EDITORIAL

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Parathyroid Hormone, Can Be a New Therapy to Overcome the Bisphosphonate Related Osteonecrosis of Jaw?

Sung-Woon Pyo

Department of Oral and Maxillofacial Surgery, The Catholic University of Korea
Bucheon St. Mary's Hospital, Bucheon, Korea

For the past 30 years, bisphosphonates (BPs) have been used routinely to control skeletal complications associated with osteoclast mediated bone loss in osteoporosis, osteolytic pathology of bone and complications of metastatic diseases. Because it is a major class of anti-bone resorptive drug, administration of BPs in these patients effectively restores bone mineral density and bone strength, reduces the incidence of bone fracture, and dramatically improves the quality of life[1].

However, recent reports show that BPs caused side effects such as acute reactions, gastrointestinal disturbances, and renal disorders including BP-related osteonecrosis of the jaw (BRONJ)[2]. Since BRONJ has been first reported in 2003[3], a number of case reports and studies on BRONJ have been published. The American Association of Oral and Maxillofacial Surgeons defined BRONJ as exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks with no history of radiation therapy to the jaws and with current or previous BP treatment[4]. Patients with BRONJ present various jaw symptoms, including pain, swelling, infection, loose teeth, and exposed bones in some severe cases. As the number of dental patients who are undergoing long term administration of BPs is increasing, the incidence of osteonecrosis of the jaws is also increasing[5].

BRONJ manifests in diverse tissue changes, including necrotic bone honey-combed with residual vital bone, inflammatory cellular elements, and fibrous tissues in histology. Most attempts to manage this disorder have not been successful, and standard osseous sequestrectomy usually results in further enlarging the bony defects[6]. Therefore, conservative nonsurgical approaches have been recommended in dealing with BRONJ patients that only slow down the deterioration but do not cure the disease. Therefore it now becomes an urgent issue that developing an effective approach to prevent and treat BRONJ.

Parathyroid hormone (PTH) is the major hormone regulating calcium metabolism, and can have both catabolic and anabolic actions in bone. While continuous exposure to PTH results in bone resorption, intermittent administration of PTH improves bone micro-architecture, mineral density and strength. This anabolic action enables PTH a particularly appealing agent to treat patients with osteoporosis. Actually, the anabolic application of PTH is FDA-approved for stimulating bone formation, and it has been shown to reduce the risks of vertebral and nonvertebral fractures in postmenopausal women in clinical trials[7-9].

In the field of dentistry, there are some preliminary clinical studies that have shown promising results with

PTH for periodontal regeneration and the treatment of BRONJ. Because of its anabolic actions, PTH has been used off-label to treat patients with BRONJ, with favorable results[10-12]. One to 6 months after PTH treatment, the most cases demonstrated clinical resolution of the signs and symptoms of BRONJ, with the exception of one. The failed response to PTH treatment in the one case was speculated to be associated with the concomitant use of immunosuppressive drugs for controlling rheumatoid arthritis. It is postulated that PTH increases bone remodeling and reduces microdamage accumulation in the bone, a possible etiology of BRONJ. As a result, PTH might assist in removing necrotic bone and accelerating healing in BRONJ patients. Still, large scale studies and/or well-characterized animal models are necessary to evaluate the efficacy of PTH for treating or even preventing the occurrence of BRONJ.

Further studies are demanded to optimize the timing and duration of PTH therapy for treatment procedures of BRONJ. There is no information is available with regard to the temporal administration of PTH therapy to achieve optimal results. The optimal duration of the PTH treatment for BRONJ is another unsolved question. It is reasonable to assume that PTH treatment should not extend beyond 6 months, which is the normal time range for bone healing. However, how short should the treatment be to minimize possible adverse outcomes, patient discomfort, and optimize patient compliance?

Moreover, PTH is currently administered systemically, which has drawbacks-including the requirement for self-injection and the exposure of drug to non-targeted sites-rendering it less than ideal for enhancing localized bone regeneration. A local therapy has many potential advantages, such as circumventing possible adverse side-effects resulting from systematic administration, decreasing dose or number of dosages, and maintaining local agent levels within a desirable range. It is recommended to develop the proper local delivery system which enables the pulsatile release of PTH in the body.

In summary, new insights with emerging clinical studies supports the merit of PTH for improving BRONJ, the short-term use of PTH might be beneficial to the resolution of BRONJ lesions with sharpened the level of scrutiny of the current widespread use of BP therapy.

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