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Case Report

Use of Teriparatide, Denosumab, and Romosozumab in a Postpartum Monogenic Osteoporosis With a *WNT1* Pathogenic Variation

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Abstract

Early-onset osteoporosis (EOOP) is a form of osteoporosis (OP) that affects young people, and its etiologies include subclinical diseases, nutritional deficiencies, medications, or even genetic variants. We present a case of a 28-year-old woman with a history of vertebral and rib fractures immediately post partum. Although negative evaluation for secondary causes of OP, her bone densitometry showed a *Z* score of −4.7 in the lumbar spine (LS) and −3.3 both in the total hip (TH) and femoral neck (FN). Classified as very high-risk OP, anabolic treatment with teriparatide was initiated, with the addition of denosumab. At the end of this initial treatment, the patient showed partial improvement in her bone densitometry, leading to further investigation with a genetic panel. A pathogenic variant of the *WNT1* gene (Chr12:48 981 551 AC > A) was identified. Consequently, romosozumab was considered, despite its absence in the official indication for such or similar cases, due to biological plausibility since it inhibits sclerostin, an inhibitor of the WNT pathway. Finally, the patient showed significant improvement in bone densitometry, with a total increase of +42.1% in lumbar spine bone mineral density (BMD) and +16.6% in total hip BMD.

Key Words: osteoporosis, WNT, β-catenin, romosozumab, denosumab, teriparatide

Abbreviations: BMD, bone mineral density; EOOP, early-onset osteoporosis; FN, femoral neck; LS, lumbar spine; OI, osteogenesis imperfecta; OP, osteoporosis; PLO, pregnancy and lactation-associated osteoporosis; RR, reference range; SC, subcutaneously; TH, total hip.

Introduction

Osteoporosis (OP), a condition characterized by the deterioration of bone microstructure, low bone mineral density (BMD), and fractures, most commonly affects postmenopausal women and its incidence increases with age [1]. There is, however, an entity called early-onset osteoporosis (EOOP) that affects children, premenopausal women, and men younger than 50 years [1].

EOOP can be secondary to nutritional deficiencies, malabsorption diseases, prolonged use of some medications, or may present as a primary condition due to genetic variants, such as WNT signaling pathogenic variations [1]. Heterozygous *WNT1* variants occur in up to 8.5% of patients with EOOP [2].

WNT1 overexpression in mice models leads to increased bone formation through higher number and activity of osteoblasts. *WNT1* deletion in mice, on the other hand, results in low bone mass and increased bone fractures [3].

There are 19 known *WNT* genes in humans [4]. Its pathogenic variations have been implicated in endocrinologic, cancers, and tissue and bone diseases [5]. *WNT1* pathogenic variations have associated with osteogenesis imperfecta (OI) type XV when in homozygosis or compound heterozygosis and EOOP when in heterozygosis [6], suggesting *WNT1* as an important factor for bone homeostasis [7]. Pathogenic variations in *WNT6*, *10a*, *10b*, *11*, and *16* have also been linked to OP [6]. The WNT signaling pathways have been classically divided into canonical, which involves WNT/β-catenin [8], and noncanonical, WNT–planar cell polarity [9], and WNT-calcium [10]. Some WNT primarily activates the canonical WNT signaling pathway, such as WNT*1*, *2*, *3*, and *8a*. Some activate primarily the noncanonical, such as WNT*4*, *5a*, *5b*, *6*, *7a*, *7b*, *10b*, *11*, and *16*. Some activate both, such as the WNT*3a* [11].

The WNT canonical pathway binds to Frizzled, a transmembrane receptor, and the coreceptor LRP5/6, which results in the transfer of Axin-mediated destruction complex from cytosol to plasmatic membrane, increasing β-catenin in the cytosol by diminishing its degradation. β-Catenin in the nucleus activates the transcription of genes responsible for osteoblast differentiation and function and inhibits osteoclast differentiation, thereby enhancing bone formation and decreasing bone resorption. It also inactivates the gene repressor Groucho/TLE [12]. However, *WNT1* variation leads to a loss of WNT1's ability to activate the LRP5/6-mediated WNT pathway, reducing β-catenin in the cytosol and decreasing bone formation.

Part of this pathway includes sclerostin, a protein encoded by the *SOST* gene, which inhibits the WNT pathway by binding to the LRP5/6 coreceptors and is targeted by the therapeutic monoclonal antibody drug called romosozumab. This inhibition increases Axin-mediated destruction complex

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activity in the cytosol, decreasing β-catenin plasmatic concentration [1, 12, 13]. Sclerostin is secreted by mature osteocytes and osteoblasts and is shown in lower concentrations in patients with *WNT1* pathogenic variations, due to its impaired process of osteogenic cell maturation [7].

To date, there are no records on the use and efficacy of this drug in human cases of *WNT1* variants, only in *WNT1* knockout mice, with a good response [3]. This article will demonstrate the use of romosozumab, along with teriparatide and denosumab for a patient with a variant of the *WNT1* gene.

Case Presentation

A 28-year-old previously healthy woman presented with right hypochondrial and lumbar pain immediately after delivery the week prior. On physical examination, tenderness and pain was noted on palpation of the ribs, with no visible changes. Imaging studies, including abdominal/lumbar computed tomography and thoracic/lumbar spine radiography (Fig. 1A), revealed multiple fragility fractures involving the rib and 2 vertebrae, consistent with the clinical presentation. Magnetic resonance imaging performed 2 weeks later identified T8, T12, and L2 fractures with associated bone marrow edema, consistent with recent injury (Fig. 1B-1D). The patient did not report any complaints prior to this period; however, no imaging studies were conducted during the pregnancy. She opted to cease breastfeeding after 2 months and sought expert medical consultation 6 months after the onset of symptoms. There was no history of parental consanguinity, OP, or fragility fractures in other members of her family. Initially, bone metabolism tests and bone densitometry were ordered.

Diagnostic Assessment

Her initial bone densitometry showed a *Z* score of −4.7 (bone mineral density [BMD] 0.608) in the lumbar spine (LS) and −3.3 (BMD 0.568) in the femoral neck (FN) and −3.3 (BMD 0.585) in total hip (TH). Secondary causes were investigated through bone metabolism tests, including serum calcium (9.7 mg/dL [2.42 mmol/L]; reference range [RR], 8.6-10.3 mg/dL [2.1-2.6 mmol/L]), intact parathyroid hormone (17.6 pg/mL [1.86 pmol/L]; RR: 19-64 pg/mL [2.0-6.8 pmol/L]), phosphorus (3.2 mg/dL [1.03 mmol/L]; RR: 2.5-4.5 mg/dL [0.80-1.45 mmol/L]), 25-OH-vitamin D (26 ng/mL [65 nmol/L]; RR: >20 ng/mL [>50 nmol/L]), 24-hour urine calcium (162 mg/24 hours [4 mmol/24 hours]; RR: 55-220 mg/24 hours [1.37-5.49 mmol/24 hours], resulting in 2.9 mg/kg/24 hours [0.071 mmol/kg/24 hours]), alkaline phosphatase (95 U/L [1.58 μkat/L]; RR: 30-130 U/L [0.50-2.16 μkat/L]), C-terminal telopeptide (0.678 ng/mL [678 pmol/L], RR: 0.025-0.573 ng/mL [25-573 pmol/L]), renal function (serum creatinine 0.91 mg/dL [0.08 mmol/L], RR: 0.60-1.10 mg/dL [0.05-0.09 mmol/L], Chronic Kidney Disease–Epidemiology Collaboration estimated glomerular filtration rate = 88 mL/min/1.73 m^2 [1.47 mL/s/1.73 m^2]), thyroid function (thyrotropin 0.660 μUI/mL; RR: 0.45-4.5 μUI/mL and free thyroxine 0.89 ng/dL [11.45 pmol/L]; RR: 0.9-1.7 [11.58-21.88 pmol/L]), and

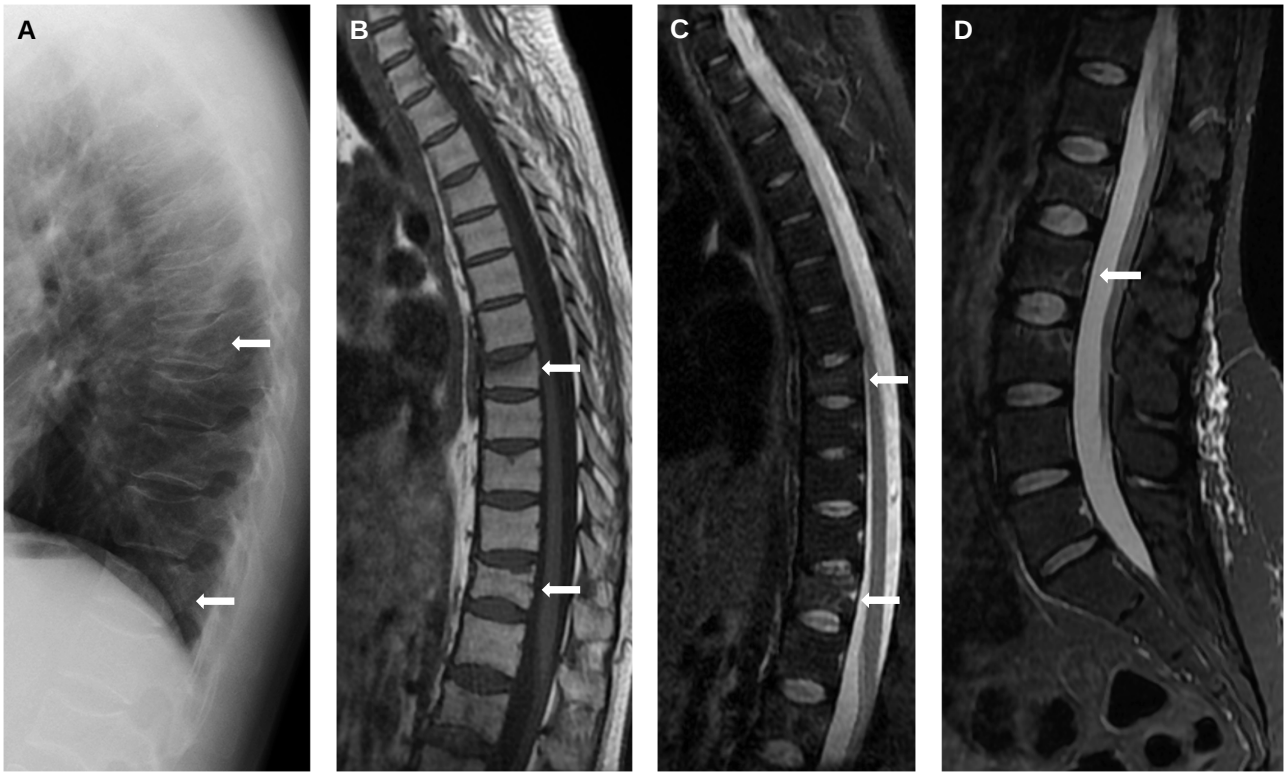

Figure 1. A, Lumbar plain radiography showing T8 and T12 vertebral fractures. B, T1-weighted MRI demonstrating vertebral fractures at T8, centered at the superior end plate and anterior column, with mild wedging and an estimated height reduction of 35%, without significant retropulsion of the posterior wall and at T12, exhibiting a biconcave morphology, with an estimated height reduction of 30%, also without significant retropulsion of the posterior wall. C, T2-weighted fat-suppressed Dixon/IDEAL MRI demonstrating vertebral fractures at T8 and T12, with associated bone marrow edema at both levels. D, STIR-weighted MRI demonstrating L2 vertebral body fracture with associated bone marrow edema, exhibiting a biconcave morphology and an estimated height reduction of 25%, without significant retropulsion of the posterior wall. IDEAL, iterative decomposition of water and fat with echo asymmetry and least-squares estimation; MRI, magnetic resonance imaging; STIR, short τ inversion recovery.

Table 1. Evolution of the patient's bone densitometry values

Region	A		B			C			D			Total variation (D-A)
	BMD	Z score	BMD	Z score	Δ (B-A)	BMD	Z score	Δ (C-B)	BMD	Z score	Δ (D-C)	Δ
Lumbar spine[a] (L1-L4)	0.608 g/cm^2 (6.08 kg/m^2)	− 4.7	0.749 g/cm^2 (7.49 kg/m^2)	−3.6	0.141 g/cm^2 (1.41 kg/m^2) (23.2%)	0.794 g/cm^2 (7.94 kg/m^2]	−3.2	0.045 g/cm^2 (0.45 kg/m^2) (6.0%)	0.864 g/cm^2 (8.64 kg/m^2)	−2.7	0.07 g/cm^2 (0.7 kg/m^2) (8.8%)	0.256 g/cm^2 (2.56 kg/m^2) (42.1%)
Femoral neck	0.568 g/cm^2 (5.68 kg/m^2)	−3.3	0.664 g/cm^2 (6.64 kg/m^2)	−2.6	—	0.664 g/cm^2 (6.64 kg/m^2)	−2.5	—	0.679 g/cm^2 (6.79 kg/m^2)	−2.4	—	—
Total hip[a]	0.585 g/cm^2 (5.85 kg/m^2)	−3.3	0.668 g/cm^2 (6.68 kg/m^2)	−2.6	0.083 g/cm^2 (0.83 kg/m^2) (14.2%)	0.665 g/cm^2 (6.65 kg/m^2)	−2.6	−0.003 g/cm^2 (−0.03 kg/m^2) (0.0%)	0.682 g/cm^2 6.82 kg/m^2)	−2.5	0.017 g/cm^2 (0.17 kg/m^2) (2.6%)	0.097 g/cm^2 (0.97 kg/m^2) (16.6%)
Radius 33%	—	—	—	—	—	0.743 g/cm^2 (7.43 kg/m^2)	−1.6	—	0.720 g/cm^2 (7.20 kg/m^2)	−1.9	—	—[a]

Abbreviation: BMD, bone mineral density.
[a]Least significant change = 3% in lumbar spine and 5% in total hip.

screening for malabsorption, including celiac disease (tissue transglutaminase IgA negative, RR negative and total immunoglobulin A 260 mg/dL [16.25 µmol/L]; RR 50-400 mg/dL [3.13-25 µmol/L]). Thus, the initial diagnostic hypothesis was established as a very high-risk primary OP.

Considering the severity of the low BMD and the negative search for secondary etiologies, a genetic panel was requested through next-generation sequencing. This test detected a variant in the *WNT1* gene (Chr12:48 981 551 AC > A) in heterozygosis, suggesting monogenic early-onset OP (EOOP).

Treatment

Initially, due to the very high-risk nature of her OP, the patient was treated with the anabolic agent teriparatide, 20 µg/day subcutaneously (SC) for 24 months and vitamin D replacement was started. However, due to the severity, denosumab 60 mg, SC every 6 months, was added after 14 months of teriparatide treatment with a good response. Using the same equipment, with the least significant change of 3% in LS and 5% in TH, there was an improvement in LS BMD of 23.2% and 14.2% in TH, as shown in Table 1 and Fig. 2.

After the genetic diagnosis and considering the need for further improvements in BMD, the patient was prescribed romosozumab 210 mg SC monthly for 12 months. After this period, her new bone densitometry showed an improvement in LS BMD of 8.8% and 2.6% in TH.

Outcome and Follow-up

The total increase was +42.1% in lumbar spine BMD and +16.6% in total hip BMD. Denosumab was reintroduced after romosozumab treatment to prevent bone mass loss and promote further gains. The patient had no new fractures after more than 4 years of follow-up.

Discussion

We present a novel case of a severe monogenetic EOOP possibly worsened by the peripartum period. A multicenter study detected pathogenic variants of bone-related genes in half of the patients with pregnancy and lactation-associated OP (PLO), the *LRP5* and *WNT1* genes being the most common loci affected, encompassing together a quarter of all the patients, closely followed by *COL1A1/A2* with 7%. These had also a worse bone profile than the nongenetic forms [14].

It is recognized that WNT signaling is a key pathway in osteometabolism. LRP5 is a coreceptor in the WNT pathway that binds to WNT ligands, such as WNT1, one of the most important among them. Disturbances in WNT1's ability to activate the WNT pathway is mediated by LRP5/6's decreased β-catenin in the cytosol, which leads to reduced bone formation. Part of this pathway includes sclerostin, an inhibitor of the WNT pathway [13, 15].

Our patient had a Chr12:48 981 551 AC > A (alternatively c.1026deLC-ENST00000293549) sequence variation, classified as pathogenic according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines [16]. This deletion of a single nucleotide in the 1026 position of chromosome 12 in a stop codon leads to an erroneous downstream translation, thus classified as frameshift, creating an anomalous protein (p.Glu343Serfs*50)

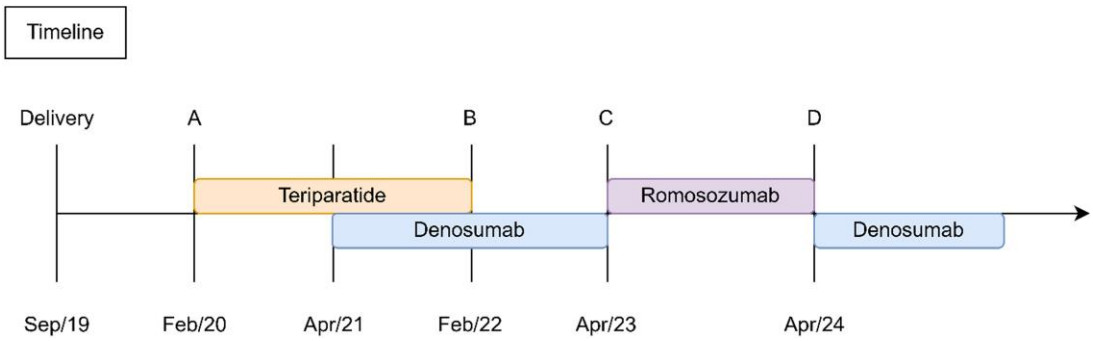

Figure 2. Timeline of the medications used.

with the next stop codon appearing 50 positions after. This sequence change has been associated with short stature and EOOP when in heterozygosis [17]. Another disruption (p.Val355Phe) of this same region of the WNT1 protein has already been determined pathogenic [18, 19], suggesting clinical relevance of this region. *WNT1* pathogenic variations in homozygosis or compound heterozygosis have been associated with OI type XV [20, 21]. This patient's pathogenic variation has once before been identified in homozygosis as a probable cause of OI in the National Center for Biotechnology Information ClinVar database-VCV000180210.2.

Given the low BMD and multiple recent fractures, configuring a very high-risk OP, there was clear indication for anabolic drug therapy [22]. Considering treat-to-target approaches to OP treatment [23], anabolic treatment with teriparatide achieved a great response in what seems to be the best predictor for major fracture recurrence, total hip BMD [24]. A previously reported *WNT1* pathogenic variation-associated case with postpartum vertebral fractures showed a similar teriparatide response, although without denosumab association [25]. However, considering that all of our patient's fractures were vertebral, an absence of enough LS BMD improvement [24] raised concerns and led us to recommend a second anabolic drug, raising the doubt about how a WNT pathway enhancer medication would behave in a patient with a pathogenic variation. If the patient had no prior vertebral fractures, we might not have followed this approach, and would have considered the teriparatide response enough and switched to an antiresorptive drug, which has been shown to improve BMD in patients with WNT1 mutations [26]. This choice led to another substantial improvement in our patient's densitometry, particularly relevant after an exclusive antiresorptive period, which could diminish its effect, suggesting a possible eminent role of romosozumab in this context.

Although we have no before pregnancy densitometry, bone mass loss during pregnancy tends to be around 3% to 5% [27], decreasing another 3% to 10% during lactation [28]. Our patient presented with a Z score of −4.7 in the LS, indicating a degree of bone mass loss incompatible with this context alone. Additionally, most fractures related to pregnancy occur during lactation (70%-90%), whereas our patient experienced fractures immediately post partum, supporting that there was likely a preexisting condition, which was then confirmed through genetic testing [12, 29].

It is possible that the recovery of postpartum BMD changes contributed to the patient's improvement, but not to the extent of the considerable difference observed at the end of treatment. Therefore, it seems that teriparatide, denosumab, and romosozumab had a significant therapeutic response.

We believe that, despite the latter acting on the canonical pathway, where the patient had a monoallelic loss of function, and probably diminished sclerostin concentration [7], the target protein for romosozumab, the enhancing effect on the other WNT that interacts with bone and use of the pathway, including the wild-type monoallelic *WNT1* the patient had, could explain the significant clinical response [12, 30].

This conclusion is also supported by previous reports of the use of this drug with significant improvement in bone mass and decrease in fracture rate in a mouse model of global *WNT1* loss [3], although we found no other human use reports. Further studies are still warranted.

Learning Points

- Romosozumab may be a promising therapy in cases of suspected genetic decreased WNT function.
- Even in the context of a possible secondary OP explanation such as pregnancy and lactation, genetic testing may be needed to further explain unusually severe results in dual-energy x-ray absorptiometry after negative investigation of other etiologies, as up to half of PLO patients may have an undiagnosed pathogenic variant, especially the most severe cases.
- The target of OP treatment should be individualized for each patient. Total hip BMD is probably the best target based on recent treatment goal guidelines for OP, but LS BMD should be considered in cases of multiple prior vertebral fractures.
- Antiresorptive therapies represent a robust choice for patients with *WNT1* pathogenic variations. However, in cases of very high fracture risk, anabolic therapies should be considered as first-line treatment.

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Contributors

T.C.M.: writing—original draft, data curation, and investigation; M.K.G.D.: writing—original draft, data curation, and investigation; and A.S.F.: writing—original draft, investigation, data curation, and supervision.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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