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Burosumab - new potent treatment for X-linked hypophosphatemia and tumor-induced osteomalacia

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Summary:

Introduction and purpose:

Elevated FGF23 in X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO) leads to systemic hypophosphatemia, several musculoskeletal manifestations and rickets in children. In this review we describe advances in the management of XLH and TIO using burosumab, which is a new therapeutic option approved both for adults and children. A search was conducted using PubMed and Google Scholarship databases.

Brief description of the state of knowledge:

Patients with XLH and TIO exhibit a similar clinical picture and way of treatment. Although in TIO surgery is the only definitive treatment, some tumors cannot be removed due to their location. In this case oral conventional therapy is used in treating both in TIO and XLH. Another approved treatment option is the use of burosumab, which is a fully humanised FGF23-antibody. This therapy led to normalisation of phosphate homoeostasis and resulted in improvement of bone turnover, fracture healing, subjective pain, and physical function. Compared to conventional, oral therapy burosumab has been shown to be superior for treatment of XLH and TIO.

Conclusions:

While burosumab appears to improve treatment outcomes, the effects of chronic or lifelong use have yet to be established. Long term follow-up studies would be necessary to assess especially the potential risk of nephrocalcinosis and cardiac calcification.

Key words: XLH; TIO; burosumab; health;

1. Introduction

The fibroblast growth factor 23 (FGF23) participates in maintaining the proper calcium-phosphate balance in the body by reducing phosphate reabsorption in the kidneys and synthesis of 1,25-dihydroxyvitamin D inhibiting. Physiologically, FGF23 is secreted by osteocytes under the influence of high concentrations of calcitriol in the plasma [1]. However, high levels of FGF23 may appear in many diseases including: X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, fibrous dysplasia/McCune-Albright syndrome and tumor-induced osteomalacia (TIO). Currently, supplementation and symptomatic treatment are used in patients with calcium and phosphate dysregulation. In recent years, burosumab has been approved for the treatment of patients with XLH and TIO. Burosumab is a fully human IgG1 monoclonal antibody to FGF23 [2]. This is a new and promising treatment method aimed at reducing the symptoms of hypophosphatemia resulting from the activity of FGF23 and its consequences, such as bone and muscle pain which may lead to bone deformities, and early degenerative arthropathy [3,4].

2.1 Burosumab in the treatment of adult XLH

First clinical trial that evaluated the effectiveness of burosumab was released in 2014. This double blind placebo controlled trial aimed to assess the activity of this antibody on patients diagnosed with XLH depending on the method and route of administration. This study cohorted 38 patients with XLH that received either a single dose of burosumab KRN23 (0.003-0.3 mg/kg i.v. or 0.1-1 mg/kg s.c.) or placebo. Positive results -significant increase of the maximum renal tubular threshold for phosphate reabsorption (TmP/GFR), serum Pi, and 1,25(OH)2D - were noted in both groups - the one that received drug subcutaneously and also in a group that received it intravenously although positive effects lasted longer in a group with subcutaneous administration. The group with subcutaneous administration gained maximum serum level later. The mean T1/2 of KRN23 was 8-12 days after intravenous (i.v.) administration and 13-19 days after subcutaneous (s.c.) administration. Patients were observed within a period of 50 days while the pharmacokinetics, pharmacodynamics, immunogenicity, safety and tolerability of burosumab were also examined. Patients did not exhibit serious side effects, mostly reported nausea (24%) and headache (18%) in the i.v. group, elevated serum amylase (17%) and back pain (17%) in the s.c. group, but none of this led to discontinue the involvement in a trial. The results suggested that burosumab should be taken into consideration as a favourable drug in patients with XLH [5].

The conclusions from this study were further supported by papers published by Zhung et al. Authors focused on pharmacokinetic and pharmacodynamic values of burosumab. Typical time to reach maximum serum KRN23 levels was 7.0 to 8.5 days and its half-life mean time was 16.4 days [6,7].

Burosumab turned out to be safe also in a prolonged observation in an open-label trial. Twenty-eight adults with XLH were cohorted to participate in a 4-month dose-escalation study (0.05–0.6 mg/kg); 22 out of them entered a 12-month extension study (0.1–1 mg/kg). They received drug subcutaneously every 28 days. During this study high incidence of adverse events (AE) were recognized although most of them were mild or unrelated to the drug. Two participants had mild intermittent hypercalcemia, one patient had persistently elevated urinary calcium excretion, three subjects had solitary hypercalciuria and one intermittent hypercalciuria [8]. Participants of this study were later measured with the SF-36v2 (Short Form Health Survey) and WOMAC (Western Ontario and McMaster Universities Index of Osteoarthritis) tools for assessing health related quality of life in XLH. Patient's view of their Physical Functioning and Stiffness changed positively [9].

Following the positive results of previous papers, the first study conducted on Asians was published in 2018 and also noted similar positive treatment responses with adverse events that were described as not clinically meaningful [10].

In 2018 another study conducted in multiple countries on 134 adults aged between 18 and 65 years with XLH was published. Participants were also the ones with confirmed PHAX mutation. The group that received burosumab showed significant improvement in phosphate level. The burosumab group also noted an improvement in pain and had better results in WOMAC scale. This study also did not recognize serious AE although the frequency of them was high [11].

Beneficial effects of burosumab were recently evaluated by Kamenicky et al. Authors concluded that favourable effects of this drug on patients with XLH should be maintained with long-term treatment for best results. During this study higher levels of serum phosphate, serum 1,25 dihydroxyvitamin D and renal phosphate reabsorption at 96 weeks of treatment were maintained through the 48-week prolongation. Results were also preserved in stiffness and

physical function measured with the Western Ontario and McMaster Universities Osteoarthritis Index, pain and fatigue endpoints measuring using the Brief Pain Inventory short-form and Brief Pain Inventory, respectively, and in ambulatory function (6-Minute Walk Test). Authors of this paper established that long-term treatment of burosumab is needed to keep up therapeutic effects [12].
Further research supported the previously made conclusion that burosumab is safe and effective treatment without serious AE even with long-term use- the cohort of patients with XLH were examined within a period of 184 weeks without alarming occurrences that would bring into question burosumab usage [13].
Another long study with similar results was the one conducted by Briot et al. Patients were observed over a duration of 96 weeks. Participants noted continuous improvement since week 24 [14].
In 2019 Brandi et al. started the 10-year retrospective and prospective cohort study utilising data from the International XLH Registry. Results are expected to come in 2028 and they will enrich current knowledge about burosumab safety and potency[15].
As burosumab is gaining more attention worldwide, recently, the efficacy and safety of self- administration was evaluated in two open-label, single-arm clinical trials and the results revealed that burosumab can be successfully self-managed by patients without significant impact on effectiveness. Studies also did not highlight serious AE [16].
Although clinical trials show mostly positive impact on treating XLH with burosumab, further research is needed to evaluate its specific role in different phenotypes of XLH. Zegari et al. described the clinical case of two patients whose after ineffective treatment of XLH with phosphates started therapy with burosumab. Symptoms were relieved, but biochemical parameters did not change significantly. Authors draw the conclusion that the poor treatment effect could be associated with the missense "de novo" mutation, c.250G>C (p.Ala84Pro) in the PHEX gene and more data is needed to explore the possible link [17].

2.2 Burosumab in the treatment of pediatric XLH

In 2018 Carpenter et al. conducted a trial, which aimed to compare 2 and 4 week dosing schedules of burosumab in children with XLH. The primary outcome was assessed with the Thacher rickets severity score, biochemical markers such as serum Pi and serum alkaline phospatase, as well as functional measures of physical ability. Burosumab therapy resulted in a decrease in rickets severity by Thacher score in both groups and while the 2 week group showed a lower mean than the 4 week group, this was not reported to be statistically significant. Moreover, burosumab normalised biochemical measures, however serum Pi fluctuated considerably less with 2 week dosing compared to every 4 weeks. In this trial adverse events and serious adverse events were recorded and a range of minor AEs were reported, such as injection-site reactions, headaches and cough, although these were less common in the 4 week dosing group. Once there was a serious AE noticed - one patient was hospitalized for myalgia and fever that were of moderate severity and potentially linked to treatment. Despite this, the patient continued with treatment and no AEs reoccurred [18].
Radiographic, biochemistry and safety outcomes of burosumab therapy were also analyzed in toddlers by Whyte et al. A small group of 13 children with XLH were examined during 64 weeks of treatment and an optional 96 week extension period. The results were similar to the previously mentioned trial - normalisation of serum Pi and improvement in Thacher rickets severity score at 40 and 64 weeks were observed. Also a range of mild to moderate AE were noticed for all patients which include: cough, pyrexia and respiratory tract infections. Additionally, two cases of injection site erythema were reported, which are likely related to treatment and one severe adverse reaction (a food allergic reaction) was noticed, but unrelated to burosumab therapy [19].
A similar protocol to prior groups was used by Ramos et al. in the group of five children aged 6-16 with confirmed PHEX mutations who received burosumab therapy. It resulted in a positive effect on growth in 3/5 children, where a marked improvement was noted. In all children normalisation of serum phosphate in association with marked increase of tubular reabsorption of phosphate and reduction of elevated serum alkaline phosphatase levels were observed. As reported, the biggest benefit of burosumab treatment for children and their
families was the elimination of the need for routine oral phosphate supplementation [20].
In 2019 Imel et al. compared burosumab and conventional therapy (CT) in children with XLH. Children aged 1-12 had been taking part in this trial for 64 weeks, although the primary outcome was assessed at 40 weeks. In addition to biochemical and radiographic changes a statistically significant improvement in height was noticed in children treated with burosumab. They also showed a significantly greater improvement in distance walked during a 6-min walk test [21].
Burosumab also turned out to be more effective in treating children with XLH compared to CT with phosphate salts and active vitamin D (Pi/D) in another study. Ward et al. found normalisation of phosphate homeostasis and declines in ALP , however they were consistently greater with burosumab than Pi/D. These changes were also reflected in clinical and radiographic characteristics including improved growth, rickets healing, and lower limb

deformity. Moreover, serum ALP was lower at week 64 in children who received burosumab compared with those who received CT, reflecting a decrease in bone turnover and this decline was greater in the older group compared with younger children receiving burosumab. However, this observation might be also explained as the normal decrease in bone turnover that occurs in older children as they approach skeletal maturity [22].

Following these promising results in 2022 Linglart et al. conducted an open-label, multicenter, randomized, dose-finding trial of the efficacy and safety of burosumab in 52 children aged 5-12 with XLH. Firstly they were randomized to receive burosumab injections subcutaneously either every 2 weeks (Q2W) or every 4 weeks (Q4W) for the first 64 weeks and during an initial 16-week dose-escalation period, the dose of burosumab was increased. Then because of biochemical evidence that serum phosphorus concentrations were more stable over time with the Q2W regimen, children in the Q4W group transitioned to the Q2W regimen at week 64 and were administered 60% of their established Q4W total dose (rounded to the nearest 10 mg) biweekly through week 160. As reported, burosumab induced an increase in serum phosphorus levels and nearly all (96%, 50/52) children achieved a normal serum phosphorus level well before week 160. The other 2 nevertheless showed improvements in rickets severity as assessed by change from baseline in RSS scores and in the RGI-C. Also serum 1,25(OH)2D concentrations increased significantly from baseline ($P < 0.05$) for both dose groups and burosumab was also associated with significant decrease in ALP activity, which is a rickets severity marker. This study also reported an increase of mean standing height z-score and growth velocity (centimeters/year). All children experienced ≥ 1 AEs, however most of them were mild to moderate in severity. One child had 2 AEs, which were classified as serious because of brief hospitalizations (fever/muscle pain at week 48 and headache at week 182); each resolved within 1 week and neither were considered related to burosumab. No child discontinued therapy, presented hyperphosphatemia, or had clinically meaningful increases in serum calcium concentration, urine calcium excretion, or circulating PTH [23].

The study conducted by Ertl et al. aimed to examine the growth patterns of 36 children affected by XLH who were treated with burosumab after switching from CT. Aditionally it also analyzed the growth response and the safety of rhGH in XLH children treated with the combination of burosumab and rhGH for at least 1 year after switching to burosumab. Children treated with burosumab alone showed a minimal change in height SDS after 1 year (mean ± SD 0.0 ± 0.3 prepubertal vs. 0.1 ± 0.3 pubertal participants), while the others, who continued rhGH therapy after switching to burosumab, clearly improved height during the first year of treatment before initiating burosumab (mean ± SD of height gain 1.0 ± 0.4); patients continued to gain height during the year of combined burosumab and rhGH therapies (mean ± SD height gain 0.2 ± 0.1). In this study it was proven, that burosumab therapy alone does not have any visible effect on height SDS, but that rhGH therapy led to catch-up growth during conventional therapy, as expected, an effect that was maintained throughout when patients were switched to burosumab therapy [24].

As Brener et al. revealed, burosumab may have beneficial impact on body composition of pediatric patients with XLH. This observational real-life study was conducted on 15 children, in whom baseline BIA revealed an unfavorable physique, with increased body fat percentage in five patients and decreased muscle mass in six. The findings of this analysis showed improvement of body composition as evidenced by decreased adiposity with a simultaneous increase in muscle mass. After 12 months under burosumab treatment linear growth and severity of the rickets were improved. These findings also presented that the greater improvement in rickets score under burosumab treatment was associated with older age and with a less pronounced improvement in the composite index of MFR and highlighted the need to initiate burosumab treatment at a younger age when rickets is less severe [25].

Originally, burosumab was approved to be administered by a healthcare professional, but the possibility of self-administration might be beneficial for patients as it can provide easier access to treatment. As mentioned, the study conducted in Japan and Korea by Kubota et al. which has assessed the safety and efficacy of self-administration of burosumab, proved that it is a viable option also for children with XLH [16].

The effect of burosumab on dental health in ten children with XLH has been assessed by Brener et al. This trial revealed that dental morphology of XLH patients, distinguished by increased pulp-coronal ratios compared to controls ($p=0.002$), remained larger after the first year of treatment ($p<0.001$) and did not attain the decrease expected with age after three years of treatment. Moreover, five children suffered from recurrent dental abscesses, with three having undergone at least one episode during the year before burosumab therapy. One of the children sustained recurrent abscesses throughout three years of treatment. This prospective study is the first, which reveals that the unique dental morphology of excessively larger pulp dimensions in patients with XLH persisted during three years of burosumab therapy [26].

Previously mentioned dental abscesses frequently accompany rickets in XLH and increase the risk of tooth loss and may lead to facial cellulitis. A retrospective study by Gadion et al. analyzed the incidence of dental abscesses in 71 children with XLH treated with either CT or burosumab, who were observed for at least 1 year. Burosumab therapy resulted in reduced mean number of dental abscesses per month of dental follow-up compared with CT group [27].

Although these results are encouraging, they need to be confirmed in other studies. Therefore, as well as adults, children have been also assessed in the previously mentioned 10-year retrospective and prospective cohort study in order to evaluate the safety outcomes of burosumab administration [15].

2.3 Burosumab in the treatment of tumor induced osteomalacia

Tumor-induced osteomalacia is a rare disease that is diagnosed about 2.9 years after the onset of symptoms [28]. The pathomechanism of osteomalacia in this disease is related to an excessive production of FGF23 from tumor, which is physiologically secreted by osteocytes under the influence of high concentrations of calcitriol in plasma. FGF23 regulates the mineralization process in bones by reducing renal phosphate reabsorption, vitamin D3 homeostasis, and Klotho protein expression [29,30,31]. Attempts to use burosumab in the treatment of TIO are based on the assumption that excessive FGF23 activity is responsible for the symptoms of osteomalacia, and the binding of FGF23 through the monoclonal antibody may weaken them. The complete tumor resection is the first line treatment for patients with a TIO. In cases where a tumor is unresectable or cannot be located, pharmacological treatment with burosumab subcutaneously is approved. The drug Crysvita containing burosumab has been approved for use in the EU by the EMA since July 25, 2022 in children and adolescents from 1-17 years of age and in adults with a phosphaturic mesenchymal tumor [2]. The efficacy of burosumab was evaluated in two single-arm clinical trials with 27 adult participants.

In Study UX023T-CL201 14 patients were treated with burosumab subcutaneously every 4 weeks for 144 weeks starting at 0.3 mg/kg. During the study, in half of the patients, the level of serum phosphorus increased above the lower limit of normal and the histopathological examination showed an improvement in parameters such as OV/BV-Osteoid volume/bone volume, O.Th-Osteoid thickness and mineralization lag time. Furthermore whole-body bone scans using 99mTc-MDP showed that the use of burosumab contributes to the healing of fractures and pseudofractures, which in 33% were fully healed at the end of the study. Patients reported reduced pain intensity, improved motor skills and reduced fatigue [32].

In the KRN23-002 study 13 adults from Japan and South Korea diagnosed with TIO were treated with burosumab. The serum phosphate level was assessed as the primary endpoint, which increased above the lower limit of normal after the first administration of the drug. In addition, improved motility in patients and accelerated fracture healing were observed [33].

Due to the fact that burosumab is a new drug, the studies discussed above are the only ones that have examined the effectiveness of burosumab in patients with TIO. For this reason, clinical case reports have an especially important role. The case of a 52-year-old patient was described by Alvin Lee Day in 2020. The patient was diagnosed with two meningiomas. The TIO was suspected due to FGF-23 levels, which was 225 RU/ml (≤ 80 RU/mL). Due to the difficulty in surgical resection and the unclear source of FGF-23 production, it was decided to use burosumab subcutaneously at a dose of 70 mg per month. At the beginning of the treatment, the patient used a wheelchair and after 23 weeks of treatment, the patient was able to use a walker. In addition, the serum phosphate level increased to 4.3 mg/dL after 5 months of treatment [34]. Daichi et al. described the case of the 58-year-old man who had suffered from non-remission TIO for 15 years. The patient was treated with burosumab instead of CT. The drug was administered subcutaneously every 4 weeks at a dose of 0.3 mg/kg. During the treatment the parameters of the phosphate-calcium metabolism in bones were improved: serum phosphate, bone mineral density (BMD) and bone Gla protein (BGP) [35].

The effects of long-term use of burosumab are still unknown. In the described case from 2022, a 46-year-old patient was treated for 2 years with burosumab at a dose of 0.3 mg/kg/month, gradually increased to 0.8 mg/kg/month due to TIO caused by tumor recurrence. The treatment was well tolerated by the patient. It is worth noting that the patient had treatment interrupted for some time due to COVID-19 pneumonia. Serum-phosphate levels then deteriorated and normalized after treatment was resumed [36].

3. Conclusions:

Treating patients with XLH and TIO remains a challenge due to the complex mechanisms involved in calcium and phosphate metabolism disorders. Conventional treatment, aimed at addressing deficiencies, often proves inadequate and fails to prevent the occurrence of adverse disease complications.

Studies and clinical cases have shown remarkable outcomes compared to traditional treatment approaches. Most XLH patients experienced improvements in calcium and phosphate metabolism parameters, reduction in disease symptoms, and enhanced physical function, resulting in an improved quality of life. Similarly, in TIO patients who are not suitable candidates for surgery as the primary treatment option, studies indicate not only an enhancement in the quality of life but also improvements in serum calcium and phosphate metabolism markers and bone

histopathological test results. Nevertheless, several unknown factors remain regarding the long-term use of burosumab, including its efficacy and potential side effects that may manifest over time. Additionally, the impact of different XLH phenotypes on treatment effectiveness remains unclear.
Burosumab represents a medication capable of revolutionising the treatment approach for diseases associated with elevated levels of FGF23. Its straightforward administration route and promising results from studies, demonstrating significant improvements among patients, raise hopes for a paradigm shift in the treatment of these conditions.

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