

# Bisphosphonate treatment: An orthodontic concern calling for a proactive approach

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The purpose of this article is to raise awareness among orthodontists of the effects of bisphosphonates, a commonly prescribed type of drug that can inhibit tooth movement and increase serious osteonecrosis risks in the alveolar bones of the maxilla and the mandible. Common medical uses of bisphosphonates, applicable pharmacology, pharmacokinetics, reports of impaired bone healing and induced osteonecrosis, and a drug effect accumulation theory are reviewed. Potential orthodontic issues and proposed orthodontic recommendations for intravenous and oral bisphosphonate treatments are discussed. Bisphosphonate medication screening, patient counseling, informed consent, and, perhaps, changes in treatment planning might be considered. (*Am J Orthod Dentofacial Orthop* 2007;131:311-20)

**B**isphosphonates are drugs used to treat bone metabolism disorders such as osteoporosis, bone diseases, and bone pain from some types of cancer. Because bisphosphonates work by inhibiting bone resorption by osteoclasts, they can have side effects in dental treatment, including inhibited tooth movement, impaired bone healing, and induced osteonecrosis in the maxilla and the mandible. As orthodontists, we need to know the pharmacology of drugs that can change bone physiology because they can hinder treatment and increase morbidity. These effects could mean additional patient counseling is needed, along with informed consent, enhanced monitoring techniques, reporting of side effects, and, perhaps, changes in treatment planning.

Bisphosphonate types include alendronate (Fosamax and Fosamax Plus D, Merck, Whitehouse Station, NJ) tablets; etidronate (Didronel, Procter & Gamble, Cincinnati, Ohio) tablets and intravenous (IV); ibandronate (Boniva, Roche, Basel, Switzerland) tablets and IV; pamidronate (Aredia, Novartis, Basel, Switzerland) IV; risedronate (Actonel, Procter & Gamble, Cincinnati, Ohio) tablets; tiludronate (Skelid, Sanofi-Aventis, Paris, France) tablets; and zoledronic acid (Zometa, Novartis, Basel, Switzerland) IV.<sup>1,2</sup>

Bisphosphonates are administered intravenously to treat severe medical conditions such as multiple myeloma, bone metastases of various cancers, hypercalcemia, and severe Paget's disease.<sup>1</sup> Systemic levels of

bisphosphonates are up to 12 times greater than from oral uses.<sup>1,3</sup> This higher drug level greatly decreases bone turnover to limit bone destruction, fractures, hypercalcemia, and pain from multiple myeloma and might decrease bone formation to slow cancers from metastasizing into the bone.<sup>4,5</sup> These bisphosphonates have been given to children for osteoporotic or lytic bone conditions such as osteogenesis imperfecta, fibrous dysplasia, juvenile or glucocorticoid osteoporosis, and Gaucher's disease.<sup>6</sup>

Alendronate, risedronate, and ibandronate are commonly administered orally to treat osteoporosis and osteopenia in peri- and postmenopausal women.<sup>1</sup> Osteoporosis affects 8 million women and 2 million men in the United States. Osteoporosis is defined as bone density of 2.5 SD below the mean or the presence of a fragility fracture.<sup>7,8</sup> Osteopenia is bone density between 1 and 2.5 SD below the mean.<sup>8</sup> At least 1.5 million bone fractures occur each year in the United States from osteoporosis. Vertebral, thoracic, pelvic, hip, and humerus fractures are associated with long-term morbidity and sometimes mortality. Oral bisphosphonates have been shown to decrease fractures up to 50%.<sup>7</sup> Nitrogen-containing bisphosphonates can cause esophagitis and limit their oral use if not taken properly.<sup>9</sup>

In 2005, alendronate was the 15th most commonly prescribed drug, with approximately 18 million prescriptions, and risedronate was 37th, with almost 10 million prescriptions.<sup>10</sup> A 40% increase in the use of risedronate for the treatment of osteoporosis has occurred since 2003.<sup>11</sup>

## PHARMACOLOGY OF BIPHOSPHONATES

Bisphosphonates, analogues of inorganic pyrophosphates, have a high affinity to calcium and are targeted

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to areas of bone turnover having preferential uptake on the exposed hydroxyapatite actively undergoing bone resorption.<sup>12,13</sup>

The major action of bisphosphonates is to decrease the resorption of bone by directly inhibiting osteoclastic activity.<sup>2</sup> The antiresorption effect on bone is mediated by intracellular uptake of the drug, which decreases osteoclastic cell function.<sup>12,14</sup> The antiresorptive action to bone is the premise for the lower doses of oral bisphosphonate used to treat osteoporosis.<sup>7,9</sup> This antiresorption action was also demonstrated with acute IV pamidronate administration to rats over 5 days to decrease bone resorption and increase bone formation by 20% to 30% during osseous distraction of the mandible.<sup>15</sup> After 6 to 12 months of oral bisphosphonate administration, a clinical improvement of periodontal disease occurred.<sup>16,17</sup> An expected decrease in N-telopeptide, a bone marker for resorption, and an increase in bone mineral density were found after 6 months of oral bisphosphonates.<sup>16</sup> At 2 years of oral bisphosphonate treatment, periodontal patients showed improvement compared with controls.<sup>18</sup>

Other articles discuss the complex mechanisms of bone regulation and metabolism that are not included here.<sup>19,20</sup>

As bisphosphonates are given in higher, more potent IV doses for longer periods of time, osteoclastic activity becomes much decreased. Hence, these drugs are used to treat severe bone disorders such as multiple myeloma and bone metastases from other cancers.<sup>1,5,21,22</sup> IV pamidronate given to stage 4 breast cancer patients showed decreases in bone pain and healing of lytic bone lesions, whereas the bone-specific alkaline phosphatase, a marker of bone formation, decreased by 41%.<sup>23</sup> During the oral alendronate phase III clinical trials for osteoporosis, after 3 years, a decrease in bone formation was found based on biochemical bone markers.<sup>24</sup> When bisphosphonates are given long term, it was suggested that, when osteoclastic activity decreases sufficiently, decreased osteoblastic activity might follow, caused by the coupling effect through intercellular mediators.

The relative potencies of osteoclastic inhibition for bisphosphonates are etidronate, 1; tiludronate, 10; pamidronate, 100; alendronate, 100-1000; risedronate, 1000-10,000; ibandronate, 1000-10,000; and zoledronic acid, 10,000+.<sup>2</sup> The chemical structures of bisphosphonates and the different nitrogen side groups that determine potency have been known for many years.<sup>9</sup> Nitrogen in the side groups, especially a cyclic nitrogen group, has a major role to increase its osteoclastic inhibition.<sup>9,12</sup> These nitrogen bisphosphonates, after being transported intracellularly, primarily inhibit farnesyl pyrophosphate syn-

thetase and geranylgeranyl pyrophosphatase in the mevalonate pathway responsible for the prenylation of small GTP-binding proteins that are responsible for cytoskeletal integrity and intracellular signaling.<sup>12,14</sup> Bisphosphonates might also prevent osteoclast activating factors, such as receptor activator of nuclear factor KB ligand (RANKL), the primary mediator of osteoclastic differentiation, activation, and survival.<sup>21</sup> Histologically, the osteoclasts lose their ruffled borders, become inactive, and undergo programmed cellular death, or apoptosis.<sup>12,14</sup>

Tooth movement was decreased by 40% after administration of subcutaneous bisphosphonate was given every other day for 3 weeks in rats.<sup>25</sup> After a single dose of IV pamidronate during tooth movement, fewer osteoclasts were observed in the alveolar bone next to the periodontal ligament.<sup>26</sup> Histologic degenerative structural changes, such as loss of ruffled borders, were observed in osteoclasts and attributed to loss of function.<sup>26</sup> It appears that a decrease in osteoclastic activity occurs early in the bisphosphonate accumulation effect and can be observed as decreased tooth movement.

Bisphosphonates have antiangiogenic properties that inhibit endothelial proliferation and decrease capillary formation.<sup>27,28</sup> The high concentrations of bisphosphonates in bone were sufficient to have antiangiogenic properties.<sup>27</sup> In alveolar bone, overaccumulation of bisphosphonates might cause lack of capillary formation and decreased blood flow, and contribute to the avascular condition in osteonecrosis.<sup>22</sup> Because of the short half-life of the drug in the plasma, it is unlikely that the low transient levels found in soft tissues (noncalcified) affect endothelial proliferation.<sup>27</sup> In patients taking long-term bisphosphonates, it appears that we should be concerned about possible decreased blood flow during new bone formation.

## PHARMACOKINETICS OF BISPHOSPHONATES

Pharmacokinetics is the study of a drug's action in the human body, including absorption, distribution into tissues, metabolism, and elimination.<sup>29</sup>

Bioavailability is the fraction of the drug that reaches systemic circulation after oral intake, and it depends on the amount absorbed and the amount that escapes the first-pass liver metabolism.<sup>29</sup> The bioavailability of oral bisphosphonates is very low, usually less than 2%; that of a standard IV dose is 100%.<sup>2,29</sup> The drugs are poorly absorbed in the upper portion of the small intestine because of their low lipophilicity, which limits transcellular transport.<sup>30</sup> When these drugs are given orally in higher doses, they bind to cations between cells, increase paracellular space, and might

increase bioavailability up to 5%.<sup>30</sup> The paracellular absorption of the drug is limited at normal dosages because of the high molecular weight, negatively charged, and high binding affinity to divalent cations (eg, calcium, iron, magnesium) in the intestinal tract.<sup>30</sup> This explains why the absorption of these drugs can be decreased an additional 40% to 60% if taken near mealtime or with orange juice, milk, or antacids.<sup>1</sup> Because these drugs are not affected by metabolism of the liver, there is no first-pass effect after oral absorption.

After bisphosphonate is in the bloodstream, it quickly binds to the exposed hydroxyapatite in the osseous matrix, and the excess drug leaves the body through the kidneys. Generally, 50% to 60% of the drug is bound to bone, with the remainder excreted through the kidneys rapidly over several hours.<sup>2</sup> However, more drug can be selectively bound to bone if more sites of active bone turnover exist during this distribution time or if the patient's renal function is decreased. Drug distribution to noncalcified tissues is transient.<sup>2</sup> In the skeleton, bone is either cortical or trabecular bone. Trabecular bone, accounting for only 20% of the skeleton, has 80% of bone turnover.<sup>31</sup> Alendronate was shown to concentrate 2 to 3 times higher in trabecular bone.<sup>31</sup>

After the drug is bound to bone, it is considered inactive until it is released during bone remodeling. The released drug might be transported into the osteoclast, rebound to another site of exposed hydroxyapatite, or be eliminated by the kidneys. When transported into the osteoclast cell, it inhibits cell function and shortens cell life span.<sup>2,14</sup> The amount of drug released from bone depends on the rate of bone turnover.<sup>32</sup>

The terminal bone elimination half-life of this drug group is variable but can be extremely long: ibandronate, 10-60 hours; zoledronic acid, 146 hours; risedronate, 480 hours; pamidronate, 300 days; and alendronate, more than 10 years.<sup>1,2,30</sup> However, terminal half-life data can be confusing for clinical relevancy. These figures were derived from animal studies or complex human third-compartment bone elimination estimates that might not necessarily depend on the specific drugs as much as on the physiological rates of bone turnover during these assays. On a given site of trabecular bone surface, a human undergoes remodeling once every 2 years vs once every month in rats.<sup>31</sup> This explains the variable terminal bone half-life of alendronate, which has been reported to be 200 days in rats, 3 years in dogs, and 12 years in humans.<sup>31</sup> Generally, this drug group, although having elimination variability among its types, is presumed to be sequestered in bone as an inactive drug and

retained for an extended time until the active drug is released by normal bone turnover.<sup>2,9</sup>

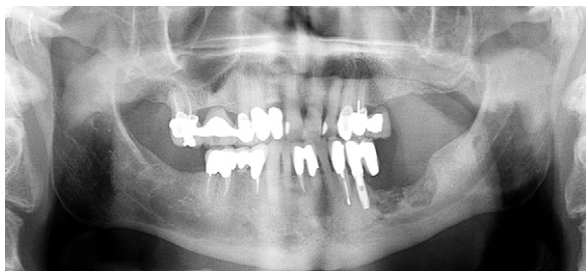
### IMPAIRED BONE HEALING

In the treatment of osteoporosis, oral bisphosphonates are used to decrease bone loss, increase bone density, and thereby decrease the risk of bone fractures.<sup>9</sup> Ironically, diminished or absence of healing for nonspinal bone fractures was reported during routine activities for 9 patients taking oral alendronate for 1 to 8 years.<sup>33</sup> Five patients resumed normal bone healing after discontinuing alendronate for 3 to 8 months. Four patients continued to have decreased healing for up to 12 months. Although the authors noted a 50% reduction in serum biochemical markers, a 95% reduction of bone turnover was found at the bone site. The difference was attributed to variable bone turnover at different skeletal sites. Also, prolonged high doses of IV bisphosphonates in children have been reported to cause brittle bones that are more susceptible to fractures.<sup>6</sup> In patients receiving long-term bisphosphonates, clinicians should be aware of impaired bone healing because of the reported decreased bone and capillary formation.

### BISPHOSPHONATE-INDUCED OSTEONECROSIS

Bisphosphonate osteonecrosis is strikingly similar to the "phossy jaws" found during the 19th century in match, fireworks, and brass industrial workers who were overexposed to white phosphorous.<sup>34</sup> Bisphosphonate osteonecrosis appears as chemically induced osteopetrosis in which the microcirculation of the bone is decreased until the endpoint of necrosis is reached.<sup>21</sup> If the mineral matrix is not absorbed by the osteoclast, new bone growth and capillary formation will not be stimulated properly; this eventually leads to acellular and avascular bone.<sup>21</sup> The vasculature in the surrounding mucosa appears clinically normal and unaffected.<sup>21</sup>

Many factors can contribute to osteonecrosis after IV bisphosphonate use, such as cancer chemotherapy, glucocorticoids, peripheral vascular disorders, and infection. However, bisphosphonate was the only variable always present in all these otherwise rare osteonecrosis cases in the maxilla and the mandible.<sup>21,22</sup> Currently, no contributing factors alone have caused this type of bisphosphonate osteonecrosis to be clinically observed in this location and at this increased incidence.<sup>21,22</sup> Glucocorticoid osteonecrosis occurs in the long bones but rarely in the jaws.<sup>21</sup> Radiation osteonecrosis, which clinically presents similar to bisphosphonate osteonecrosis, occurs in the mandible but is uncommon in the maxilla because of the high vascularity.<sup>22</sup>

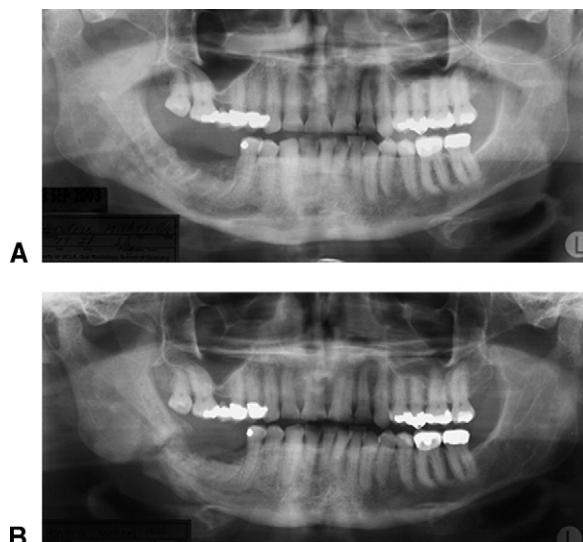


**Fig 1.** After long-term IV administration of pamidronate and zoledronic acid for multiple myeloma, tooth pain and infection resulted in extractions in mandibular left quadrant. Osteonecrosis presented with loss of alveolar bone. Grafting procedures are not expected to be successful. Several root canals were unsuccessful in resolving pain (radiograph courtesy of Sanford Ratner).

### OSTEONECROSIS PRESENTATION

In patients who received intravenous bisphosphonate, typical osteonecrosis presentations are painful abscessed teeth that, when extracted, expose the underlying necrotic bone, furthering bone loss without normal healing (Fig 1).<sup>21,22,35,36</sup> Osteonecrosis appears as exposed bone (68%), at least 1 mobile tooth (23%), and fistulas (17%) in patients after IV bisphosphonate treatment of severe bone disorders.<sup>21</sup> Most open tissue lesions with exposed necrotic bone were observed on the posterior lingual area of the mandible near the mylohyoid ridge and on the mandibular tori.<sup>3,21</sup> Dental radiographs that demonstrate a widened periodontal ligament space at the molar furcation have a strong association with osteonecrosis.<sup>21</sup> Patients with advanced osteonecrosis have developed mandibular fractures (Fig 2).<sup>22</sup> Aggressive surgical treatments for the necrosis and the resulting infection usually worsen the situation.<sup>21</sup> Once the mucosa surrounding the necrotic alveolar bone is not intact, it is an often painful condition that can be susceptible to severe infections (Fig 3). This can result in a long-term debilitating condition.<sup>21</sup> In patients taking bisphosphonates, osteonecrosis symptoms can mimic dental or periodontal disease. Bisphosphonate osteonecrosis should be considered as a possible diagnosis if routine treatment does not resolve the symptoms, even in the absence of exposed bone.<sup>37</sup>

This osteonecrosis was reported only in the maxilla and the mandible—in alveolar bone—and not in any other bones of the body.<sup>21,22,36,38</sup> Osteonecrosis was located in the mandible (68%), the maxilla (28%), and both jaws (4%). Necrosis was found predominantly in the posterior alveolar regions of the maxilla and the mandible.<sup>21</sup> A pharmacologic explanation of why os-



**Fig 2. A,** After 2 years of IV zoledronic acid for treatment of multiple myeloma, tooth infection required extractions in mandibular right quadrant. **B,** Osteonecrosis was found, and excessive alveolar bone loss continued postextraction. Spontaneous fracture of mandible occurred. No normal healing of fracture site was observed, and mandible will be stabilized with titanium frame (radiographs courtesy of Sanford Ratner).

teonecrosis is found at these sites could be that alveolar bone, with constant masticatory functions, contributes to accelerated drug uptake because its bone turnover rate is 10 times greater than in the tibia.<sup>13,39,40</sup> Since bisphosphonate decreases normal physiologic bone deposition and remodeling, the constant force of mastication could cause unrepaired microfractures, possibly setting the stage for osteonecrosis.<sup>35</sup> Trauma and infection can increase the demand for osseous repair that exceeds hypodynamic bone capability, resulting in localized alveolar bone necrosis.<sup>3</sup>

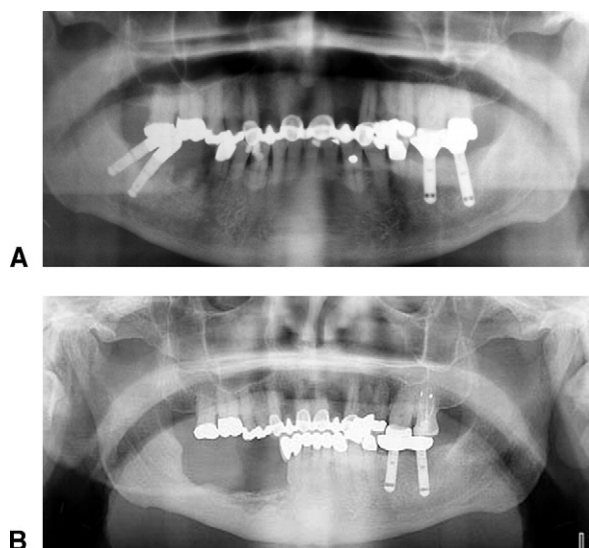
The events that precipitated necrotic bone exposure were tooth extraction (37%), existing periodontal disease (28%), periodontal surgery (11%), implant placement (3%), apicoectomy (1%), and spontaneous occurrence (25%).<sup>21</sup> Tissue pressure from poorly fitting dentures was also reported to cause exposed necrotic bone.<sup>36</sup> The most common dental comorbidity factor was clinical and radiographic periodontitis.<sup>21</sup>

Only the more potent nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, alendronate, risedronate, and ibandronate) have been linked to osteonecrosis in the maxilla and the mandible.<sup>3,21,22</sup>

### INTRAVENOUS VS ORAL ADMINISTRATION

Most osteonecrosis cases were reported after IV administration of bisphosphonate for the treatment of





**Fig 3. A,** After 4 years of IV zoledronic acid treatment for multiple myeloma, right mandibular first molar was extracted due to abscess that did not respond to treatment (patient had existing stable implants with nonideal placement in mandibular right quadrant). **B,** Osteonecrosis was observed, and serious bone infection required block resection of alveolar bone. Infection was controlled, but bone remained exposed. No bone or soft-tissue grafting procedures were done (radiographs courtesy of Sanford Ratner).

multiple myeloma and bone metastases from cancers.<sup>21,22,36,38</sup> Several authors reported relatively high incidences (4%-10%) of severe osteonecrosis after IV bisphosphonates.<sup>41-43</sup> These patients had other factors that might have contributed to the high incidence of osteonecrosis: cancer chemotherapy, compromised immune systems, glucocorticoid administration, or infections.<sup>21,22</sup>

As of March 2006, after oral bisphosphonate treatment for osteoporosis, the numbers of osteonecrosis cases reported were 170 for alendronate, 12 for risedronate, and 1 for ibandronate.<sup>37</sup> The reported incidence of osteonecrosis after oral administration appears low at approximately 0.7 cases per 100,000 patient-years exposure.<sup>37</sup> This incidence might increase as oral bisphosphonate treatment exceeds 3 years. The authors found no osteonecrosis in the jaws during a 10-year double-blind study of more than 900 postmenopausal women treated for osteoporosis with alendronate.<sup>44</sup> This study was most likely completed before the first reports of osteonecrosis in 2003.<sup>45</sup> Osteonecrosis cases are being reported more frequently from oral use, because the problem is recognized more by practitioners.

The reported mean times of necrotic bone exposure

were 9 to 14 months (zoledronate and pamidronate, respectively) after IV therapy for severe bone disorders and 3 years (alendronate) after oral administration for osteoporosis.<sup>21</sup> The earliest cases of osteonecrosis were observed at 4 months after IV administration and at 2 years after oral use.<sup>3</sup> As expected, a controlled study found no osteonecrosis in 335 patients with moderate to severe periodontal disease taking alendronate up to 2 years.<sup>18</sup>

### IRREVERSIBLE VS REVERSIBLE DAMAGE

The osteonecrosis from prolonged IV bisphosphonate administration for severe bone disorders does not appear to be preventable or treatable with extensive bone debridement, hyperbaric oxygen, bone grafting, tissue grafting, or even discontinuation of the drug. Except in rare anecdotal situations, osteonecrosis is considered irreversible.<sup>46</sup> This appears to be a long-term, often painful, secondary infection source that is manageable only with chlorhexidine rinses and antibiotics.<sup>21,22</sup>

Oral bisphosphonates given for osteoporosis seem to be causing less severe osteonecrosis than that with IV use. A more focal type of osteonecrosis can be seen and treated.<sup>47</sup> This might be associated with the relatively lower amount of bisphosphonate absorbed and subsequently less drug delivered to the alveolar bone. Perhaps this osteonecrosis is reversible.<sup>46</sup> After osteonecrosis is presented, it was suggested to perform surgery procedures, such as implants or grafts, after discontinuing the oral bisphosphonate for at least 6 months and monitoring the C-telopeptide to a blood level greater than 150 pg/mL.<sup>46</sup> The prescribing physician must decide to change or discontinue bisphosphonate treatment after weighing all risks and benefits for each patient.

### ORTHODONTIC ISSUES

Recently, there have been orthodontic concerns for patients receiving bisphosphonates.<sup>48-50</sup>

Successful orthodontic treatment depends on osteoclastic activity to allow tooth movement. The amount of tooth inhibition should depend on the specific drug potency of osteoclastic inhibition and the amount of drug at the specific site. Inhibition of tooth movement should be presumed to occur to a greater degree and sooner with high IV doses than lower oral doses. Although the bisphosphonate inhibition of tooth movement was reported in animals, it was not quantified for any dose or duration of bisphosphonate treatment in humans.

A single-blind study was performed on 50 patients with 210 implants; half of the patients took oral

bisphosphonates (alendronate or risedronate) for 1 to 4 years before implant placement, and the other half took no bisphosphonates.<sup>18</sup> Both groups were observed for at least 3 years after implant placement and had success rates greater than 99%. This study suggests that implant osseointegration might not be affected by oral bisphosphonates taken 1 to 4 years previously. Although the 3-year bisphosphonate administration prior to implants was not part of the controlled study, the patients' histories of consistent administration were verified by the medical prescribers.<sup>51</sup> Patients might be at more risk with extensive implant placement, guided bone regeneration, and longer oral bisphosphonate treatment.<sup>37</sup> They should be informed of the current incidence of osteonecrosis and that, if it occurs, the implants could be lost.

The accumulated pharmacologic effects of bisphosphonates appear to affect bones in stages influenced by dose and potency, route of administration, continuous administration, duration of treatment, a drug group that specifically binds to bone and is released during turnover, and degree of turnover in a specific bone. In the skeletal framework, new bone might be laid over the sequestered drug, and no accumulation effects are observed as the active drug is released in small amounts during normal bone resorption. Alveolar bone, with constant tooth function and greater bone turnover, might have more of the drug bound and released near osteoclasts and new bone formations. These cycles of higher active drug concentration could be continuously bathing the cells and vascular components, leading to stages of decreasing function by not allowing normal cellular regeneration.

In the initial stage of lower drug concentrations, osteoclastic activity is decreased with the balance shifting to more osteoblastic activity, causing increased bone formation.

In the midstage, drug concentrations rise, causing osteoclastic activity to decrease further. This might start to decrease both osteoblastic activity and new capillary formation in new bone, observed as decreased bone turnover and bone repair.

In the later stage, the drug might greatly accumulate in alveolar bones in the maxilla and the mandible. Osteoclastic activity is decreased enough not to allow normal removal of diseased bone. New bone is laid over defective bone with decreased capillary formation and blood supply. This can be observed as induced osteopetrosis.

In the final stage of excessive drug accumulation, programmed cell death occurs more rapidly, and vascular compromised bone might not be able to regenerate from the micro-trauma of continuous mastication.

This can ultimately be observed as osteonecrosis. The addition of extractions, trauma, secondary infection, periodontal disease, and bone augmentation might accelerate osteonecrosis by exceeding the osseous repair capacity of hypodynamic bone.<sup>3</sup>

Although not proven, this bisphosphonate effect accumulation theory (BEAT) seems to agree with the inherent pharmacologic effects described in the literature. Future observations and studies will determine the validity of this theory.

Orthodontic tooth movement causes greater alveolar bone turnover and might further increase the uptake of bisphosphonates locally. If bone apposition covers the sequestered inactive drug during tooth movement, no effect can be clinically observed. However, orthodontic movement and continuous administration of bisphosphonate could create an even more exaggerated cycle of continuous increased uptake and release of the active drug locally. Presently, it is difficult clinically to determine the local stage of active drug accumulation as the bone changes from augmentation to avascular necrosis. Intuitively, sufficiently decreased osteoclastic activity will be observed as slower tooth movement and might be the first sign in the early midstage of drug accumulation. It is not known how quickly hypodynamic alveolar bone will progress to end-stage necrosis with continued active drug release, existing periodontal disease, prior tooth trauma, infection, surgical procedures, or tooth movement. No studies have attributed orthodontic treatment to increased osteonecrosis risks. Future studies are needed to correlate histology, bone-mineral densities, radiographic markers (such as technetium<sup>99</sup>), and biochemical markers for bone deposition (bone-specific alkaline phosphatase or osteocalcin) and bone resorption (N or C telopeptides) to provide information about drug accumulation staging to determine procedural risks.

#### **LONG-TERM ORAL BIPHOSPHONATE TREATMENT**

It is expected that more osteonecrosis cases will be reported in the future for the following reasons.

1. More patients are being treated with oral nitrogen-containing bisphosphonates that can preferentially accumulate in the alveolar bones of the maxilla and the mandible.
2. Constant administration of oral bisphosphonates might allow them to remain in the alveolar bone for long periods. There might be local cycles of binding and releasing the drug in higher concentrations due to increased alveolar bone turnover through normal mastication, trauma, and infection.

3. The dental community is increasingly aware of osteonecrosis linked to oral bisphosphonate treatment.

Many pertinent questions arise without clear answers for the many women (and smaller number of men) who take oral bisphosphonates and seek orthodontic treatment. How much will orthodontic movement be inhibited in each patient? Even if initial tooth movement appears normal, will bisphosphonate continue to accumulate and be released in the alveolar bone surrounding the periodontal ligament and impede successful orthodontic completion? When should orthodontic treatment be stopped if tooth inhibition is noted? Because orthodontic treatment stimulates more alveolar bone turnover and possibly causes more bisphosphonate uptake and release, will more localized osteonecrosis occur? Will appliances that place pressure on the palate disrupt the mucosa and expose underlying necrotic bone? Will bone healing be impaired after orthognathic or dental alveolar surgery? How much risk are we imposing for elective surgery procedures—eg, orthognathic surgery, extractions, periodontal surgery, and implants?

#### PROPOSED ORTHODONTIC RECOMMENDATIONS

I propose the following recommendations for patients receiving bisphosphonate treatment. These recommendations are to be used for professional guidance and are not to be interpreted as the standard of care.

1. Ask all patients whether they currently take or have ever taken IV or oral bisphosphonates (include all generic and trade names) and ask the medical reason for treatment (severe bone disorders, cancers, osteoporosis/osteopenia) on your screening/medical history form.
2. Determine the risk of osteonecrosis and the level of osteoclastic inhibition: route of administration and reason for bisphosphonate treatment (IV bisphosphonate treatment for severe bone disorders and cancers has high risk of osteonecrosis and high level of osteoclastic inhibition. Oral bisphosphonate treatment for osteoporosis or osteopenia has a lower risk of osteonecrosis and lower level of osteoclastic inhibition); duration of treatment (longer duration is associated with more risk); and dose and frequency (presume that a higher dose or more frequent administration leads to higher risks).
3. Evaluate treatment plan based on risk group.
  - (A) If a patient has high risk/high level of osteoclastic inhibition (IV bisphosphonates), avoid orthodontic treatment. Because of their severe medical conditions, few of these patients will seek elective orthodontics. I believe

it is prudent to avoid elective orthodontic treatment because of possible strong inhibition of tooth movement, intensifying local bisphosphonate uptake and release, and increasing demand for osseous repair that might exceed compromised alveolar bone capability. Orthodontic treatment should begin only after discussions with the oncologist, the dentist, and the patient to determine that more benefit will occur than risk. Patients who have started IV bisphosphonate treatment need retainers checked for passive retention and be relieved of any tissue pressure; they also need areas monitored for open necrotic bone, especially in posterior, lingual mandibular areas, mandibular tori, and midline palatal tori. Passive tooth-borne retainers can be considered. Elective surgeries should be avoided (extractions, implants, periodontal surgeries) after IV bisphosphonates.<sup>21</sup> The objective is to keep the mucosa intact and avoid exposing any underlying necrotic bone. Root canal treatment is considered more conservative than extraction. Teeth with grade 1 or 2 mobility can be splinted. Teeth with grade 3 mobility are strongly associated with periodontal abscesses and osteonecrosis. Dental alveolar surgeries or extractions are recommended only when infection cannot be managed by conservative measures and should be performed by a specialist knowledgeable about bisphosphonate osteonecrosis.

- (B) If there is low risk/lower level of osteoclastic inhibition (oral bisphosphonates), in my opinion, this large group of patients poses a challenge for treatment planning because of possible pharmacologic inhibition of tooth movement and reported osteonecrosis. Counsel patients about inhibited tooth movement, osteonecrosis, and impaired bone healing with elective surgery procedures—eg, orthognathic surgery, extractions, implants, and periodontal grafts. Discuss the potential surgery risks with all applicable dental providers. Revise your orthodontic treatment plan based on your assessment of potential risks. Options might include avoiding or minimizing elective surgery and extractions, favoring interproximation over mandibular incisor extraction, minimizing tooth movement, minimizing pressures on tissues during treatment and retention, or avoiding treatment. Informed consent should include all potential risks of

bisphosphonates. Watch for slower than expected tooth movement. Monitor for signs and symptoms of later drug accumulation effects and possible osteonecrosis—excessive tooth mobility, furcal involvement of posterior teeth shown on panoramic radiographs, unresolved pain from root-canal treatments, periodontal symptoms unresolved by routine treatment, fistulas, exposed areas of necrotic bone on the posterior lingual mandibular teeth and all tori, and unhealed or resorbing alveolar bone after extraction. Routine dental and periodontal examinations for these patients are even more important during orthodontic treatment. Before extractions or dental alveolar surgeries to treat refractive infections, the patient should be informed of the possibility of osteonecrosis and that treatment could worsen the situation. Report patients with osteonecrosis during or after bisphosphonate use to their prescribing physicians and to the Food and Drug Administration's Med Watch at [www.fda.gov/MedWatch/report.htm](http://www.fda.gov/MedWatch/report.htm) or call 800-FDA-1088.

4. Read articles for the interesting history of white phosphorus toxicity and the histology of osteonecrosis<sup>3</sup>; the comprehensive review of bisphosphonates and dental recommendations before and during IV bisphosphonate use<sup>35</sup>; dental recommendations during oral bisphosphonate use<sup>37</sup>; better understanding of bisphosphonate osteonecrosis with excellent categorization of presentation, treatment, and dental recommendations<sup>21</sup>; and bisphosphonate osteonecrosis presentation and treatment.<sup>22</sup> Read future articles for information that will help you determine risks vs benefits of orthodontic and auxiliary surgery procedures.
5. Watch for new drugs prescribed to treat bone disorders. Many new drugs for the treatment of osteoporosis and serious bone disorders might have osteoclastic inhibitions as part of their pharmacologic actions and should be looked at closely. Denosumab, now in clinical trials as an osteoporosis treatment, is a human monoclonal antibody that selectively binds to RANKL and decreases bone turnover for 6 months after 1 subcutaneous administration.<sup>52</sup>

## CONCLUSIONS

Orthodontic treatment depends on the normal physiologic processes of bone. Every day, we alter growth of the jaws, perform sutural osseous distractions, and orchestrate complex bone changes for even the simplest

movement of 1 tooth. We redirect these biological processes so routinely that it is easy to take them for granted until inhibition or morbidity occurs. The opening of the human genome will lead to the discovery of new proteins and hormones that can change the human body's physiologic functions in dramatic ways. A physician's responsibility is to balance the therapeutic effects of drugs with their unwanted side effects to determine whether to order drug holidays, discontinue drugs, or choose alternative medications. This was demonstrated by the recent Mayo Clinic treatment adjustment of IV bisphosphonates for multiple myeloma patients based on the incidence of jaw osteonecrosis.<sup>53</sup> The dentist's responsibility is to observe and report osteonecrosis and other side effects. Dentists have access and the knowledge to detect the transition of alveolar bone from normal to pathologic conditions. A national registry would help to establish the true incidence of side effects attributed to these drugs and future ones.<sup>34</sup> The orthodontist's responsibility is to evaluate any effects of these drugs on alveolar bone during routine orthodontic treatment. Future research must have clear goals of rapidly integrating data from radiographic and bone markers, bone densities, and animal histology into clinical practice. The practicing orthodontist must be able to determine treatment success and risk of procedures by a simple blood or radiographic screen of patients receiving bisphosphonates and other drug groups that will follow. Once established, these tools can be given to our dental and medical colleagues to help them monitor for potential side effects in the jaws. Our orthodontic specialty was formed from 3 disciplines: medicine, dentistry, and engineering. Let this article remind us that the roots of our specialty have always been firmly embedded in medicine.

This article was written to inform orthodontists of potential issues and concerns of bisphosphonate treatment that can affect our patients' treatments. As yet, there have been no reports of orthodontic-related problems associated with bisphosphonate treatment. Increasing our knowledge of bisphosphonates is critical because these drugs can impede orthodontic treatments and increase morbidity to the maxilla and the mandible. This article was not intended to change the medical community's prescribing habits of effective drugs used to treat difficult medical conditions, which, if left untreated, can result in much greater morbidity and possible mortality. However, bisphosphonate complications might develop under our direct observation. As orthodontists, we must be aware of, document, and report any problems to the FDA and to our medical and dental colleagues so that the risks and benefits of



bisphosphonate treatment can be fully understood. Discussing the potential risks with our patients and dental referrals will help ease our difficult treatment decisions. Communication of any future discovered risks with our dental and medical colleagues will ultimately improve patient care. The members of our specialty should strengthen their knowledge, awareness, and communication of these issues and adhere to the primary principle, "first, do no harm."

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