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The Effect of Teriparatide for the Treatment of Multiple Spontaneous Clinical Vertebral Fractures after Discontinuation of Denosumab in a Female Patient with Rheumatoid Arthritis: A Case Report

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Discontinuation of denosumab is associated with the risk of rebound in bone turnover and rebound-associated spontaneous clinical vertebral fractures. This case report presents an 86-year-old woman with rheumatoid arthritis who experienced rebound-associated spontaneous clinical vertebral fractures at 9 months after denosumab discontinuation. Following 5-year bisphosphonate treatment, the patient had 9 injections of 60-mg denosumab every 6 months. Because of tooth extraction, denosumab treatment was discontinued, and raloxifene was administered. At 9 months after the last denosumab injection, the patient experienced severe low back pain. Magnetic resonance imaging (MRI) and radiograph demonstrated clinical fracture at the fourth lumbar vertebra. MRI performed at 3 months after first fracture showed two additional fractures at the second and third lumbar vertebrae. Teriparatide was administered for management of rebound-associated spontaneous clinical, multiple vertebral fractures. Teriparatide was effective for accelerating the fracture healing and suppressing the occurrence of new fractures. However, 2-year treatment of teriparatide did not have suppressive effect of rebound in bone turnover and general bone loss. This case suggested that teriparatide was effective for suppression of new rebound-associated spontaneous clinical vertebral fractures, but not effective in prevention of general bone loss after denosumab discontinuation.

Keywords: denosumab discontinuation; osteoporosis; rebound effect; spontaneous multiple vertebral fracture; teriparatide
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Introduction

Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor *κ*-B ligand; it is the most potent anti-resorptive agent (Bone et al. 2008). Several studies have reported the efficacy of denosumab for the treatment of osteoporosis and prevention of osteoporotic fractures (Cummings et al. 2009; Papapoulos et al. 2015; Bone et al. 2017). Denosumab was also demonstrated to be effective for the prevention of bone erosion in patients with rheumatoid arthritis (Takeuchi et al. 2016; Mori et al. 2021). However, the discontinuation of denosumab has been reported to be related with increased markers for bone resorption, rebound in bone turnover, and subsequent general bone loss (Bone et al. 2011).

Some recent reports have demonstrated rebound-associated spontaneous clinical vertebral fractures (RVF) and multiple RVFs after denosumab discontinuation (Lamy et al. 2019; Anastasilakis et al. 2020; Kashii et al. 2020; Niimi et al. 2020). Appropriate management of RVFs is not to be determined yet (Lamy et al. 2019). In the clinical setting, bisphosphonates have been administered for osteoporotic patients who have discontinued denosumab for the prevention of rebound in bone turnover and RVFs (McClung 2016). Previous studies reported that a daily recombinant form of human parathyroid hormone (1-34) (teriparatide) stimulated bone formation and reduced osteoporotic fractures (Neer et al. 2001; Girotra et al. 2006). Teriparatide

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may be considered as a treatment alternative for these patients with RVFs. In contrast, the result of switching therapy from denosumab to teriparatide showed general bone loss with rebound in bone turnover (Leder et al. 2015). Physicians may have concerns about increasing the risk of rebound in bone turnover and subsequent RVFs induced by switched teriparatide after denosumab discontinuation, and thus the treatment effect of teriparatide for prevention of RVFs after denosumab discontinuation has not been reported, although teriparatide has been demonstrated to accelerate fracture healing in an experimental animal model (Mognetti et al. 2011). Therefore, the effect of teriparatide for the treatment of RVFs remains unclear.

These fractures have been reported in patients with postmenopausal osteoporosis, but several studies reported these fractures in patients with rheumatoid arthritis or glucocorticoid-induced osteoporosis (Florez et al. 2019; Anastasilakis et al. 2021; Tripto-Shkolnik et al. 2021). This case report presents a patient with rheumatoid arthritis who experienced multiple RVFs after denosumab discontinuation due to tooth extraction. Teriparatide was administered for the treatment of RVFs and was effective for stopping subsequent multiple RVFs. However, bone mineral density (BMD) decreased to the baseline, even with 2 years administration of daily teriparatide.

Case Presentation

An 86-year-old woman with 20-year treatment history of rheumatoid arthritis had the treatment of osteoporosis with a weekly risedronate (an oral bisphosphonate) for 5 years. The height and body weight were 149.9 cm and 63.1 kg (Body mass index: 28.1). After the bisphosphonate treatment was discontinued, she had 9 subcutaneous injections of 60-mg denosumab every 6 months for 4 consecutive years for both treatment of osteoporosis and rheumatoid arthritis with 0.75 μg of eldecalcitol (an orally active analogue of active vitamin D). The last denosumab was administered in September 2017. For treatment of rheumatoid arthritis, she had 1,000 mg of salazosulfapyridine and 5 mg of methylprednisolone with denosumab administration. Anti-cyclic citrullinated peptide antibody was 56.2 U/mL (reference range: 0-4.4 U/mL) at baseline of denosumab treatment. Steinbrocker classification was class II and stage II. The disease activity of rheumatoid arthritis was controlled.

Baseline imaging and laboratory studies before beginning denosumab treatment showed the following results. Dual-energy x-ray absorptiometry (DEXA) revealed bone mineral density (BMD) of 0.596 g/cm^2 (T score: −2.5) in lumbar spine, 0.528 g/cm^2 (T score: −2.4) in the femoral neck, and 0.671 g/cm^2 (T score: −1.6) in total hip. Tartrate-resistant acid phosphatase 5b (TRACP-5b) was 430 mU/dL (reference range: 120-420 mU/dL); bone alkaline phosphatase (BAP) was 12.9 U/L (reference range: 9.6-35.4 U/L) (Table 1).

At one-year follow-up after denosumab initiation, TRACP-5b was decreased to 234 mU/dL and BAP was 9.4 U/L. At 2-year follow-up, the patient's BMD was improved by denosumab treatment, as evident by these DEXA results: 0.788 g/cm^2 (T score: −1.9) in lumbar spine, 0.534 (T score: −2.3) g/cm^2 in femoral neck, and 0.694 (T score: −1.5) g/cm^2 in total hip. There were no disturbance of renal function and hypocalcemia during denosumab treatment (Table 1). At 4.5 years after denosumab administration, the patient had a planned tooth extraction, so the scheduled denosumab injection was discontinued and 60 mg raloxifene (selective estrogen receptor modulator) was administered instead. Raloxifene and eldecalcitol have been reported to have no risks associated with medication related osteonecrosis of the jaw (MRONJ) after tooth extraction (Yoneda et al. 2010; Taguchi et al. 2019), therefore raloxifene and eldecalcitol were administered for treatment of osteoporosis avoiding the risk of MRONJ. No vertebral fractures were demonstrated before denosumab discontinuation (Fig. 1A).

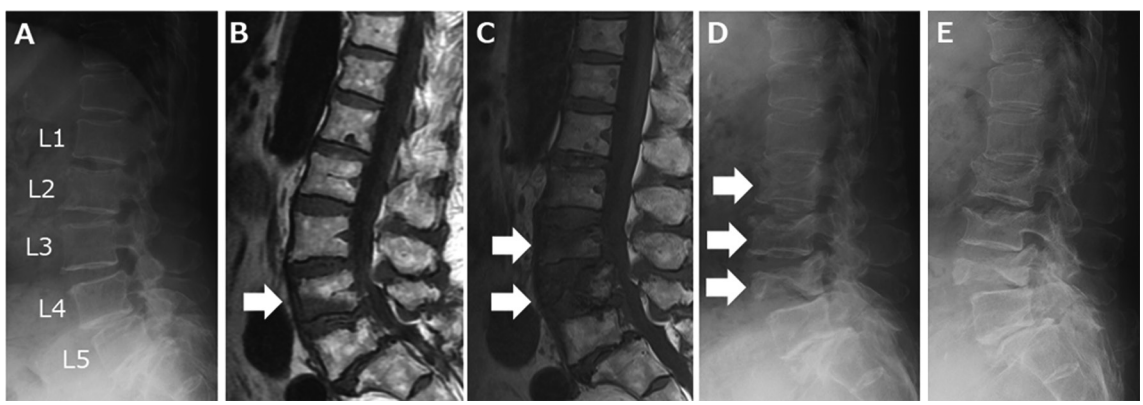

Fig. 1. Radiographs and sagittal MRI show rebound-associated spontaneous clinical vertebral fractures.
(A) Radiograph before denosumab discontinuation. (B) MRI at 9 months after last denosumab administration; an arrow indicates L4 fracture. (C) MRI at 3 months after first fracture; arrows indicate L3 and L4 fractures. (D) Radiograph at 4 months after first fracture; arrows indicate vertebral fractures at L2, L3, and L4. (E) Radiograph at 2 years after teriparatide treatment. L2, second lumbar vertebra; L3, third lumbar vertebra; L4, fourth lumbar vertebra; MRI, magnetic resonance imaging.

Table 1. The assessment of clinical measurements in the treatment course of switching denosumab to daily teriparatide.

	Baseline	1 year after Dmab	2 years after Dmab	4 years after Dmab	Occurrence of RVFs	1 year after teriparatide	2 years after teriparatide
TRACP-5b (mU/dl)	430	234			1283	666	775
P1NP (mg/l)					180.1	89.2	81.1
BAP (U/L)	12.9	9.4			25.1	17.6	17.5
25OHD (ng/ml)					15.3	15.8	15.7
Serum Ca (mg/dl)	9.5	9.4	9.6	9.7	9.8	9.8	9.7
eGFR	58	55	56	57	60	56	56
Bone mineral density							
Lumbar (g/cm^2)	0.596		0.788	0.816		1.125	1.12
T score	−2.5		−1.9	−1.8		1.1	0.9
Femoral neck (g/cm^2)	0.528		0.534	0.539		0.508	0.476
T score	−2.4		−2.3	−2.3		−2.6	−2.9
Total hip (g/cm^2)	0.671		0.685	0.694		0.655	0.629
T score	−1.6		−1.5	−1.4		−1.9	−2.1
DAS28-CRP	2.61	2.09	2.33	2.21	3.1	1.84	1.94

Dmab, denosumab; RVFs, rebound-associated spontaneous clinical vertebral fractures; TRACP-5b, tartrate-resistant acid phosphatase 5b; P1NP: N-terminal propeptide of type I collagen; BAP, bone alkaline phosphatase; 25OHD: 25-hydroxyvitamin D; DAS28-CRP: C-reactive protein based (CRP) Disease activity score (DAS) 28.

Nine months after denosumab discontinuation, the patient had a severe low back pain with the spontaneous onset. Her pain score of the visual analog scale (VAS) was 95. Magnetic resonance imaging (MRI) revealed vertebral fracture at the fourth lumbar vertebra (L4) (Fig. 1B). Conservative treatment was performed, and the low back pain was gradually improved within 2 months (VAS score, 51).

The decision was made to continue raloxifene and eldecalcitol treatments and not to reinitiate the denosumab because of the dental treatment. However, 12 months after denosumab discontinuation, the low back pain flared up; MRI revealed new vertebral fracture at the third lumbar vertebra (L3) (Fig. 1C); TRACP-5b increased to 1,283 mU/dL; and BAP increased to 25 U/L; and N-terminal propeptide of type I collagen (P1NP) increased to 180.1 μg/L (reference range: 26.4-98.2 μg/L). 25-hydroxyvitamin D (25OHD) (Serum vitamin D) was low, 15.3 ng/ml (reference range: 30-60 ng/ml). C-reactive protein (CRP) based Disease activity score (DAS) 28 increased to 3.1 (Table 1). At the next 1-month follow-up, radiograph demonstrated a new vertebral fracture at the second lumbar vertebra (L2) (Fig. 1D). A diagnosis of multiple RVFs was made, and treatment with daily teriparatide was initiated for the prevention of new vertebral fracture occurrence.

At 2-month follow-up after daily teriparatide initiation, the low back pain was improved: her VAS score was 32. No advanced deformity of RVFs and no new vertebral fractures were shown on radiograph after 2-year treatment of daily teriparatide (Fig. 1E). However, the results of DEXA were 1.125 g/cm2 (T score: 1.1) in lumbar spine, 0.508 g/cm2 (T score: −2.6) in femoral neck, and 0.655 g/cm2 (T score: −1.9) in total hip after one-year treatment of daily teriparatide. The results of DEXA after 2 years of daily teriparatide treatment were 1.12 g/cm2 (T score: 0.9) in lumbar spine, 0.476 g/cm2 (T score: −2.9) in femoral neck, and 0.629 g/cm2 (T score: −2.1) in total hip. The BMD of the lumbar spine was elevated due to the fracture. In contrast, hip BMD had decreased at 1 year and 2 years after teriparatide treatment initiation. In the assessment of bone metabolic markers, TRACP-5b decreased to 666 mU/dL; and BAP decreased to 17.6 U/L; and P1NP decreased to 89.2 μg/L atfter1-year treatment of daily teriparatide. However, in the results of bone metabolic markers after 2-year treatment of daily teriparatide, TRACP-5b increased to 775 mU/dL. Although the teriparatide treatment successfully prevented the occurrence of new consecutive RVFs, the score of BMD had decreased compared with baseline values, even with 2 years of daily teriparatide treatment. After teriparatide treatment, risedronate was administered for sequential treatment of osteoporosis. Written informed consent was obtained from the patient included in the study.

Discussion

This patient with rheumatoid arthritis discontinued denosumab after 9 injections to undergo dental treatment and subsequently experienced RVFs. Teriparatide treatment prevented the occurrence of successive RVFs; however, DEXA demonstrated a lower BMD for the hip compared with baseline values. Teriparatide might contribute to prevention of RVFs and acceleration of the fracture healing; however, teriparatide could not prevent the loss of hip BMD after denosumab discontinuation.

In the postmenopausal osteoporosis patients with denosumab discontinuation, a transient rise of bone turnover and the occurrence of RVFs have been demonstrated

(Lamy et al. 2019; Anastasilakis et al. 2020; Kashii et al. 2020; Niimi et al. 2020). Previous study reported that younger postmenopausal patients were at higher risk of RVFs after denosumab discontinuation compared with elderly patients (Lamy et al. 2019). Similarly, there are concerns about rebound in bone turnover and RVFs after denosumab discontinuation in patients with secondary osteoporosis, including rheumatoid arthritis and glucocorticoid-induced osteoporosis. In general, these patients have a high risk of general bone loss and osteoporotic vertebral fractures, and long disease duration, low body mass index, and long glucocorticoid treatment duration were demonstrated as risk factors for general bone loss and osteoporotic vertebral fractures (Mori et al. 2017, 2020). Large-scale study results on the treatment effects of denosumab among the patients with glucocorticoid-induced osteoporosis indicated favorable treatment effects compared with bisphosphonate and did not demonstrate RVFs in the cases of denosumab discontinuation (Saag et al. 2019). Several reports were previously found about RVFs in patients with rheumatoid arthritis and glucocorticoid-induced osteoporosis (Florez et al. 2019; Anastasilakis et al. 2021; Tripto-Shkolnik et al. 2021). It is not unclear whether rheumatoid arthritis or glucocorticoid use is associated as an obvious risk for RVFs after discontinuation of denosumab. However, physicians should consider the risks of RVFs after discontinuation of denosumab in patients with rheumatoid arthritis, like as patients with postmenopausal osteoporosis.

Appropriate management of RVFs after denosumab discontinuation remains undetermined (Lamy et al. 2019). Bisphosphonates have been administered for the prevention of RVFs in osteoporotic patients who discontinue denosumab (McClung 2016). Previous report demonstrated that delayed denosumab administration was not effective for the prevention of RVFs (Niimi et al. 2020). Teriparatide and romosozumab are treatment alternatives for patients who discontinue denosumab. However, a previous study has reported that sequential therapy of teriparatide after denosumab discontinuation induced rebound in bone turnover and loss of BMD in the lumbar spine and hip (Leder et al. 2015). There are no reports of therapeutic effects of teriparatide given for 2 years after RVF. In this case, 2-year treatment of teriparatide prevented the occurrence of sequential multiple RVFs; however, bone loss in the hip was not prevented. Teriparatide might have a contribution to the treatment of RVF with prevention of new fractures and pain relief. In other study, romosozumab could not prevent the occurrence of subsequent RVFs after denosumab discontinuation (Kashii et al. 2020). The effects of teriparatide and anti-sclerostin antibody have been proven to accelerate fracture healing in animal models (Mognetti et al. 2011; Ominsky et al. 2011). In contrast, it had been reported that inhibition of excessive bone resorption resulted in inhibition of fracture healing, and denosumab and bisphosphonates might have negative effects on fracture healing (Kamimura et al. 2015). Therefore, treatment with teriparatide and anti-sclerostin antibody may contribute to fracture healing in the setting of RVFs. However, 24-months daily teriparatide treatment was not effective to maintain BMD improved by denosumab treatment. Authors considered that teriparatide might improve the bone quality and strength of lumbar spine regardless of the loss of hip BMD. Previous studies reported that parathyroid hormone (1-34) treatment suppressed the production of advanced glycation end products (AGEs) in the animal models, including homocysteine and pentosidine those were used as bone quality markers reflecting bone strength (Saito et al. 2010, 2011). Although the measurements of homocysteine and pentosidine were not performed in this case, a possible mechanism for the improvement in bone strength was that teriparatide might improve the bone quality by inhibiting the production of homocysteine and pentosidine. Further prospective cohort studies should be required to determine the adequate treatment for patients after denosumab discontinuation and the suppression of subsequent RVFs.

Author Contributions

Yu Mori: Conceptualization, data curation, writing original draft, and supervision. Takuya Izumiyama: Writing, review and editing. Naoko Mori: Writing, review and editing. Toshimi Aizawa: Writing, review and editing. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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