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CASE STUDY

ROMOSOZUMAB AS A NEW THERAPEUTIC OPTION IN POSTMENOPAUSAL OSTEOPOROSIS WITH VERY HIGH FRACTURE RISK: A CASE REPORT

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Summary

Osteoporosis is a metabolic bone disease characterized by increased risk of fractures. Bisphosphonates and denosumab are widely used in the pharmacotherapy of osteoporosis. In severe cases, anabolic drugs and romosozumab (ROMO) – a monoclonal antibody that acts bi-modularly, blocking the sclerotin pathway, leading to bone formation and reduced bone resorption – are used. The paper presents data from one of the first post-trial ROMO therapies in Poland under real-data follow-up. The research paper presents a 61-year-old woman with severe postmenopausal osteoporosis and multiple osteoporotic fractures (MOF) of the thoracic and lumbar vertebrae after 5 times of vertebroplasty. The patient underwent a full differential diagnosis because of a suspected secondary cause of the disease, which was ruled out. Because of the patient's contraindication to bisphosphonates and very high fracture risk, denosumab was used in the treatment. Due to a decrease in bone mineral density (BMD) in the follow-up, dual-energy X-ray absorptiometry (DXA) and treatment with ROMO was started (Mar 2024). The treatment was well tolerated. No early adverse effects were observed. Due to its strong antifracture efficacy and the bi-modal mechanism of the latest guidelines for the diagnosis and

management of osteoporosis in Poland, ROMO was recommend. This could be the first-line treatment in postmenopausal women at very high risk of fracture.

Keywords: romosozumab, postmenopausal osteoporosis, DXA, fracture risk, BMD

Introduction

Osteoporosis is a metabolic bone disease characterized by low bone mass, with consequent excessive bone loss and architecture deterioration and increased risk of fractures. Osteoporotic vertebral fractures (VF) are the most common site of osteoporotic fractures [1]. The incidence of osteoporotic vertebral fractures in Europe is 18-26% of all osteoporotic fractures [2]. The most common symptom of fractures is back pain (85%), decreased height, increased thoracic kyphosis and neurological deficits [3]. Typically, osteoporotic fractures are described using the Genant scale. This classifies the shape of the fracture (wedge, biconcave, crush) and, based on the deformity of the bone, assesses its severity (mild, moderate, severe). In the treatment of osteoporotic fractures, pharmacological treatment, conventional surgery and minimally invasive techniques (vertebroplasty, kyphoplasty) are used. Treatment of osteoporosis itself is extremely important. In severe cases, therapy includes romosozumab (ROMO), a monoclonal antibody that acts against the sclerostin pathway, leading to increased bone formation and decreased bone resorption in patients with osteoporosis [4].

Case Description

A 61-year-old woman with severe postmenopausal osteoporosis and MOF of the thoracic and lumbar vertebrae (9 fractures) was referred to the Department of Rheumatology for diagnosis of osteoporosis due to low-energy compression fractures after 5 times of

vertebroplasty. She developed complaints of pain in the thoracic spine in August 2018 after lifting a light weight. She reported difficulty sitting up and when standing upright. In addition, the patient suffered from hypertension, hypercholesterolemia, carbohydrate intolerance and gastroesophageal reflux. There was a family history of osteoporosis in her mother and sisters. On physical examination, thoracic kyphosis and increased tension of the paraspinal muscles in the pectoral and lumbar regions were noted, along with limited mobility of the spine. Regarding the shoulder joints, abduction was limited.

In laboratory tests, slightly reduced levels of vitamin D (29.9 ng/ml) were noted, while calcium and phosphorus were normal. Hypoparathyroidism was ruled out. MRI and CT imaging of the spine showed osteoporosis with multiple compression fractures of the Th-L spine: Th7-12, L2-5 vertebrae with reduced height, L4/5 herniation, osteophyte on the posterior-upper edge of L5 protruding into the spinal canal by 7 mm with compression of the meningeal sac and reduced height of the L5/S1 intervertebral disc.

The patient has had vertebroplasty performed several times: Th8 and Th9 (Jan 2019); L2, L3 (Apr 2019); Th7, Th8, L2-L4 (May 2019); Th7, Th10 (Jan 2023). After the procedures, the patient experienced significant improvement in pain and reduced difficulty in verticalization. No new pathological fractures were observed.

The patient was secured with a corset. Therapy included vitamin D3 and calcium at a tolerable dose (at a higher dose, the patient had gastrointestinal side effects). Since the patient had contraindications to bisphosphonates (active GERD), the treatment included denosumab every six months subcutaneously.

She received 9 doses of denosumab with good tolerance, but due to lack of improvement and a 3.9% drop in-dual-energy X-ray absorptiometry (DXA) (Table 1), the drug was changed to ROMO. On March 11, 2024, the patient was administered the first dose of ROMO. The

patient is currently on the fourth dose of ROMO (15 Jun 2024). She reports no adverse effects after taking the drug.

Table 1. Bone mineral density (BMD) changes in the proximal end of the femur

Date of survey	Patient's age	BMD	% change in BMD from previous study	T- score
Jan 12, 2024	62	0.388	-7.4	-4.1
Apr 12, 2023	62	0.465	10.9	-3.5
Dec 08, 2021	60	0.413	-1.6	-3.9
Feb 22, 2021	60	0.419	-0.1	-3.9
Feb 24, 2020	59	0.419	-	-3.9

Notes: Spine not evaluable due to vertebroplasty and multiple fractures.

Case Analysis

Despite numerous tests, multidisciplinary consultations and hospitalization, the cause of such severe osteoporosis could not be determined. However, genetic testing, specifically for the COL1 mutation typical of osteogenesis imperfecta, was not included in the diagnostic arsenal. Type 1 of this disease can even occur in younger adults and present with a similar course. In the treatment of those at very high risk of fracture, the time to reduce fracture risk and the strong effect on BMD is crucial for secondary fracture prevention. In this group of patients, treatment should be started with anabolic drugs. There are no such drugs available in Poland, thus the hope in therapy is to use ROMO. After one year of ROMO, therapy should be continued with denosumab (DMAB) or bisphosphonates (BP) (Table 2).

Table 2. Preferred therapy according to osteoporotic fracture risk category

Risk category	Criteria of fracture risk	Preferred therapy
Very high	- Fracture within 12 months - Multiple fractures - Fx on osteoporosis treatment - Fx on pro osteoporotic medications - T-score <-3.0 - FRAX >30% for major, >4.5% hip - Recurrent falls	- ROMO 1x1 per month for 12 months - PTH analogs - DMAB 2x a year
High	- T-score < -2.5 - A history of fracture in the primary location within 2 years - T-score -1.0 to - 2.5 and FRAX ≥20% for MOF or ≥3% hip	- BP or - DMAB 2x a year
Low	- Without fractures - T-score > -1.0 and FRAX probability <20% MOF and <3% hip	calcium/vitamin D only

Notes: FRAX – Fracture Risk Assessment Tool, ROMO – romosozumab, PTH analogs – Parathyroid Hormone analogs, DMAB – denosumab, BP – bisphosphonates.

ROMO is a humanized monoclonal antibody that inhibits the activity of the osteocyte protein sclerostin, thereby exerting a dual effect of stimulating bone formation while inhibiting bone resorption. Sclerostin inhibits the Wnt/β-catenin pathway in osteoblasts through competitive binding of lipopolysaccharide-binding protein 5/6, and thus inhibits osteoblast differentiation. Inhibition of sclerostin activates osteoblasts and promotes bone formation. Because of its efficacy, the latest guidelines for the diagnosis and management of osteoporosis in Poland recommend ROMO as first-line treatment in postmenopausal women with very high fracture risk [5]. Sequential use of ROMO-DMAB results in a steady, strong increase in BMD even after the 3rd year of therapy (20% increase in spine BMD and 6% in neck), which is not

observed after BP [6]. Citation No. 6 comes from the original publication of the clinical trial and was the most important registration trial. The reduction in the risk of compression and non-vertebral fractures with this therapy is visible as early as 12 months and increases with continued therapy [7]. ROMO in the ARCH trial showed a nearly 49% higher reduction in vertebral fracture risk than alendronate after 2 years of treatment. Earlier, in the FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) trial, ROMO resulted in a rapid and significant reduction in the incidence of morphometric and clinical VF over 12 months of treatment compared to placebo [8]. The efficacy of such therapy has been proven in patients who have never used any osteoporosis treatment and were previously treated with BP or denosumab, as in the case of our patient [9].

In this case, the evaluation of the effectiveness of the treatment, most often based on the result of DXA, was crucial. A decrease in BMD below precision error (PR) may be the basis for changing therapy. At the author's center, the PR of measurement of BMD at the lumbar spine and hip is 1.5%, and calculated least significant change (LSC) is 4.16%. The observed decline of 7.9% met these criteria.

Conclusions

ROMO therapy is an attractive and safe new option for the treatment of osteoporosis in postmenopausal women at very high risk of fracture, but due to lack of reimbursement and high treatment costs, the post-trial experience in Poland is limited. Our case of a patient with multimorbidity and polytherapy differs from the typical trial patient but confirms the safety of ROMO even in a medically complex patient.

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