Adjunct teriparatide therapy with monitoring of bone turnover markers and bone scintigraphy for bisphosphonate-related osteonecrosis of the jaw

Yumiko Ohbayashi, DDS, PhD, Minoru Miyake, DDS, PhD, Fumi Sawai, DDS, Yuko Minami, DDS, Akinori Iwasaki, DDS, PhD, and Yoshiro Matsui, DDS, PhD

The management of bisphosphonate-related osteonecrosis of the jaw (BRONJ) is still difficult in many cases that do not respond to conservative treatments. We report a case of BRONJ treated by adjunctive teriparatide therapy for 6 months with monitoring of bone turnover markers (at baseline, at 1, 3, and 6 months of treatment, and after 9 months off therapy) and bone scintigraphy (at baseline, 3 and 6 months, and after 9 months off therapy). The patient was a 78-year-old woman with osteoporosis and BRONJ. She had not responded to previous conventional treatment. Teriparatide was added for resolution of BRONJ. The pain disappeared after 1 month, and remarkable bone regeneration was obtained after 6 months, with significantly increasing bone formation and resorption markers. Bone scintigraphy showed regression of the uptake area. This case suggests the usefulness of monitoring bone turnover markers and using bone scintigraphy to increase the effectiveness of teriparatide therapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e31-e37)

The American Association of Oral and Maxillofacial Surgeons and the Canadian Association of Oral and Maxillofacial Surgeons have proposed a strategy to treat BRONJ. It includes patient education, antibacterial mouth rinse, antibiotic therapy, pain control, and surgical debridement/resection. These treatments should be conducted according to the stage of BRONJ. The standard therapy, however, has not yet been established.

Intermittent administration of teriparatide (recombinant human parathyroid hormone 1-34) is used for the treatment of osteoporosis because it predominantly stimulates bone formation. Several recent studies have demonstrated that teriparatide therapy can be an effective treatment for BRONJ[1-8] periodontal osseous defects[9] and assist in osseointegration of titanium implants.[10] Teriparatide therapy may promote bone remodeling in BRONJ by directly stimulating osteoblasts and bypassing their dependence on local osteoclasts for optimal reciprocal stimulation.[11] It not only reduces the expression of sclerostin, a Wnt antagonist, thus augmenting Wnt signaling and bone formation, but also increases the recruitment and activation of osteoclasts from the circulation to remove the necrotic bone effectively. In addition, teriparatide directly increases the production of Wnt10b from bone marrow CD8+ T cells and the activation of Wnt signaling in osteoblastic cells by T-cell–produced Wnt10b.[12]

Teriparatide therapy for osseous issues of the jaw, including BRONJ, is speculated to provide at an early tipping point in therapeutic intervention.[13] Teriparatide therapy has been successful for some patients with BRONJ; a lack of response to 8 months of teriparatide therapy for BRONJ has also been reported.[14] The latter report stated that the ineffectiveness of teriparatide therapy could be attributed to the immunosuppressive effects of riximab and methotrexate. To explain this discrepancy, it is necessary that teriparatide treatment efficacy be always monitored.

Bisphosphonates inhibit bone resorption for low bone turnover,[15] although teriparatide promotes bone formation for high bone turnover.[16] Biochemical markers of bone turnover are products released from osteoblasts and osteoclasts or collagen breakdown products.[17] Biochemical markers reflect osteoporotic risk and are used to monitor the efficacy of osteoporosis treatment.[17] Furthermore, they reflect bone structure during anabolic treatment.[18] Bone formation and bone resorption markers indicate bone turnover and therefore may be useful not only to manage the efficacy of osteoporosis treatment, but also to monitor the effect of teriparatide therapy for BRONJ. Subramanian et al. describe the possible effectiveness of monitoring bone turnover markers and functional imaging in teriparatide therapy for BRONJ.[19]

We report a case of BRONJ treated by teriparatide therapy with monitoring of the bone turnover markers (at baseline, at 1, 3, and 6 months of treatment, and

Presented as a poster to the XXIst Congress of the European Association for Craniomaxillofacial Surgery 11 − 15 September 2012 Dubrovnik, Croatia.
Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Kagawa University, Kagawa, Japan
Received for publication Jul 13, 2012; returned for revision Sep 5, 2012; accepted for publication Sep 9, 2012.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2012.09.006

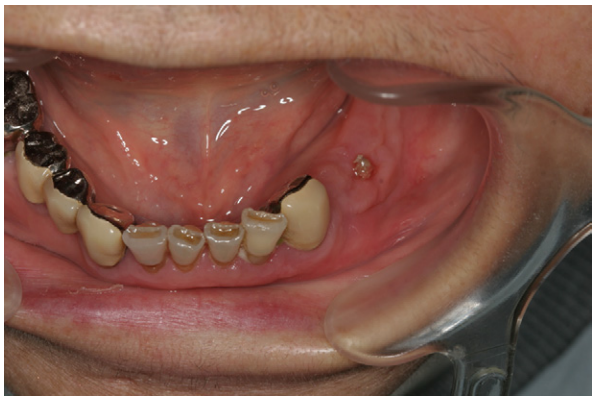

Fig. 1. Clinical picture of the patient. The gingival mucosa showed mild erythematous swelling with pus discharge from the fistula on initial examination.

after 9 months off therapy) and bone scintigraphy (at baseline, 3 and 6 months, and after 9 months off therapy), in which additional bone formed even after teriparatide therapy was completed.

CASE REPORT

A 78-year-old Japanese woman suffered from dull spontaneous pain in the left mandible for 5 months after extraction of the left first and second premolars. Antibacterial mouth rinse and antibiotic therapy given at another dental clinic for 5 months were ineffective. The patient suffered from osteoporosis, diabetes mellitus, hypertension, and dysuria. Her medication was as follows: alendronate (35 mg once weekly for 66 months), voglibose, benidipine hydrochloride, amlodipine besylate, and solifenacin succinate. She had no history of cancer or irradiation to the jaw. She had never had renal dialysis, obesity, or anemia. Alcohol drinking and cigarette smoking were not habituated, and she had not taken steroids or other immunosuppressive agents.

The physical examination revealed no facial swelling or asymmetry. Oral function, including the movement of the jaw and tongue, was normal. Paresthesia of the left chin and lip was noted. The gingival mucosa showed mild erythematous swelling with pus discharge from the fistula (Figure 1). Computerized tomography (CT) examination revealed that the osteolysis extended to the inferior alveolar canal. The buccal and lingual cortical bone was partially destroyed. A thin or small sequestrum was presented (Figure 2). Sclerotic bone was noted below the left inferior alveolar canal. Bone scan with Tc-99m methylene diphosphonate showed intense uptake in almost the entire body of the left mandible (Figure 3, *A*). *Prevotella bivia*, an anaerobic gram-negative bacilli, was detected by culturing of the pus. The patient was diagnosed with stage III BRONJ based on her medical history and the clinical and radiographic findings.

The patient had not responded to simple conservative management, and bone destruction was progressive. Therefore, she gave informed consent for off-label therapy with teriparatide after being informed about the possible benefits, side effects, and risks. Her alendronate therapy for osteoporosis was discontinued. She started receiving daily injections of 20 μg teriparatide, and this continued for 6 months. In addition, conservative treatment including saline-blended 7% povidone-iodine irrigation from the fistula to the osteolysis area and the administration of 400 mg clarithromycin. We monitored the patient's serum and uric acid during treatment for assessment of adverse events. The spontaneous pain disappeared, and a small part of the sequestrum was spontaneously eliminated 1 month later. After 2 months of treatment, the paresthesia of the chin and lip gradually disappeared. Pus discharge from the fistula continued for 4 months, and CT examination showed that most of the detached sequestrum remained. The largest mobile segment of the sequestrum was removed under local anesthesia without exposing uninvolved bone. The fistula then disappeared. Antibiotics were continuously administrated for 4 months with the weekly irrigation. Six months after the combination of teriparatide and conservative treatment, CT showed evidence of bone regeneration and the intraoral wound was completely healed (Figures 4 and 5). Bone scan with Tc-99m methylene diphosphonate showed that mild uptake remained in the body of the left mandible (Figure 3, *C*). Adverse events related to teriparatide treatment were not observed.

After the patient had been off therapy for 9 months, CT showed subsequent osteogenesis occurring after the teriparatide therapy (Figure 6). The uptake area of Tc-99m methylene diphosphonate showed a reduction compared with that at 6 months (Figure 3, *D*).

Biochemical bone formation markers (intact amino-terminal propeptide of type 1 procollagen [intact P1NP], bone-specific alkaline phosphatase [BAP], and serum osteocalcin) and bone resorption markers (urinary N-telopeptide [uNTX], urinary free deoxypyridinoline, and tartrate-resistant acid phosphatase 5b [TRACP-5b]) were monitored at 0, 1, 3, and 6 months of therapy and after 9 months off therapy. All of the bone formation and resorption markers except uNTX were elevated at 1 month. Almost all of the markers showed an increasing incidence of bone formation and resorption during teriparatide treatment. After 9 months off therapy, most markers decreased, except for BAP and TRACP-5b. However, compared with the baseline, all of the markers remained at a high level (Figure 7).

Using repeated-measures analysis of variance, there was no significant difference in the percentage change between the bone formation markers and bone resorption markers. Variation in percentage change measured over time was statistically significant in each marker during teriparatide administration ($P < .005$).

DISCUSSION

Treatment of BRONJ remains an intractable problem in many cases. The standard of care includes symptomatic control, treatment of dental infections, and conservative surgical intervention.[20] Teriparatide has been used in the therapeutic regimen for BRONJ,[2] and it was effective in the present patient, who was not responsive to