Treatment of Medication-Related Osteonecrosis of the Jaw Around the Dental Implant With a Once-Weekly Teriparatide: A Case Report and Literature Review

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Managing medication-related osteonecrosis of the jaw (MRONJ) around a dental implant can be difficult. Although conservative treatment of MRONJ is recommended as the first-line form of management, many patients exhibit no improvement. The human recombinant parathyroid hormone teriparatide has recently been introduced for the management of MRONJ. Teriparatide is effective in the treatment of postmenopausal osteoporosis and is the only US Food and Drug Administration–approved anabolic agent that directly affects osteoblast function and contributes to bone remodeling. Herein we describe a case of MRONJ in an 85-year-old woman who was successfully treated with teriparatide. Teriparatide was administered once per week without any surgical interventions such as a sequestrectomy. Compared with most recently reported cases involving daily treatment with teriparatide, once-weekly administration of teriparatide may minimize side effects and patient discomfort. Once-weekly teriparatide application without sequestrectomy may be effective in the management of MRONJ around a dental implant.

Key Words: bisphosphonate, implant, osteonecrosis of the jaw, osteoporosis, teriparatide

INTRODUCTION

After Marx[1] described medication-related osteonecrosis of the jaw (MRONJ) as a "growing epidemic" in 2003, it has since been reported by many physicians that it is a difficult disease to treat. Bisphosphonate therapy affects osteoclasts and interferes with normal bone metabolism and remodeling, and it can reportedly affect the balance of osteoclasts, osteoblasts, and osteocytes—especially in the context of necrosis of the jawbone—which has added to dentists' concerns.[2] The placement of dental implants in patients using bisphosphonate or antiresorptive agents has been discussed extensively in the literature.[3,4] Currently, conservative patient management consisting of systemic antibiotics, analgesics, chlorhexidine gargle, maintenance of oral hygiene, and/or sequestrectomy is suggested.[5,6] Notably, however, even after these treatments, many patients' symptoms do not improve, and they can develop more severe osteonecrosis. In patients with widespread necrosis in the jawbone, segmental resection is necessary, and importantly, setting the resection margins and determining the appropriate timing of the operation is often difficult. For this reason, many researchers are investigating new potentially more effective treatments.

Teriparatide is a recombinant form of a human parathyroid hormone that facilitates bone formation. In 2007, Harper and Fung[7] described a patient with MRONJ who was successfully treated with teriparatide, and similar cases have since been reported.[8–12] Teriparatide is effective for the treatment of postmenopausal osteoporosis, and it is the only available anabolic agent that directly affects osteoblast function and contributes to bone remodeling.[13,14] Continuous use of parathyroid hormone reduces bone mineral density but activates osteoblast function when used intermittently at a low dose.[15] Several studies have investigated the daily injection of teriparatide (20 μg).[7,16,17] Notably, however, daily injections impose a considerable treatment burden on patients. Recently, a once-weekly teriparatide (56.5 μg) regimen has been developed for clinical use. In 2015, Korea's Ministry of Food and Drug Safety approved the sale of teriparatide (Teribone, 56.5 μg) for the treatment of osteoporosis in postmenopausal women.

Herein we describe the case of a patient with MRONJ who was successfully treated via weekly administration of teriparatide.

CASE REPORT

An 85-year-old woman visited the Department of Oral and Maxillofacial Surgery in November 2017 with pain, bone

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exposure, and pus discharge around a left mandibular molar implant site. Two implants had been placed at the location 1 year prior at a local dental clinic. The patient had been diagnosed with osteoporosis and was treated with oral risedronate (35 mg per week) for the preceding 4 years. The T-score of her total lumbar spine bone mineral density in quantitative dual-energy x-ray absorptiometry was −3.8 (the normal range is less than −1.0). Clinical examination revealed necrotic bone exposed on the lingual side of dental implants (Figure 1). There was paresthesia in the left lower lip and chin region, and mobility of the implant was observed. A panoramic X ray performed at the initial visit depicted extensive bone destruction involving the upper cortex of the inferior alveolar canal and sequestrum formation (Figure 2). Because the lesion extended beyond the alveolar portion, the patient was diagnosed with stage 3 MRONJ.[5] Serum collagen cross-linked C-telopeptide (CTx) and osteocalcin were examined to evaluate the bone turnover rate. Serum concentrations are affected by circadian rhythms and diet, and accordingly, the samples were consistently collected in the morning before anything other than water had been ingested by mouth that day. Serum samples were refrigerated at −20°C and analyzed in a clinical laboratory located within the same hospital. Serum concentrations of CTx and osteocalcin were measured. Serum CTx and osteocalcin were measured by an electrochemiluminescence immunoassay (E801 Modular System; Roche, Mannheim, Germany). The initial serum type I collagen CTx level was 121 pg/mL, and the initial osteocalcin level was 12.0 ng/mL. Conservative care was performed with a drug holiday rather than immediate surgery because the serum CTx level was lower than 150 pg/mL. Risedronate was discontinued after consultation with the patient's physician. Teriparatide treatment was recommended to the patient, but she declined it. Chlorhexidine mouth rinse, antibiotics, and analgesics were administered for the relief of symptoms and pain, but there was no significant improvement in the subsequent 3 months. The patient then opted for treatment with teriparatide. Before teriparatide treatment, her serum CTx was 149 pg/mL and her serum osteocalcin was 12.8 ng/mL. The patient did not want to inject teriparatide herself daily, and after consultation with an endocrinologist, we decided to instigate a treatment regimen involving once-weekly injection of teriparatide. Thereafter, teriparatide acetate (Teribone, 56.5 μg) was injected subcutaneously by medical staff. On each occasion, 1 vial of teriparatide acetate was dissolved in 1 mL of saline solution prior to administration. After dissolution, the drug was injected subcutaneously into the abdomen, and it was injected slowly in order to minimize any potential pain. The patient agreed to recline on a bed for approximately 30 minutes after each injection so that she could be monitored for potential adverse effects such as temporary hypotension, nausea, malaise, or vomiting, none of which were observed. After 4 weeks of weekly teriparatide injections, the sequestrum on the lingual side disappeared spontaneously, and spontaneous exfoliation of the dental implant occurred at 6 weeks (Figure 3). After 8 weeks of weekly teriparatide injections, the CTx level was 294 pg/mL and the osteocalcin level was 18.5 ng/mL (Figure 4). After weekly teriparatide administration, increases in CTx and osteocalcin were observed in conjunction with an increase in bone turnover rate. The patient was treated with teriparatide for 8 weeks without additional surgery, and oral wound healing was observed and maintained for 6 months (Figures 5 and 6).

This case study was conducted in accordance with the tenets of the Declaration of Helsinki, and the publication of it was approved by the Ethics Review Board of Yonsei University Dental Hospital (IRB No. 2-2019-0015). The patient whose case is described in the report has provided informed consent for its publication.

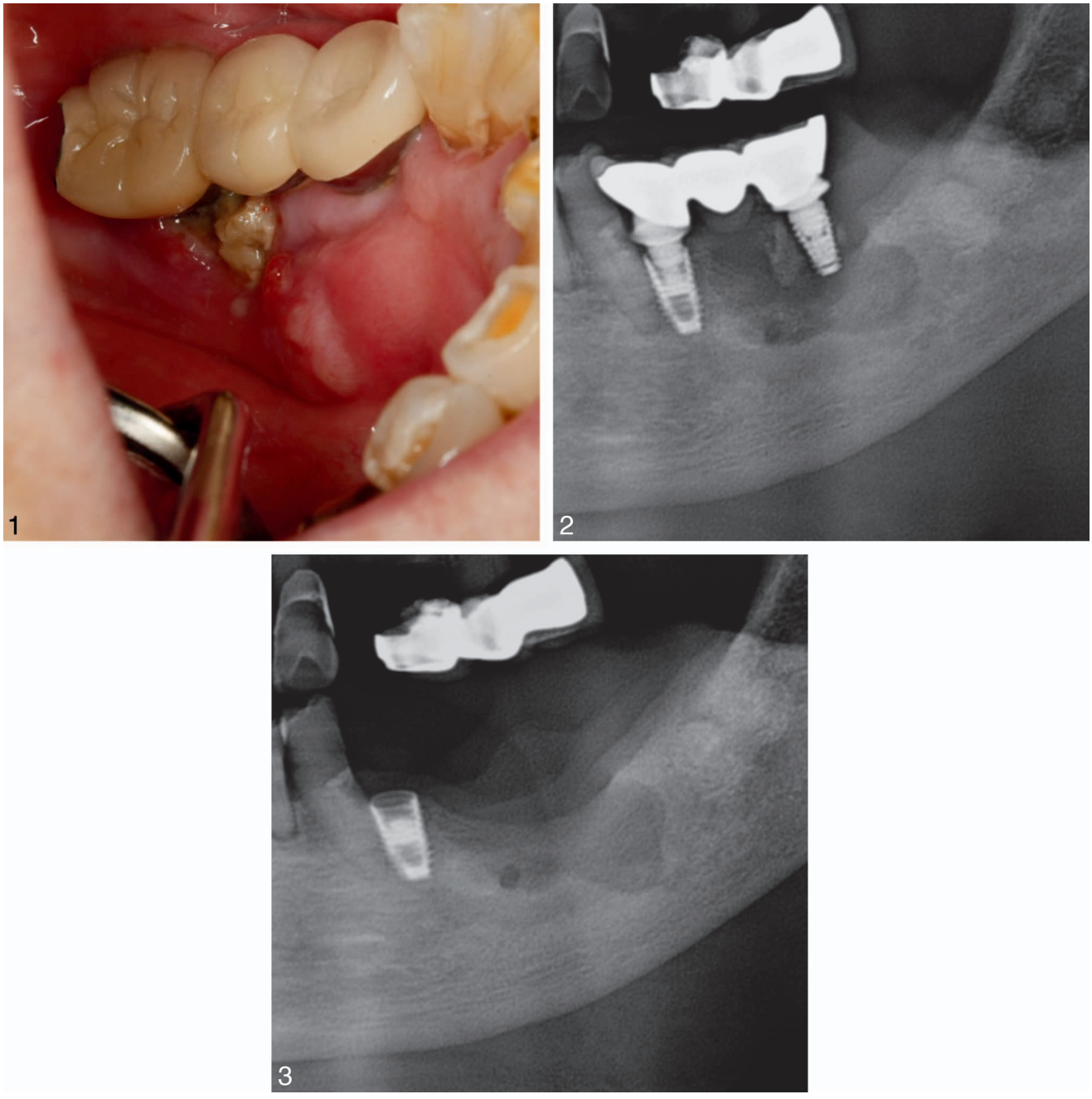
Discussion

The most commonly used drug to prevent bone mineral density reduction and fractures in patients with postmenopausal osteoporosis and metastatic bone disease is bisphosphonate. Notably, however, many clinicians have expressed concern over its use with reference to potentially associated osteonecrosis of the jaw. Although the pathophysiology of MRONJ has not yet been elucidated, numerous studies have indicated that bisphosphonate inhibits osteoclasts in the bone-remodeling process and interferes with interactions between osteoclasts and osteoblasts, thus negatively affecting bone turnover.[18] Bisphosphonate also plays roles in antiangiogenesis and anti-infection.[18,19]

Many clinicians use drug holidays to prevent and treat MRONJ. Bisphosphonate has a high affinity with bone because of its structural similarity with pyrophosphate; thus, it accumulates in bone and exhibits a long half-life in vivo. It is difficult to determine when to use a drug holiday and what an effective duration might be. In addition, drug holidays may lead to complications that increase the risk of fractures of the spine, femur, and hip in patients with existing osteoporosis.

Treatment methods for MRONJ are classified on the basis of disease stage, in accordance with a position paper by the American Association of Oral and Maxillofacial Surgeons.[5] Occasionally, however, patients with early-stage MRONJ do not respond to conservative treatment with systemic oral antibiotics, analgesics, and antimicrobial oral rinsing, and subsequently, the lesions deteriorate further and require extensive resection and reconstruction. The development and application of more effective MRONJ treatment methods for use in such cases is required. Teriparatide is currently the only approved medication that exerts anabolic effects in the treatment of osteoporosis. It stimulates the bone formation function of osteoblasts, increases calcium reabsorption and phosphate excretion in the renal tubules, and increases the intestinal absorption of calcium via effects on 1,25-dihydroxyvitamin D production.[20] Unlike bisphosphonate and a commercially available monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (denosumab), teriparatide inhibits apoptosis while stimulating osteoblast activity. Its influence on osteoblasts is thought to be more effective in regions with continuous bone remodeling such as extraction sockets, implant surgery sites, and periapical lesions.

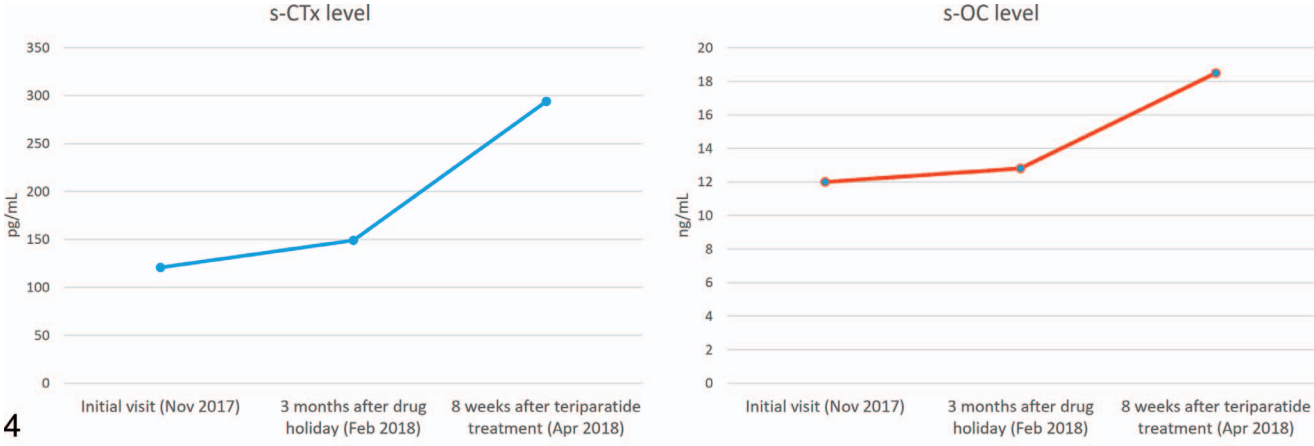
Several cases of the administration of teriparatide to the jawbone have been reported. Low-dose intermittent daily teriparatide has been used to treat MRONJ without surgery.[9,11,12,16] In addition, teriparatide has recently been reported to be an effective treatment for osteoradionecrosis

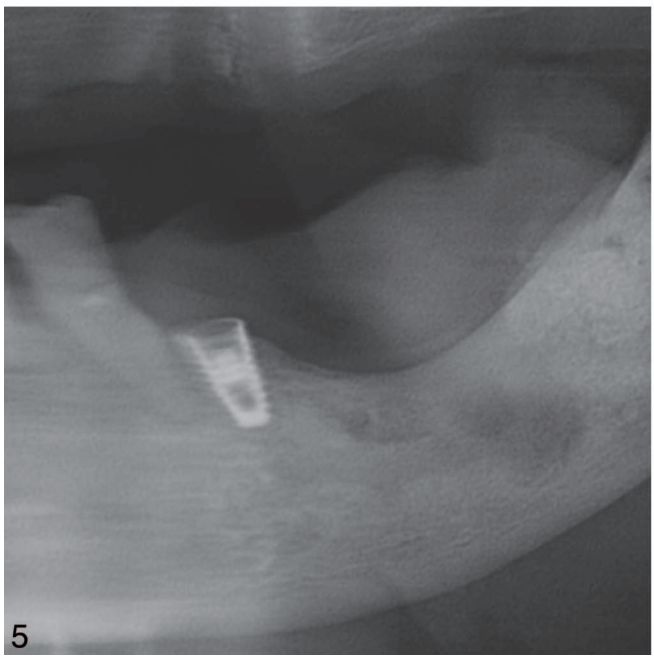


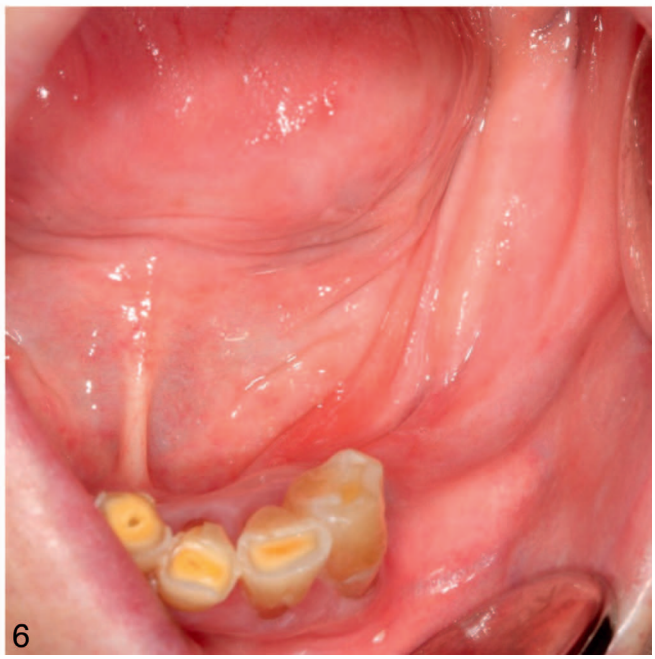
Figures 1–3. Figure 1. Initial intraoral photograph showing soft-tissue erythema, swelling, and exposed necrotic bone around the dental implant. **Figure 2.** Initial panoramic radiograph depicting an extensive lesion with sequestrum around the dental implant. **Figure 3.** Panoramic radiograph 6 weeks after once-weekly teriparatide treatment showing spontaneous exfoliation of the implant and sequestrum.

patients.[21] In animal studies, intermittent administration of teriparatide has reportedly facilitated mandibular bone healing in ovariectomized mice.[22,23] Zandi et al[22] and Keskinruzgar et al[23] have also suggested that teriparatide has an anabolic effect and that teriparatide before and after extraction could reduce the risk of osteonecrosis.

In most patients treated with teriparatide, it is administered daily. Despite the advantages of weekly administration of teriparatide compared with daily administration, the number of case reports of patients prescribed weekly teriparatide as MRONJ therapy is small.[24] In the present case, teriparatide was administered to an MRONJ patient once per week without surgical intervention. Unlike daily teriparatide, which is generally administered by the patient, it is feasible for weekly teriparatide to be administered by medical staff. This may be advantageous because the doctor can observe the patient's progress each week. There is an additional advantage in that the incidence of side effects due to injection can be reduced because of the reduced frequency of administration, and the patient's discomfort may thus be reduced.







Figures 4–6. Figure 4. Changes in bone turnover markers during treatment. **Figure 5.** Panoramic radiograph after 6 months of treatment showing complete bone healing. **Figure 6.** Intraoral photograph after 6 months of treatment showing complete mucosal healing without bone exposure.

With regard to CTx as a bone turnover marker, Marx et al[25] noted a relationship between low serum CTx values and the incidence of MRONJ. They reported that serum levels less than 100 pg/mL indicated a high risk, and values between 100 and 150 pg/mL indicated a moderate risk. Serum osteocalcin level is associated with bone formation, and Nakamura et al[26] reported that in patients who used teriparatide once per week, it had increased by approximately 24.6% after 4 weeks of administration. It then gradually decreased but remained moderately elevated. In the present case, serum CTx and osteocalcin were elevated, suggesting that bone remodeling may have been promoted at the defect site.

Despite its many advantages, clinicians should consider the side effects and contraindications of teriparatide. It is contraindicated in patients with metastatic bone disease, Paget's disease, osteosarcoma, and hypercalcemia. Notably, this is not based on clinical observations in humans but an increased risk of osteosarcoma that has been reported in animal studies.[27,28] It is also recommended that the maximal period of once-weekly teriparatide use be limited to 72 weeks, and nausea, malaise, and/or vomiting during the injection therapy are known potential side effects. Temporary hypotension may occur after the administration of teriparatide; thus, observation is required. Because most of the teriparatide administered is processed within 6 hours, however, there are no significant side effects.

Only limited conclusions can be drawn from a single case report. Therefore, a well-designed prospective randomized study and additional long-term studies are needed. Appropriate dosing and duration of use, as well as additional comparisons with existing drugs, should be further investigated.

In conclusion, in MRONJ patients, once-weekly teriparatide treatment may be a good adjunctive pharmacological treatment because of its anabolic action and promotion of bone remodeling, with associated positive effects on bone and

mucosal healing. In some cases, it may eliminate the need for surgical intervention.

Abbreviations

MRONJ: medication-related osteonecrosis of the jaw

CTx: serum type I collagen cross-linked C-telopeptide

Note

No financial compensation was derived from this work. All authors declare that they have no conflict of interest.

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