Successful Treatment of Advanced Bisphosphonate-Related Osteonecrosis of Mandible with Adjunctive Teriparatide Therapy

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Key Words:	osteoporosis, alendronate, parathyroid hormone, jaws, tooth extraction

**Successful Treatment of Advanced Bisphosphonate-Related
Osteonecrosis of Mandible with Adjunctive Teriparatide Therapy**

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Running title: Teriparatide for BRONJ

Keywords: osteoporosis; alendronate; parathyroid hormone; jaws; tooth extraction.

Abstract

Background. The management of bisphosphonate-related osteonecrosis of the jaws (BRONJ) is challenging and controversial. At present, there is no established medication treatment for the disease.

Methods. A 78-year-old osteoporotic woman with osteonecrosis of the mandible related to alendronate therapy was referred for treatment. The disease was unresponsive to conservative therapy including antibacterial mouth rinse, antibiotics and minor surgical debridement. Teriparatide, a human recombinant parathyroid hormone peptide 1-34, was then used for treatment.

Results. The oral mucosa completely regrew and pain subsided 4 weeks after the initiation of teriparatide administration. Progressive bone regeneration was found during and after the 6-month period of teriparatide therapy.

Conclusion. Our case demonstrated that teriparatide can be an important adjuvant in the management of advanced BRONJ and should be considered prior to major resection with reconstruction. Its true value in the treatment of BRONJ for non-cancer patients with osteoporosis warrant future studies.

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INTRODUCTION

During the past decade, bisphosphonates (BPs) have been widely used for the treatment of bone resorption diseases, such as osteopenia and osteoporosis, and bone malignancies, such as multiple myeloma and metastatic carcinomas.^{1,2} The mechanisms of action of BPs are not yet fully understood. They inhibit bone resorption by means of direct effects on osteoclasts or other bone cells. BPs accumulate to sites of active bone formation, making the sites more resistant to dissolution by osteoclasts, and are internalized by osteoclasts, in which they inhibit specific cell pathways, modulate signaling from osteoblasts to osteoclasts, and lead to osteoclast inactivation and apoptosis.^{1,2} However, osteoclasts are critically important in the inflammatory and remodeling phases of bone healing.³ Other studies also revealed the antiangiogenic nature of BPs, expressed by interference with endothelial cell proliferation⁴ and capillary neoangiogenesis.⁵ The anti-osteoclast and antiangiogenic activities together with the fact that BPs are not metabolized, leads to the potential risk of avascular osteonecrosis because of the decreased vascularity and long-standing, continuous interference with bone turnover and remodeling.

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) was first reported by Marx⁶ in 2003 and numerous cases were subsequently identified.^{7,8} This severe complication occurs most frequently in patients on intravenous zoledronate (Zometa®;

Norvatis Pharmaceutical, East Hanover, NJ, USA) or pamidronate (Aredia®; Norvatis Pharmaceutical, East Hanover, NJ, USA) treatment for malignant diseases.⁷⁻⁹ However, reports of osteonecrosis occurred in long-term users of oral alendronate (Fosamax®, Merck, Whitehouse Station, NJ, USA) have also been published.^{8,10} The anatomical and physiological features of mandibular bone incur a higher risk of osteonecrosis and BRONJ affects the mandible about twice as often as the maxilla.¹¹ Many authors have reported cases where tooth extraction was a precipitating event in the development of BRONJ.⁷⁻⁹

Management of BRONJ is challenging and controversial. The current consensus is to treat patients conservatively, consisting primarily of antibiotics, analgesics, chlorhexidine mouth rinse, maintenance of good oral hygiene and superficial debridement.⁷⁻⁹ However, even after treatment, a number of patients still present with, or progress to more severe bone necrosis. Although some authors found that hyperbaric oxygen (HBO) was beneficial,^{12,13} other investigators reported a less successful result with HBO in patients with BRONJ.^{14,15} In advanced and symptomatic mandibular osteonecrosis cases, bone resection followed by immediate reconstruction with a rigid plate or bone and soft tissue grafts are often required.^{16,17} Nevertheless, it is difficult to decide the extent of resection because BP is deposited uniformly within the entire jaws and necrotic bone may be present or develop later at

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the resection margin.¹⁸ In addition, aggressive mandibular resection often results in extreme morbidity.

Teriparatide (Forteo[®]; Eli Lilly, Indianapolis, IN, USA) is a synthetic polypeptide hormone that contains the 1-34 amino acid fragment of recombinant human parathyroid hormone (rhPTH 1-34). Although PTH has been generally considered catabolic in the mobilization of calcium from bone, intermittent low-dose of teriparatide has been shown to directly stimulate new bone formation and produce rapid gains in bone mass with improved microarchitecture. Teriparatide therapy in osteoporotic patients increases mechanical bone strength without impairing osteoclast function and reduces the risk for both vertebral and nonvertebral fractures.¹⁹⁻²¹ In view of its anabolic effect to bone, teriparatide may be beneficial for BRONJ, especially in osteoporotic patients with advanced mandibular lesions because it may provide protection against pathologic fractures.

The purpose of this report is to present our experience of using teriparatide to treat BRONJ occurred after tooth extraction in an osteoporotic patient. The rationale for treatment is discussed.

CASE REPORT

A 78-year-old Taiwanese woman was referred on June 5, 2008, for treatment of unhealed tooth extraction wound in the mandible. She received extraction of the mandibular right second molar 8 months earlier because of high tooth mobility. Before tooth extraction there was no obvious pain or soft tissue swelling in the area and preoperative radiograph shows bone destruction limiting to the periodontal region (Figure 1). After extraction the wound was persistently painful. Numbness, mucosal swelling and multiple fistulas later developed in that region. The symptoms did not improve following incisional drainage, alveoloplasty and surgical debridement performed at other hospitals. The past medical history was positive for coronary artery disease s/p percutaneous transluminal coronary angioplasty (PTCA) 6 years ago with regular use of aspirin since then. She had been taking oral alendronate 70 mg once weekly for 5 years to treat osteoporosis, but 4 months before the referral an examination revealed a low bone mineral density (total lumbar spine BMD with quantitative dual-energy x-ray absorptiometry, T-score = -2.8). She denied any other medication and systemic diseases such as diabetes. She had no history of cancer or previous irradiation to the head and neck region and did not have the habits of alcohol drinking and cigarette smoking.

On clinical examination, soft tissue swelling in right mandibular and

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submandibular region was noted. The overlying skin was erythematous and tender to palpation. There were no regional lymphadenopathies. Jaw and tongue movements were normal. Teeth posterior to the right lower lateral incisor were missing. Over the edentulous ridge multiple fistulas with purulent discharge were noted (Figure 2a). The painful lesion was ulcerative and an area of exposed bone measuring approximately 10 x 5 mm² was found under the swollen tissues.

A panoramic x-ray taken on June 11, 2008, showed a moth-eaten osteolytic lesion measuring about 3.5 x 1.5 cm² in the posterior edentulous ridge of right mandibular body (Figure 3a). A biopsy was done on the same day and the report showed chronic inflammation and sequestrum. Based on the medical history and clinical and radiographic findings, the diagnosis of stage 2 BRONJ was made.⁸ After discussion with the family physician, oral alendronate therapy was discontinued and conservative treatment including 0.12% chlorhexidine rinses and a 3-week course of amoxicillin 500 mg q8h was started. The symptom did not improve after conservative therapy. A panoramic x-ray taken on August 18, 2008, showed progressive bone destruction extending below the mandibular canal with apparent sequestration (Figure 3b). Therefore the patient was arranged to receive surgical debridement and sequestrectomy under general anesthesia on August 19, 2008. For fear of pathologic fracture only limited debridement was performed and two pieces of sequestrum were

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4 removed (Figure 2b). Postoperative antibiotic therapy was given for 2 weeks but the
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7 wound was not healed well and painful bone exposure persisted (Figure 2c).
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10 At a recall on September 30, 2008, the patient complained of pain at right
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12 mandibular body during chewing. Swelling, erythema and tenderness of the skin
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14 overlying right mandibular body were also noted (Figure 2d). However, the occlusion
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16 and mandibular movement were grossly normal. Panoramic radiography disclosed
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18 bone destruction close to the mandibular border (Figure 3c). In order to prevent
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20 disease progression and pathologic fracture of the mandible, daily subcutaneous
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22 injection of 20 µg teriparatide, as usually recommended for treatment of osteoporosis,
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24 was initiated on October 7, 2008. During the course of teriparatide therapy, daily
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26 mouth rinse with chlorhexidine was continued but antibiotics were not used. After a
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28 4-week treatment with teriparatide, pain in the right mandible disappeared and the
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30 exposed bone was covered by soft tissues (Figure 2e). A panoramic film taken on
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32 November 12, 2008 showed evidence of bone regeneration (Figure 3d). Six months
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34 after the initiation of teriparatide therapy the intraoral wound was completely healed
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36 (Figure 2f) and panoramic radiography demonstrated continuous bone regeneration
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38 (Figure 3e). Therefore, administration of teriparatide was discontinued. Seven months
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40 after the cessation of teriparatide the intraoral condition remained stable and
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42 progressive bone regeneration was noted on panoramic film (Figure 3f). Moreover,
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the T-score of total lumbar spine BMD with quantitative dual-energy x-ray absorptiometry increased to -2.2.

For Peer Review

DISCUSSION

Alendronate is among the most widely prescribed drugs in the market for patients with postmenopausal osteoporosis.⁷ Although the incidence of BRONJ related to oral alendronate was significantly lower than that reported for intravenous pamidronate or zoledronate in cancer patients, the alendronate-related problem cannot be neglected in view of the large number of patients who take the drug.

The current treatment strategies recommended for stage 1 and 2 BRONJ, including antibacterial mouth rinse, oral antibiotics and superficial debridement,⁷⁻⁹ are somewhat passive in nature. In our patient, conservative therapy failed to alleviate the symptoms and bone destruction. HBO therapy may hold some promise^{12,13} but its exact role in the management of BRONJ is still controversial.^{14,15} Gradual improvement of BRONJ has been reported in some cases after the discontinuation of oral bisphosphonate.^{10,11} However, since alendronate has a bone half life of 10.9 years and bone turnover markers remain reduced for up to 5 years after abstaining from alendronate,² the short-term benefit of its discontinuation on BRONJ management is unpredictable.¹¹ Cessation of alendronate therapy did not help to arrest the disease in our patient. The lesion aggravated in the 2 to 3 months following drug discontinuation and extended close to the mandibular border, increasing the risk of pathologic fracture. At this stage, mandibulectomy followed by complex reconstructive procedures might

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be needed. Since surgical resection does not guarantee the eradication of necrotic bone⁹ and is associated with significant morbidity, other treatment options were sought.

In addition to the effects on fracture prevention,¹⁹⁻²¹ teriparatide has also been shown to accelerate healing of vertebral and long bone fractures.^{22,23} A previous study showed that intermittent administration of teriparatide increased new bone formation and mechanical strength of tibial fractures in rats.²² Although the anatomic characteristics of mandible differ from those of the proximal metaphysis of the tibia, similar results have been found for the mandible. Intermittent teriparatide have therapeutic effects for restoration of osseous tissues in the oral cavity in aged ovariectomized rats.²⁴ It also stimulates bone formation in the mandibles of aged ovariectomized rats, similar to that observed in long bones.²⁵

More importantly, teriparatide is able to reverse the antiresorptive effect of BPs. In an in vitro study, it was shown that viable osteoblastic cells grown from alveolar bone of chronic BP users had PTH responses similar to those of normal osteoblastic cells in terms of alkaline phosphatase activity, cell proliferation and viability.²⁶ Teriparatide indirectly increases the metabolic activity and number of osteoclasts by affecting osteoblast function.²⁷ The results of *in vivo* studies are consistent with the *in vitro* findings. Ma et al. demonstrated that before treatment with teriparatide,

alendronate strongly suppressed activation frequency and bone formation rate in the proximal tibia metaphysis in ovariectomized rats. After 2 months of teriparatide administration there was an increase in mineral apposition and bone formation.²⁸ Suppression of bone turnover by BPs is associated with increased bone microdamage.²⁹ Teriparatide reduces microdamage accumulation in the iliac crest of patients previously treated with alendronate.³⁰ All these works provide a rationale for the clinical use of teriparatide in BRONJ treatment.

Although it is well approved that teriparatide can effectively enhance bone regeneration and counteract the anti-osteoclast effect of BPs, its role in the management of BRONJ has seldom been mentioned. Harper et al. reported a case of BP-related osteonecrosis of the mandible in a 75-year-old female user of oral alendronate.³¹ After seven months of conservative therapy, painful ulcerations with bone exposure persisted on the alveolar ridge. Teriparatide therapy was therefore initiated and superficial sequestrectomy was performed 3 months later. After a 10-month course of teriparatide the patient presented with normal mucosa and panoramic x-ray showed healed extraction sites. Nevertheless, in that case the therapeutic effect of teriparatide was not definite. The ulcerative lesion was superficial and no radiographic bone destruction was demonstrated before treatment. Moreover, sequestrectomy was done in addition to the hormone therapy. In contrast,

in our patient the osteonecrotic lesion was large and continued to progress even after conservative sequestrectomy. After a 4-week treatment with teriparatide, pain disappeared and the alveolar ridge began to heal. Although a number of interventions were performed in a relatively narrow time frame, teriparatide was likely to play a certain role in the remission of osteonecrosis considering the dramatic bone regeneration observed after a 6-month course of teriparatide without further surgery and antibiotics. In addition, the drug is an effective replacement of alendronate for the treatment of osteoporosis.

Teriparatide 20 µg daily subcutaneous injection is usually taken for a period of 18 to 24 months for the treatment of osteoporosis,^{21, 32} but the optimum duration and dosage of teriparatide therapy for BRONJ is unknown. In the case reported by Harper et al., a 2-year course of treatment was recommended and the lesion was resolved after 10 months of drug administration. In the present report, clinical improvement was noted 1 month after the initiation of treatment and complete resolution of osteonecrosis was observed after a 6-month teriparatide therapy.

It should be pointed out that teriparatide is not recommended for patients with hypercalcemic disorder, osteosarcoma, metastatic bone disease, Paget’s disease of bone, pregnancy, and radiation therapy to the skeleton or to soft tissue in which a skeletal port is exposed.^{32,33} Patients with severe renal or hepatic impairment also

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4 should not receive teriparatide.^{32,33} However, adverse events associated with the drug
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7 were usually mild in patients without these contraindications and teriparatide therapy
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10 is generally well tolerated.²⁰
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14 In conclusion, teriparatide can be an important adjuvant to other measures in the
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16 management of BRONJ and should be considered prior to major resection with
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18 reconstruction. Its exact role in the treatment of BRONJ for non-cancer patients with
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23 osteoporosis warrant future studies.
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Figure Legends

- Figure 1.** The periapical radiograph of mandibular right second molar taken before extraction showing bone destruction limiting to the periodontal region.
- Figure 2.** Clinical pictures of the patient. (a) Multiple fistulas with purulent discharge over the right mandibular ridge on initial examination. (b) Sequestra and infected tissues removed by superficial debridement. (c) Unhealed surgical wound 2 weeks after debridement. (d) Swelling and erythema of the skin overlying right mandibular body 6 weeks after surgical debridement. (e) Intraoral wound covered by soft tissues 4 weeks after the initiation of teriparatide treatment. (f) Completely healed intraoral wound after a 6-month course of teriparatide therapy.
- Figure 3.** Panoramic radiographs of the patient. (a) A moth-eaten osteolytic lesion measuring about 3.5 x 1.5 cm² in the posterior edentulous ridge of right mandibular body on initial examination. (b) Progressive bone destruction after 9 weeks of conservative therapy. (c) Bone destruction extended close to the mandibular border 6 weeks after surgical debridement. (d) Subtle bone regeneration 5 weeks after the initiation of teriparatide treatment. (e) Remarkable bone regeneration after a 6-month course of

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4 teriparatide therapy. (f) Continued bone consolidation 7 months after the
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For Peer Review

Figure 1. The periapical radiograph of mandibular right second molar taken before extraction showing bone destruction limiting to the periodontal region.
80x68mm (300 x 300 DPI)

Figure 2. Clinical pictures of the patient. (a) Multiple fistulas with purulent discharge over the right mandibular ridge on initial examination. (b) Sequestra and infected tissues removed by superficial debridement. (c) Unhealed surgical wound 2 weeks after debridement. (d) Swelling and erythema of the skin overlying right mandibular body 6 weeks after surgical debridement. (e) Intraoral wound covered by soft tissues 4 weeks after the initiation of teriparatide treatment. (f) Completely healed intraoral wound after a 6-month course of teriparatide therapy.
170x170mm (300 x 300 DPI)

Figure 3. Panoramic radiographs of the patient. (a) A moth-eaten osteolytic lesion measuring about 3.5 x 1.5 cm² in the posterior edentulous ridge of right mandibular body on initial examination. (b) Progressive bone destruction after 9 weeks of conservative therapy. (c) Bone destruction extended close to the mandibular border 6 weeks after surgical debridement. (d) Subtle bone regeneration 5 weeks after the initiation of teriparatide treatment. (e) Remarkable bone regeneration after a 6-month course of teriparatide therapy. (f) Continued bone consolidation 7 months after the cessation of teriparatide.

170x140mm (300 x 300 DPI)