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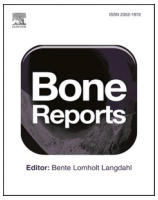

Case Report

Effectiveness of romosozumab in primary biliary cholangitis at half the recommended dose in an underweight patient

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ABSTRACT

Romosozumab (RSB) is a monoclonal antibody to sclerostin that is approved for post-menopausal osteoporosis at high fracture risk. It is administered as a monthly 210 mg subcutaneous injection for 12 months. We report the response to half the standard dose of RSB in an underweight patient with severe osteoporosis and primary biliary cholangitis (PBC). Using half dose RSB (approximately 3 mg/kg RSB), she demonstrated significant improvement in lumbar spine BMD, paralleling the results of phase III trials. This case highlights the effectiveness of RSB in a patient with concomitant PBC, in addition to its effectiveness at half the recommended dose in an underweight patient.

1. Introduction

Romosozumab (RSB) is a monoclonal antibody used to treat osteoporosis in postmenopausal patients with a high risk of fractures. It binds and inhibits sclerostin, thereby increasing bone formation and decreasing bone resorption. It was approved by FDA in 2019 at a dose of 210 mg, administered monthly, for 12 months. It is recommended that treatment with RSB should always be followed with an anti-resorptive medication such as bisphosphonates or denosumab.

We present a case of a 76 y.o. underweight female with primary biliary cholangitis (PBC), Sjogren's syndrome and severe osteoporosis, with history of intolerance to multiple medications. She was administered half the recommended monthly dose of RSB due to extreme reluctance and concern about side effects with the approved 210 mg monthly dose. We hereby report the response of her bone density to the treatment regimen. This case report highlights the effectiveness of RSB treatment in patients with PBC, and the significant response achieved with half the recommended dose of RSB in our underweight patient.

2. Case description

A 76-year-old female with a history of PBC, Sjogren's syndrome, hemorrhagic duodenal ulcer, and history of subtotal gastrectomy in 1962 presented for evaluation of severe osteoporosis. Fracture history was significant for a T11 compression fracture in 2020 requiring kyphoplasty, and a T10 inferior endplate compression fracture requiring vertebroplasty in 2022. Her history was also significant for biopsy-proven stage I primary biliary cholangitis complicated by hepatic cirrhosis, diagnosed when she was about 55 years old, for which she was maintained on ursodiol with normalization of her liver enzymes. She was up-to-date with dental care and engaged in daily physical activity by walking. She had no family history of osteoporosis, fractures, or kidney stones. She denied alcohol, tobacco, or recreational drug use. Secondary causes of osteoporosis including hyperthyroidism, hyperparathyroidism, celiac disease, hypercalciuria, and multiple myeloma were ruled out. She did not have much dairy intake and was initiated and maintained on 500 mg of calcium as calcium citrate twice daily and 800 units of vitamin D3.

Prior treatment history was significant for being diagnosed with osteoporosis in 2005, when she was tried on teriparatide. This was discontinued after six months due to significant nausea, hypercalcemia, fatigue, and cramps in the extremities. She was not prescribed oral bisphosphonates at the time due to a history of hemorrhagic duodenal ulcers. Zoledronic acid (ZA) was administered in 2006 and 2008, with good tolerance, but without any improvement in bone density. Baseline bone resorption markers before ZA were low as measured by fasting second void urine N-telopeptide cross-links (NTX) of 18 nm BCE/mm creatinine, which decreased to 10 nm BCE/mm creatinine while on ZA. Hence, further ZA infusions were withheld. Denosumab was offered after it was approved in the United States, which she declined due to

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concern about side effects. Teriparatide was tried again in 2013 which she could not tolerate due to similar side effects as in the past. She received ZA again in 2016. BMD did not improve on ZA and she declined further infusions.

On examination, she was frail, with BMI of 16.6 mg/kg^2 (weight 37.8 kg). She had mild kyphoscoliosis of the spine with no spinal or paraspinal tenderness. The remainder of the exam was unremarkable. Laboratory evaluation showed normal serum calcium, albumin and 25 OH vitamin D level (25-OHD), with bone specific alkaline phosphatase (BSAP) of 22.7 U/L and 2nd fasting urine N-telopeptide (NTX) of 23 nm BCE/mm creatinine (Table 1). Other secondary workups were unremarkable including parathyroid hormone and serum protein electrophoresis. Bone mineral density (BMD) done by dual x-ray absorptiometry (DXA) in January 2022 using the GE Lunar Prodigy machine showed a lumbar spine (LS) BMD of 0.613 g/cm2 (T-score − 4.7) and a total hip BMD of 0.575 g/cm^2 (T-score − 3.4) (Table 2).

Our patient was reluctant to consider any medications due to concerns about side effects but after much discussion, finally agreed to a trial of RSB at half the recommended dose only. She had no cardiovascular co-morbidities that precluded the use of RSB. She received RSB 105 mg injection monthly for 12 months. BMD checked a year later showed a remarkable 17 % increase in her lumbar spine BMD (0.715 g/cm^2, T-score − 3.9), with stable total hip BMD (Table 2). Bone markers showed relatively stable bone specific alkaline phosphatase (BSAP) and a significant 25 % reduction in 2nd fasting urine NTX from baseline pre-RSB values (least significant change of urine NTX measured by the VITROs immunodiagnostic quantitative NTX assay is 15 %). She was then transitioned to denosumab, which she was now agreeable to take.

3. Discussion

Romosozumab is a humanized monoclonal sclerostin antibody, approved by the FDA in 2019 for the treatment of osteoporosis in postmenopausal women who are at a high risk of fracture. Sclerostin, produced by osteocytes, inhibits bone formation by blocking the wnt-signaling pathway. RSB binds to the sclerostin, preventing it from interacting with its receptor and the LRP-5 and LRP-6 co-receptors, thus neutralizing its inhibitory effect. This leads to increased bone formation and decreased bone resorption by decreasing RANKL production (Lim and Bolster, 2017). The recommended monthly dosage of RSB is 210 mg, administered through two pre-filled syringes, each containing 105 mg. It is given as a once-a-month subcutaneous injection for 12 months. No dose adjustment is recommended based on weight, renal or hepatic function.

In the phase I trial or RSB, 72 healthy subjects received either AMG 785 (later known as RSB) or placebo in ascending weight- based single doses either subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg) or intravenously (1 or 10 mg/kg). DXA scans were conducted pre-dose and on days 29 and 57. Compared with placebo, single doses of AMG 785 at 3 mg/kg body weight did increase BMD at the lumbar spine and total hip. It also increased the bone-formation markers Procollagen 1 Intact N-Terminal Propeptide (P1NP), BSAP, and osteocalcin, and decreased the bone-resorption marker serum C-terminal telopeptide, resulting in a large anabolic window (Padhi et al., 2011).

During phase II trials, participants were randomly assigned to receive subcutaneous RSB monthly (at a dose of 70 mg, 140 mg, or 210 mg) or every 3 months (140 mg or 210 mg), subcutaneous placebo, or an open-label active comparator (oral alendronate (70 mg weekly) or subcutaneous teriparatide (20 μg daily)) (McClung et al., 2014). According to FDA recommendations, the optimal dose of the drug is 210 mg per month, with no specific guidelines for adjusting the dose for individual patients. Assuming an average weight of 70 kg, the recommended monthly dose of 210 mg equates to approximately 3 mg/kg body weight for the average patient.

Our patient had unusually low bone density, likely due to a combination of autoimmune disease and biopsy-proven stage 1 PBC, complicated by hepatic cirrhosis. She achieved significant improvement in lumbar spine BMD with half the recommended dose of RSB, comparable to results in phase 3 trials. Based on her weight of 37.8 kg, she received almost 3 mg/kg body weight dose of RSB, as most of the average weight phase III trial patients. After 12 monthly doses of 105 mg of RSB, 2nd fasting urine NTX (bone resorption marker) was 25 % lower from baseline, while lumbar spine BMD had increased by 17 %, indicating a significant clinical response.

Even though phase III trials (Cosman et al., 2016; Saag et al., 2017) have demonstrated an increase in BMD at the hip with romosozumab, the results of the DXA showed no improvement in BMD at the hip. This lack of progress could be due to the blunting effect of bisphosphonates, as the patient had previously received treatment with ZA 5 years before romosozumab, and ZA has a long half-life.

In conclusion, this case report demonstrates the success of RSB in treating severe osteoporosis in patients with underlying primary biliary cholangitis. Further research is required to assess the effectiveness of the approved dose of romosozumab at 210 mg each month for 12 months in a larger cohort of patients with PBC. There is also a need for future studies with RSB at weight-based doses in underweight patients, which may potentially reduce treatment costs.

Table 1
Laboratory values pre- and 1-year after treatment with RSB.

Laboratory value	Units	Before treatment with RSB	After 12 months of RSB	Reference range
Calcium	mg/dl	9.5	9.7	8.4–10.2
Albumin	g/dl	4.2	4.1	3.8–5.3
25-Hydroxy vitamin D	ng/ml	36	51	30–80
Urine calcium/ creatinine	(mg/g)	120	300	
Bone specific ALP	U/L	22.7	19.6	14.2–42.7
Urine N telopeptide collagen cross link (NTx)	nM BCE/ mM Cr	23	17	14.2–42.7

Table 2
Bone mineral density (BMD) before and 1 year after treatment with RSB.

Site	BMD before RSB		BMD after 12 months of RSB	
Lumbar spine	BMD (g/cm^2)	T-score	BMD (g/cm^2)	T-score
L1	0.581	−4.6	0.638	−3.7
L2	0.615	−4.9	0.728	−3.9
L3	0.597	−5.0	0.717	−4.0
L4	0.651	−4.6	0.724	−4.0
Total (L1-L4)	0.613	−4.7	0.715	−3.9
Femur				
Neck	0.570	−3.4	0.595	−3.2
Total	0.575	−3.4	0.563	−3.5

Informed consent

The patient has given their consent for these findings to be published, with a full understanding of the implications of such publication.

CRediT authorship contribution statement

Bhanvi Ramchandani: Writing – original draft. **Faryal Sardar Mirza:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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