COULD TERIPARATIDE BE THE TREATMENT FOR OSTEONECROSIS OF THE JAWS?

To the Editor:

We read with great interest the case reported by Lee et al[1] in the Early View section of the journal, presenting a case of aledronate-induced osteonecrosis of the jaws (ONJ), which healed following teriparatide administration.

The authors conclude that teriparatide can be an important adjuvant to other measures in the management of ONJ that should be considered prior to major resection with reconstruction and aspire for future studies.[1] Overall, these are true and teriparatide might be the best news for pharmaceutical treatment of ONJ since its recognition.

Lee et al[1] discuss 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. This might be correct, although it is based on insufficient or nonexisting evidence. To date, there are no clinical trials examining the efficacy of teriparatide in patients with cancer-related skeletal events. Of note, ONJ has mainly been described in the latter population that—for the most part—comprises patients with multiple myeloma, breast cancer, and prostate cancer.[2,3]

The breast functions as an accessory parathyroid gland during lactation, producing parathyroid hormone–related peptide (PTHrP).[4] Thus the administration of parathyroid hormone (PTH) or teriparatide in patients with breast cancer could be expected to interfere with the disease. However, contradictory evidence exists with regard to the association between PTH and breast cancer.[4] No evidence exists with regard to teriparatide administration in patients with prostate cancer or multiple myeloma. The single malignancy that has been reported to be associated with teriparatide administration is osteosarcoma.[5] This association has been reported in Fisher rats in a single study,[6] but not in primates in a number of experimental studies.[6,7] Large power epidemiological studies were also not able to detect any association that would change the risk–benefit profile for teriparatide.[5] Teriparatide is metabolized in the liver and kidneys.[8] Thus, future clinical trials for the use of teriparatide in cancer patients would need to designate these toxicities as safety issues.

In primate experimental models, teriparatide was reported to increase bone mass and strength, an effect that was lost during the withdrawal phase, for the vertebrae but not for the proximal femur.[7] This effect of withdrawal would probably be insignificant for its utility for the treatment of ONJ. Importantly, both published case reports indicate that healing of ONJ occurs well before the 18-month FDA-approved administration period.[1,9]

PTH is an 84–amino acid peptide, produced by the parathyroid glands, that plays a major role in the regulation of calcium and phosphate metabolism.[8] Teriparatide is the N-terminal (1–34) fragment of the human PTH peptide biosynthesized using *Escherichia coli* as a host.[8] It has been proposed that the complete PTH peptide has additional biological actions to teriparatide—attributed to a putative C-terminal PTH receptor—that are often in opposition to those that occur following PTH-1 receptor activation. For example, C-terminal PTH fragments may blunt the increase in serum calcium levels induced by teriparatide, inhibit bone resorption, and stimulate apoptosis in bone cells.[6] The lack of these additional biological responses in teriparatide, along with others, unknown to date, may lie beneath the ability of teriparatide to cure ONJ. Lee et al[1] comment that teriparatide has been reported to reduce microdamage accumulation. Microdamage accumulation, or "fatigue,"[10] was reported to have a role in the aetiopathogenesis of osteonecrosis of the jaws based on experimental and clinical data.[10,11] Importantly, teriparatide could be able to revert the "fatigue" process induced by bisphosphonates through the above-mentioned biological actions.[6]

Lee et al[1] appositely report that treatment options for osteonecrosis of the jaws are controversial and management of these patients is an important problem for head and neck surgeons, endocrinologists, and oncologists.[2] Nowadays, it could be justified to prescribe teriparatide to patients with bisphosphonate-treated osteoporosis who already have ONJ. Given that (1) teriparatide is licensed for the treatment of osteoporosis and is considered a second-line treatment,[8] (2) the limited evidence of a potential protective effect for ONJ,[1,9] and (3) the lack of appropriate treatment modalities for ONJ,[1,2] its prophylactic use also in patients who need to undergo oral cavity surgery might be recommended instead of bisphosphonates.

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A similar case was reported almost 3 years ago,[9] although this novel treatment option was probably overlooked back then. On the publication of a better-documented case in *Head & Neck*, it is imperative that this option is adequately elucidated.

Moreover, cancer patients who developed ONJ following bisphosphonate administration may be candidates for participation in well-designed phase II clinical trials with teriparatide following informed consent. The possibility of yet to be described adverse effects may be secondary to those cancer patients who already have the additional burden of ONJ.

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Reply

In accord with the U.S. Food and Drug Administration label, teriparatide (FORTEO) is approved only for patients with osteoporosis at high risk of fracture. Carcinogenicity bioassays revealed that teriparatide caused an increase in the incidence of osteosarcoma in rats. Although the relevance of these animal findings to humans is uncertain, the FDA label puts forth a warning that teriparatide should not be used for patients at increased baseline risk of osteosarcoma. These include: Paget's disease of bone, pediatric and young adult patients with open epiphyses, and prior external beam or implant radiation therapy involving the skeleton. The label further states that patients with bone metastases or a history of skeletal malignancies should not be treated with teriparatide. We agree with Drs. Kyrgidis and Antoniades that the precautions are based on insufficient evidence. It is therefore reasonable to undertake clinical trials to evaluate the effect of teriparatide on cancer patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ), provided that the participants are fully informed about the possible risks.

On the other hand, although the incidence of BRONJ related to oral alendronate was significantly lower than that reported for intravenous pamidronate or zoledronate in patients with cancer, the alendronate-related problem cannot be neglected in view of the large number of patients who take the drug. As a matter of fact, about 70% of the BRONJ cases treated at our clinic are osteoporosis patients who have been exposed to oral alendronate only. Furthermore, previous in vivo studies have shown that teriparatide can reverse the adverse effects of alendronate on bone.[1,2] Therefore, to use teriparatide in patients with osteoporosis who developed BRONJ after oral alendronate treatment is more justifiable and clinical trials on this aspect are warranted.

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