

Review Article

The Efficacy of Burosumab Treatment for Hypophosphatemic Rickets: Systemic review

Abstract

Background/objective: The approval of burosumab for the treatment of X-linked hypophosphatemia (XLH) in adults and children is a significant milestone. Nevertheless, there is a scarcity of data regarding its safety and efficacy in adolescents. The primary objective of this research is to assess the safety and effectiveness of burosumab in the treatment of hypophosphatemia rickets in adolescents. **Methods:** An extensive and comprehensive search was carried out primarily utilizing the PubMed database, in accordance with the PRISMA criteria. The search parameters were confined to studies conducted in the English language that investigated the effectiveness and safety of burosumab in the treatment of hypophosphatemic rickets. Specific criteria for inclusion and exclusion were established to guarantee the quality and relevance of the research under evaluation. **Results:** The study encompassed a broad spectrum of research from various geographical regions across the globe, with no particular focus on gender or age. A discernible pattern emerged, indicating a favorable efficacy of burosumab as a therapeutic intervention for hypophosphatemic rickets. **Conclusion:** Burosumab seems to enhance results in both younger and older children with hypophosphatemic rickets. **Keywords:** Hypophosphatemic Rickets, Burosumab, Efficacy, FGF-23, Dose, Conventional Therapies.

Introduction

Rickets is a widespread condition that has a significant negative impact on the growth, development, and health of children and teenagers

worldwide[1]. It is caused by anomalies in the growth plate cartilage, which mainly affect longer bones, resulting in inadequate mineralization, poor bone development, and skeletal malformations, including knock-knees and bow-legs[2]. The primary cause of rickets is typically a shortage of calcium and phosphorus, which are essential for healthy bone development and mineralization [3].

Bones are made up of cells that play numerous roles during the bone production process. Osteoclasts degrade the bone matrix as a result of illness, aging, or remodeling, while osteoblasts build bone and secrete the extracellular matrix, mineralizing the osteoid. Calcium salts must mineralize the organic component of the bone matrix, the osteoid, for bone formation [3]. In rickets, this process is impeded, resulting in the accumulation of osteoid behind the growth plate, which leads to softening of the bone over time. Rickets can be divided into two main subgroups: phosphopenic and calcipenic. This article will focus mainly on the phosphopenic form [4].

Phosphorus is a structural element present in all bodily tissues and is essential for the mineralization of bone [5]. The bone is maintained in a healthy, functioning state by both calcium and phosphorus. Increased renal excretion of phosphate is often the cause of the problem in phosphopenic/hypophosphatemic rickets [2]. Urinary phosphate loss can occur as part of generalized tubular dysfunction, as seen in *Fanconi* syndrome, or as a result of increased synthesis or reduced catabolism of FGF-23, or inactivating mutations in genes encoding sodium-dependent phosphate transporters in the proximal renal tubule. Reduced phosphate concentration is the common mechanism in the development of both the phosphopenic and calcipenic types of rickets [6].

The primary abnormality in hypophosphatemic variants of rickets is the increased loss of phosphate through the urine. Genetic mutations in phosphate-regulating neutral endopeptidase, dentin matrix acidic phosphoprotein 1 (DMP1), or FGF23 are the causes of hereditary hypophosphatemic rickets, which are caused by X-linked dominant, autosomal recessive (ARHR), or autosomal dominant [7]. The condition

known as hypophosphatasia, which results from the ineffectiveness of the tissue nonspecific alkaline phosphatase enzyme, is not to be confused with hypophosphatemic rickets [8], which is the main point of our article.

Based on clinical indicators of rickets and/or osteomalacia, hypophosphatemia, and renal phosphate loss without lack of calcium or vitamin D, the diagnosis of X-linked hypophosphatemic rickets is made, in accordance with the European evidence-based guideline for the diagnosis and therapy. Before starting treatment, genetic testing or monitoring FGF-23 levels should be used to confirm the diagnosis of Xlinked hypophosphatemic rickets. The cornerstone of therapy continues to be phosphate supplementation, which involves giving 3-to 5-doses of elemental phosphorus (20–60 mg/kg each day). The majority of them also gain by supplementing with calcitriol (20–30 ng/kg daily) or alfacalcidol (30–50 ng/kg daily), as FGF-23 inhibits the production of 1,25 dihydroxy cholecalciferol. Urinary calcium levels should be regularly examined if calcitriol is being supplemented to prevent nephrocalcinosis [9].

The release of burosumab (KRN23), a human monoclonal antibody against FGF-23 that has been shown to be effective in children with X-linked hypophosphatemia, is a significant recent discovery [10].

61 children with X-linked hypophosphatemia from 16 clinical locations participated in a phase 3 trial that was randomized, active-controlled, open-label, and examined the safety and effectiveness of burosumab vs. oral phosphate and active vitamin D supplements as the standard of care. When compared to the group receiving standard therapy, the burosumab group had a substantial improvement in growth, serum biochemistries, and the severity of rickets [11].

52 children with Xlinked hypophosphatemia were randomly allocated, in a 1:1 ratio, to receive subcutaneous burosumab every 2 weeks or every 4 weeks in another open-label phase 2 study. The dosage of burosumab was adjusted to attain a low normal blood phosphorus level. When compared to the every 4 weeks regimen, treatment with burosumab every 2 weeks

resulted in a more sustained increase in phosphorus levels and rickets recovery [10].

In children with X-linked hypophosphatemia, burosumab was found to be beneficial in enhancing renal tubular phosphate reabsorption, blood phosphorus levels, linear development, and physical function. It also lessened rickets severity and discomfort. The cost-effectiveness and long-term outcome data of burosumab treatment are still being gathered. Injection site responses, headaches, and discomfort in the limbs are the most frequent adverse effects of burosumab treatment [10].

The U.S. Food and Drug Administration recently granted approval for it to be used for the indicated purpose in patients one year of age and older in 2018. Moreover, burosumab received conditional marketing clearance from the European Medicines Agency in February 2018. The evidence-based European guidelines advise X-linked hypophosphatemic children aged one year or older who have growing skeletons, overt bone disease visible on radiographs, refractoriness or complications, or noncompliance with conventional treatment to begin burosumab therapy at a dose of 0.4 mg/kg subcutaneously every two weeks. Burosumab dose modifications are advised no more frequently than every four weeks, with increments of 0.4 mg/kg to a maximum of 2 mg/kg, in order to keep fasting serum phosphate levels below the lower bound of the age-appropriate normal range [10]. Therefore, the present work observes the efficacy of BUROSUMAB as a new treatment for hypophosphatemic rickets.

Methods:

For this systematic review, we followed the PRISMA (Preferable Reporting Items for Systematic Reviews and Meta-Analyses) standards.

Search tactics:

A comprehensive search was conducted across multiple databases, primarily using PubMed as the study search engine, to find relevant studies. Our search was limited to English results. The following keywords were translated into PubMed Mesh terms to locate relevant studies:

"rickets," "burosumab," "hypophosphatemic," "FGF23," "X linked hypophosphatemia," and "efficacy." Boolean logic operations "OR" and "AND" were used to match the necessary keywords. The search results included human trials, articles written entirely in English, and publicly accessible materials.

Selection criteria:

Inclusion criteria for this review included studies demonstrating the efficacy of burosumab as a new treatment for hypophosphatemic rickets, clinical studies, observational studies, easily accessible and free articles, and Research carried out on a global scale has shown.

We excluded systematic reviews, meta-analyses, review articles, case reports, editor letters, and dispute resolution statements. Studies in languages other than English were also excluded.

Data extraction:

Rayyan (QCRI) was used to identify duplicates in the search strategy output [12]. The researchers filtered the combined search results using a set of inclusion/exclusion criteria to assess the relevance of the titles and abstracts. Reviewers read all papers that met the inclusion criteria in their entirety. The authors provided other methods for resolving purposeful disagreements. The researchers gathered information on the titles, authors, study year, nation, gender, participants, main outcomes, and conclusions.

Data synthesis technique:

A qualitative overview of the study's results and components was created by generating summary tables using information from relevant research. After data extraction for the systematic review, the most effective technique for using the data from the included study articles was selected.

Risk of bias assessment:

A quality assessment of the included studies was conducted using the ROBINS-I risk of bias assessment approach for non-randomized treatment trials [13]. Seven factors were assessed: confounding, selection of study

subjects, classification of interventions, deviations from planned interventions, incomplete data, assessment of outcomes, and selection of published results.

Results

Search results

A total of 340 research articles were identified through the systematic search; 120 of those were automatically excluded. After screening the titles and abstracts of 220 papers, 80 studies were deemed unsuitable for publication. Only 45 publications were found out of the 140 studies that were requested for retrieval. 87 out of the 95 publications screened for full-text review were rejected due to inappropriate study designs or conclusions. Eight research papers met the eligibility criteria for this systematic review. A summary of the research selection process is depicted in **Figure 1**.

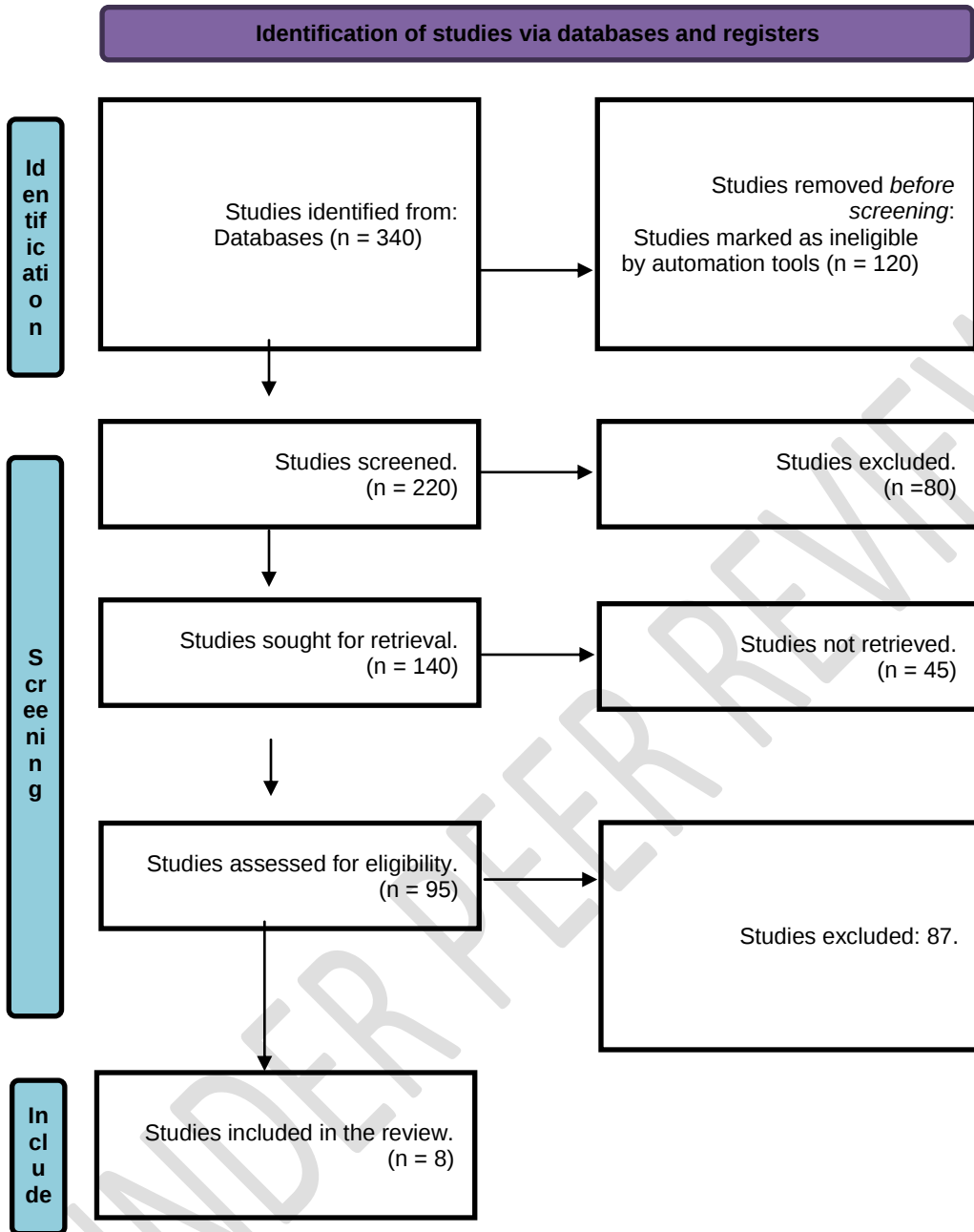


Figure (1): PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table 1: Socio-demographic Characteristics of Participants

The socio-demographic information of participants from eight distinct research studies is included in Table (1), which summarizes the small number of patients from references [14–21]. These studies' geographic scope is expansive, encompassing countries such as the UK [14], Milan [15], and Japan [17].

The research methodology of the reviewed studies [14,15,17,20] used a retrospective cohort study, while other studies [16, 18, 19] were trials.

The age range of patients was without restrictions, including patients from 1 year to 70 years. Walker, Emma Yi Xiu, et al 2023 [14], Carpenter, Thomas O., et al 2018 [16], Harada, Daisuke, et al. 2021[17], Ward, Leanne M., et al. 2022 [18], and Levy-Shraga, Yael, et al. 2023 [20] focused on children in their studies, with median ages of 11.7 years, 5 - 12 years, 10.4 ± 1.9 years, 1-12 years, and 7.5 ± 4.4 years, respectively. Additionally, according to Arcidiacono, Teresa, et al. 2023 [15], Briot, Karine, et al. 2022 [19], and Kamenicky P, Briot K, Brandi ML, et al. 2022 [21], the studies were conducted on elders with age ranges of 20 - 59 years, 18.5–65.5 years, and 18.5–59.9 years, respectively.

Table (2): Treatment -related information and the form of rickets of the included participants.

The studies detailed the treatment steps for hypophosphatemic rickets, particularly X-linked hypophosphatemic rickets [14-21]. Most studies in principle, before starting with burosumab utilized conventional therapies such as phosphorus supplements, vitamin D, and growth hormones, as outlined in Walker, Emma Yi Xiu, et al 2023 [14], Harada, Daisuke, et al. 2021[17], and Levy-Shraga, Yael, et al.2023 [20].

The doses of burosumab administered to patients varied, with Walker, Emma Yi Xiu, et al 2023 [14], Arcidiacono, Teresa, et al. 2023 [15], and Kamenicky P, Briot K, Brandi ML, et al. 2022 [21] reporting doses of 1.17 mg/kg per dose, 1 mg/kg s.c. every 28 days, and 0.9 to 1.5mg/kg, respectively. Harada, Daisuke, et al. 2021[17] and Ward, Leanne M., et al. 2022 [18] indicated doses of 0.8 mg/kg every two weeks. Carpenter,

Thomas O., et al 2018 [16] and Levy-Shraga, Yael, et al.2023 [20] mentioned initial doses (0.1 mg / kg every 2 weeks or 0.2 mg /kg every 4 weeks), escalating to doses of 0.2 or 0.3 mg /kg every 2 weeks, or 0.4 or 0.6 mg /kg every 4 weeks.

The duration of burosumab treatment which were adopted varied across studies. Walker, Emma Yi Xiu, et al 2023 [14] and Levy-Shraga, Yael, et al.2023 [20] noted a duration of around 3 years. Carpenter, Thomas O., et al. 2018 [16] and Ward, Leanne M., et al. 2022 [18] reported a duration of 64 weeks to observe the drug's efficacy. Briot, Karine, et al. 2022 [19] and Kamenicky P, Briot K, Brandi ML, et al. 2022 [21] indicated a duration of 96 weeks for the drug.

Table (3): Extent of burosumab effect and major outcomes of the included participants.

The efficacy of burosumab in treating rickets, particularly X-linked hypophosphatemic form, has been shown to significantly improve serum phosphate levels and physical performance[15, 19, 20, 21]. It has also been found to enhance linear growth[20] in both adults[15] and children[17], as well as significantly improve the RGI-C rickets total score[18].

The studies have highlighted the positive effects of regular burosumab treatment on patients with X-linked hypophosphatemia. For instance, studies by Walker et al. [14] and Levy-Shraga et al. [20] in 2023 showed a significant increase in height in children treated every 2 weeks with burosumab. Additionally, a six-month burosumab treatment was found to significantly improve the general condition and physical performance of adult patients with XLH, as reported by Arcidiacono et al. [15] in 2023. Carpenter et al. [16] in 2018 and Harada et al. [17] in 2021 also noted that burosumab treatment was associated with an increase in renal tubular phosphate reabsorption and the correction of hypophosphatemia in children with XLH. However, Ward et al. [18] in 2022 reported that pain occurred more frequently with burosumab than Pi/D in older children, and dental abscesses were common in older children who received burosumab.

Cough and headache were also frequently reported among children who received burosumab. Nevertheless, Briot et al. [19] in 2022 confirmed that there was a statistically significant improvement in 6 Min Walk Test distance and percent predicted at all-time points from 24 weeks. Kamenicky et al. [21] in 2022 also stated that long-term treatment with burosumab helped maintain Serum 1,25(OH)₂ D concentrations.

Table (1): Socio-demographic characteristics of the included participants.

Study	Country	Study design	Sample size	Age	Gender	Duration of study
Walker, Emma Yi Xiu, et al 2023 [14]	UK	retrospective cohort study	55 patients	median age of 11.7 years	21 male and 34 female	December 2014 and August 2022
Arcidiacono, Teresa, et al. 2023 [15]	Milan, Turin	Cohort study	8 patients	20 - 59 years	5 male and 3 female	NA
Carpenter, Thomas O., et al 2018 [16]	NA	randomized, open-label, parallel-group, phase 2 trial	52 patients	5 - 12 years	46% male	NA
Harada, Daisuke, et al. 2021[17]	Japan	Retrospective study	8 patients	10.4 ± 1.9 years	2 male, 6 female	December 2016- July 2017
Ward, Leanne M., et al. 2022 [18]	NA	open-label, randomized controlled study	61 patients	1-12 years	NA	August 3, 2016, to May 8, 2017
Briot, Karine, et al. 2022 [19]	NA	randomised phase 3 trial and open-label extension	134	18.5–65.5 years	87 female	NA
Levy-Shraga, Yael, et al.2023 [20]	Israel	multi-center retrospective study	35 patients	7.5 ± 4.4 years	51% male	January 2018 and January 2021
Kamenicky P, Briot K, Brandi ML, et al.	NA	randomised, double-blind, placebo controlled study	31	18.5–59.9 years	68% female	

2022 [21]						
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Table (2): Treatment related information and the form of rickets of the included participants.

Study	conventional therapies	Dose of burosumab	Duration of treatment with burosumab	Form of rickets
Walker, Emma Yi Xiu, et al 2023 [14]	phosphate supplements and vitamin D.	1.17 mg/kg per dose	Median duration was 3.3 years	X-linked hypophosphatemia rickets
Arcidiacono, Teresa, et al. 2023 [15]	NA	1 mg/kg s.c. every 28 days	NA	X-linked hypophosphatemia rickets
Carpenter, Thomas O., et al 2018 [16]	NA	initial doses (0.1 mg / kg every 2 weeks or 0.2 mg /kg every 4 weeks) , escalating doses (0.2 or 0.3 mg /kg every 2 weeks, or 0.4 or 0.6 mg /kg every 4 weeks)	64 weeks	X-linked hypophosphatemia rickets
Harada, Daisuke, et al. 2021[17]	alfacalcidol (150.9 ± 43.9 ng/kg per day) and phosphate (27.5 ± 6.3 mg/kg per day)	0.8–1.2 mg/kg every two weeks	NA	X-linked hypophosphatemia rickets
Ward, Leanne M., et al. 2022 [18]	NA	0.8 mg/kg every 2 weeks	64-week	X-linked hypophosphatemia rickets
Briot, Karine, et al. 2022 [19]	NA	NA	96 weeks	X-linked hypophosphatemia rickets
Levy-Shraga, Yael, et	oral phosphate supplement and	mean initial dose of 0.8 ± 0.3 mg/kg, which	2.9 ± 1.4 years	X-linked hypophosphatemia

<i>al. 2023 [20]</i>	alfacalcidol/ growth hormone	was subsequently increased to 1.1 ± 0.4 mg/kg every 2 weeks		rickets
Kamenicky P, Briot K, Brandi ML, et al. 2022 [21]	NA	0.9 to 1.5mg/kg	96 weeks	X-linked hypophosphatemia rickets

Table (3): Extent of burosumab effect and major outcomes of the included participants.

Study	Extent of burosumab effect	Major outcomes
Walker, Emma Yi Xiu, et al 2023 [14]	the effect of burosumab improve rickets condition	significant although modest change in height in children treated with regular (every 2 weeks) burosumab.
Arcidiacono, Teresa, et al. 2023 [15]	the effect of burosumab on serum phosphate and physical performance was evaluated in adult patients with XLH to identify which one was more indicative of its therapeutical efficacy	a six-month burosumab treatment may significantly improve the general condition and physical performance of adult patients with XLH; this improvement was more stable and more indicative of treatment efficacy than that of serum phosphate.
Carpenter, Thomas O., et al 2018 [16]	By week 40, rickets was significantly ameliorated, with a mean Thatcher rickets severity total score of 0.8 in the every-2-week dosing group and 1.1 in the every-4-week dosing group	inhibition of FGF-23 activity with burosumab, was associated with an increase in renal tubular phosphate reabsorption and the correction of hypophosphatemia in children with X-linked hypophosphatemia.
Harada, Daisuke, et al. 2021[17]	Burosumab tended to improve rickets in partly controlled XLH children	burosumab improved the renal reabsorption of P (TmP/GFR and %TRP) compared to that at the baseline, which was unchanged by conventional therapy
Ward, Leanne M., et al. 2022 [18]	burosumab, compared with Pi/D, significantly improved LS mean (SE) RGI-C rickets total score, at week 64 both in younger children and in older children	pain occurred more frequently with burosumab than Pi/D in older children but not in younger children. dental abscesses occurred in 53% of the older children who received burosumab. Cough and headache were frequently reported among children who received burosumab
Briot, Karine, et al. 2022 [19]	Burosumab treatment improved phosphate homoeostasis	Burosumab treatment was associated with a steady and consistent improvement in PROs and ambulatory function. Improvement in 6MWT distance and percent predicted were statistically

		significant at all time points from 24 weeks.
<i>Levy-Shraga, Yael, et al. 2023 [20]</i>	Burosumab treatment in a real-life setting improved phosphate homeostasis and rickets severity, and enhanced linear growth.	despite treatment with conventional therapy for a mean 5.4 years, some patients still presented with persistent rickets and short stature at the initiation of burosumab treatment
<i>Kamenicky P, Briot K, Brandi ML, et al. 2022 [21]</i>	burosumab treatment was associated with initial improvements and then maintenance of serum phosphate and 1,25(OH) ₂ D concentrations and phosphate reabsorption (TmP/GFR)	the correction of serum phosphate concentrations to above the LLN observed in the phase 3 trial through to week 96 is maintained with long-term burosumab treatment for a further 48 weeks in the open-label extension. Serum 1,25(OH) ₂ D concentrations were also maintained with long-term treatment

Discussion

Oral phosphate salts and active vitamin D have been the mainstay of treatment for X-linked hypophosphatemia for over 40 years with Multiple daily doses are required. Because of the difficulties associated with several daily doses, parental supervision, and inadequate phosphate preparations, this technique is sometimes hard to sustain, especially in younger kids [22]. Newly, Burosumab, a FGF-23 monoclonal antibody, has been shown to enhance phosphate metabolism, lessen the severity of rickets, promote development and activity, and lessen discomfort in patients with hypophosphatemia rickets [16].

Burosumab is being registered in other GCC nations after being approved by regulatory bodies in Europe, the USA, the UAE, and Oman. The Food and Drug Administration (FDA) and the European Medicines Authority (EMA) have authorized burosumab for the treatment of XLH in children and adults starting at age six months, as well as in adolescents with expanding bones and toddlers starting at age one year. Since burosumab is a novel medication, information about its real-world, long-term effectiveness, and post-marketing pharmacovigilance should be gathered via global and local XLH registries. Injection site responses, headaches, toothaches, and myalgia are examples of short-term adverse effects [11].

The first clinical trial assessing burosumab's efficacy was published in 2014. The purpose of this double-blind, placebo-controlled study was to evaluate the antibody's efficacy in treating patients with XLH based on the mode and route of administration. 38 XLH patients were included in this trial and were given either a placebo or a single dosage of burosumab KRN23 (0.003-0.3 mg/kg i.v. or 0.1-1 mg/kg s.c.). Positive outcomes, including a significant increase in serum Pi, 1,25(OH)₂D, and the maximum renal tubular threshold for phosphate reabsorption (TmP/GFR), were observed in both the subcutaneous and intravenous drug groups. However, the subcutaneous group's benefits persisted longer. Subcutaneously administered groups reached their maximal serum level later. After intravenous and subcutaneous injection, the mean T_{1/2} of KRN23 was shown to be 8–12 days and 13–19 days, respectively. Over the course of 50 days, patients were monitored as burosumab's pharmacokinetics, pharmacodynamics, immunogenicity, safety, and tolerability were also investigated. The majority of patients experienced nausea (24%) and headaches (18%) in the intravenous group, raised serum amylase (17%) and back pain (17%) in the SC group, however none of these adverse effects were severe enough to prevent the patients from continuing in the experiment. The outcomes showed that burosumab ought to be regarded as a beneficial medication for XLH patients [23].

The patient's weight and the blood phosphate concentrations while fasting are used to calculate the burosumab dosage. Every two weeks for children and every four weeks for adults, it is administered by subcutaneous injection. It takes 7–13 days following the injection for burosumab to reach its optimum concentration. Its half-life is around eighteen days, and it is most likely eliminated like other antibodies. Patients with significant renal impairment should not be treated with burosumab. Co-administration of vitamin D and phosphate is another contraindication. Stopping these supplements one week before to beginning burosumab is recommended [24].

In the phase 2 trial, burosumab medication normalized fasting blood phosphate levels, decreased serum alkaline phosphatase, and reduced the severity of rickets in children with XLH, aged 1 to 12 years. In the phase 3 randomized open-label research, children with XLH aged 1 to 12 received burosumab treatment in addition to standard therapy. Prior to being enrolled in the study, each individual had received traditional treatment. According to the findings, burosumab outperformed traditional therapy in reducing the severity of rickets, reducing alkaline phosphatase and serum phosphate levels, and promoting development, mobility, and deformities in the lower limbs [11].

Serum phosphate and physical tests revealed different responses to burosumab during the six-month follow-up period, indicating that quality-of-life surveys and physical testing may be better indicators of burosumab's effectiveness in XLH patients than serum phosphate levels. Therefore, physical recovery may be considered a primary goal of burosumab therapy, and results from physical performance assessments could be the most useful indicators of this medication's clinical effectiveness in adult XLH patients. Skeletal muscle performance tests may need to be included in clinical follow-ups to fully assess individuals with XLH. The results were related to patients' tubular phosphate reabsorption and blood phosphate concentrations, suggesting that the walking test seemed to be a better indicator of burosumab's impact [15].

Burosumab-induced improvements in skeletal muscle performance were not attributed to changes in muscle mass but rather to enhanced muscle cell function, as supported by the restoration of serum phosphate and vitamin D levels [25]. This allowed for increased availability of these nutrients for metabolic processes and the deactivation of FGF23's inhibitory effect on skeletal myocytes. Research revealed that skeletal myocytes possess the FGF23 receptor, which can directly influence myocyte activity. Additionally, FGF23 was found to induce premature senescence in mesenchymal stem cells derived from skeletal muscle through an oxidative stress pathway in in vitro studies [26].

Regarding future research on burosumab, Many of the published studies are expected to provide further research and follow-up of adult and pediatric XLH patients receiving burosumab to evaluate the long-term benefits and any concerns related to long-term use. Several additional clinical trials aiming to address more specific issues have also been filed.

Conclusion

The breakthrough of burosumab as a medicinal treatment has completely transformed the way XLH is treated and is much better than the traditional methods for both adults and children. Even though the impact on serum phosphate levels may lessen after the first few weeks of treatment, it improves the overall health and physical abilities. In medical practice, evaluations for skeletal muscle function, discomfort, and disability can be used to evaluate people with XLH and to guide burosumab therapy for these patients.

References

1. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. *Nature Reviews Disease Primers*. 2017 Dec 21;3(1):1-20.
2. Jagtap VS, Sarathi V, Lila AR, Bandgar T, Menon P, Shah NS. Hypophosphatemic rickets. *Indian journal of endocrinology and metabolism*. 2012 Mar;16(2):177.
3. Vupperla D, Lunge SB, Elaprolu P. Vitamin D-dependent rickets Type II with alopecia: a rare case report. *Indian Journal of Dermatology*. 2018 Mar;63(2):176.
4. Tiosano D, Hochberg ZE. Hypophosphatemia: the common denominator of all rickets. *Journal of bone and mineral metabolism*. 2009 Jul;27:392-401.
5. Goldsweig BK, Carpenter TO. Hypophosphatemic rickets: lessons from disrupted FGF23 control of phosphorus homeostasis. *Current osteoporosis reports*. 2015 Apr;13:88-97.
6. Mughal MZ. Rickets. *Current osteoporosis reports*. 2011 Dec;9:291-9.
7. Sabbagh Y, Carpenter TO, Demay MB. Hypophosphatemia leads to rickets by impairing caspase-mediated apoptosis of hypertrophic chondrocytes. *Proceedings of the National Academy of Sciences*. 2005 Jul 5;102(27):9637-42.
8. Whyte MP. Hypophosphatasia: an overview for 2017. *Bone*. 2017 Sep 1;102:15-25.

9. Imel EA, Liu Z, Coffman M, Acton D, Mehta R, Econs MJ. Oral iron replacement normalizes fibroblast growth factor 23 in iron-deficient patients with autosomal dominant hypophosphatemic rickets. *Journal of Bone and Mineral Research*. 2020 Feb;35(2):231-8.
10. Carpenter TO, Whyte MP, Imel EA, Boot AM, Höglér W, Linglart A, Padidela R, van't Hoff W, Mao M, Chen CY, Skrinar A. Burosumab therapy in children with X-linked hypophosphatemia. *New England Journal of Medicine*. 2018 May 24;378(21):1987-98.
11. Imel EA, Glorieux FH, Whyte MP, Munns CF, Ward LM, Nilsson O, Simmons JH, Padidela R, Namba N, Cheong HI, Pitukcheewanont P. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *The Lancet*. 2019 Jun 15;393(10189):2416-27.
12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Systematic reviews*. 2016 Dec;5:1-0.
13. Jüni P, Loke Y, Pigott T, Ramsay C, Regidor D, Rothstein H, Sandhu L, Santaguida PL, Schünemann HJ, Shea B. Risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance. *Br Med J*. 2016;355:i4919.
14. Walker EY, Lindsay TA, Allgrove J, Marlais M, Bockenbauer D, Hayes W. Burosumab in management of X-linked hypophosphataemia: a retrospective cohort study of growth and serum phosphate levels. *Archives of Disease in Childhood*. 2023 May 1;108(5):379-84.
15. Arcidiacono T, Foligno NE, Brioni E, Bologna A, Weber G, Mora S, Pitea M, Vitale C, Vezzoli G. Different Efficacy of Burosumab on Physical Performance and Serum Phosphate in Adult Patients with X-Linked Hypophosphatemic Rickets during the First Six-Month of Treatment. *Journal of Clinical Medicine*. 2023 Apr 17;12(8):2906.
16. Carpenter TO, Whyte MP, Imel EA, Boot AM, Höglér W, Linglart A, Padidela R, van't Hoff W, Mao M, Chen CY, Skrinar A. Burosumab therapy in children with X-linked hypophosphatemia. *New England Journal of Medicine*. 2018 May 24;378(21):1987-98.
17. Harada D, Ueyama K, Oriyama K, Ishiura Y, Kashiwagi H, Yamada H, Seino Y. Switching from conventional therapy to burosumab injection has the potential to prevent nephrocalcinosis in patients with X-linked hypophosphatemic rickets. *Journal of Pediatric Endocrinology and Metabolism*. 2021 Jun 25;34(6):791-8.
18. Ward LM, Glorieux FH, Whyte MP, Munns CF, Portale AA, Höglér W, Simmons JH, Gottesman GS, Padidela R, Namba N, Cheong HI. Effect of burosumab compared with conventional therapy on younger vs older children with X-linked hypophosphatemia. *The Journal of Clinical Endocrinology & Metabolism*. 2022 Aug 1;107(8):e3241-53.
19. Briot K, Portale AA, Brandi ML, Carpenter TO, Cheong HI, Cohen-Solal M, Crowley RK, Eastell R, Imanishi Y, Ing S, Insogna K. 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 Sep 1;7(3):e001714.
20. Levy-Shraga Y, Levi S, Regev R, Gal S, Brenner A, Lebenthal Y, Gillis D, Strich D, Zung A, Cleper R, Borovitz Y. Linear growth of children with X-linked hypophosphatemia treated

with burosumab: a real-life observational study. *European Journal of Pediatrics*. 2023 Sep 14:1-2.

- 21.** Kamenicky P, Briot K, Brandi ML, Cohen-Solal M, Crowley RK, Keen R, Kolta S, Lachmann RH, Lecoq AL, Ralston SH, Walsh JS. Benefit of burosumab in adults with X-linked hypophosphataemia (XLH) is maintained with long-term treatment. *RMD open*. 2023 Feb 1;9(1):e002676.
- 22.** Linglart A, Bioso-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, Kamenicky P, Nevoux J, Prié D, Rothenbuhler A, Wicart P. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocrine connections*. 2014 Mar 3;3(1):R13.
- 23.** Carpenter TO, Imel EA, Ruppe MD, Weber TJ, Klausner MA, Wooddell MM, Kawakami T, Ito T, Zhang X, Humphrey J, Insogna KL. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. *The Journal of clinical investigation*. 2014 Apr 1;124(4):1587-97.
- 24.** Whyte MP, Carpenter TO, Gottesman GS, Mao M, Skrinar A, San Martin J, Imel EA. Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *The lancet Diabetes & endocrinology*. 2019 Mar 1;7(3):189-99.
- 25.** Brener A, Lebenthal Y, Cleper R, Kapusta L, Zeitlin L. Body composition and cardiometabolic health of pediatric patients with X-linked hypophosphatemia (XLH) under burosumab therapy. *Therapeutic Advances in Endocrinology and Metabolism*. 2021 Mar;12:20420188211001150.
- 26.** Avin KG, Vallejo JA, Chen NX, Wang K, Touchberry CD, Brotto M, Dallas SL, Moe SM, Wacker MJ. Fibroblast growth factor 23 does not directly influence skeletal muscle cell proliferation and differentiation or ex vivo muscle contractility. *American Journal of Physiology-Endocrinology and Metabolism*. 2018 Oct 1;315(4):E594-604.