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Case Report

Monoclonal antibody anti-sclerostin for treatment of pelvic insufficiency fractures in adult hypophosphatasia: A case report

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ABSTRACT

Hypophosphatasia is a rare inherited metabolic disease leading to inhibition of bone and teeth mineralization that can be complicated by multiple insufficiency fractures. Treatment is currently limited to enzyme replacement therapy using bone-targeting recombinant human alkaline phosphatase, or asfotase alfa. Romosozumab is a monoclonal anti-sclerostin antibody originally indicated for the treatment of osteoporosis in postmenopausal women with high-risk of fracture. Recently its indication had been expanded to other metabolic bone disorders such as osteogenesis imperfecta. We report a unique case of a 67-yer-old female with hypophosphatasia complicated by multiple delayed-union and nonunion insufficiency fractures of the pelvis. After 12-month therapy with Romosozumab to address her osteoporosis, the patient healed her fractures and increased her bone mass density. Our case report shows interesting effects of Romozumab in an adult patient with hypophosphatasia. It not only helped increase bone density, but also help in the healing process of delayed-union and nonunion insufficiency fractures of the pelvis and prevented the occurrence of new fractures during the treatment period. To our knowledge, this is the first report describing the potential effect of Romosozumab on insufficiency fractures in patients with hypophosphatasia.

Background

Hypophosphatasia (HPP) is a rare autosomal recessive inherited metabolic disease affecting bone and teeth [1]. It is characterized by low activity of the tissue non-specific isoenzyme of alkaline phosphatase (TNSALP), bound to the outer surface of osteoblasts, due to mutation at the *ALPL* gene. HPP leads to a high level of inorganic pyrophosphate which inhibits bone and tooth mineralization by reducing the formation of hydroxyapatite. Worldwide incidence is unknown, but in the United States, it affects approximately 500 to 600 individuals per year [1]. HPP occurs in all races, but it appears that the disease is more prevalent in Japan and in specific Mennonite populations in Canada. Males and females are equally affected, and it affects all age groups. Five forms have been identified: perinatal, infantile, juvenile, adult, and odontohypophosphatasia (dental only) [2].

The clinical presentation of HPP varies from devastating prenatal intrauterine disease to mild manifestations in adulthood. Adult

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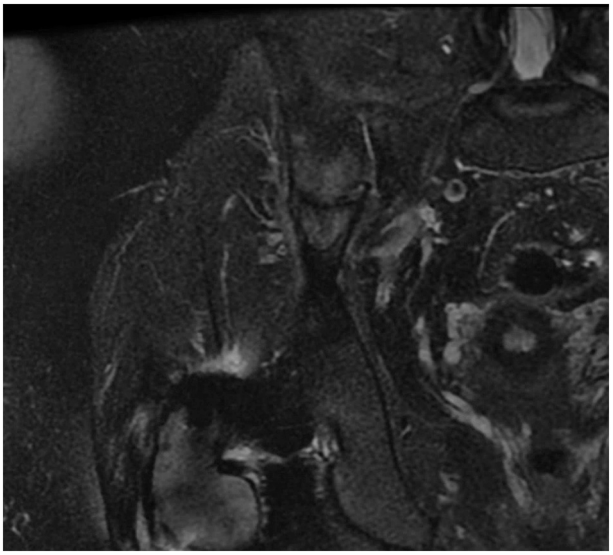

Fig. 1. MRI T2 coronal image of the right hip showing insufficiency fracture of the right iliac wing.

forms of HPP have a vast clinical heterogeneity. Adults may be asymptomatic, have early loss of their secondary teeth, osteopenia/osteoporosis, chronic muscle pain, or reduced muscular strength. They are also at increased risk of joint pain as a consequence of chondrocalcinosis. HPP can be associated with deposition of hydroxyapatite crystals in the rotator cuff, elbow, and Achilles tendons. Some adults may also experience painful delayed union or nonunion insufficiency fractures of the feet, lateral aspect of the proximal femur, or pelvis [2]. Laboratory studies in these patients show low serum alkaline phosphatase, elevated serum pyridoxal-5′-phosphate (vitamin B6), and/or elevation of urinary phosphothanolamine [3].

Treatment of adult patients with HPP is currently limited to enzyme replacement therapy using bone-targeting recombinant human alkaline phosphatase, or asfotase alfa (Strensiq; Alexion Pharmaceutical, New Haven, CT, USA), which was approved by the Food and Drug Administration in 2015 [4].

Over the past decade, the use of Romosozumab (Evenity; Amgen, Thousand Oaks, CA, USA), originally indicated for the treatment of osteoporosis in postmenopausal women with high fracture risk, has been expanded to other metabolic bone disorders such as osteogenesis imperfecta [5,6]. It is a monoclonal antibody that inhibits sclerostin, a regulatory factor in bone metabolism, resulting in increased bone formation and, to a lesser extent, decreased bone resorption. Its use has been shown to increase trabecular and cortical bone mass, as well as bone structure and strength [5]. Medication is administered subcutaneously monthly by a healthcare professional with two separate 105-mg prefilled syringes for a total dose of 210 mg per month [7]. Romosozumab is contraindicated in patient with hypocalcemia, a history of stroke or myocardial infarction in the past year, or a history of hypersensitivity to Romosozumab or any component of its formulation [8].

Treatment of HPP patients with Romozumab has been seldomly reported in the literature. Seefried et al. reported a 29-week treatment of 8 adult patients with HPP with a monoclonal anti-sclerostin antibody (BPS804) [9]. The therapy resulted in increased bone formation markers as well as a transient decrease in the bone resorption marker C-telopeptide. Lumbar spine bone mass densitometry showed a mean increase of 3.9 % at the end of the study. To our knowledge, the potential effect of Romosozumab on insufficiency fractures in HPP patients has not been described in the literature. We report a unique case of adult hypophosphatasia complicated by multiple delayed-union and nonunion insufficiency fractures of the pelvis who after a 12-month therapy with Romosozumab healed her fractures and increased her bone mass density.

Case presentation

The patient was a 67-year-old Caucasian female with surgical history of right and left femur subtrochanteric insufficiency fractures fixed with cephalomedullary nails. Her medical history was significant for hiatal hernia, reflux disease, hypertension, hyperlipidemia, menopause, bilateral rotator cuff tendinopathy, left distal radius fracture, and right foot insufficiency fractures. She also had severe periodontal disease and benefited from dentures in the past. She was a former smoker and social history was otherwise negative for alcohol or recreational drugs use. Family history was notable for hypophosphatasia in her sister and her sister's daughter who were both treated with enzyme replacement therapy.

At the time of her subtrochanteric fractures, routine labs revealed reduced serum alkaline phosphatase levels between 11 and 18 U/L (normal range: 45–117 U/L) and 25-OH-D as low as 24 ng/mL (normal range: 30–100 ng/mL). The diagnosis of hypophosphatasia was made based on labs and family history. She was started on calcium and vitamin D supplementation for vitamin D deficiency and osteopenia. At follow-up visits, her 25-OH-D improved to 29 ng/mL and later normalized to 31 ng/mL.

At age 71, she presented to the general orthopaedic clinic with new right hip pain that had been present for one month. X-ray of the

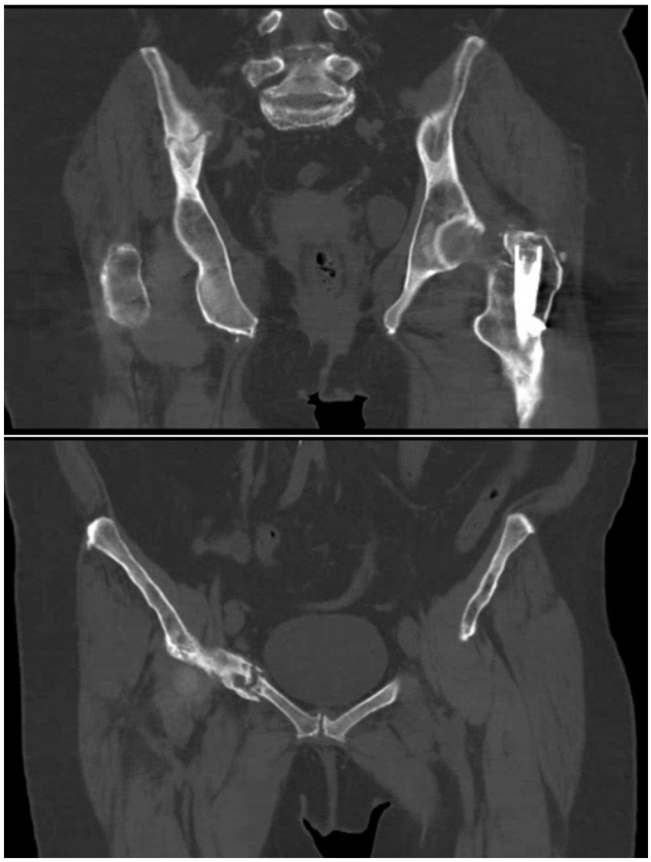

Fig. 2. CT-scan coronal images of the pelvis showing delayed union of insufficiency fracture of the right iliac wing and the right superior ramus.

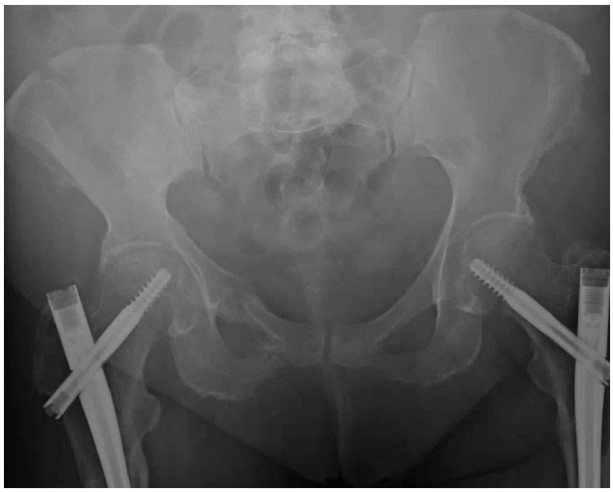

Fig. 3. Anteroposterior radiographic view of the pelvis showing insufficiency fractures of the right superior ramus and right iliac wing and acute fractures of the right inferior ramus and left superior and inferior rami.

right femur revealed healing insufficiency fractures of the right superior rami and an MRI of the right hip showed a nondisplaced fracture of the right iliac wing (Fig. 1). These fractures were treated conservatively with continuation of calcium and Vitamin D. However, she visited the office an additional three times over a 3-month period with no improvement in her pain. She ultimately underwent a CT-scan of the bony pelvis which revealed delayed healing of the insufficiency fractures (Fig. 2).

Given the lack of clinical and radiological improvement of her insufficiency fractures, the patient was referred to the orthopaedic

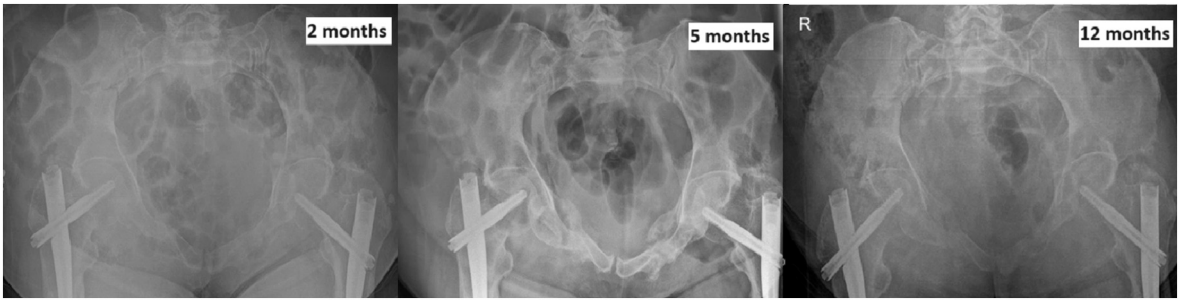

Fig. 4. Inlet radiographic view of the pelvis showing healing of the insufficiency fractures after two, five and twelve months of treatment with Romosozumab.

traumatology service for potential fixation of her pelvic fractures and was also referred to the endocrinology team for further evaluation of her hypophosphatasia. Under the care of the endocrinology team, a DEXA-scan showed a lumbar T-score of +1.0 with lumbar spine bone mineral density (BMD) of 1.100 g/cm^2 and proximal radius BMD of 0.500 g/cm^2. Enzyme replacement therapy with asfotase alfa and referral to a higher center was suggested, but the patient declined. She did, however, agree to be started on Romosozumab, 210 mg subcutaneously monthly, for her osteopenia and increased risk of fracture.

When she visited the orthopaedic traumatology service for surgical evaluation of her delayed union stress fractures, she reported significant new pain in the left groin area. Her right-sided hip pain had been present for six months and was still incapacitating, rated as a 10/10 on visual analogic scale (VAS). She was using an electric wheelchair to move around. Pelvic X-rays obtained the same day revealed new non-displaced left superior and inferior pelvic rami insufficiency fractures (Fig. 3). Her first dose of Romosozumab injection was planned for later that month, and the decision was made to wait for the medication to improve her biology prior to doing any type of stabilization procedures.

Two months after the initial visit, she had already received two doses of Romozumab. Her pain had progressively improved, rated 6/10 on the VAS; she was also no longer in a wheelchair and was ambulating with a cane. Pelvic X-ray obtained the same day showed interval bony callus formation with early obliteration of the fracture lines in her pelvis (Fig. 4).

Five months after her initial clinic visit, she had completed a total of five doses of Romozumab. She reported her pain was completely resolved, but she still was ambulating with a cane. A repeat pelvic X-ray demonstrated interval bony callus formation with maintained stable overall alignment of the pelvic ring (Fig. 4). Her right ilium had near complete obliteration of the fracture line. The rami fracture lines could still be seen but with good surrounding bony callus. A repeat DEXA-scan showed a lumbar T-score of +1.1, a lumbar spine BMD of 1.327 g/cm^2 and proximal radius BMD of 0.764 g/cm^2.

After her 12th and final dose of Romozumab, she was seen again at the orthopaedic trauma clinic for her fourth visit. Her pain was rated 0/10 on the VAS, she was walking without any assistive device, and she was back to her baseline activity of daily living. Pelvic X-ray demonstrated stable healed fractures (Fig. 4). A final DEXA scan showed a lumbar T-score of 1.2, lumbar spine BMD of 1.443 g/cm^2, and proximal radius BMD of 0.852 g/cm^2. At that time, she was released from clinic and was invited to follow as needed.

Discussion

Hypophosphatasia is a rare genetic disease that can be complicated by delayed union or nonunion of insufficiency fractures. Romosozumab (Evenity) is a monoclonal anti-sclerostin antibody that improves bone density in osteoporosis by increasing bone formation and decreasing bone resorption. Our case report shows that Romosozumab can be effective in healing delayed union/nonunion insufficiency fractures of the pelvis in hypophosphatasia. To our knowledge, this is the first time delayed union/nonunion insufficiency fractures have been successfully treated pharmacologically with an anti-sclerostin antibody in a patient with hypophosphatasia.

The use of Romozumab has been reported in other clinical settings of fracture. Uemura et al. reported a case where they achieved successful union using combination of spanning distraction plate, bone graft, and a 6-month course of Romosozumab in a 61-year-old male smoker with distal radius fracture non-union [10]. Similarly, Lee et al. reported a 67-year-old male with humerus fracture in whom bone union could not be obtained after 11 months of conservative management [11]. Successful bone healing was achieved after a 6-month treatment with Romosozumab. Two recent randomized controlled trials using anti-sclerostin antibody on acute hip and tibia fractures suggested that Romosozumab might be more useful in patients in need of increased biologic healing potential, such as in delayed healing or nonunion fractures. [12,13] Various reports showed that targeting sclerostin to recover bone mass, restore bone strength, prevent fragility fracture, and heal fracture in patient with osteogenesis imperfecta [5,6,14].

After literature review, only one article has previously studied the effect of a monoclonal anti-sclerostin antibody in HPP. Seefried et al. studied the effect of Romozumab in 8 adult patients with HPP, but without any particular bone injuries [9]. They showed that overall, a 29-week treatment increased bone formation and decreased bone resorption marker C-telopeptide. Lumbar spine bone mass densitometry showed a mean increase of 3.9 % at the end of the study.

Our case report shows similar results in a now 72-year-old female with hypophosphatasia, who had sustained multiple insufficiency fractures, delayed-healing fractures, and nonunion fractures of the pelvis, all effectively treated with a 12-month course of the anti-

Table 1
Timeline.

Ortho visits	Initial visit	Second visit	Third visit	Fourth visit
Timeline	0 month	2 months	5 months	12 months
Romosozumab dose	None	Second	Fifth	Twelfth
VAS pain	10/10	6/10	0/10	0/10
Ambulatory status	Wheelchair use	Cane use	Cane use	No assistive device

VAS: Visual Analogic Scale.

Table 2
DEXA scan results.

DEXA scan timeline	T-Score lumbar spine	Lumbar spine BMD (g/cm^2)	BMD improvement from baseline	T-Score proximal radius	Proximal radius BMD (g/cm^2)	BMD improvement from baseline
Beginning	+1.0	1.100		−1.6	0.500	
6 months	+1.1	1.327	20.6 %	−1.3	0.764	52.8 %
12 months	+1.2	1.443	31.2 %	−1.1	0.852	70.4 %

DEXA: Dual-Energy X-ray Absorptiometry, BMD: Bone Mass Density.

sclerostin antibody. During this treatment period, the patient's ambulatory status went from being wheelchair-bound to walking without any assistive device. Ratings on the VAS for pain went from 10/10 at the beginning of the treatment to 0/10 at the end (Table 1). Radiographic studies of the pelvis showed progressive filling of the facture lines with surrounding bony callus formation (Figures). In addition, Romosozumab treatment successfully improved the bone density in our patient. The T-score went from 1.0 to 1.2 and −1.6 to −1-1 for the lumbar spine and proximal radius respectively. BMD of the lumbar spine and distal radius had a 31.2 % and 70.4 % improvement from the beginning to the end of treatment (Table 2).

Among other molecules tried to treat insufficiency fractures in hypophosphatasia, Teriparatide is one of them. Earlier case reports showed good response to Teriparatide, improving the biology with increase bone remodeling and skeletal mineralization [15]. However, current literature is more mitigated on the effect of Teriparatide on healing insufficiency fractures in hypophosphatasia with variable clinical and biochemical effect depending on the severity of the disease [16]. Romosozumab is an emerging osteoporotic treatment that now offers a new alternative options to improve biology in hypophosphatasia in order to heal insufficiency fracture, delayed union, and nonunion associated with this condition.

As demonstrated by our case report, Romosozumab shows great potential in treating pelvic insufficiency fractures in patients with impaired bone metabolism. Romosozumab might aid in recovering bone mass density, restoring bone strength, and promoting healing of delayed and nonunion pelvis fractures in patients with hypophosphatasia. This report paves the way for future more robust assessment of Romosozumab for hypophosphatasia with randomized controlled trial to confirm its effects.

CRediT authorship contribution statement

Pierre-Emmanuel Schwab: Writing – review & editing, Writing – original draft, Methodology. **Alicia Dessain:** Writing – review & editing. **Joshua Milby:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors have no conflict of interest to disclose.

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