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ORIGINAL ARTICLE

Distinctive role of 6-month teriparatide treatment on intractable bisphosphonate-related osteonecrosis of the jaw

K. M. Kim · W. Park · S. Y. Oh · H.-J. Kim · W. Nam · S.-K. Lim · Y. Rhee · I. H. Cha

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Abstract

Summary The administration of teriparatide (TPTD) in conjunction with periodontal care could provide faster and more favorable clinical outcomes in previously refractory bisphosphonate-related osteonecrosis of the jaws (BRONJ) cases compared to conventional dental care, combination of surgery and antimicrobial treatment. We also found that underlying vitamin D levels might influence the response to TPTD treatment.

Introduction Treatment of BRONJ is quite challenging and there are no standard treatment modalities. In this retrospective, longitudinal study, we examined whether additional TPTD administration could be beneficial for the resolution of BRONJ lesions compared to conservative management, such as antimicrobial treatment with or without surgery, and also studied the factors influencing the response to TPTD.

Methods Twenty-four cases of intractable BRONJ were included: 15 subjects were assigned to the TPTD group and the other 9 subjects, who refused TPTD administration, were assigned to the non-TPTD group. All subjects in both groups continued calcium and vitamin D supplementation and the TPTD group additionally received a daily subcutaneous injection of 20 μg TPTD for 6 months.

Results While 60.0 % of the non-TPTD group showed one stage of improvement in BRONJ, 40.0 % of the group did not show any improvement in disease status. In the TPTD group, 62.5 % of the treated subjects showed one stage of improvement and the other 37.5 % demonstrated a marked improvement, including two stages of improvement or complete healing, and there was not a single case that did not improve. The clinical improvement of BRONJ was statistically better in the TPTD group after the 6-month treatment ($p<0.05$). Moreover, patients with higher baseline serum 25(OH)D levels showed better clinical therapeutic outcomes with TPTD.

Conclusions We observed the beneficial effects of TPTD on BRONJ, and subjects with optimal serum vitamin D concentrations seemed to reap the maximum therapeutic effects of TPTD. A prospective, randomized, controlled trial should be needed to further evaluate the therapeutic efficacy of TPTD in the resolution of BRONJ.

Keywords Bisphosphonate · Jaw · Osteonecrosis · Teriparatide · Vitamin D

Abbreviations

BRONJ	Bisphosphonate-related osteonecrosis of the jaws
BMD	Bone mineral density
BMI	Body mass index
TPTD	Teriparatide
CTX	C-telopeptide of type I collagen
OCN	Osteocalcin
PTH	Parathyroid hormone
25(OH)D	25-Hydroxyvitamin D

K. M. Kim and W. Park contributed equally to this study.

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Introduction

Osteoporosis and related fractures are a serious, worldwide health problem in aged societies, causing increased morbidity and mortality; so treating osteoporosis and preventing related osteoporotic fractures are urgent tasks in caring for the health of the elderly [1, 2]. Bone loss resulting from a negative bone balance between resorption and formation is an inevitable change associated with aging [3]. Therefore, antiresorptive therapy has been one of the main effective strategies for treating osteoporosis [4]. Among several antiresorptive agents, bisphosphonates have been widely used over the past decades as a major drug for osteoporosis. They have demonstrated superior effects in increasing bone mineral density (BMD) and decreasing the number of fractures, ultimately becoming a fundamental, therapeutic approach for osteoporosis [5].

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) was defined as a condition of exposed bone in the maxillofacial region that did not heal within 8 weeks in a patient who had been exposed to bisphosphonates by the American Society for Bone and Mineral Research [6] and emerged as a grave side effect of bisphosphonate use after the first report by Marx et al. in 2003 [7]. The risk factors and clinical stage according to symptom and sign had been also defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS) [8]. BRONJ occurs more frequently in patients receiving higher doses of intravenous bisphosphonate, but also happens in patients administered with lower doses in oral forms [6, 9].

The current consensus on treating patients with BRONJ is conservative management with antibiotics, analgesics, and occasionally surgical intervention [8]. However, managing BRONJ is quite challenging and an ideal standard treatment modality does not yet exist. The condition in a number of patients thus persists or progresses to a severe stage, even after long-term, conventional treatment [5].

Teriparatide (TPTD), a drug composed of the first 34 amino acids of recombinant human parathyroid hormone, initially stimulates bone formation by osteoblasts and subsequently bone resorption by osteoclasts and thus can reactivate suppressed bone remodeling and exert anabolic effects on bone [10]. Because of this mechanism, it has been anecdotally suggested as a beneficial drug in situations that need stimulation of bone remodeling. TPTD has clinically demonstrated greater resolution of alveolar bone defects and accelerated osseous wound healing in the oral cavity of chronic periodontitis cases [11]. Moreover, several case reports have disclosed favorable therapeutic outcomes with TPTD in BRONJ [12–14].

The aims of this study were to determine whether the addition of TPTD to conventional treatment could provide better outcomes in managing intractable cases of BRONJ and to investigate any predictive factors on therapeutic effects of TPTD.

Materials and methods

Study design and participants

The study design and treatment schedules for both groups are shown in Fig. 1a, b. This was a retrospective, longitudinal study and included advanced BRONJ cases diagnosed between January and December 2011 at Severance Hospital. We included patients with intractable BRONJ whose condition did not recover after a few months or up to more than

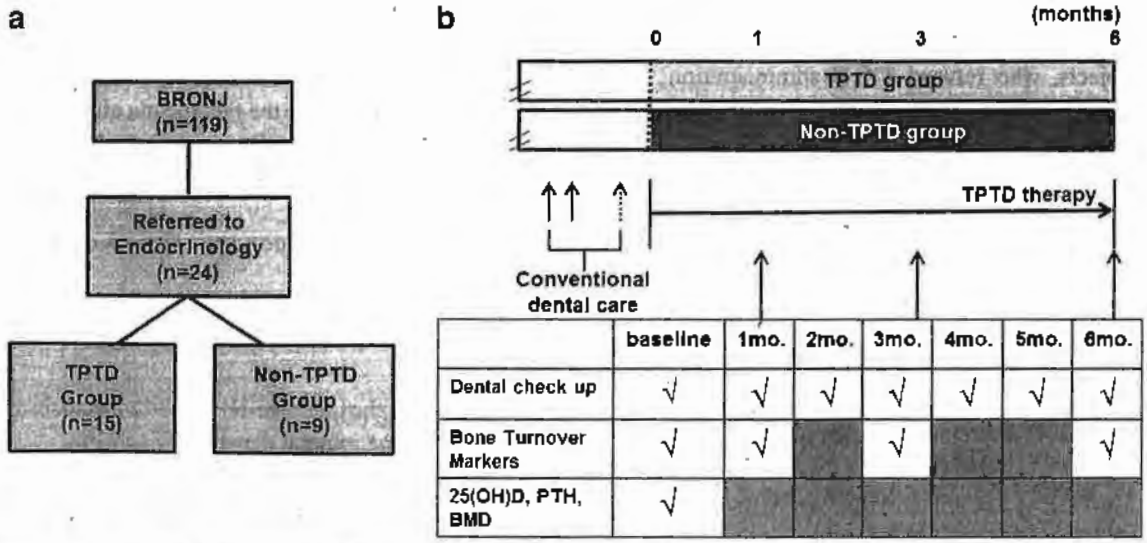

Fig. 1 Study participants and treatment schedule. **a** Among the 119 BRONJ cases, 24 advanced cases were included, with 15 subjects assigned to the TPTD group and 9 subjects to the non-TPTD group. **b** Assessment of the resolution of BRONJ was assessed monthly and bone turnover markers were checked at baseline, 1 month, 3 months, and 6 months. *BRONJ*, bisphosphonates-related osteonecrosis of the jaws; *TPTD*, teriparatide; *25(OH)D*, 25-hydroxyvitamin D; *PTH*, parathyroid hormone; *BMD*, bone mineral density

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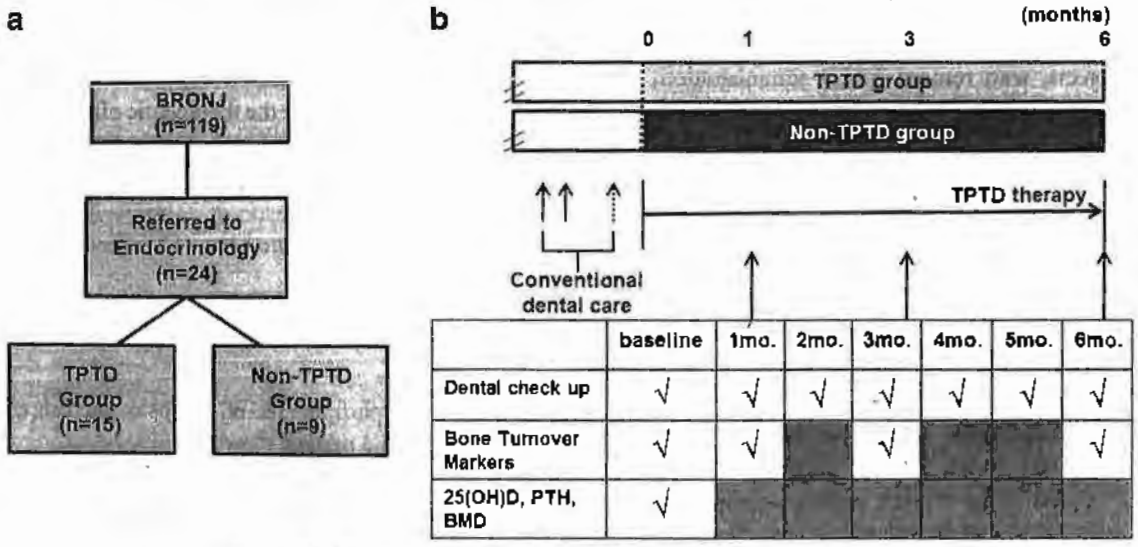

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2 years of conventional care with or without sequestrectomies after the diagnosis of BRONJ. All patients enrolled had been recommended for TPTD treatment for 6 months. The subjects who agreed to the TPTD therapy received a daily subcutaneous injection of 20 μg TPTD (Forsteo®, Eli Lilly, Indianapolis, IN, USA) with calcium and vitamin D supplementation for 6 months, and this group was designated as the TPTD group. The remaining subjects, who refused the use of TPTD, were only prescribed calcium and vitamin D supplementation and were designated then as non-TPTD group. Periodic follow-up visits were the same for both groups and scheduled at 1, 3, and 6 months after the initiation of therapy. All participants underwent a monthly dental examination, including panoramic radiographs, during the entire treatment period. Associated clinical aspects of the lesions, including size, site, and signs of secondary infection were monitored and recorded. We only included primary osteoporosis patients and excluded the subjects who had other contributable factors for developing BRONJ including glucocorticoid exposure or chemotherapy. Therefore, indications for previous bisphosphonate usage by the study subjects were postmenopausal osteoporosis for all female subjects and age-related male osteoporosis for the two male subjects. This study protocol was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine, Severance Hospital (4-2011-0908).

Assessment of BRONJ resolution

The clinical and radiographic resolution of the lesion at each scheduled visit was blindly reviewed by two separate dentists. Stage of BRONJ was defined according to the definition of the AAOMS [8].

Healing status at the final sixth month visit was assessed as the primary endpoint. The outcome variable was the improvement of BRONJ stage, and the evolution of the disease after 6 months of treatment was stratified as follows (Fig. 2):

"No improvement"—no improvement or worsening of BRONJ status (Fig. 2a)
"Moderate improvement"—one stage of improvement of BRONJ status (Fig. 2b)
"Marked improvement"—improvement of two stages of BRONJ or complete healing (Fig. 2c)

Assessment for bone-related markers and BMD

Bone turnover markers, including c-telopeptide of type I collagen (CTX, Roche Diagnostics, Indianapolis, IN, USA), osteocalcin (OCN, Roche Diagnostics, Indianapolis, IN, USA), 25-hydroxyvitamin D (25(OH)D, D_3-RIA-CT, Biosource, Belgium, Europe), and parathyroid hormone (PTH) (Elecsys System; Roche, Mannheim, Germany), were checked at baseline (visit 0). The bone turnover markers were then regularly monitored at the 1-, 3-, and 6-month follow-up

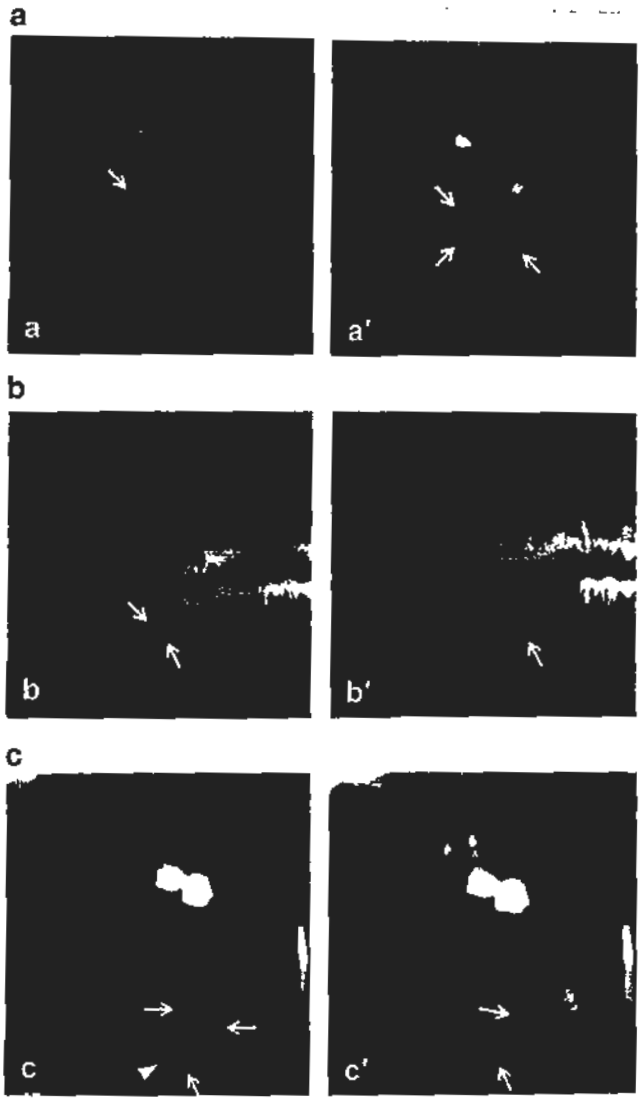

Fig. 2 Assessment of BRONJ resolution. **a** A case from the no improvement group. Initial diagnosis was stage 1 with bone exposure in the mandibular right posterior region after implant placement (*white arrow, a*). Though implant removal and sequestrectomy were performed, symptoms such as pain and discharge of pus became worse and osteonecrosis spread to the adjacent teeth and inferior alveolar nerve, which was diagnosed as stage 3 (*white arrows, a'*). **b** A case from the moderate improvement group. Initial diagnosis was stage 2 with bone exposure in the mandibular right posterior region after implant placement (*white arrows, b*). After TPTD injection, implant removal, and sequestrectomy, no further progress of osteonecrosis was observed and mucosal healing was achieved finally down to stage 1 (*white arrows, b'*). **c** A case from the marked improvement group. Initial diagnosis was stage 3 in the mandibular right posterior lower region after implant placement (*white arrows, c*). Even though sequestrectomies had been performed several times, osteonecrosis extended to the inferior border of the mandible (*arrowhead, c*). After TPTD injection, bone healing was observed radiographically, mucosal healing was achieved, and inflammation was not observed clinically, indicating an improvement of more than two stages (*white arrows, c'*)