Romosozumab treatment in osteogenesis imperfecta type I: a case report

Francesca Giusti [1,2], Francesca Marini [3], Maria Luisa Brandi [2,3]

[1] Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [2] Bone Clinic, Villa Donatello Private Hospital, Sesto Fiorentino (FI), Italy; [3] Fondazione F.I.R.M.O. Onlus, Italian Foundation for Research on Bone Diseases, Florence, Italy

ABSTRACT

The term osteogenesis imperfecta (OI) refers to a heterogeneous group of genetic diseases characterized by defective mineralization of calcified tissues, leading to increased bone fragility and susceptibility to pathological fractures.

There is currently no specific therapy for OI. Applied therapies are solely focused on alleviating symptoms, slowing disease progression, and preventing/delaying the most serious consequences of the disease. Patients with OI require life-long supplementation with calcium and vitamin D to compensate for the deficiency of these two molecules. Standard therapy consists of the administration of bisphosphonates to reduce bone resorption. Other drugs, such as denosumab or bone anabolic agents, are potential alternatives in selected patients. Additional drugs, such as anti-sclerostin agents and transforming growth factor beta antagonists, are being studied in clinical trials.

We report the case of a female patient diagnosed with OI type I, due to a heterozygous germline mutation of the *COL1A1* gene (c.1821+1G>A), associated with multiple fragility fractures, occurring from childhood. After treatment with bisphosphonates, denosumab, and an anabolic drug, the patient was prescribed romosozumab for 24 months, showing an improvement in the quality parameters of trabecular bone, no new fractures, a clear reduction of bone pain (not obtained with previously administered drugs), and a generally improved quality of life.

KEYWORDS

Osteogenesis imperfecta, rare bone disease, fractures, bone mineral density, bisphosphonates, denosumab, teriparatide, abaloparatide, romosozumab.

Introduction

The term osteogenesis imperfecta (OI) refers to a heterogeneous group of diseases characterized by defective mineralization of calcified tissues, prevalently due to altered synthesis or incorrect assembly of type 1 collagen, the main protein component of the extracellular matrix of bone and teeth. Germline inactivating mutations in specific genes are responsible for defective synthesis of the mature collagen molecule and, consequently, the development of OI. Over 80% of OI cases are caused by heterozygous germline inactivating mutations of the *COL1A1* or *COL1A2* genes that encode, respectively, the alpha 1 and alpha 2 chains of type 1 collagen. In addition to these two major genes, a further 20 genes have been associated with other, rarer, forms of OI or OI-like pathologies in case reports and genetic studies of OI families. To date, 23 different OI types have been reported, characterized by variable age at onset, clinical presentation, and degree of severity. Genetic transmission varies between different clinical forms and can be autosomal dominant, autosomal recessive, or, very rarely, X-linked recessive. Mutational screening of *COL1A1*, *COL1A2*, and other OI-associated genes is important for genetic diagnosis of the disease, differential diagnosis with other phenotypically similar bone diseases, and correct clinical management of affected patients [1,2]. The most prominent clinical sign in all types of OI is early-onset skeletal fragility, due to decreased mineralized bone matrix and osteomalacia, associated with skeletal deformities and variable degrees of susceptibility to bone fractures occurring after minor or no trauma [3]. Clinically, the presentation of OI is highly variable, ranging from mild forms with normal stature, absence of deformities, and normal life expectancy to perinatally lethal forms.

Currently, there is no specific therapy for OI; treatments are administered with the sole aims of minimizing fracture risk by increasing bone mineral density (BMD), reducing bone pain, and increasing the patient's mobility and autonomy. The medications used to improve skeletal health in OI patients are ones originally developed to treat osteoporosis. In OI patients, therapies may include calcium and vitamin D supplementation, antiresorptive and/or osteoanabolic drugs, physical therapy and rehabilitation, and orthopedic interventions.

Oral or intravenous bisphosphonates are the most commonly used antifracture drugs in OI patients, even though these molecules do not specifically treat the disease. Substantial evidence supports the efficacy of bisphosphonates in improving BMD, but it is not known whether increased BMD translates

Article history
Received 12 Nov 2024 – Accepted 17 Mar 2025

Contact
Francesca Giusti; francesca.giusti@unifi.it
Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

into protection against fragility fractures [4-7]. The risks of osteonecrosis of the jaw and atypical femur fracture do not appear to be greater in adults with OI treated with long-term bisphosphonate therapy compared with treated patients without OI. Since individuals with OI may have a higher incidence of gastroesophageal reflux disease and gastrointestinal symptoms that may be exacerbated by oral bisphosphonates, intravenous bisphosphonates generally have better adherence rates and may be more effective in increasing BMD in OI [8]. Additionally, scoliosis and the inability to stand may complicate oral bisphosphonate administration in OI patients.

Teriparatide and abaloparatide, respectively a human 1-34 PTH and a synthetic peptide analog of PTHrP, are two osteoanabolic drugs that showed fracture-protective effects in patients with osteoporosis [9-11]; despite the current absence of specific clinical trials in OI, they are administered as treatment alternatives in adults with type I OI who have high vertebral fracture risk and poor therapeutic response to bisphosphonates. Similar to their use in osteoporosis, a treatment duration of 18–24 months followed by an antiresorptive agent appears prudent. The usefulness of abaloparatide has not been studied specifically in OI, but conceptually there is no reason to consider it less effective than teriparatide [12,13].

Although there are currently no data to support the use of denosumab in the treatment of OI [14], it may be an option for adults with OI who have renal insufficiency, drug intolerance, or poor therapeutic response to bisphosphonates and/or teriparatide. Increased bone resorption and subsequent bone loss after denosumab discontinuation are of particular concern in patients with OI. In this situation, the use of a potent bisphosphonate (e.g., zoledronic acid), with careful monitoring of BMD and possibly biochemical markers of bone resorption to help determine the optimal frequency of bisphosphonate dosing, would be appropriate.

Finally, romosozumab is a monoclonal antibody that inhibits sclerostin, increases bone formation, and decreases bone resorption. It is an effective and FDA-approved treatment for postmenopausal osteoporosis [15] and has been shown to significantly improve lumbar spine, total hip, and femoral neck BMD in osteoporosis patients, according to real-world data [16]. The literature suggests that romosozumab could be an effective therapy for subjects with OI; off-label use of romosozumab could be considered in adults with OI at high risk of fracture, who are not good candidates for bisphosphonate or teriparatide therapy [17-19].

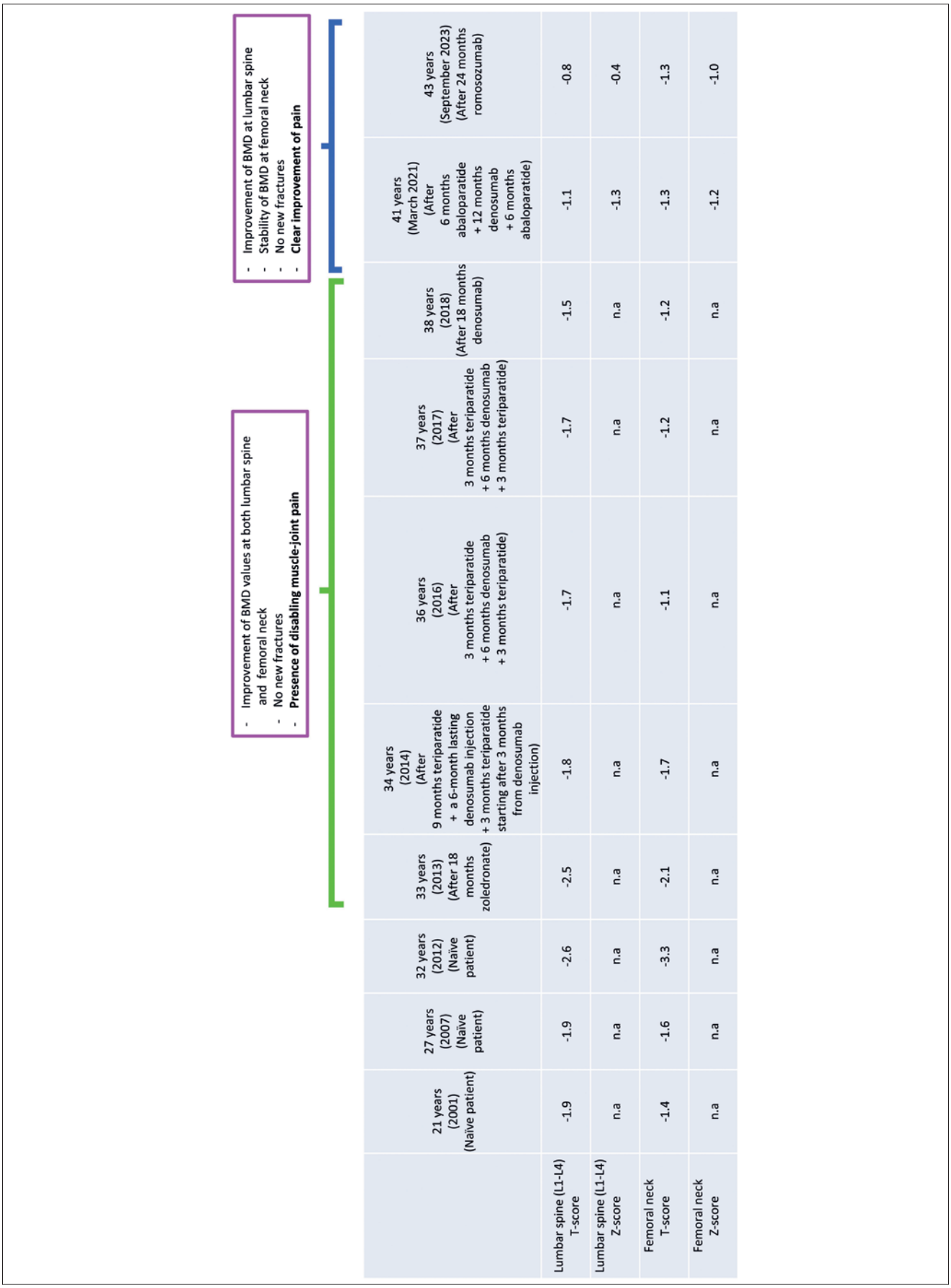
Case report

We here report the case of a female patient who was first referred to our clinical center at the age of 31 years, and was diagnosed with OI on the basis of a clinical history of multiple fragility fractures and the presence of blue sclera. A year later, the diagnosis of OI type I was genetically confirmed by a positive genetic test, which identified a heterozygous germline pathogenic variant in intron 7 of the *COL1A1* gene (c.1821+1G>A), altering the splicing site at the exon 7-intron 7 junction.

The patient reported the occurrence of multiple pathological fractures, either in the absence of trauma or with minimal trauma, starting from childhood (i.e., tibia, both humeri, hip). An initial DXA evaluation, performed at the age of 21 years, showed reduced BMD at both the lumbar spine and the femoral neck (T-score -1.9 and -1.4, respectively). Repeat DXA assessments, at 27 and 32 years, showed a progressive and significant decrease in BMD at both the lumbar spine and the femoral neck (Figure 1). Spine morphometry, performed at the age of 32 years, showed fractures at T5, T6, T7, T9, T11, and T12. At this time, the patient was initially treated with zoledronic acid for 18 months (two intravenous infusions, at baseline and after 6 months) which led to a BMD improvement, mostly at the femoral neck (Figure 1). At the end of the 18 months, she began the following 15-month lasting treatment plan: 9 months of teriparatide followed by a 6-month covering injection of denosumab, and 3 months of teriparatide started at the 4th month after the denosumab administration. At the end of these 15 months, DXA assessment at lumbar vertebra and femoral neck level showed a further improvement of BMD values (Figure 1). As a result, the patient continued therapy for a further 24 months, consisting of two annual cycles each of 3 months of teriparatide, followed by 6 months of denosumab, and 3 months of teriparatide. After these two cycles, BMD showed a further improvement, especially at femoral neck level; this improvement was already present after the first year of treatment and remained constant during the second year (Figure 1). This treatment was followed by 18 months of therapy with denosumab, at the end of which the lumbar T-score showed a slight improvement, while the femoral neck T-score remained unchanged (Figure 1). Subsequently, the patient received 6 months of abaloparatide followed by 24 months of sequential therapy with abaloparatide and denosumab, as follows: 6 months of abaloparatide, 12 months of denosumab and 6 months of abaloparatide, at the end of which BMD at the lumbar spine showed a further improvement, while the femoral neck T-score diminished slightly from -1.2 to -1.3 (Figure 1).

Despite the evident improvement in densitometric values and the absence of new fractures, the patient complained of muscle and joint pain, sometimes disabling, from the beginning of the antifracture therapies. This pain was only partially reduced during treatment with anabolic drugs. To try to solve pain issue, in September 2021, the patient started a 24-month treatment with romosozumab, administered at half the dosage commonly used for osteoporosis (105 mg/month). Before romosozumab administration, the patient underwent thorough cardiovascular screening. No adverse cardiovascular events occurred during the 24-month treatment period. During romosozumab treatment, no new fractures occurred and the patient reported a clear improvement in her pain symptoms, as assessed through specific questionnaires administered at the beginning of the therapy, at 12 months, and at 24 months. This led to a notable improvement in her general quality of life, allowing her to carry out daily activities that had been precluded in previous years. Densitometrically, we observed BMD stability at the femoral neck (T-score -1.3) and a further improvement at the lumbar spine (T-score -0.8). Moreover, the patient underwent high-resolution peripheral quantitative computed tomography screenings, both at the beginning and after 24 months of romo-

Figure 1 Schematic representation of over-time changes in T-score values at vertebral and femoral level in our OI patient before and during anti-fracture therapies.



	21 years (2001) (Naïve patient)	27 years (2007) (Naïve patient)	32 years (2012) (Naïve patient)	33 years (2013) (After 18 months zoledronate)	34 years (2014) (After 9 months teriparatide + a 6-month lasting denosumab injection + 3 months teriparatide starting after 3 months from denosumab injection)	36 years (2016) (After 3 months teriparatide + 6 months denosumab + 3 months teriparatide)	37 years (2017) (After 3 months teriparatide + 6 months denosumab + 3 months teriparatide)	38 years (2018) (After 18 months denosumab)	41 years (March 2021) (After 6 months abaloparatide + 12 months denosumab + 6 months abaloparatide)	43 years (September 2023) (After 24 months romosozumab)
Lumbar spine (L1-L4) T-score	-1.9	-1.9	-2.6	-2.5	-1.8	-1.7	-1.7	-1.5	-1.1	-0.8
Lumbar spine (L1-L4) Z-score	n.a	n.a	n.a	n.a	n.a	n.a	n.a	n.a	-1.3	-0.4
Femoral neck T-score	-1.4	-1.6	-3.3	-2.1	-1.7	-1.1	-1.2	-1.2	-1.3	-1.3
Femoral neck Z-score	n.a	n.a	n.a	n.a	n.a	n.a	n.a	n.a	-1.2	-1.0

sozumab therapy, which showed an improvement of trabecular bone quality parameters. Table I summarizes the trend of bone turnover markers and mineral metabolism during the therapy with romosozumab.

Discussion

Treatment of OI is not easy to manage: the timing of osteoprotective therapy in OI patients as well as the choice of the most suitable drug(s) for the single patient are still unresolved medical challenges.

Bisphosphonates, denosumab, and synthetic parathyroid hormones are currently commonly used for reducing bone mass loss and fracture risk in OI patients, although in some cases these therapies have disadvantages, showing relatively weak efficacy and lack of effects in some patients. Indeed, none of these drugs exerts a direct pharmacological action on the pathogenic mechanism of the disease, which is altered collagen synthesis. In practice, while all these molecules may control/reduce some consequences of OI, such as reduced BMD, osteomalacia, risk of fragility fractures, and vertebral pain, they fail to act on the intrinsic mechanism of the disease, restoring correct synthesis of type 1 collagen. To act more effectively, the genetic defect should be corrected and/or effective collagen secretion should be ensured in the correct locations and at a very early age. Promising strategies for the future treatment of OI and other genetic bone diseases are based on stem cell transplantation, genetic engineering, and the use of molecular chaperones. However, most of these approaches are still at the basic research stage and many further investigations are needed to confirm their therapeutic benefits and translate their results into clinical practice.

Pending the development and approval of an effective and targeted therapy for OI, currently available antiresorptive and/or osteoanabolic drugs should always be considered an integral part of the multidisciplinary approach, alongside the program of corrective surgery, physiotherapy, and occupational therapy, with the overall aim of reducing fracture occurrence, deformities, disability, and pain, and granting each patient the best quality of life possible.

Antisclerostin antibodies, by exerting both anabolic and antiresorptive properties, may be a novel treatment option for patients with OI. They include romosozumab, a dual-action humanized antisclerostin monoclonal antibody, currently approved for the treatment of severe postmenopausal osteoporosis. Romosozumab is not conventionally used in OI. Off-label treatment of OI patients with romosozumab showed significant improvement of BMD in a few case reports [17-19]. Another fully humanized monoclonal antisclerostin antibody, setrusumab, is currently under trials as a potential treatment for OI. In October 2024, it was granted Breakthrough Therapy Designation by the FDA, after the preliminary clinical results of the Orbit study (phase 2/3) showed a rapid and clinically meaningful decrease in fracture rate in treated patients with OI types I or III/IV [20], and those of the ASTEROID study (phase 2b) showed significant improvements in bone strength and areal BMD in adult patients diagnosed with OI types I, III, or IV and carrying a pathogenic variant in *COL1A1/A2* [21].

In our patient with OI type I, we demonstrated the efficacy of both antiresorptive and osteoanabolic drugs in improving BMD values at the lumbar spine and femur and in preventing new fragility fractures over an overall treatment period of 9 years, starting from the age of 32 years. However, the patient reported persistence of osteoarticular pain, and subsequent limitation in her daily activities and autonomy, during treat-

Table I Trend of bone turnover markers and mineral metabolism during therapy with romosozumab.

DATE OF BIOCHEMICAL ANALYSES	SERUM TOTAL CALCIUM	SERUM PHOSPHATE	25(OH)-VITAMIN D	PTH	TOTAL ALP	BALP	CTX	P1NP	URINARY CALCIUM	URINARY PHOSPHATE
	Ref. range: 8.4–10.4 mg/dl	Ref. range: 2.5–4.5 mg/dl	Sufficiency: 30–100 ng/ml	Ref. range: 15–65 pg/ml	Ref. range: 30–120 U/L	Ref. range: 3.0–19.0 mcg/L in premenopausal women	Ref. value < 0.573 ng/ml in premenopausal women	Ref. range: 2.9–8.1 mcg/L	Ref. range: 100–300 mg/24h	Ref. range: 400–1300 mg/24h
March 2021 (before starting therapy with romosozumab)	8.1	3.0	37.5	16.4	37 (55.0% of BALP)	n.a.	0.072	n.a.	232	810
June 2021 (before starting therapy with romosozumab)	9.0	2.7	n.a.	24.3	n.a.	8.5	0.122	4.7	n.a.	n.a.
June 2022 (after 9 months of romosozumab therapy)	9.4	3.9	57.1	65	64	n.a.	0.129	n.a.	n.a.	n.a.
September 2023 (after 24 months of romosozumab therapy	9.7	3.4	51.0	15.3	51 (51.5% of BALP)	n.a.	0.169	n.a.	95	359

Abbreviations: **PTH** = parathyroid hormone; **ALP** = alkaline phosphatase; **BALP** = bone alkaline phosphatase; **CTX** = C-terminal telopeptide of collagen type 1; **P1NP** = procollagen type 1 N propeptide; **n.a.** = not available

ment with bisphosphonates and denosumab. Only osteoanabolic therapy with teriparatide produced a slight improvement of her pain symptoms. Given its bone-forming action and its demonstrated efficacy in increasing bone strength in some OI patients, we decided to prescribe our OI patient a 24-month course of treatment with romosozumab, administered at the half the dosage commonly used for osteoporosis. Romosozumab, in addition to being well tolerated over the entire treatment period, and associated with absence of new fragility fractures, maintenance of BMD at the femur, improvement of BMD at the lumbar spine, and improvement of trabecular bone quality, was also found to have an effective analgesic effect, notably improving our patient's general quality of life, allowing her to carry out daily and work activities that had been precluded in previous years.

In conclusion, our case report suggests that therapy with romosozumab could be a valid alternative treatment in some OI patients in whom pain symptoms are not sufficiently alleviated by antiresorptive and osteoanabolic drugs.

References

1. Marom R, Rabenhorst BM, Morello R. Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol. 2020; 183(4):R95-R106.
2. Jovanovic M, Marini JC. Update on the genetics of osteogenesis imperfecta. Calcif Tissue Int. 2024;115(6):891-914.
3. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet. 2016;387 (10028):1657-71.
4. Ralston SH, Gaston MS. Management of osteogenesis imperfecta. Front Endocrinol (Lausanne). 2020;10:924.
5. Anissipour AK, Hammerberg KW, Caudill A, et al. Behavior of scoliosis during growth in children with osteogenesis imperfecta. J Bone Joint Surg Am. 2014; 96(3):237-43.
6. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev. 2016; 10(10):CD005088.
7. Adami S, Gatti D, Colapietro F, et al. Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res. 2003;18(1):126-30.
8. LoTurco HM, Carter EM, McInerney DE, Raggio CL. Patient-reported prevalence of gastrointestinal issues in the adult skeletal dysplasia population with a concentration on osteogenesis imperfecta. Am J Med Genet. 2022;188(5):1435-42.
9. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434-41.
10. Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87(10):4528-35.
11. Gatti D, Rossini M, Viapiana O, et al. Teriparatide treatment in adult patients with osteogenesis imperfecta type I. Calcif Tissue Int. 2013;93(5):448-52.
12. Brent MB. Abaloparatide: a review of preclinical and clinical studies. Eur J Pharmacol. 2021;909:174409.
13. Miller PD, Hattersley G, Riis BJ, et al.; ACTIVE Study Investigators. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316(7):722-33.
14. Hoyer-Kuhn H, Netzer C, Koerber F, Schoenau E, Semler O. Two years' experience with denosumab for children with osteogenesis imperfecta type VI. Orphanet J Rare Dis. 2014:9:145.
15. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017;377(15):1417-27.
16. Kobayakawa T et al. Real-world effects and adverse events of romosozumab in Japanese osteoporotic patients: a prospective cohort study. Bone Rep. 2021:14:101068.
17. Uehara M, Nakamura Y, Nakano M, Miyazaki A, Suzuki T, Takahashi J. Efficacy of romosozumab for osteoporosis in a patient with osteogenesis imperfecta: a case report. Mod Rheumatol Case Rep. 2022;6(1):128-33.
18. Dattagupta A, Petak S. Osteoporosis improved by romosozumab therapy in a patient with type I osteogenesis imperfecta. AACE Clin Case Rep. 2023;9(6):209-12.
19. Kusakabe T, Ishihara Y, Kitamura T, et al. Beneficial effects of romosozumab on bone mineral density and trabecular bone score assessed by dual-energy X-ray absorptiometry in a family with osteogenesis imperfecta. Osteoporos Int. 2024;35(7):1303-4.
20. Gottesman GS, Carpenter TO, Wallace M, et al. 6820 Assessing the efficacy and safety of setrusumab for osteogenesis imperfecta: updated phase 2 data from the phase 2/3 Orbit study. Abstract. J Endocr Soc. 2024;8(Suppl 1):bvae163.358.
21. Glorieux FH, Langdahl B, Chapurlat R, et al. Setrusumab for the treatment of osteogenesis imperfecta: 12-month results from the phase 2b Asteroid study. J Bone Miner Res. 2024;39(9):1215-28.

Disclosure: *The authors declare that they have no conflicts of interest to disclose.*
Funding: *The authors report no forms of financial support involved in the production of this case report.*
Consent: *The authors attest that this study complies with the requirements of human research ethics committees, including obtaining patient consent where appropriate.*