



# Long-term use of burosumab for the treatment of tumor-induced osteomalacia

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## Abstract

**Summary** Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by tumoral overproduction of FGF-23. Due to local recurrence, we describe the long-term efficacy and safety profile of burosumab, an anti-FGF-23 monoclonal antibody, in a TIO patient after three unsuccessfully surgical attempts.

**Introduction** TIO is a rare paraneoplastic syndrome caused by tumoral overproduction of fibroblast growth factor 23 (FGF23), resulting in hyperphosphaturia, hypophosphatemia, and osteomalacia. Surgery is the only definitive treatment, but tumor can locally recur, even after years from primary surgery. Furthermore, some tumors cannot be removed by surgery due to their location.

**Methods** We describe the case of a 54-year-old woman affected by recurrent TIO who, after three unsuccessful surgical attempts of tumor removal, was treated with burosumab, an anti-FGF-23 monoclonal antibody.

**Results** The patient was referred to our Bone Unit after experiencing several fractures in different sites, both traumatic and non-traumatic. At the time of first evaluation, at the age of 46, serum-phosphate (SP) was 1.2 mg/dL (reference range (RR) 2.5–4.5), 24-h urinary phosphate was 842 mg (RR 400–1000), and intact-FGF-23 was 117 pg/mL (RR 25–45). Imaging showed a metabolic pre-sacral lesion that firstly underwent to exploratory laparotomy. Then, patient underwent to surgical excision of tumor. After 18 months of well-being, tumor relapsed and even the subsequent surgery was not able to completely remove it. Since 2015, patient was maintained in phosphorus supplements and 1,25(OH)<sub>2</sub>vitamin D<sub>3</sub>, but SP levels never normalized. In September 2019, she was started on burosumab, initially at the dose of 0.3 mg/kg/month, progressively increased to the current 0.8 mg/kg/month, with great improvement of pain, physical performance, and normalization of SP levels. Burosumab was temporary and cautionary discontinued for COVID-19 pneumonia, with a worsening of SP. After restart of burosumab, biochemistry returned to normal.

**Conclusions** To our knowledge, this is the first European patient affected by TIO treated with burosumab for more than 2 years. Burosumab is a promising therapy in the medical treatment of TIO refractory or not eligible for definitive surgery, with good efficacy and safety profile.

**Keywords** Burosumab · FGF23 · Osteomalacia · Tumor-induced bone disease

## Introduction

Tumor-induced osteomalacia (TIO) is an acquired rare paraneoplastic disease caused by tumors overproducing fibroblast growth factor 23 (FGF23) [1]. The excess of FGF23 leads to renal phosphate wasting, reduced active vitamin D synthesis, and chronic hypophosphatemia [1–3]. The hallmark biochemical characteristics are hypophosphatemia and inappropriately normal or frankly low 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) [2]. In addition to chronic hypophosphatemia, the net effect of FGF23 overproduction is rickets, osteomalacia, and possible secondary hyperparathyroidism [1, 2]. Clinical features

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include fractures and pseudofractures; fatigue; musculoskeletal pain, widespread or mostly localized in weight-bearing areas; and severe myopathy; these characteristics burden the health-related quality of life, due to the rapid clinical deterioration of patients [3, 4]. TIO diagnosis is often quite challenging and the disease is frequently misdiagnosed or diagnosed late. The omission of blood phosphate on many standard chemistry panels added to non-specific symptoms of hypophosphatemia contributes to a delayed diagnosis of TIO in many patients [5], taking up to 20 years [5, 6]. The causative tumors are now classified among mesenchymal tumors known as Phosphaturic Mesenchymal Tumor-Mixed Connective Tissue variant (PMT-MCT) [7, 8], which are typically small size, benign, slow growing, and potentially located almost everywhere in the body. PMT-MCT are quite difficult to identify with standard imaging techniques [1]. A gradual and integrated diagnostic approach, combining functional and anatomical imaging, is recommended [1, 2, 5]. To date,  $^{68}\text{Ga}$ -DOTA-based PET/CT has been shown to have the greatest sensitivity and specificity in TIO localization [9, 10]. If tumors can be identified and if they are accessible, management is straightforward, because surgical complete resection is the recommended treatment choice and the standard of care [1, 2]. In case of comorbidities or unresectable masses, alternative therapies include radiotherapy, cryoablation, or radiofrequency ablation. After complete resection, blood FGF23 levels decrease and biochemical parameters commonly return to normal levels [11]. Furthermore, some tumors cannot be found and others cannot be removed resulting in a persistence or recurrence of the disease [12]; the first choice is to treat patients with oral inorganic phosphate and/or active vitamin D supplements [1]. In some cases, adjuvant therapy with cinacalcet, an agonist of the calcium-sensing receptor, has shown some benefit but monitoring and managing of possible hypercalciuria are needed.

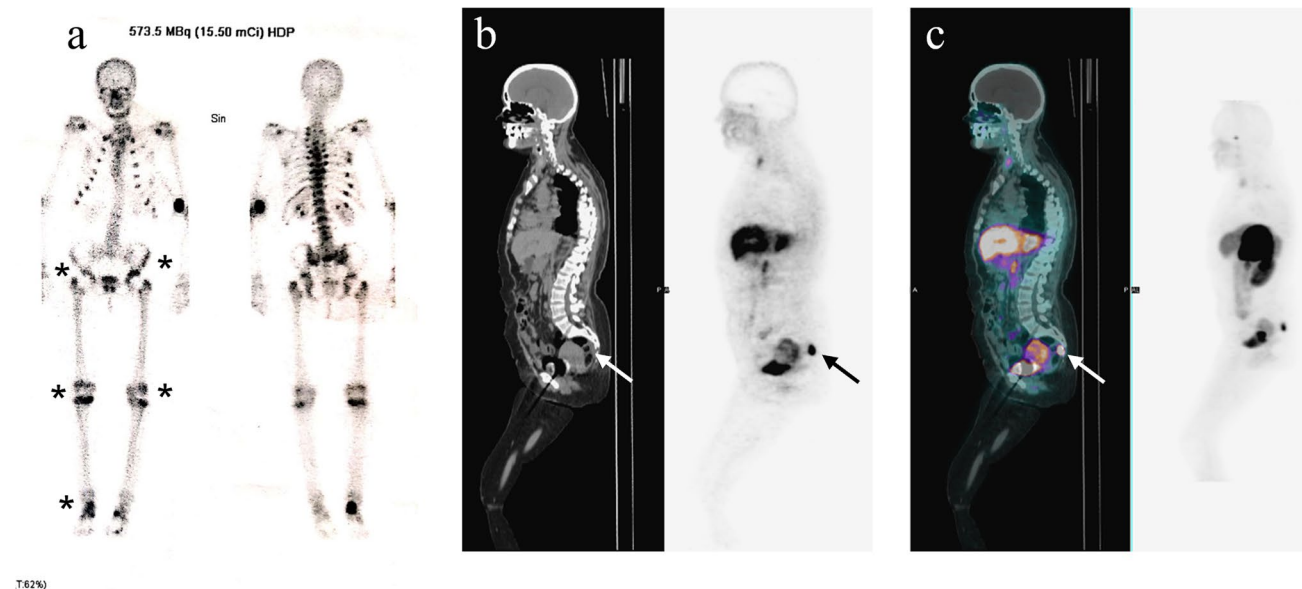
Burosumab (KRN23), a fully human monoclonal antibody targeted against FGF23 [13], is approved for X-linked hypophosphatemic rickets and has been recently approved also for TIO patients in the USA and Japan [14, 15], with promising results in clinical practice [16].

We describe a patient diagnosed with TIO, who unsuccessfully underwent to three surgical attempts of tumor resection, and she has been on Burosumab since September 2019.

## Case report

In May 2013, a 46-year-old Caucasian female was referred to our Bone Unit after experiencing several fractures at different sites. She reported being in good health until 3 years prior consultation. At the time of symptoms onset, she experienced progressive muscle pain, not allowing her to stand for a long period. In May 2011, during imaging evaluation for atraumatic fracture of the great trochanter

of right femur, the abdomen magnetic resonance imaging (MRI) with and without contrast administration showed a pre-sacral lesion confirmed as a metabolic active lesion (21 × 25 mm) at the  $^{18}\text{F}$ FDG- PET-CT evaluation and described as a pre-sacral lesion with enhanced uptake. She unsuccessfully underwent to an exploratory laparotomy. In March 2012, she suffered from atraumatic pertrochanteric fracture of the right femur, surgically treated with endomedullar nail, and after 3 months, she had an atraumatic basicervical left femoral neck fracture, surgically treated with total hip prosthesis. Furthermore, she experienced six left, two right ribs, and T7, T8, T9, and T10 vertebral fractures without significant trauma. At the time of first evaluation, lab works showed serum-phosphate (SP) 1.2 mg/dL (RR 2.5–4.5 mg/dL), 24-h urinary phosphate (PU) 842 mg (RR 400–1000), tubular reabsorption of phosphate (TRP) 46%, alkaline phosphatase (ALP) 565 UI (RR < 300), 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> 27 ng/L (RR 25–86.5), PTH 24 (RR 10–75 pg/mL), intact-FGF-23 117 (RR 25–45 pg/mL), normal serum calcium (9.3 mg/dL, RR 8.5–10), and 24-h urinary calcium (221.9 mg/24 h, RR 50–300). Patient underwent to  $^{68}\text{Ga}$ -DOTATATE-PET-CT that confirmed the lesion, located in the pre-sacral adipose tissue (25 × 15 mm of diameter) that was further investigated with MRI and CT before surgery. Figure 1 shows bone scan and  $^{68}\text{Ga}$ -DOTATATE-PET-CT at baseline. In November 2013, patient underwent surgical excision of the pre-sacral region with a rapid and progressive recovery of well-being. After 18 months of well-being and biochemical remission, patient complained worsening of joint pain and muscle weakness, and further atraumatic fractures (5 right ribs and 2 left ribs, IV left metatarsal bone, III right metatarsal bone fractures). Another  $^{68}\text{Ga}$ -DOTATATE-PET-CT reported a relapse of the previous pre-sacral lesion (32 × 12 × 47 mm). At the same time, a new decline of SP (1.2 mg/dL) and an increase of FGF-23 levels (54.6 pg/mL) were shown. Even the subsequent surgery in October 2015 was not able to remove the tumor definitely. Since 2015, patient was treated with phosphorus supplements (2 g/daily of dihydrogen phosphate) and 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> (calcitriol 1 mcg/daily), but SP levels never normalized. Thereupon, we asked for compassionate use of burosumab and, after our ethical committee approval and signature of informed consent, she was started on burosumab in September 2019, at the recommended dose of 20 mg per month (0.3 mg/kg) [17]. At baseline, she had SP 1.2 mg/dL, PU 1874 mg/24 h, and TRP 25.96%. After 2 months, she experienced significant pain symptom improvement (visual analogic scale (VAS) [from 0 = no pain to 100 = maximal pain] reduction from 65 to 12 mm, Fig. 2a), which allowed her to walk and stand without crutches. She did not normalize her SP levels that were still lower than normal (1.3 mg/dL), while PU was 1000 mg/24 h. We titrated burosumab dose at 40 mg per



**Fig. 1** Patient's bone scan and  $^{68}\text{Ga}$ -DOTATATE-PET-CT at time of TIO diagnosis in 2013. **a** Bone scan shows uptake of the tracer ( $\text{Tc}^{99}$ ) in the fracture/pseudofractures areas. Patient has a rachitic rosary at the costochondral junctions, which is an evocative sign in adults with TIO. Asterisk highlights fractures and pseudofractures.  $^{68}\text{Ga}$ -DOTATATE-PET-CT (**b**)  $^{68}\text{Ga}$ -DOTATATE-CT and **c**  $^{68}\text{Ga}$ -DOTATATE-

PET) shows the oval pre-sacral lesion with enhanced uptake (white arrows). The lesion is located in the pre-sacral adipose tissue, closely adherent to the anterior wall of sacrum and anteriorly related to the rectus intestinus, which imprints but does not infiltrate. Plane of cleavage with the left piriformis muscle is preserved

month (0.6 mg/kg) and the patient experienced a further improvement of pain, enhancing physical performance and SP levels came back to normal. In October 2020, patient had experienced fever no higher than  $38.5\text{ }^{\circ}\text{C}$ , pharyngeal discomfort, dry cough, muscle pain, and fatigue. A pharyngeal swab SARS-CoV-2 ribonucleic acid (RNA) test was performed and was tested positive. Chest computed tomography scans showed initial ground glass opacity of inferior lobe of the left lung. Patient was treated with antibiotics (levofloxacin) and antipyretics; she did not require hospitalization, and after 20 days of quarantine, she had a negative swab. During that period, patient suspended burosumab and SP levels returned below the normal range (SP 1.6 mg/dL). After the negative swab, burosumab was started again at 40 mg/every 4 weeks with normalization of SP levels in 4 months (SP 2.5 mg/dL) (Fig. 2b). In June 2021, due to a new and persistent decline of SP levels (1.8 mg/dL), burosumab dosage was increased at 60 mg/4 weeks (0.8 mg/kg) with good laboratory response in 2 months (SP 3.0 mg/dL).

On burosumab, FGF-23 levels (both intact and C-terminal) were extremely high, well above the reference range (mean FGF23 intact  $662.5 \pm 443.5$  pg/mL; FGF23 C-terminal mean  $264.9 \pm 119.2$  RU/mL).

After more than 2 years on burosumab, patient experienced a significant improvement of VAS pain (Fig. 2a), and SP levels were persistently in the normal range (Fig. 2b).

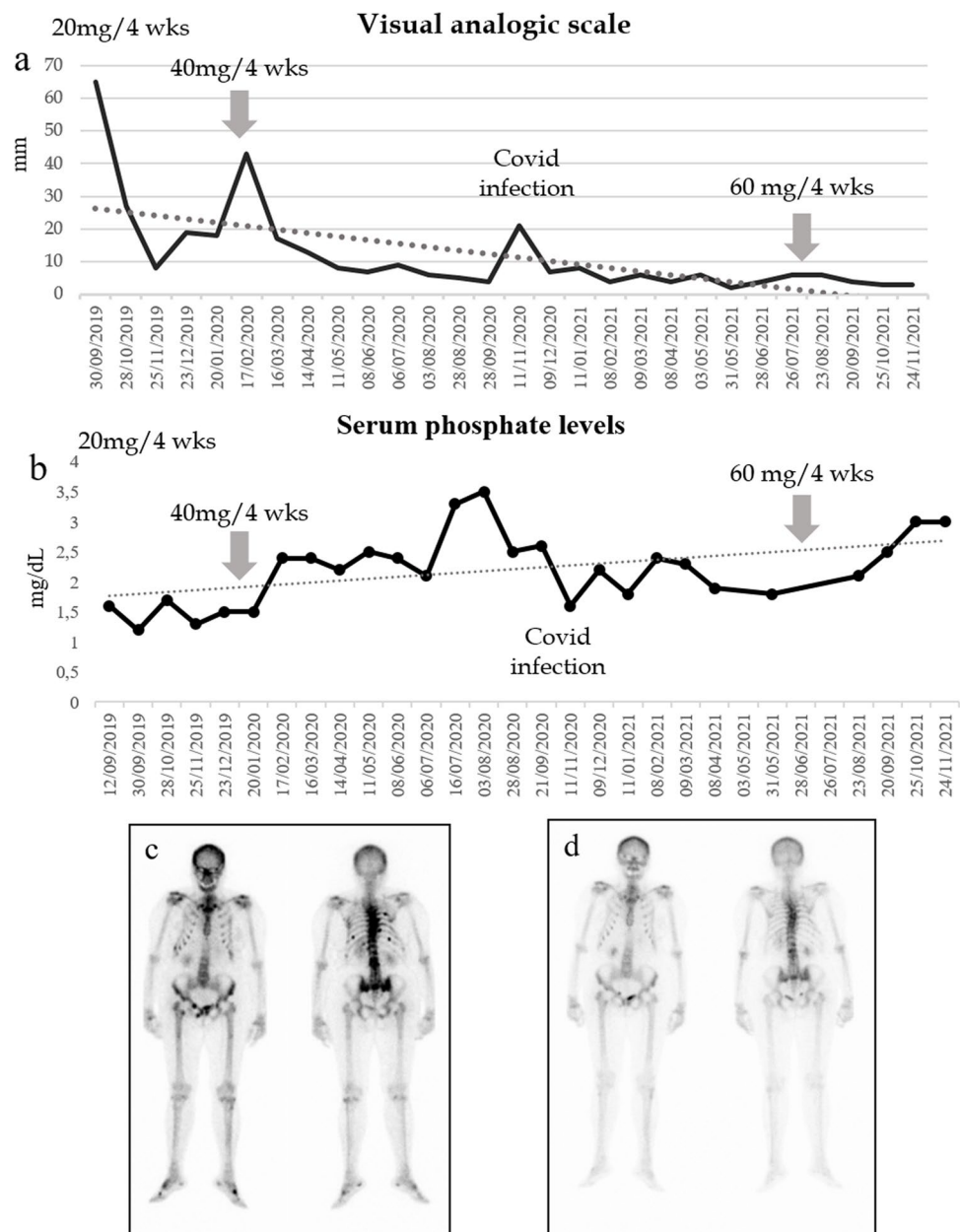
A new MRI was performed showing a slight increase in tumor size compared with the previous evaluation ( $36 \times 28 \times 57$  mm vs  $32 \times 12 \times 47$  mm).

During the follow-up, the patient underwent yearly to abdomen ultrasound and no signs of nephrocalcinosis or nephrolithiasis were reported. Likewise, patient underwent an echocardiogram at baseline and after 1 year without any signs of valve calcifications. Changes in bone scan over time are shown in Fig. 2c. No significant changes in renal function or any calcium-related parameters were observed.

## Discussion

To our knowledge, this is the first European patient on Burosumab for almost 2 years. Our patient had a recurrent TIO and, although she was treated in the past with active vitamin D and phosphate, she never normalized SP levels until burosumab administration. After burosumab start, pain score decreased (Fig. 2a), no new fractures occurred, and the bone scintiscan significantly improved, likely related to the fractures' healing (Fig. 2c). These findings suggest the efficacy of burosumab and its potential to restore normal SP levels, providing clinical benefit to patients with recurrent TIO and patients without a feasible surgical approach. Our data are consistent with the data available in literature on efficacy of

**Fig. 2** VAS pain change (**a**) and serum phosphate change (**b**) from baseline to the last evaluation. Changes in bone scan at baseline (**c**) and 1 year after burosumab start (**d**). **a** shows the VAS trend during 2 years. **b** shows the serum phosphate levels during the 2 years. Gray arrows indicate burosumab dose escalation. Burosumab was stopped at the beginning of October 2020 due to COVID-19 infection and restarted on 11–11-2020. Bone scan shows the uptake of tracer at fracture sites (left and right foot, ribs, bilateral iliopubic branch) before burosumab onset in September 2019 (**c**). **d** shows the reduction of radiotracer uptake particularly at lower limbs and ribs 1 year later



burosumab, both from clinical trials and few published case reports [14–16]. To the best of our knowledge, it is the first to describe the variation of FGF-23 levels during therapy and try to provide some explanation on this issue.

Complete tumor resection is clearly the first treatment option and surgical resection with large free margins is considered as the gold standard therapy; even alternative therapies are also possible (radiotherapy, cryoablation, or radiofrequency ablation) [2]. Our patient underwent an exploratory laparotomy and two surgical attempts of removal without complete resolution. Furthermore, the second surgical attempt was complicated by a massive intraperitoneal hemorrhage. That is the reason why the patient asked not to undergo further surgical attempts and was treated with

phosphate plus calcitriol despite the multiple fractures that have already occurred (Fig. 2c). However, over time, the patient's physical condition had progressively deteriorated; patient could not stand for long period or walk without crutches, felt pain, severe fatigue, and impaired physical functioning with progressive reduction in her work and daily activities. In fact, in patients with unresectable tumors or those in whom causative tumors are not found, currently available treatments have limited efficacy in healing osteomalacia, reducing symptoms, and maintaining biochemical tests within the normal range [1, 2]. Burosumab administration was initially started at a dose of 0.3 mg/kg and then titrated according to SP level. Our patient progressively recovered performance status and experienced a good

control of pain (Fig. 2a). The efficacy of burosumab was maintained even after the temporary suspension for COVID-19-related pneumonia, with a rapid restoration of normal SP levels after starting it over.

SP should always be monitored because, as our patient experienced, levels can decline even after a phase of persistent stability and good clinical response, in the absence of changes in patient's physical characteristics or dietary habits.

The clinical utility of FGF23 levels on burosumab warrants further study. In our patient, FGF-23 levels were consistently higher compared to reference range. These altered results can be explained by the possible immunological interference in immunoassays, as already described in X-linked osteomalacia, where it has been suggested to consider heterophilic binding tubes pretreatment and dilution assays [18]. Conversely, a particular analytical protocol for FGF23 measurement in TIO patients has not been defined yet. As a further hypothesis, the extremely high FGF23 concentrations might be biochemically ineffective, not reflecting the *in vivo* effect on SP levels. The discrepancy between high FGF23 levels and normal SP levels *in vivo* needs to be better clarified; however, it is possible to speculate that circulating FGF23 is being complexed and neutralized by burosumab that can make it biologically ineffective. In X-linked osteomalacia, it has been proposed to monitor SP, ALP, and 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> as the *in vivo* control in clinical practice [19]. Based on our results, it could be the same approach also into the TIO context.

While burosumab is clinically and biochemically effective, it does not stop tumor growth, which, albeit slowly, continues, as MRI data of our patient have shown. It might be useful, speculatively and when possible, to think about using this drug while waiting for the tumor to be potentially surgically managed again.

Recent findings on PMT tumorigenesis paved the way to other possible therapies, for example, targeting FGFR1 to block tumor growth and FGF23 secretion [20]. However, to date, the trial on infigratinib, a pan-FGFR tyrosine kinase inhibitor, was stopped early for incidence of adverse events and lack of permanent biochemical remission. Infigratinib could only be considered in life-limiting metastatic disease [21, 22].

Given the abovementioned, burosumab may satisfy this unmet need for TIO recurrent or persistent patients even if the surgical resection, whenever possible, remains the treatment of choice.

Burosumab was well tolerated, with no treatment-related adverse events. Serum calcium, urinary calcium, and intact parathyroid hormone did not show relevant changes throughout the patient's follow-up. Furthermore, no evidence of ectopic renal or heart calcifications by ultrasound was detected.

Although burosumab appears to be a promising therapy, information on its long-term efficacy and safety is still lacking. Moreover, burosumab does not affect the natural course of the

underlying disease not halting progression or growth of the causative tumor. Considering these data, its use should be limited to patients with unresectable or unidentified tumors, while continuing to try to locate the tumor [2]. Although burosumab is not curative, it provides meaningful improvements in overall patient's health and health-related quality of life.

## Conclusion

In conclusion, this is the first European patient affected by TIO treated with burosumab for over 2 years. Burosumab could be a promising therapy in the medical treatment of TIO not eligible for definitive surgery or not detected tumors. Further data are needed to standardize the proper dose regimen and to improve observation on its long-term efficacy and safety.

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## Declarations

**Conflict of interest** Massimo Varenna has received advisory board honoraria from Kyowa Kirin. Chiara Crotti has received speaker honoraria from Kyowa Kirin. All other authors have no conflicts of interest to declare.

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