

Optimizing orthodontic treatment in patients taking bisphosphonates for osteoporosis

James J. Zahrowski

Tustin, Calif

Bisphosphonates have unique pharmacological characteristics unlike those of any other drug group. Millions of adults take oral bisphosphonates for long-term treatment of osteoporosis and osteopenia; some of these people will most likely also seek orthodontic treatment. Adverse dental effects from bisphosphonates have been reported, including decreased tooth movement, impaired bone healing, and osteonecrosis in the mandible and the maxilla. Osteonecrosis has been rarely observed after bisphosphonate use for osteoporosis. However, adverse drug effects might occur more frequently in orthodontic patients, and they would probably be noted before the end-stage pathology of osteonecrosis. Adverse effects during orthodontic treatment, including decreased tooth movement, could last for years after the drug therapy is stopped. Successful orthodontic treatment requires optimal bone healing to prevent excessive tooth mobility. Bisphosphonates appear to have 2 bone elimination rates—a fast elimination of weeks from the bone surface and a slow elimination of years after incorporation into the bone structure. This article presents methods to clinically and radiographically monitor orthodontic patients who are taking oral bisphosphonates. Efforts to minimize adverse effects and optimize orthodontic procedures with physician-approved drug holidays are discussed. The orthodontic treatment results of 3 patients who received bisphosphonate therapy are reported. (*Am J Orthod Dentofacial Orthop* 2009;135:361-74)

Bisphosphonate (BP) is used for the long-term treatment of osteoporosis and osteopenia by millions of adults who might also seek orthodontic treatment.¹⁻⁴ Approximately 1.5 million osteoporotic fractures occur annually in the United States, with the incidence projected to rise.⁵ Osteoporotic fractures are a principal cause of disability and death.⁶ Although a higher fracture risk is noted in those with osteoporosis than osteopenia, an estimated 33 million people in the United States—80% of them women—have osteopenia with more fracture risk than the normal population.⁷ After menopause, decreased estrogen secretion leads to relatively increased osteoclastic activity and increased bone resorption.^{3,4} The internal cross-links break because of more resorption in trabecular bone than in cortical bone.⁸ The destabilized bone structure allows more fractures to occur in the hip and the lumbar vertebral regions.^{8,9} Bone density in these regions is usually measured by dual-energy x-ray absorptiometry.⁴ Osteopenia is defined as decreased bone density of 1 to 2.5 SD below the mean. Osteoporosis is defined as a further decrease of bone density more than 2.5 SD below the

mean. Patients with severe osteoporosis and a previous fragility fracture are at higher risk for future fractures. Oral BP treatment has been related to a 50% decrease of bone fractures in the hips and the vertebrae.³ Intravenous BP, such as zoledronic acid given yearly or ibandronate given every 3 months, have been recommended for osteoporosis treatment by increasing compliance and decreasing fractures up to 70%.^{10,11} Oral BP is 1 of the 15 most prescribed drugs in the United States and a primary long-term osteoporosis treatment that reduces morbidity and mortality with few adverse medical effects.^{2,7}

The BP pharmacological site of action is in the osteoclast, which removes the outer ruffled border, inactivates function, and decreases the lifespan of the cell.¹²⁻¹⁴ The drug enters the osteoclast through endocytic vacuoles.¹⁵ Commonly used BP, containing a nitrogen group, primarily inhibits farnesyl pyrophosphatase synthetase and geranylgeranyl pyrophosphatase.^{15,16} Enzyme inhibition causes a decrease of proteins responsible for cytoskeletal integrity and intracellular signaling.^{12,16} There is some evidence that this drug group might also inhibit osteoclast precursors and osteoblast communication with osteoclasts.^{15,16} Absorption of BP through the small intestine is low. Approximately 0.06% of the oral dose reaches the bloodstream as opposed to 100% when given intravenously.^{13,17} Once the drug is in the bloodstream, approximately 50% is excreted within hours by the kidneys, and the other

Private practice, Tustin, Calif.

Reprint requests to: James J. Zahrowski, 13372 Newport Ave E, Suite E, Tustin, CA 92780; e-mail, jzahrowski@aol.com.

Submitted, April 2008; revised and accepted, August 2008.

0889-5406/\$36.00

Copyright © 2009 by the American Association of Orthodontists.

doi:10.1016/j.ajodo.2008.08.017

half is preferentially bound to the surfaces of high bone turnover.¹² Preferential drug binding was documented by a 3-times higher alendronate concentration in trabecular bone, which has a 3-times greater bone turnover rate than cortical bone.⁸ Various locations in the body have different bone repair rates. It was reported that alveolar bone has up to a 10-times greater bone turnover rate than skeletal bones because of the constant masticatory forces.¹⁸ After BP is incorporated into the bone, drug elimination occurs slowly and is regulated by the physiologic rate of bone turnover.^{9,17,19} Since high bone turnover occurs during orthodontic treatment, more BP might be bound and incorporated around the teeth than in other bone areas of the body.

After 3 months of oral BP use, bone resorption decreased by 50% to 75% as measured by osteoclastic systemic bone markers, carbon or nitrogen telopeptide.²⁰ After 6 months of oral drug use, bone formation also decreased by 50% as measured by an osteoblastic systemic bone marker, bone-specific alkaline phosphatase.²¹ The resultant decrease in bone formation was thought to be indirectly caused by intercellular osteoclastic mediators suppressing osteoblastic activity. The systemic bone markers stabilized at these levels and did not decrease further after long-time oral BP use.^{22,23} One study noted that nonhealing skeletal fractures occurred after many years of continuous oral BP use.²⁴ Fracture site biopsies showed a 95% decrease in bone formation, whereas the systemic marker of bone formation decreased by only 50%. Therefore, systemic bone function tests might not accurately describe locally decreased bone function around the teeth caused by BP.

Adverse dental effects of BP were reported to decrease tooth movement, impair bone healing, and induce osteonecrosis in the mandible and the maxilla.²⁵⁻²⁷ This drug group causes decreased tooth movement rapidly and was reported to interfere with orthodontic results.^{28,29} Optimal tooth movement and bone healing, which are dependent upon osteoclastic and osteoblastic activity, are important for a successful orthodontic treatment result. Although BP-induced osteonecrosis was first reported in 2003, similar nonhealing extraction sites with jaw necrosis was reported in 19th century factory workers who were overexposed to white phosphorus.^{30,31} BP-induced osteonecrosis is currently defined as exposed necrotic bone in the mandible or the maxilla for at least 8 weeks with prior BP use and no history of radiation treatment to the jaws.³² The soft-tissue exposure of necrotic bone usually was observed after extractions but also was noted with periodontal disease and periodontal surgery, or occurred spontaneously over tori or posterior lingual of the mandible.³³ Untreatable jaw osteonecrosis

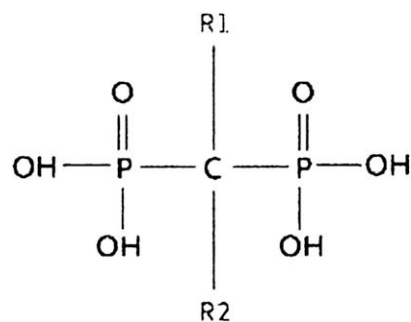




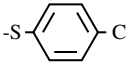
Fig 1. BP structure. Carbon between the phosphate groups allows no metabolism in the body (pyrophosphate contains oxygen between phosphate groups). Pharmacology of different types depends on R1 and R2 groups attached to carbon. R1 group increases binding to bone (calcium), especially when OH is present; R2 group increases potency, especially when nitrogen is present.

was reported with an incidence of 4% to 10% in bone cancer patients who received continuous large intravenous doses of BP, zoledronic acid or pamidronate.^{27,33-36} The reported high incidence and severity of osteonecrosis is probably due to the 12 to 50 times greater systemic BP dose given to treat bone cancer than osteoporosis.^{37,38} Bone cancers, such as multiple myeloma or metastatic breast cancer, treated with BP given intravenously usually contraindicate any orthodontic or elective dental surgery procedures.^{25,33} BP pharmacology is important for the orthodontist to understand to evaluate adverse drug effects to the bone around the teeth.

BP STRUCTURE RELATES TO PHARMACOLOGICAL ACTIVITY

BP has a chemical structure change in which carbon, substituted for oxygen in pyrophosphate, is between 2 phosphates as shown in Figure 1.¹² Pyrophosphate, rapidly inactivated into 2 phosphates by tissue alkaline phosphatase, is secreted by the smooth muscle and can prevent vascular or soft-tissue calcification.³⁹ BP affects bone regulation because of the structural carbon change.^{9,12} The drug cannot be metabolized by the tissue or the liver and can only be eliminated through the kidneys. BP has R1 and R2 groups attached to the carbon; these increase bone affinity and drug potency, respectively (Fig 1). The common medical uses, bone affinity, potency, and R group structures of the BP types are shown in Table I. A greater affinity to human bone was found when a hydroxyl group (OH) was present in the R1 group, as

Table I. Comparison of BP types

Types ¹	Common use ¹		R1 group* ¹²	Bone affinity ^{40†}	R2 group ^{12‡}	Potency ^{3,17,41§}
	Cancer	Osteoporosis Pagets, hypercalcemia				
Alendronate (Fosamax [Merck, Whitehouse Station, NY], oral)		X	-OH	1.5	-(CH ₂) ₃ -NH ₂	700
Risedronate (Actonel [Proctor & Gamble, Cincinnati, Ohio], oral)		X	-OH	1.1	-CH ₂ - 	2000
Ibandronate (Boniva [Roche, Basel, Switzerland], oral and IV)		X	-OH	0.8	-(CH ₂) ₂ -N-CH ₃ (CH ₂) ₄ -CH ₃	4000
Zoledronic acid (Reclast [Novartis, Basel, Switzerland], IV) (Zometa [Novartis], IV)	X	X	-OH	1.1	-CH ₂ - 	10,000
Pamidronate (Aredia [Novartis], IV)	X		-OH	1.1	-(CH ₂) ₂ -NH ₂	325
Etidronate (Didronel [Proctor & Gamble], oral and IV)		X	-OH	1.0	-CH ₃	1
Tiludronate (Skelid [Sanofi-Aventis, Paris, France], oral)		X	-H	0.5	-S- 	10
Clodronate (Bonefos [Berlex Inc, Schering, NJ], oral)		X	-Cl	0.1	-Cl	10

IV, Intravenous; Ki, human bone affinity.

*R1 group: hydroxyl (OH) increases binding to bone; †Bone affinity: relative bone affinity compared to etidronate as 1 (etidronate Ki divided by type Ki); ‡R2 group: nitrogen (N) increases drug potency; §Potency: relative drug potency compared to etidronate as 1.

demonstrated by the 15 times stronger affinity of alendronate to bone than clodronate.⁴⁰ The BP types used for osteoporosis have strong affinities to bone with smaller variations, since they all have an OH group in R1. Alendronate has the strongest affinity to bone, 30% stronger than risedronate or zoledronic acid and almost 2 times stronger than ibandronate. Since these drugs have a high affinity to calcium, they are quickly targeted and bound to the exposed hydroxyapatite of actively resorbing bone in the body.¹² When nitrogen was present in the R2 group, drug potency was increased.^{12,13,17,41} Increased potency corresponds to a smaller amount of the drug needed to suppress osteoclastic function. Zoledronic acid is the most potent type due to a cyclic nitrogen group in R2. The relative systemic effects per dose for the BP types used in osteoporosis are compared in Table II. Higher-potency drug types are usually given at lower dosages to provide sim-

ilar medical treatment efficacy and fewer adverse effects. Similar systemic effect doses for alendronate, risedronate, and ibandronate are noted when comparing daily dosages. A higher systemic dose is given as the time between doses is increased. This can be noted when comparing the increased weekly dose of alendronate or risedronate to the respective daily dose. The 150-mg monthly dose of ibandronate is given at twice the expected oral dose from a simple calculation of the daily dose multiplied by 30 days. A larger monthly dose is needed for effectiveness, probably due to ibandronate's lower bone affinity that allows the active drug on the bone surface to leave more rapidly and be eliminated. Although this article discusses the entire BP drug group, the severity of adverse dental effects might be different for each BP type based on differences in systemic effective dose, bone affinity, and other inherent characteristics.

Table II. Comparisons of BP types used for osteoporosis treatment

Types ^{1,10,11,43}	Potency ^{13,17,41}	Dose (interval) ^{1,10,11,43}	Systemic absorption ^{13,17}	Relative systemic effect per dose*
Oral treatment for osteoporosis				
Alendronate (Fosamax)	700	10 mg (daily)	0.6%	1
		70 mg (weekly)	0.6%	7
Risedronate (Actonel)	2,000	5 mg (daily)	0.6%	1.4
		35 mg (weekly)	0.6%	10
Ibandronate (Boniva)	4,000	2.5 mg (daily)	0.6%	1.4
		150 mg (monthly)	0.6%	90
Intravenous treatment for osteoporosis				
Ibandronate (Boniva)	4,000	3 mg (3 months)	100%	286
Zoledronic acid (Reclast)	10,000	5 mg (12 months)	100%	1190

Higher systemic effect dose is given as dosage interval increased.

*Potency x dose x systemic absorption and compared to alendronate as 1.

BP HAS FAST AND SLOW ELIMINATION RATES FROM BONE

The bone elimination half-lives for BP have been reported over an extremely wide range from several days for ibandronate to over 10 years for alendronate.^{13,17} However, the different methodologies of the elimination studies are often overlooked. The BP drug group appears to have 2 bone elimination rates: fast and slow.^{13,17,37,42}

The short BP half-life was documented by short-term blood studies of ibandronate (37-157 hours), zoledronic acid (146 hours), and risedronate (224-561 hours).^{11,13,43,44} Alendronate was observed to have a similar short half-life when compared with risedronate over a 30-day period.⁴² The documented short half-lives for the BP types provide additional information for the entire drug group regarding bone surface elimination. By pharmacokinetic principle, drug concentration would be estimated to decrease 94% after the drug is discontinued for a time period of 4 half-lives.⁴⁵ Most active BP, that is on the bone surface, should be eliminated rapidly after the drug is stopped for a period of 4 half-lives. A biphasic bone elimination of alendronate was reported in rats with approximately 40% of the drug leaving in 30 days, and the rest leaving at a much slower rate.⁸ The blood concentration decreased rapidly and could not be accurately measured 30 days after drug discontinuation. A biphasic bone elimination rate was also established for osteoporosis patients taking alendronate.⁴⁶ Forty percent of alendronate bound to the skeleton was rapidly excreted in the urine during a 3-month period. The rapid elimination rate was interpreted to be alendronate leaving the bone surfaces before bone incorporation. The rest of the alendronate was estimated to be slowly excreted over decades after bone incorporation. Therefore, stopping oral BP for 3 months would appear to decrease the active drug to a minimum level on the bone surface and in the blood.

A long BP half-life was documented by long-term urine collections of alendronate and pamidronate.^{13,47}

It is believed that the BP drug group, once incorporated in the bone as an inactive drug, would be released slowly as an active drug during normal bone repair.^{8,9,19}

Since the active drug release would slow bone turnover, it would also slow its own elimination from the bone. This could explain the estimated long drug elimination half-life of more than 10 years.⁴⁸ The BP, incorporated into the bone, continued to decrease skeletal fractures for 5 years after drug discontinuation.²³ Orthodontic treatment, as teeth are moved into the BP incorporated bone, might be adversely affected years after the drug is stopped.

OSTEONECROSIS OCCURS RARELY AND MIGHT BE PREVENTABLE

During oral BP treatment for osteoporosis, osteonecrosis has been noted rarely and is usually treatable. The length of continuous oral BP use and type of dental procedure are important to note. Most osteonecrosis cases were discovered in patients who had taken oral BP continuously for more than 3 years and had extractions.³³ Other factors that increase osteonecrosis risk might be diabetes, periodontal disease, glucocorticoids, alcohol, and smoking. No large prospective study has carefully evaluated the incidence of osteonecrosis after long-term continuous oral BP treatment for osteoporosis. Osteonecrosis incidence was first reported: 0.7 cases per 100,000 patient years of drug exposure.⁴⁹ Some investigators suggested that this incidence was underreported.^{26,50,51} Recent reports suggested that the osteonecrosis incidence of approximately 1:5000 occurs after 2 to 3 years of continuous oral BP use with increased incidence after extractions, as shown in **Table III**. In a large Australian survey of patients taking weekly oral alendronate for more than 2 years, an osteonecrosis

Table III. Osteonecrosis incidence and prevention during oral BP treatment for osteoporosis

<u>Osteonecrosis incidence^{50,51} (after 2-3 years continuous oral BP use)</u>	
<u>No drug holiday</u>	<u>Drug holiday</u>
Usually rare, extractions may dramatically increase incidence Higher risk with glucocorticoid use, diabetes, PDL radiographic changes	Decreased drug: PDL bone surface and blood Less risk of osteonecrosis, Optimized bone healing
<u>Osteonecrosis prevention (AAOMS guidelines)³²</u>	
(continuous BP more than 3 years or less than 3 years with glucocorticoid use)	
<u>Drug holiday 3 months before and 3 months after elective dental alveolar surgery</u>	
Any drug holiday must be done with the knowledge and consent of the prescribing physician If drug holiday not authorized: osteonecrosis risk explained, usually treated successfully if occurs No drug holiday needed for routine root canals, root scaling, or restorative procedures ⁴⁹	

incidence of 1:2300 to 1:8500 was reported; it increased up to 1:300 when extractions were performed.⁵⁰ A retrospective institutional study reported osteonecrosis from oral bisphosphonates occurred frequently after extractions, with a high incidence of 1:20.⁵¹ This study also reported that no osteonecrosis was found after 4384 extractions in patients never using oral bisphosphonates. Osteonecrosis has been successfully treated with necrotic bone removal and bone grafting after an oral drug holiday of 6 months, with the drug restarted 3 months after the surgery.^{26,32} Chlorhexidine 0.12% rinses and appropriate antibiotics were used to help control secondary infections.

The American Association of Oral Maxillofacial Surgeons (AAOMS) recommends osteonecrosis prevention through a drug holiday if oral BP has been taken continuously for more than 3 years or less than 3 years with glucocorticoids, such as prednisone, as shown in Table III.³² After physician approval, a drug holiday is requested 3 months before and 3 months after elective dental surgery. The AAOMS recommendations for osteonecrosis prevention were based on successful treatment of BP-induced osteonecrosis in osteoporosis patients after an oral drug holiday. A drug holiday is not needed before routine root canal treatment, root scaling, or tooth restorative procedures.⁴⁹ A study of 98 published cases of oral BP-induced osteonecrosis found that 50% of the patients were concurrently taking glucocorticoids, which might be a contributing factor.⁵² Long-term glucocorticoids are used to treat chronic inflammatory conditions and might chemically induce osteoporosis, which is commonly treated with oral BP.⁵³ Glucocorticoids directly decrease osteoblastic activity and increase the oral absorption of alendronate by 20% to 44%.^{48,53}

Most BP-induced necroses commonly seem to involve the bone surrounding the teeth with later progression into the alveolar bone in the jaws.²⁶ BP might also

inhibit normal vascularization at high concentrations found in bone.⁵⁴ These reports support a theory that greater adverse effects of BP occur in areas of high bone repair. An exaggerated cycle of the active BP being bound and released might decrease cellular bone function more in high bone-turnover areas than in low areas.²⁵ Nontooth-bearing areas having lower bone turnover might explain why prospective and retrospective studies of implant placements have not reported adverse effects from oral BP use.^{55,56} However, caution is needed, since implant failures have been reported after long oral BP use.^{26,57,58} Dental procedures that involve the bone around the teeth, such as extractions, periodontal surgery, and tooth movement, appear to be more susceptible to adverse BP effects and are commonly included in orthodontic treatment plans.

ADVERSE EFFECTS OF INTRAVENOUS BP

The osteonecrosis incidence after long-term BP given intravenously for osteoporosis treatment is unknown but presumed to be rare. In a 3-year, double-blind study, 3889 women were given 5 mg of zoledronic acid yearly for osteoporosis intravenously and 3876 were given a placebo. Two osteonecrosis cases were found and treated successfully. One osteonecrosis patient was found with zoledronic acid treatment and the other with a placebo.⁵⁹ The study's methodology contained no routine dental screenings and no comments about prior BP use for the placebo patient. The osteonecrosis incidence might have increased if the study had been longer than 3 years, since almost all osteonecrosis cases from oral BP were noted after 3 years of continuous use.³³ Although the systemic effect per dose is much higher from intravenous when compared with oral usage, the time interval between doses is longer (Table II). The long dosage interval

should result in a low active drug level retained on the bone surfaces and allow a more normal cellular function to return between doses. Until 5- to 10-year studies with routine dental screenings are performed, both intravenous and oral BP used for osteoporosis treatment are presumed to have similar rare occurrences of osteonecrosis.

Orthodontists should proceed with caution regarding decreased tooth movement and bone formation after intermittent intravenous BP administration for osteoporosis with ibandronate (Boniva) and zoledronic acid (Reclast). Ibandronate is more frequently administered probably because of lower bone affinity and effective systemic dose than zoledronic acid (Tables I and II). Higher effective systemic doses noted from intravenous than from oral administration could greatly inhibit tooth movement (Table II). During orthodontic treatment, concurrent intravenous BP could highly elevate the bone surface levels around teeth and lead to more drug incorporation. This might limit present and future tooth movement more rapidly and profoundly. Ibandronate at the 3-mg dose given intravenously every 3 months and perhaps the monthly 150-mg oral dose would lead to higher initial bone surface levels that might remain elevated enough to slow tooth movement until the next dose is given. Zoledronic acid, at a 5-mg dose intravenously every 12 months, should immediately increase the lamina dura surface level but decrease 3 months after the initial dose. Intuitively, a limited orthodontic treatment plan might be successful if started 3 to 6 months after the previous dose and finished before the next dose is given. Since 1 dose of zoledronic acid sustains a 12-month reduction of bone turnover, it is uncertain how much tooth movement or bone healing would occur between doses. A small amount of a highly potent BP, remaining on the bone surface or released from the bone could be enough to interfere with orthodontic treatment.

RADIOGRAPHIC CHANGES: SIGN OF DECREASED BONE FUNCTION DURING BP USE

A radiographic hyper-mineralized area might signify osteoclastic activity that has been dramatically decreased from BP use.²⁶ The sclerotic areas might not have enough osteoclastic activity to remove diseased bone and form proper vascular structures. BP slows bone formation, but mineralization is unaffected.^{19,21} Sclerosis was reported as a beginning BP toxicity in alveolar bone before osteonecrosis.^{26,33,60} Sclerotic bone was observed when no orthodontic tooth movement occurred during BP use.²⁹ The sclerotic areas can appear around teeth or obscure the periodontal liga-



Fig 2. Obscured PDL with sclerosis might signify early BP toxicity. After long-term continuous BP use, osteonecrosis presented on the contralateral side following a molar extraction.

ment (PDL) space.³³ A widened PDL space might be a sign of decreased bone formation before osteonecrosis.²⁶ The lamina dura around the PDL and the PDL space should be closely examined in initial and progress radiographs, especially in the mandibular molar regions. The bone surrounding the mandibular molars might be more susceptible to adverse BP effects because posterior occlusal forces cause higher bone turnover, and the mandible has a lower vascular supply than the maxilla.^{26,27}

After long-term continuous BP use, radiographically obscured PDL space and sclerosis of the lamina dura were noted in the left posterior region, signifying possible local BP toxicity (Fig 2). Osteonecrosis was observed after the extraction of a painful mandibular molar on the contralateral side.

PATIENT 1: COMPROMISED NONEXTRACTION RESULT WITH ORAL BP USE

Oral BP use during orthodontic treatment would sustain a high blood concentration with presumably more active drug bound and incorporated into the bone surrounding teeth. Progressively slower tooth movement could occur with continued BP administration. Slow tooth movement can continue years after stopping the drug.

A 60-year-old woman, completing nonextraction, nonsurgical orthodontic treatment that lasted 4.5 years with compromised results, requested a second opinion (Fig 3). Her concerns were uneven posterior occlusion, heavy occlusal contact on anterior bridge, minor posterior spacing, slow tooth movement, long treatment time, and reports of BP inducing osteonecrosis. Before her orthodontic treatment, she had a significant right posterior open bite and used alendronate for osteoporosis for 18 months. No signs or symptoms of osteonecrosis were apparent from a clinical exam or history. The beginning panoramic radiograph showed mild sclerosis within normal limits on the mandibular right second molar,

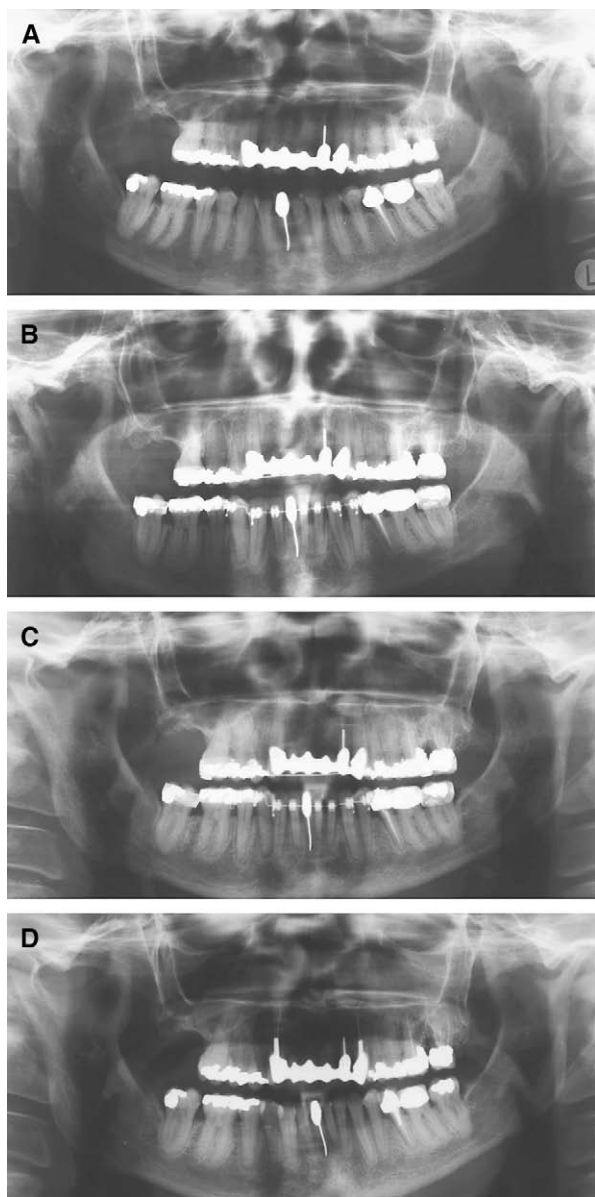


Fig 3. Patient 1: 60-year-old woman requested a second opinion after compromised nonextraction result with concurrent BP use. **A**, Initial panoramic radiograph shows periodontal bone loss between the maxillary left first and second molars and a small left condyle. Prior continuous BP use of 18 months. Sclerosis in mandibular region is within normal limits. **B**, Profound sclerotic areas (greater in the mandible) surrounding the PDL and widened PDL spaces are present after 2 years of orthodontic treatment and concurrent BP use (3.5 years total). **C**, Diffuse sclerosis and widened PDL spaces are present after 3.5 years of orthodontic treatment. BP was discontinued 18 months earlier. **D**, Diffuse sclerosis and widened PDL spaces are noted after 4.5 years of orthodontic treatment. Decreased movement was noted after BP was discontinued 2.5 years ago.

a small left condyle, and a periodontal defect between the maxillary left first and second molars (Fig 3, A). After 2 years of orthodontic treatment and concurrent alendronate use, pronounced sclerotic bone around the teeth and widened PDL spaces were observed, especially in the mandible (Fig 3, B). The physician, unaware of the changed radiographic signs, stopped alendronate and started teriparatide treatment to achieve higher bone density for her osteoporosis treatment. After 3.5 years of orthodontic treatment, widened PDL spaces and diffuse sclerotic areas were present (Fig 3, C). After 4.5 years of orthodontic treatment, diffuse sclerosis and widened PDL spaces were present after alendronate was stopped for 2.5 years (Fig 3, D). Orthodontic treatment was discontinued by the orthodontist because of decreased tooth movement and fear of osteonecrosis. No root resorption was noted when comparing the initial and final periapical radiographs.

PATIENT 2: COMPROMISED EXTRACTION RESULT WITH CONCURRENT ORAL BP

During orthodontic extraction treatment, BP could incorporate in the extraction site and around the teeth being moved. Root translation into the extraction site might be slowed after stopping the drug. Decreased bone formation and excessive tooth mobility can occur.

A 50-year-old woman came with a Class II (3 mm left molar) malocclusion, 3 missing first premolars, moderate mandibular incisor crowding, lower midline to the right, periodontal bone loss, and no tooth mobility (Fig 4). After periodontal treatment, comprehensive orthodontic treatment was started with extraction of the remaining mandibular left first premolar. Orthodontic space closure was extremely slow. The patient had started taking alendronate approximately 6 months before the extraction and stopped 12 months later because of esophagitis, a common adverse side effect.⁹ She did not report alendronate use in her medical history because she did not believe it was an orthodontic concern. Space closure was difficult, and divergent roots were noted in the extraction site (Fig 4, B). Less inhibition of tooth movement was noted after the alendronate was discontinued for 6 months. The orthodontic appliances were repositioned to obtain parallel roots. After 7 months, little root movement occurred and a hyper-mineralized area was observed within the extraction site (Fig 4, C and D). Alendronate use had been stopped for 13 months. Excessive mobility and widened PDL spaces were noted. No traumatic occlusion or change in periodontal status was present. Orthodontic movement of the incisors

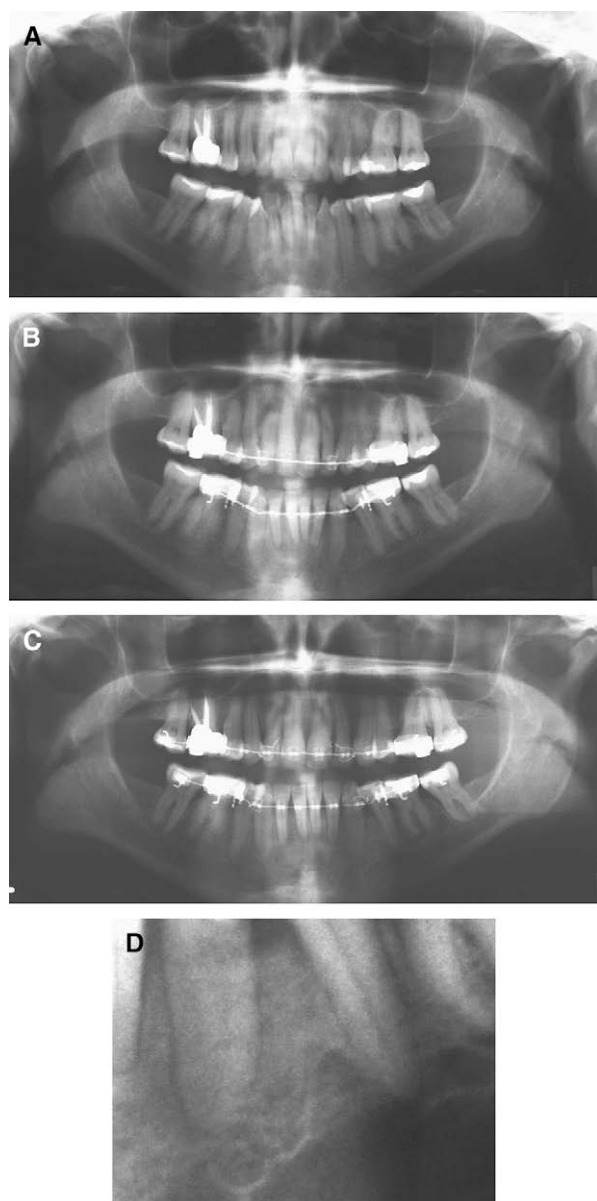


Fig 4. Patient 2: compromised extraction result with concurrent oral BP therapy. **A**, Initial panoramic radiograph of 50-year-old woman. BP use started 6 months prior to extraction of left mandibular bicuspid and orthodontic treatment. **B**, Slow space closure and divergent roots are noted in extraction site at 12 months of treatment. Mandibular incisors had excessive mobility, increased PDL spaces and decreased movement. BP was discontinued 6 months prior (12 months total use). **C**, Nonparallel roots in extraction site after brace repositioning (7 months prior) is noted at 19 months of treatment. Incisor mobility and increased PDL spaces still present. **D**, Sclerotic area is noted within the extraction site at 19 months of treatment.

was difficult, even though there was mobility. Slow tooth movement, mandibular incisor mobility, and compromised parallel roots were observed throughout the orthodontic treatment.

PATIENT 3: OPTIMIZED EXTRACTION RESULT WITH AN ORAL BP HOLIDAY

After stopping oral BP for 3 months, a minimum active drug level should be present on bone surfaces and in the blood. A BP holiday throughout orthodontic treatment should sustain a low drug level with less drug incorporation into the bone surrounding the teeth.

A 74-year-old woman presented with a Class I occlusion, severe periodontal bone loss, routine periodontal maintenance, severe mandibular incisor crowding, and a recently fractured mandibular left central incisor that was clinically unrestorable (Fig 5). She had been taking oral alendronate continuously for 3 years. Her intraoral examination was normal, without tooth pain or exposed necrotic bone. An orthodontic treatment plan was requested before further dental treatment. The beginning occlusal photograph showed the fractured incisor temporarily bonded (Fig 5, A). The initial panoramic radiograph showed mild sclerosis around the mandibular molars (Fig 5, B). The furcal radiolucency of the mandibular right first molar was under periodontal observation and present before alendronate use. The initial mandibular anterior periapical radiographs showed obscured PDL spaces (Fig 5, C). Continuous alendronate use for 3 years and the obscured PDL were interpreted as possible decreased bone function. An osteonecrosis risk was noted for the planned incisor extraction. Since there were no signs of infection, immediate extraction was thought to be unnecessary. An immediate temporary root canal was deemed unnecessary because of the obliterated root canal. The physician stopped the alendronate for 3 months before the incisor extraction according to the AAOMS oral BP prevention guidelines (Table III). The physician decided that the bone density goal was reached, and no increased patient morbidity was expected during the extended drug holiday throughout orthodontic treatment. After evaluation of the orthodontic records, limited braces were placed between the mandibular first premolars after consideration of a functional posterior occlusion, severe periodontal bone loss, age, and the patient's request not to treat the maxillary incisors. The limited orthodontic treatment was successful with normal extraction healing, space closure, and acceptable parallel roots within 14 months. Acceptable parallel roots, although not ideal, were somewhat slow to

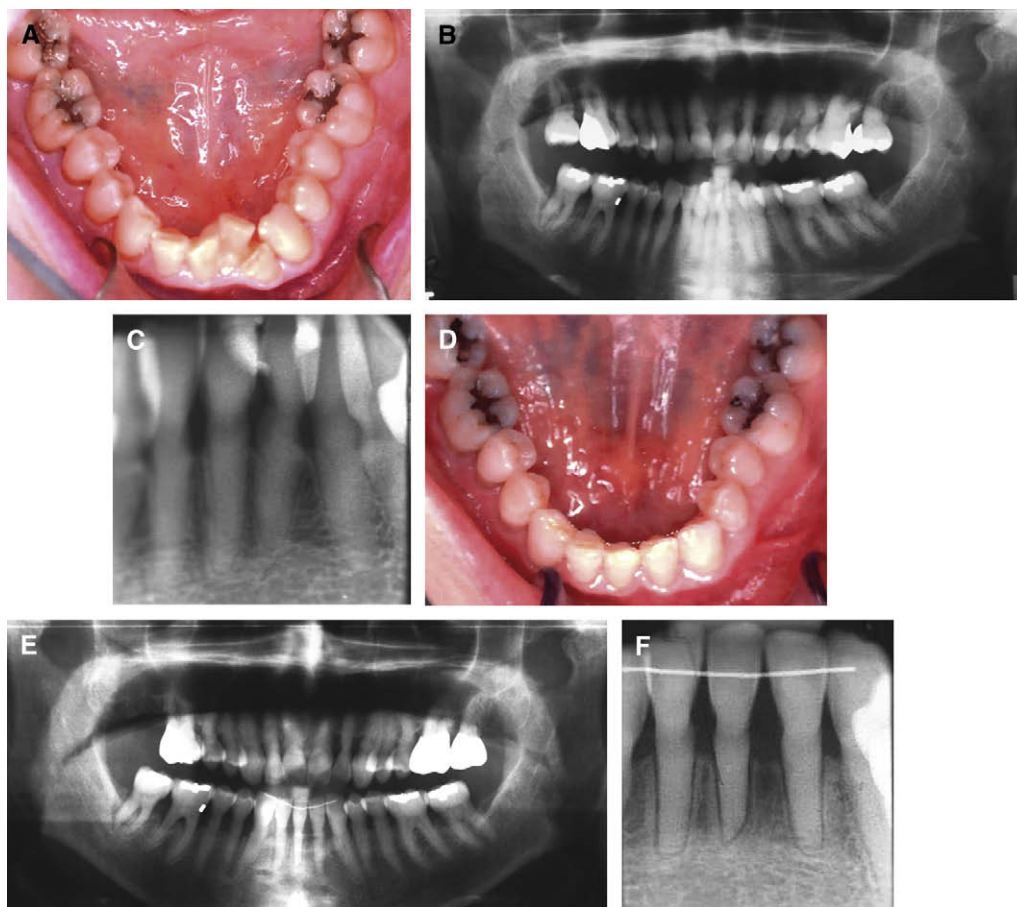


Fig 5. Patient 3: optimized extraction result with an oral BP holiday. **A**, Initial mandibular occlusal photograph shows the fractured unrestorable left central incisor. **B**, Initial panoramic radiograph shows mild sclerosis and severe periodontal bone loss. Patient had taken alendronate for 3 years. **C**, Initial mandibular incisor periapical radiograph. Obscured PDL is a possible sign of decreased bone function; the obliterated root canals are from age. **D**, Final occlusal photograph. The patient's physician authorized a drug holiday 3 months before and during orthodontic treatment. **E**, Final panoramic radiograph shows no sclerotic changes and acceptable parallel roots. This limited extraction treatment was successful in 14 months. **F**, Final lower incisor periapical radiograph shows PDL spaces and sclerosis within normal limits. Mild root resorption is noted.

obtain. The final photograph showed successful alignment and space closure (Fig 5, D). Debonding of the fixed retainer was noted and repaired. The final panoramic radiograph showed no sclerotic changes, PDL spaces within normal limits, and mild root resorption on lower central incisor (Fig 5, E). The final mandibular incisor periapical radiographs showed mild sclerosis and PDL spaces. No mobility was noted on the mandibular incisors. Mild root resorption was noted on the mandibular incisors. The patient was pleased with the limited extraction treatment result after prior counseling about possible adverse effects. The alendronate

was planned to be restarted by the physician after the orthodontic treatment with no expected adverse dental effects. A bonded retainer was used, although BP has been reported to help decrease orthodontic relapse.²⁸ The general dentist and the periodontist were asked to monitor for future radiographic signs after 3 years of continued alendronate use.

DISCUSSION

The orthodontic treatment in patient 1 could have been stopped at 2 years after excessive sclerosis was

noted around the PDL, since little tooth movement would be anticipated (Fig 3, B). An osteonecrosis risk was present after 3 years of continuous alendronate use and a changed radiographic sign denoting possible local drug toxicity. Higher osteonecrosis risk and less bone healing would be expected if extractions or periodontal surgery had been performed.²⁶ This was important, since a periodontal defect was noted between the left first and second molars. After alendronate was stopped for 3 to 6 months, the osteonecrosis risk should have decreased closer to a normal range.^{26,32} After the BP is stopped for 3-6 months, a consideration to continue orthodontics can be made if clinical and radiographic signs begin to decrease. The length of orthodontic continuation is a clinical judgement based on the occlusal improvement that can be achieved. Minor tooth movement can usually be accomplished, however major tooth movement might be slowed for years without normal bone healing, especially if sclerosis is still present (Fig 3, C and D). Ideally, initiating orthodontic treatment in patient 1 could have been delayed until 3 months after the physician discontinued the alendronate and chose an alternate osteoporosis treatment, teriparatide. Teriparatide, a recombinant parathyroid hormone, causes more bone formation by increasing osteoblastic activity. Animal experiments have shown that parathyroid hormone reverses BP depression of osteoclastic activity.⁶¹ Teriparatide was used to treat a rare osteonecrosis case that did not heal after a 6-month oral BP holiday.⁶² Since teriparatide increases osteoclastic activity, the osteonecrosis risk should decrease, and orthodontic tooth movement should increase. In this case, tooth movement continued to be inhibited from excessive bone incorporation of BP during the concurrent drug use with orthodontic treatment. Although the sclerosis appeared to be decreasing, it was observable years after the alendronate was stopped (Fig 3, C and D). Sclerosis might have a variable duration, since, in another patient, the sclerosis disappeared within a year after the alendronate was stopped.²⁹

Concurrent BP use during orthodontic extractions allows the drug to integrate into the healing bone. Extraction site closure would cause active BP release from bone resorption, decrease osteoclastic function, and inhibit further tooth movement. The incorporated BP might stay in the extraction site for years after drug is discontinued and continue to slow tooth movement. Slow tooth movement and nonparallel roots in the extraction site with concurrent BP use has been reported.²⁹ Hyper-mineralized lines were observed after tooth extractions with concurrent BP use.^{26,60} Hyper-mineralized brittle bones were found in children given long-term BP.⁶³ In patient 2, the hyper-mineralized ex-

traction site might signify decreased bone formation from BP that was not sufficient to affect healing (Fig 4, D). Inhibited movement, excessive mobility, and increased PDL spaces were noted during and after space closure. The BP, bound and incorporated into bone, could have decreased bone formation and inhibited new tooth movement even after the drug was stopped. A 95% decrease in bone formation was reported after alendronate use.²⁴ Widened PDL spaces were noted as a possible local sign of BP toxicity.²⁶ Subnormal bone formation, a decrease of 75% to 95%, would presumably occur sooner and more frequently than an end-stage necrosis or no bone formation. Detection of early warning signs can be beneficial to provide better orthodontic care and prevent end-stage pathology in patients taking oral BP.

A drug holiday was used in patient 3 to decrease the osteonecrosis risk before extraction. If the physician had decided not to stop the alendronate, the oral surgeon would have informed the patient of the osteonecrosis risk. Without a drug holiday, compromised extraction space closure would have been expected. In this case, the extraction site was closed satisfactorily. Orthodontic treatment was optimized by sustaining minimum BP concentrations on the bone surface and in blood. Mild root resorption was noted after orthodontic treatment. BP has been shown to decrease root resorption.⁶⁴ Since the active drug on the bone surface would decrease after a drug holiday, the pharmacological protection against root resorption should also decrease. Even though a drug holiday might optimize orthodontic treatment, tooth movement still might not be ideal with extended oral BP use. Longer use will cause more BP to incorporate in trabecular bone and remain for many years. Slow drug release from the skeleton into the bloodstream would allow more BP to bind during tooth movement. Drug accumulation can be significant in patients who have been taking oral BP for long periods. It has been estimated that 25% of a daily dose is released from the skeleton daily after 10 years of continuous oral administration.¹ BP might also decrease the activity of osteoclastic progenitor cells that could contribute to long-term adverse effects.^{16,65} Research is needed to understand the long-term adverse effects of BP in orthodontics.

An orthodontic screening should ask about prior BP use. A detailed history is needed to establish the specific oral or intravenous BP preparations, the duration of use, and the medical purpose of treatment (osteopenia, osteoporosis, or severe osteoporosis with prior fragility fractures). Patients with severe osteoporosis might have a greater skeletal fracture risk during a drug holiday. A notation should be made of any patient given

Table IV. Suggested orthodontic optimization guidelines during BP treatment for osteoporosis

*Drug holiday 3 months before and during orthodontic tooth movement
(decreases and maintains low active drug level: blood and PDL bone surfaces)*

<u>No drug holiday</u>	<u>Orthodontic risks</u>	<u>Drug holiday</u>
Progressively slower tooth movement More tooth mobility Teeth less likely to move in future		Closer to normal range
<u>Orthodontic treatment suggestions</u>		
Consider: delay until drug stopped or alternative drug Consider: limited, nonextraction cases with caution BP effect accumulates with continued use BP bone incorporation might limit future movement		Optimized treatment (especially extraction cases) Long prior BP use might slow tooth movement after holiday
<u>Monitoring signs: BP decreased bone function</u>		
Clinical signs: slow movement, excessive mobility Radiographic signs: sclerosis around teeth, obscured PDL, or excessive PDL space (Rule out trauma, infection, periodontal causes, and normal bone variations) If signs present, consider careful monitoring, drug holiday, and delay or discontinue orthodontics		
The suggested guidelines do not guarantee ideal results but are meant to lessen nonideal results with sound orthodontic treatment plans and continuous monitoring for adverse effects. Drug holiday must be done with the knowledge and consent of the prescribing physician		

intravenous BP (zoledronic acid or pamidronate) for cancer treatment, since orthodontic or elective dental surgery should be contraindicated, and drug holidays do not apply.^{25,27,33} Intravenous zoledronic acid is used to treat both osteoporosis and cancer patients by changing the time intervals between doses. Zoledronic acid (Reclast), 5 mg intravenously, is given every 12 months for osteoporosis treatment.¹¹ Zoledronic acid (Zometa), 4 mg intravenously, is given every 3 to 4 weeks for bone cancer treatment.¹ Bone cancer treatment requires frequent administration of zoledronic acid to sustain high surface bone levels to limit the cancer's detrimental effect on skeletal bones.

The suggested guidelines, shown in Table IV, are to optimize orthodontic treatment through appropriate drug holidays and monitor adverse dental effects during oral BP treatment of osteoporosis. The guidelines do not guarantee ideal orthodontic results but should lessen nonideal results and minimize adverse effects with sound clinical treatment plans and continued patient monitoring. The guidelines are not meant to be the standard of care and should be reevaluated as future studies dictate. The orthodontist should have the patient read and sign the American Association of Orthodontists' informed consent for BP before orthodontic treatment. Changing clinical and radiographic signs should be carefully monitored especially prior to a drug holiday, since they might suggest decreased alveolar bone function and early local drug toxicity. If positive signs occur, orthodontic treat-

ment might need to be discontinued, even if treatment goals are not achieved. Clinical monitoring should include changes in decreased movement and increased mobility. Radiographic monitoring should include changes of sclerotic or radiolucent bone surrounding teeth. Radiographic changes can be caused by other pathologies, such as infection, prior accidents, periodontal disease, or occlusal trauma. Careful evaluation of trabecular variations, lamina dura, and PDL space in routine orthodontic patients will give proper comparisons of radiographic changes caused by BP use. AAOMS osteonecrosis prevention should be considered for any extraction or periodontal surgery planned in an area of decreased bone function. After 2 to 3 years of oral BP administration, the differential diagnosis of tooth pain should include osteonecrosis. If routine dental procedures, such as root canal therapy or periodontal scaling, do not relieve symptoms, then osteonecrosis should be considered strongly in the differential diagnosis.⁴⁹ The orthodontist should not act unilaterally if any adverse drug effects are observed. The physician should be informed of any changed clinical or radiographic signs that indicate a BP drug holiday may be of value to help orthodontic treatment or decrease osteonecrosis risk.

Radiographic signs are not diagnostic for osteonecrosis but can suggest a higher risk. The clinical osteonecrosis definition, requiring tissue exposure of necrotic bone, might be a late diagnosis. Osteonecrosis has been reported before clinical signs of exposed

necrotic bone.⁶⁶ Magnetic resonance imaging (MRI) has shown all BP-induced osteonecrosis lesions before they were clinically present.⁶⁷ MRI found all necrotic bone lesions from other causes better than bone scans or computerized tomography when compared with histologic diagnosis in the hip, knee, ankle, and shoulder.⁶⁸ MRI should be considered for early recognition of osteonecrosis in the alveolar bone. MRI might have significant value, since histologic diagnosis cannot be made in a suspected BP-induced osteonecrosis for fear of worsening the situation.

The successful clinical outcome of osteonecrosis treatment from oral BP has been reported to be related to a serum C telopeptide level (CTX) level when it is greater than 150 ng per milliliter.⁶⁹ The CTX level, a systemic osteoclastic bone marker, is obtained from a fasting, early-morning blood draw. The use of the CTX is controversial, since it measures systemic osteoclastic activity from the entire skeleton and does not specifically measure the local osteoclastic function in the alveolar bone. However, the CTX level might be a sensitive measure of altered bone function caused from the active drug residing on the bone surfaces. Although controversial, the CTX level can be considered after a 3- to 6-month drug holiday to confirm that systemic osteoclastic function is normal before major dental surgical procedures when BP was taken continuously for more than 5 years.

Ideally, the orthodontist should contact the prescribing physician to discuss the planned orthodontic procedure, expected risks, and possible optimization with a drug holiday. Optimizing orthodontic treatment after BP use has different requirements than osteonecrosis prevention (Tables III and IV). Two bone elimination rates have been reported for the BP drug group. A 3-month drug holiday should lower the active drug concentration in the blood and on the bone surfaces around the teeth to lower the risk of osteonecrosis. An extended BP holiday during orthodontic treatment should sustain low active drug levels, lessen drug incorporation surrounding teeth, and optimize tooth movement and bone healing. During tooth movement, bone turnover will slowly release any previously incorporated inactive drug as an active drug. BP incorporated in the bone, which can remain for many years, should be minimized in areas where teeth are planned to be moved.

The patient's treatment goal for osteoporosis might have been reached, and the physician could decide that no further oral BP is needed during orthodontic treatment. A randomized, double-blind, multicenter study of 6459 patients concluded that there was no difference in the 10-year fracture rate comparing a group taking alendronate for 5 years with another group taking the drug continuously for 10 years.²³ However, it was

concluded that high-risk vertebral fracture patients can benefit from longer 10-year treatment.

An alternate osteoporosis treatment can be started by the physician because the treatment goal has not been reached. It is the physician's responsibility to suggest alternative osteoporosis treatments, even though alternate medications might have fewer adverse dental effects. Alternate treatments such as raloxifene, a selective estrogen receptor modulator, and estrogen both have short half-lives with no bone accumulation, and should affect tooth movement less than BP. However, alternate drugs could be less effective for osteoporosis. Treatment alternatives can also have a greater incidence of serious adverse medical effects.⁷ Estrogen can increase the risk of breast cancer, deep venous thrombosis, and stroke. Raloxifene might increase the risk of deep venous thrombosis and stroke. Teriparatide is an effective treatment for vertebral osteoporosis with shortcomings of high expense, daily subcutaneous injections, duration of treatment not to exceed 2 years, and another osteoporosis medication needed after 2 years to retain the increased bone density.⁵

It is not appropriate for all patients to have a BP holiday, and the physician might decide that the fracture risk is too high. The orthodontist can consider not treating or delaying treatment, especially in elective extraction patients, until the BP can be stopped or an alternative medication is appropriate. A consideration to treat limited, nonextraction patients could be made with the following precautions. Concurrent BP use might cause drug accumulation and progressively slower tooth movement. Slow tooth movement can continue for years after the drug is discontinued. Orthodontic treatment might have to be discontinued before the treatment goals have been accomplished. No patient should stop oral BP medication without the knowledge and consent of the primary prescribing physician because bone density might not have risen sufficiently to prevent hip and vertebral fractures. Orthodontists should understand that prevention of hip or vertebral fractures takes priority over an elective orthodontic procedure. Physicians should understand that the patient's desired orthodontic result might not be achieved if BP is continued, especially if the medication is not currently beneficial. After discussing the medical and orthodontic risks and benefits, a mutual decision can be made in the patient's best interest.

CONCLUSIONS

This article was written to begin parameters to minimize adverse effects and optimize orthodontic treatment in the millions of patients taking oral BP for

osteoporosis. Orthodontists clearly need to understand the pharmacology and adverse effects of this unique drug group to evaluate early warning signs of decreased bone function before progression to necrosis. Tooth movement, tooth mobility, and radiographic changes of the lamina dura and the PDL spaces need to be evaluated and monitored in patients taking oral BP. This drug group has many medical benefits, and the increased orthodontic risks might be small compared with the increased medical risks if the medication is stopped. No patient should discontinue BP without the knowledge and consent of the primary prescribing physician. Osteonecrosis occurs rarely during BP treatment for osteoporosis, and the AAOMS guidelines for osteonecrosis prevention and treatment should be reviewed. Ideally, the orthodontist and the physician should discuss the patient's risks and benefits of BP treatment according to the severity of the osteoporosis, the projected risks to orthodontic procedures, and the appropriateness of a drug holiday to optimize orthodontic treatment and minimize adverse dental effects.

REFERENCES

1. Burnham TH, Wickersham RM, editors. Drug facts and comparisons. 57th ed. St Louis: Wolter Kluwer; 2003. p. 336-49.
2. Ukens C. The top 200 brand drugs in 2005. *Drug Topics* 2006;150:25.
3. Lindsay R, Cosman F. Osteoporosis. In: Braunwald E, Hauser SL, Fauci AS, Longo DL, Kasper DL, Jameson JL, editors. *Harrison's principles of internal medicine*. 15th ed. New York: McGraw-Hill; 2001. p. 2226-36.
4. Raisz LG. The osteoporosis revolution. *Ann Intern Med* 1997;126:458-62.
5. Rosen C. Postmenopausal osteoporosis. *N Engl J Med* 2005;353:595-603.
6. Raisz LG. Screening for osteoporosis. *N Engl J Med* 2005;353:164-71.
7. Khosla S, Melton LJ. Osteopenia. *N Engl J Med* 2007;356:2293-300.
8. Lin JH, Russell G, Gertz B. Pharmacokinetics of alendronate: an overview. *Int J Clin Pract* 1999;101(Suppl):18-26.
9. Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin North Am* 1998;27:419-39.
10. Prescribing information for Boniva, ibandronate intravenous. Nutley, NJ: Roche Therapeutics; February 2007.
11. Prescribing information for Reclast, zoledronic acid intravenous. East Hanover, NJ: Novartis Pharmaceuticals; August 2007.
12. Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, et al. Cellular and molecular mechanisms of action of bisphosphonates. *Cancer* 2000;88(12 Suppl):2961-78.
13. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005;39:668-77.
14. Masarachia P, Weinreb M, Balena R, Rodan GA. Comparison of the distribution of 3H-alendronate and 3H-etidronate in rat and mouse bones. *Bone* 1996;19:281-90.
15. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* 2003;9:2643-58.
16. Van Beek ER, Lowik CWGM, Papapoulos SE. Bisphosphonates suppress bone resorption by a direct effect on early osteoclast precursors without affecting the osteoclastogenic capacity of osteogenic cells: the role of protein geranylgeranylation in the action of nitrogen-containing bisphosphonates or osteoclast precursors. *Bone* 2002;30:64-70.
17. Lin JH. Bisphosphonates: a review of the pharmacokinetic properties. *Bone* 1996;18:75-85.
18. Dixon RB, Tricker ND, Garetto LP. Bone turnover in elderly canine mandible and tibia. *J Dent Res* 1997;76:336 (IADR abstract 2579).
19. Rodan G, Reszka A, Golub E, Rizzoli R. Bone safety of long-term bisphosphonate treatment. *Curr Med Res Opin* 2004;20:1291-300.
20. Rocha ML, Malacara JM, Sanchez-Marin FJ, Vazquez de la Torre CJ, Fajardo ME. Effect of alendronate on periodontal disease in postmenopausal women: a randomized placebo-controlled trial. *J Periodontol* 2004;75:1579-85.
21. Meunier PJ, Arlot M, Chavassieux P, Yates J. The effects of alendronate on bone turnover and bone quality. *Int J Clin Pract* 1999;101(Suppl):14-7.
22. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT research group. *J Clin Endocrinol Metab* 2000;85:4118-24.
23. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA. Effects of continuing or stopping alendronate after 5 years of treatment. *J Am Med Assoc* 2006;296:2927-38.
24. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005;90:1294-301.
25. Zahrowski JJ. Bisphosphonate treatment: an orthodontic concern calling for a proactive approach. *Am J Orthod Dentofacial Orthop* 2007;131:313-22.
26. Marx RE. Oral and intravenous bisphosphonate-induced osteonecrosis of the jaws. Hanover Park, Illinois: Quintessence; 2007.
27. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;62:527-34.
28. Igarashi K, Mitani H, Adachi H, Shinoda H. Anchorage and retentive effects of a bisphosphonate (AHBuBP) on tooth movement in rats. *Am J Orthod Dentofacial Orthop* 1994;106:279-89.
29. Rinchuse DJ, Rinchuse DJ, Sosovicka MF, Robison JM, Pendleton R. Orthodontic treatment of patients using bisphosphonates: a report of 2 cases. *Am J Orthod Dentofacial Orthop* 2007;131:321-6.
30. Marx RE. Pamidronate (aredia) and zoledronate (zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
31. Hellstein JW, Marek CL. Bisphosphonate osteochemonecrosis (bis-phossy jaw): is this phossy jaw of the 21st century? *J Oral Maxillofac Surg* 2005;63:682-9.
32. AAOMS position paper. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 2007;65:369-76.
33. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;63:1567-75.
34. Guarneri V, Donati S, Nicolini M, Givannelli S, D'Amico R, Conte PF. Renal safety and efficacy of I.V. bisphosphonates in patients with skeletal metastases treated for up to 10 years. *Oncologist* 2005;10:842-8.

35. Durie B, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates (letter). *New Engl J Med* 2005;353:99-102.
36. Schwarz HC. Bisphosphonate-associated osteonecrosis of jaws. *J Oral Maxillofac Surg* 2005;63:1555-6.
37. Zahrowski JJ. Comment on the American Association of Oral Maxillofacial Surgeons statement on bisphosphonates. *J Oral Maxillofac Surg* 2007;65:1440-1.
38. Woo SB, Hellstein JW, Kalmar JR. Systemic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-61.
39. Lomashvili KA, Cobbs S, Hennigar RA, Hardcastle KI, O'Neill WC. Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. *J Am Soc Nephrol* 2004;15:1392-401.
40. Leu C, Luegmayr E, Freedman LP, Rodan GA, Reszka AA. Relative binding affinities of bisphosphonates for human bone and relationship to antiresorptive efficacy. *Bone* 2006;38:628-36.
41. Muhlbauer RC, Bauss F, Schenk R, Janner M, Bosies E, Strein K, et al. BM21.0955, a potent new bisphosphonate to inhibit bone resorption. *J Bone Miner Res* 1991;6:1003-11.
42. Porras A, Denker A, Santhanagopal A, Daifotis AG. Alendronate and risedronate have similar pharmacokinetic half-lives when analyzed over the same time interval. *J Bone Miner Res* 2003;18(Suppl 2):S371.
43. Prescribing information of Boniva, ibandronate tablets. Nutley, NJ: Roche Therapeutics; August 2006.
44. Prescribing information for Actonel, risedronate tablets. North Norwich, NY: Proctor & Gamble Pharmaceuticals; April 2008.
45. Wilkinson GR. Pharmacokinetics. In: Hardman JG, Limbird LE, editors. *Goodman & Gilman's the pharmacological basis of therapeutics*. 10th ed. New York: McGraw-Hill; 2001. p. 3-29.
46. Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. *J Bone Miner Res* 1997;12:1700-7.
47. Papapoulos SE, Cremers SC. Prolonged bisphosphonate release after treatment in children. *N Engl J Med* 2007;356:1075-6.
48. Prescribing information for Fosamax, alendronate tablets. Whitehouse Station, NJ: Merck; 2006.
49. Edwards BJ, Hellstein JW, Jacobsen PL, Kaltman S, Mariotti A, Migliorati CA. ADA report of the Council on Scientific Affairs: dental management of patients receiving oral bisphosphonate therapy—expert panel recommendations. *J Am Dent Assoc* 2006;137:1144-50.
50. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg* 2007;65:415-23.
51. Sedghizadeh PP, Stanley K, Caligiuri M, Hofkes S, Lowry B, Shuler CF. Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw. *JADA* 2009;140:61-6.
52. Hess LM, Jeter JM, Berham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. *Am J Med* 2008;121:475-83.
53. Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE, editors. *Goodman & Gilman's the pharmacological basis of therapeutics*. 10th ed. New York: McGraw-Hill; 2001. p. 1649-77.
54. Wood J, Bonjean K, Ruetz S. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* 2002;302:1055-61.
55. Fugazzotto PA, Lightfoot WS, Jaffin R, Kumar A. Implant placement with or without simultaneous tooth extraction in patients taking oral bisphosphonates: postoperative healing, early follow-up, and incidence of complications in two private practices. *J Periodontol* 2007;78:1664-9.
56. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants* 2006;21:349-53.
57. Wang HL, Weber D, McCauley LK. Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. *J Periodontol* 2007;78:584-94.
58. Starck WJ, Epker BN. Failure of osseointegrated dental implants after diphosphonate therapy for osteoporosis: a case report. *Int J Oral Maxillofac Implants* 1995;10:74-8.
59. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
60. Markewicz MR, Margaroni JE 3rd, Campbell JH, Aguirre A. Bisphosphonate-associated osteonecrosis of the jaws: a review of current knowledge. *J Am Dent Assoc* 2005;136:1669-74.
61. van der Pluijm G, Lowik CW, de Groot H, Alblas MJ, van der Wee-Pals LJ, Bijvoet OLM, Papapoulos SE. Modulation of PTH-stimulated osteoclastic resorption by bisphosphonates in fetal mouse bone explants. *J Bone Miner Res* 1991;6:1203-10.
62. Harper RP, Fung E. Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible application for intermittent low-dose parathyroid hormone [rhPTH(1-34)]. *J Oral Maxillofac Surg* 2007;65:573-80.
63. Marini JC. Do bisphosphonates make children's bones better or brittle? *N Engl J Med* 2003;349:423-6.
64. Igarashi K, Adachi H, Mitani H, Shinoda H. Inhibitory effect of the topical administration of a bisphosphonate (risedronate) on root resorption incident to orthodontic tooth movement in rats. *J Dent Res* 1996;75:1644-9.
65. Sahni M, Guenther HL, Fleisch H, Collin P, Martin TJ. Bisphosphonates act on rat bone resorption through the mediation of osteoblasts. *J Clin Invest* 1993;91:2004-11.
66. Junquera L, Gallego L. Nonexposed bisphosphonate-related osteonecrosis of the jaws: another clinical variant? *J Oral Maxillofac Surg* 2008;66:1516-7.
67. Garcia-Ferrer L, Bagan JV, Martinez-Sanjuan V, Hernandez-Bazan S, Garcia R, Jimenez-Soriano, et al. MRI of mandibular osteonecrosis secondary to bisphosphonates. *Am J Roentgenol* 2008;190:949-55.
68. Mont MA, Ulrich SD, Seyler TM, Smith JM, Marker DR, McGrath MS, et al. Bone scanning of limited value for diagnosis of symptomatic oligofocal and multifocal osteonecrosis. *J Rheumatol* 2008;35:1629-34.
69. Marx RE, Cillo JE, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 2007;65:2397-410.