The relationship of denosumab pharmacology and osteonecrosis of the jaws

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Denosumab is a new bone antiresorptive agent that has received approval by the Food and Drug Administration for use in patients with osteoporosis and metastatic cancer to the bones. Like the bisphosphonates that are used as antiresorptive medications, denosumab has been associated with osteonecrosis of the jaws (ONJ). However, because the pharmacodynamics and pharmacokinetics of denosumab differ from that of the bisphosphonates, ONJ related to denosumab may resolve more rapidly with a drug holiday than bisphosphonate-related osteonecrosis of the jaws (BRONJ). This paper describes the management of a patient who developed ONJ while receiving denosumab, reviews the incidence of ONJ associated with denosumab, and compares the pharmacology of denosumab and the bisphosphonates. Because the effects of denosumab on bone turnover are more rapidly reversible than the effects of the bisphosphonates, ONJ related to denosumab may resolve more quickly with a drug holiday than BRONJ. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:671-676)

Current clinical management of metastatic and fragile bone diseases such as osteoporosis targets pathways involved in bone remodeling. Bisphosphonates are potent and effective drugs used to manage these diseases.1-3 However, patients receiving bisphosphonates sometimes develop osteonecrosis of the jaws (ONJ), which can be challenging to treat.4-9 The search for medications with the same therapeutic effectiveness as the bisphosphonates but fewer side effects has resulted in the discovery of denosumab, a human monoclonal antibody that inhibits osteoclasts.10-15

The purpose of this article is to describe a patient who developed ONJ while taking denosumab and review the relationship between the pharmacology of denosumab and ONJ. The clinical presentation of the patient suggests that the osteonecrosis associated with denosumab is similar to bisphosphonate-related osteonecrosis of the jaw (BRONJ). Because of the unique pharmacokinetics and pharmacodynamics of denosumab, ONJ associated with denosumab may resolve more rapidly with a drug holiday than BRONJ.16,17

CASE REPORT

A 67-year-old male was referred to the oral and maxillofacial surgery clinic at Harborview Medical Center in Seattle, Washington, because he continued to have exposed bone in his maxilla and mandible 6 months following the extraction of teeth 3, 4, 5, and 30 by his primary-care general dentist. His medical history was significant for hypertension, obesity, and prostate cancer. He had no history of receiving bisphosphonates or radiation therapy. He reported a 40-pack-year history of tobacco use and was taking hydrochlorothiazide, lisinopril, metoprolol succinate, ibuprofen, calcium, and vitamin D supplements. He was using chlorhexidine gluconate mouth rinse for the exposed bone in his jaws. He also reported a 3-year history of hormone ablative therapy (goserelin acetate) for treatment of his prostate cancer.

The patient was enrolled in a clinical trial involving administration of denosumab to prostate cancer patients receiving hormone deprivation therapy. The study was double blind and subjects were randomized to receive either a placebo or denosumab (Xgeva, Amgen, Thousand Oaks, CA). Patients were given monthly subcutaneous injections of 120 mg of denosumab or placebo. The patient described in this report received 22 months of denosumab treatments prior to extraction of the teeth. The injections were stopped 4 months after the removal of the teeth because of the exposed bone in the
maxilla and mandible. He received a total of 26 denosumab injections before the drug treatment was stopped.

When the patient presented 6 months following removal of the teeth, he complained of moderate pain emanating from his right mandible. Physical examination revealed no facial swellings and no head and neck lymphadenopathy. He had full range of motion of his jaws and neck and opened his mouth without limitation. Intraoral exam revealed a full range of motion of his jaws and neck and opened his mouth without limitation. Microbiologic analysis revealed no acid-fast bacilli or fungal elements. Bacterial culture grew 4+ Streptococcus milleri groups of 2 colony types, 4+ mixed anaerobic floras and 1+ Neisseria species. The patient was placed on a 2-week course of oral amoxicillin/clavulanate potassium, 875 mg/125 mg twice a day, chlorhexidine gluconate 0.12% oral mouth rinse 3 times a day, and hydrocodone/acetaminophen 5 mg/500 mg every 6 hours as needed for pain. Over the next several months, the patient was maintained on daily chlorhexidine mouth rinses and antibiotics were used only during flare-ups (increased pain, erythema, purulence). He had several minor contouring procedures of the exposed bone on the right mandible because he developed sharp bony edges that irritated his tongue (Table I).

A panoramic radiograph obtained 5 months after cessation of denosumab and 3 months after the initial debridement showed enhanced demarcation of a bony sequestrum in the right mandible and decreased height of alveolar bone at the right mandible (Fig. 1, b). The left first maxillary molar spontaneously exfoliated during the 3-month period following the debridement. No bone was exposed at the left maxilla following loss of the molar. The right maxilla clinically healed 11 months after cessation of denosumab. At 22 months after the extractions and 18 months after cessation of denosumab, the patient presented with a 4 × 2 cm sequestrum of bone that had spontaneously exfoliated (Fig. 2, a). Clinical examination revealed nottender, pink mucosa and gingiva covering the exposed bone at the right maxilla and mandible. Panoramic radiograph revealed decreased height and increased radiopacity of the right mandibular body (Fig. 2, b). Shortly after complete bone healing, teeth 17, 18, 22, 23, 27, 28, and 29 were removed. The patient healed normally and did not develop ONJ (Figure 3, a and b).

**DISCUSSION**

Bisphosphonates are frequently used to prevent the skeletal complications associated with postmenopausal osteoporosis in women. They are also used to manage patients with multiple myeloma, hypercalcemia, and metastasis of cancer to the bone. Structurally, bisphosphonates resemble the endogenous molecule pyrophosphate. However, bisphosphonates possess a central carbon atom linking 2 phosphate groups instead of a central oxygen atom, which links the phosphate groups in the endogenous pyrophosphate. Bisphosphonates have a high affinity for binding to calcium and readily incorporate into bone matrix. The exact mechanism for the antiresorptive properties of the bisphosphonates has not been fully elucidated. It is believed that bisphosphonates reduce bone turnover by inhibit-
ing osteoclast recruitment to bony surfaces, decreasing osteoclast activity through interference with ruffled border formation and extracellular proton extrusion, and possibly increasing osteoclast apoptosis.1

When taken orally, the absorption of bisphosphonates is extremely poor, with less than 1% of the administered dose reaching the plasma.2 Once bisphosphonates have reached the bloodstream, the plasma half-life of the drug is extremely short because roughly 50% of the absorbed dose is incorporated into bone and the unincorporated bisphosphonate is rapidly cleared by the kidneys.2 There is no systemic metabolism of bisphosphonates because of a lack of cellular mechanisms to degrade the central phosphate–carbon–phosphate bond of the drug.3 Once incorporated into the bone matrix, the drug is cleared from the body by liberation from the bone matrix during active resorption. The half-life of bisphosphonates after incorporation into the bone matrix is >10 years.3

BRONJ was first reported in 2003.4 A recent systematic review published in 2010 suggested that the prevalence of BRONJ in cancer patients ranges from 0.7% to as high as 24.5%, depending on the parameters of the epidemiologic study and the quality of patient follow-up.5 Rates of BRONJ in noncancer patients

<table>
<thead>
<tr>
<th>Total time from extraction of teeth</th>
<th>Total time from beginning drug holiday</th>
<th>Outcome following removal of teeth at 22 months of denosumab therapy</th>
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<tbody>
<tr>
<td>6 months</td>
<td>2 months</td>
<td>Patient appeared with exposed bone and was treated with conservative debridements of bone, oral antibiotics for acute flare-ups of infection, and oral rinses with chlorhexidine</td>
</tr>
<tr>
<td>15 months</td>
<td>11 months</td>
<td>Exposed bone on maxilla healed, tooth 14 spontaneously exfoliated, and continued exposure of bone on the mandible treated with oral rinses with chlorhexidine</td>
</tr>
<tr>
<td>22 months</td>
<td>18 months</td>
<td>Spontaneous healing of the mandible and normal mucosa covering the maxillary and mandibular alveolar bone</td>
</tr>
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Fig. 2. (a) Sequestrum of bone that spontaneously exfoliated 18 months after cessation of denosumab. (b) Panoramic radiograph taken after spontaneous exfoliation of the bony sequestrum from the right mandible, which was 18 months after cessation of denosumab. The alveolar ridge height has decreased and the density of the bone has increased in the right mandible.

Fig. 3. (a) Panoramic radiograph showing the mandible following removal of the unrestorable mandibular teeth. (b) Clinical photograph of the healed right mandible showing the bone covered by normal-appearing mucosa.

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have been reported to be much lower, at 0.01 to 0.34%.19

Currently, drug holidays are recommended to allow resolution of the effects on bone turnover.6-9 However, the required length of the holiday is unknown because of the long half-life of bisphosphonates (10 years). Although bisphosphonates have proven to be extremely effective at inhibiting bone turnover, their prolonged effect on bone remains a concern for management of patients who develop BRONJ.

Denosumab and bisphosphonates have significantly different mechanisms of action. The pharmacokinetics of denosumab are more favorable for the management of ONJ than that of the bisphosphonates.16,17 Denosumab has been approved by the Food and Drug Administration for the treatment of osteoporosis in postmenopausal women at high risk for fractures and for patients with metastatic cancer to the bones. The drug is also undergoing clinical trials for management of other metabolic bone disorders, including rheumatoid arthritis, multiple myeloma, and cancer.10-13 The current formulation of denosumab is administered as a subcutaneous injection. The patient described in this report was enrolled in a clinical trial involving monthly injections of a high dose of denosumab, 120-mg.

Denosumab is a human monoclonal immunoglobulin 2G (Ig2G) antibody.10,11 It functions to decrease bone metabolism by inhibiting a critical step in the differentiation of osteoclasts. Specifically, denosumab inhibits the binding of receptor activator of nuclear factor-κB ligand (RANKL) in the cell membrane of osteoclasts to its constituent receptor activator of nuclear factor-κB (RANK) in the cell membranes of osteoclasts and osteoclast precursor cells. Pharmacologically, denosumab mimics the function of the endogenous molecule osteoprotegrin (OPG). RANK, RANKL, and OPG are all members of the tumor necrosis factor superfamily of proteins. The interaction of OPG/RANK/RANKL explains the pharmacodynamics of denosumab.

RANK and RANKL are critical in triggering the cellular pathway that leads to up-regulation of bone metabolism. RANK is a transmembrane receptor that is expressed in the cell membranes of mature osteoclasts and osteoclast precursors.19 RANKL is a membrane-bound cytokine that is found on the surface of osteoblast/stromal cells.20 The binding of RANKL to RANK triggers fusion of osteoclast precursors producing osteoclasts,21 stimulating osteoclast attachment to bone,22 promoting osteoclast activation,21,22 and inhibiting osteoclast apoptosis.23

OPG controls the interaction of RANK and RANKL. Unlike RANK and RANKL, OPG is a soluble molecule, which is produced by osteoblasts.24 OPG is similar in structure to RANK in the cell membrane of the osteoclast. However, OPG is not bound to the cell membrane and lacks the transmembrane domain of RANK.19 The OPG functions as a secreted autocrine receptor for the osteoblast-derived RANKL molecule and binds to RANKL. OPG possesses structural similarity to other proapoptotic molecules in the tumor necrosis factor; it competitively binds to RANKL on the surface of the osteoblast and prevents the RANKL from binding to the RANK receptors found on osteoclasts.23 OPG inhibits the formation of osteoclasts,21,22,25 attachment of osteoclasts to bone,26 and activation of osteoclasts22,27 and increases apoptosis of osteoclasts.23 Animal studies have confirmed the significance of OPG in controlling bone remodeling because knock-out mice unable to produce OPG demonstrate osteoporotic skeletal changes and reduced bone mineral density.28

OPG has a potent antiresorptive effect in postmenopausal women and has been tested for use in patients. Recombinant OPG was rapidly metabolized in vivo and required frequent administration to maintain adequate suppression of bone turnover.29 Because of the unfavorable pharmacokinetics of recombinant OPG, alternative therapeutic options have been pursued to produce a RANKL inhibitor with a sufficient half-life to allow for convenient dosing schedules. Monoclonal antibodies to RANKL were considered because of their longer half-life relative to recombinant OPG30 and denosumab is a monoclonal antibody to RANKL that can mimic the action of OPG.

Denosumab has nonlinear dose-related activity.14 Yonemuri et al. described the pharmacokinetics in a group of cancer patients receiving single or multiple doses of denosumab.31 The drug was absorbed rapidly with peak serum values at 8 to 10 days (single dose) or 10 to 14 days (multiple doses). The serum half-life was 25 to 29 days. No significant change of the pharmacokinetics was observed with multiple doses of the drug.

Denosumab has been shown to increase bone mineral density without incorporation into the bone matrix. In a study with “knock-in” mice with human RANKL, denosumab was found to localize in the blood vessels in the medullary cavity and cortex without incorporation into the bone matrix or cells that lined the bone surfaces.32 This is supported by treating the knock-in mice with human OPG and showing that the clearance of OPG from peripheral blood was coordinated with clearance from bone.33 Therefore, a distinct advantage of denosumab over bisphosphonates is the relatively short half-life of the drug compared with that of the bisphosphonates that are incorporated into the mineral matrix of the bone.17

Osteonecrosis of the jaws in patients taking denosumab has been identified during clinical trials to eval-
The patient receive in this report received monthly subcutaneous injections of denosumab. The ONJ in the maxilla resolved 15 months after extractions, 11 months after cessation of denosumab, and the ONJ in the mandible resolved 22 months after the teeth were removed, 18 months after cessation of denosumab. The ONJ likely had a slow resolution because multiple high doses of denosumab have a prolonged effect on bone turnover because of the slow release of the denosumab from subcutaneous sites.35

Denosumab-induced ONJ has been reported in patients treated for metastases of cancer to the bones.16,17,36,37 In a study with nearly 2000 subjects receiving denosumab or the intravenous bisphosphonate zoledronate, the incidence of ONJ was 1.5% in the denosumab group and 1.3% in the bisphosphonate group.16 Saad et al.17 reported that the incidence of ONJ was 1.8% in the denosumab group and 1.3% in the bisphosphonate group. The differences between the 2 groups were not statistically significant. In addition, Saad et al.17 found that patients taking denosumab had a more rapid resolution of ONJ than patients taking the bisphosphonate zoledronate, 40% compared with 29%. They suggested that the more rapid recovery may be related to the “reversible” inhibition of RANKL.

Theoretically, ONJ may resolve more rapidly with a drug holiday in patients taking denosumab compared with patients taking a bisphosphonate. Because denosumab has a reversible effect on RANKL, inhibition of the osteoclasts may reverse more quickly and allow for a more rapid resolution of ONJ than in patients taking bisphosphonates, which accumulates in bone, prolonging the inhibition of the osteoclasts. The reversibility of ONJ in patients receiving denosumab is supported by Taylor et al.34 in a case report of ONJ in a patient receiving denosumab. The ONJ in the patient described in this case report resolved with minimal debridements and intermittent oral antibiotic treatments. The ONJ in the maxilla resolved 11 months after cessation of denosumab and the ONJ in the mandible resolved 18 months after stopping the drug. The fact that ONJ did not develop after multiple teeth were removed 18 months after cessation of denosumab also supports the hypothesis that denosumab’s effect on bone may be rapidly reversible.

ONJ has been reported rarely in patients receiving denosumab for osteoporosis. Papapoulos et al.15 reported an incidence of 2 cases of ONJ in a total of 4550 women enrolled in a study investigating the safety and efficacy of denosumab for the treatment of osteoporosis. These patients received 60-mg denosumab injections every 6 months in contrast to 120-mg monthly injections given to patients with metastatic cancer. The greater incidence of ONJ in cancer patients may be related to the larger and more frequent dosing of denosumab. BRONJ was initially reported in patients receiving high-dose intravenous treatment and was not recognized in patients taking lower-dose oral bisphosphonates until later.18

CONCLUSION

With Food and Drug Administration approval of denosumab for treatment of osteoporosis and bone metastasis of cancer, oral health-care providers must be aware of the possibility that ONJ can develop in patients receiving denosumab. Until the incidence and treatment of ONJ in patients taking denosumab are established, it is recommended that health-care providers follow the same recommendations for prevention of BRONJ in patients taking bisphosphonates. Because the half-life of denosumab is significantly shorter than that of the bisphosphonates, ONJ in patients taking denosumab who receive conservative surgical management with a drug holiday may result in a slow but more rapid rate of healing than BRONJ in patients who stop taking bisphosphonates. Further studies using bone turnover markers are needed to verify the rate of bone turnover after cessation of denosumab in patients who develop or are at significant risk of developing ONJ.

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