Bisphosphonate-related osteonecrosis of the jaws: a potential alternative to drug holidays

Douglas D. Damm, DDS ▪ David M. Jones, DDS

In 2011, the American Dental Association Council on Scientific Affairs released an update by their expert panel on managing the care of patients receiving antiresorptive therapy for the prevention and treatment of osteoporosis. In this report, the panel found no study results that confirmed the effectiveness of *drug holidays* to prevent antiresorptive agent-induced osteonecrosis of the jaws without increasing the risks of low bone mass. The purpose of this article is to provide suggestions for a pattern of patient care for individuals who desire or require an invasive surgical procedure of the jaws, but who also have a skeleton that is at risk for osteoporotic fracture.

The authors reviewed pertinent literature related to basic bone histology, the pharmacokinetics of the aminobisphosphonates (nBP), diagnostic criteria for osteopenia/osteoporosis, and clinical applications of the antiresorptive agents. The skeletal system demonstrates a mixture of resting surfaces (osteocytes, 85%), resorbing surfaces (osteoclasts, 2%), and forming surfaces (osteoblasts, 10%-12%). Deposition of nBP is not uniform, and is highly concentrated in areas of bone remodeling.

A full understanding of bone remodeling and the pharmacokinetics of nBP allow for the modification of the antiresorptive therapy and the timing of the oral surgical procedure in a manner that minimizes the prevalence of osteonecrosis while at the same time continuing to protect the patient's skeleton from osteoporotic fracture. The lack of support for drug holidays by the ADA's expert panel is strongly consistent with the science behind bone remodeling and nBP pharmacokinetics. In spite of this, creative interdisciplinary patient care has the potential to dramatically reduce the prevalence of bisphosphonate-related osteonecrosis (BRON), while at the same time continuing to protect the skeleton of the osteoporotic patient. Creative interdisciplinary patient care may prove to be an effective intervention to reduce the prevalence of BRON of the jaws.

Received: January 7, 2013
Accepted: April 29, 2013

Key words: oral and maxillofacial pathology, bisphosphonate-related osteonecrosis, aminobisphosphonate, jaw, drug holiday

In 2011, the American Dental Association (ADA) Council on Scientific Affairs released their most recent update related to the management of patients receiving antiresorptive therapy, such as aminobisphosphonates (nBPs) for prevention and treatment of osteoporosis.[1,2] In contrast to the ADA document, the two landmark publications that initially highlighted Bisphosphonate-Related Osteonecrosis (BRON) concentrated on cancer patients utilizing the IV formulations, and little guidance existed on the management of patients utilizing bisphosphonates for prevention and therapy of osteoporosis.[3,4] The ADA must be commended for convening an expert panel to expand on the early investigations of BRON and create the standard of care where none previously existed.

Among the many changes in these recent ADA updates, one of the most controversial is the removal of support for *drug holidays.* Since nBPs are known to concentrate in sites of bone remodeling, the lack of support for drug holidays was surprising to many.[3,4] The expert panel was well aware of the pharmacokinetics of nBPs, but also understood that drug holidays have the potential to increase the skeletal-related risks of low bone mass. Osteoporosis cannot be taken lightly. Of patients who suffer a hip fracture, 20% of women and 30% of men will not survive the event, and 75% never regain full function.[5,6]

The purpose of this article is to provide suggestions for a pattern of patient care for individuals who desire or require an invasive surgical procedure of the jaws, but also have a skeleton that is at risk for osteoporotic fracture. This topic is very complicated, and requires an in-depth discussion of the basic histology of bone, skeletal remodeling, and the pharmacokinetics of the antiresorptive agents. In addition, a short case is included, which hopefully will demonstrate the adverse effects of invasive procedures in patients whose antiresorptive therapy is not modified appropriately to minimize gnathic complications.

Any understandable discussion of the pharmacokinetics of the nBP must be interwoven with a review of the basic histology of bone.[7] Within hours of intake, 50% of nBP is removed unmetabolized by the kidneys with the remainder deposited in the skeleton. Eighty-five percent of the skeleton consists of resting bone and demonstrates quiescent osteocytes within their lacunae (Fig.1). Osteocytes have a low affinity for nBP, with the medication loosely bound to resting bone, and removed from these surfaces within days. The resorbing surfaces of bone represent only 2% of the skeleton and are identified by the presence of osteoclasts within their resorptive lacunae (Fig. 1). The cells demonstrate 8 times the affinity for the medication. In spite of this high affinity, the vast majority of the medication is liberated from these cells over days to weeks, with the medication being recycled into the blood for distribution once again to the skeleton or excretion by the kidneys.

The forming surfaces of bone comprise 10%-12% of the skeleton, and are defined by the presence of osteoblasts (Fig. 1). These cells demonstrate 4 times the affinity for nBP. Unlike the osteocytes and osteoclasts, the osteoblasts do not release the medication, but incorporate it into the bone by affixing nBP to newly deposited osteoid. The buried nBP remains within the bone until osteoclasts remodel the area and release the medication for recycling to the skeleton and kidneys. Once recycled back into the blood, the medication tends to be attracted to areas of high metabolic activity, due to the increased affinity of the

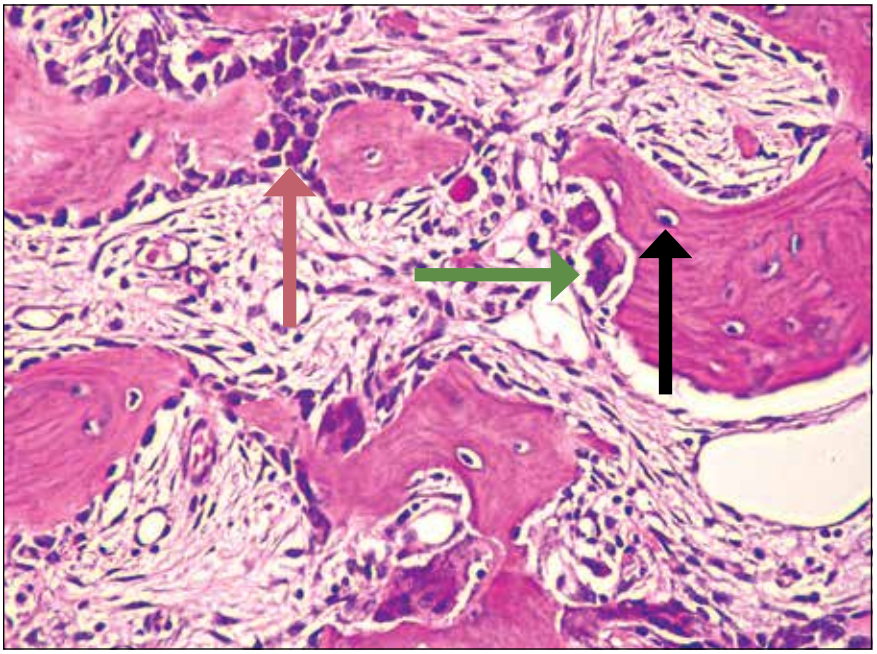

Fig. 1. Histopathologic image of remodeling bone. Note the osteocyte (black arrow), osteoclast (green arrow), and osteoblast (orange arrow). (H&E stain, magnification 20X)

cells involved in active remodeling. Once deposited into the newly formed bone, the medication has a half-life of approximately 10 years, and continues to be recycled upon each remodeling. It is critical for one to understand that the deposition of nBP in the skeleton is not uniform and tends to be highly concentrated in areas of remodeling.[7]

The effects of nBP on the crucial osteoclasts vary with the local concentration of the medication.[7] With low deposition, the ability of the osteoclasts to accomplish bone mineral resorption and collagen degradation is diminished. With increasing nBP deposition, osteoclastic differentiation from the stem cell pool is inhibited; ultimately, osteoclastic apoptosis is induced. Since the majority of the skeleton consists of resting bone with relatively low deposition of the drug, the desired pharmacologic effect of reduced resorption with increased bone mass is achieved in most sites that are not undergoing significant remodeling.

The nBP pharmacokinetics is only half of the story, and one must understand the basics of bone remodeling to design an appropriate pattern of patient care. When the bone is disturbed, as in an extraction site, or in preparation for implant placement, the surgical defect fills with extravasated blood, leading to formation of a hematoma. An inflammatory phase follows clot formation. During this time, the inflammatory cells remove bacteria and foreign debris from the surgical site. Macrophages within the infiltrate release growth factors that activate fibroblasts and endothelial cells, leading to formation of granulation tissue. Pluripotential mesenchymal cells form collagen and, ultimately, woven bone. This immature bone gains full strength only after complete remodeling.[8]

Final remodeling is accomplished by a cell packet known as the *basic multicellular unit* (BMU).[8,9] This unit is an organized synergism, in which osteoclasts, osteoblasts, osteocytes, and the local vascular supply work in an organized and tightly controlled pattern. The BMU is a discrete and narrow "cutting cone" that burrows through the immature woven bone and replaces it with well-organized and strong lamellar bone. Numerous BMU cones traverse the woven bone in the healing surgical site to accomplish final remodeling. Each BMU consists of a leading phalanx of osteoclasts that resorb the woven bone, and these octeoclasts are followed by newly formed blood vessels and osteoblasts. The osteoblasts advance centripetally around the central vascular supply, and fill in the resorptive defect with well-organized lamellar bone. Despite the attention on the osteoclasts and osteoblasts, angiogenesis also is an important component of bone remodeling. The BMU is a moving structure, and requires continual replacement of osteoclasts and osteoblasts at exactly the correct time and place in an ever-changing location. In addition to transporting needed cells to the site, the vascular system supplies bone components to the area, and assists in the removal of degradation products. All the while, new growth of blood vessels, nerves, and connective tissue must occur at the proper rate as the BMU progresses through the healing bone.

The life span of the involved cells in a BMU mandates frequent replacement. The average life span of an osteoclast is only 2 weeks.[8] Osteoblasts have a life span of 1-3 months, unless incorporated into the newly formed bone.[8] Those incorporated into the bone become osteocytes, which are permanent cells, and have the potential to live as long as the organism itself. Most osteocytes live until removed from the bone during remodeling, and demonstrate a life span which varies from a few years to decades.[8-10] The remodeling period is defined as the shortest period of time when, after disturbing the bone, a new steady-state can be guaranteed to exist.[11] Although the time period varies from 2-8 months, 4 months is the normal remodeling period in the human skeleton.[8,12]

The basic knowledge of bone remodeling is critical to planning presurgical and postsurgical antiresorptive therapy. The following case report will demonstrate the adverse outcomes associated with failure to develop an interdisciplinary approach to patient care in individuals receiving antiresorptive therapy and undergoing an oral surgical procedure.

Case report

In 2004, a 70-year-old female presented for comprehensive dental care. At that time, she reported a diagnosis of osteoporosis in the late 1990s, at which point she began therapy. Since that diagnosis,

the patient had changed physicians and attempts to obtain a more detailed medical history were unsuccessful. At this presentation, she utilized weekly oral risedronate for her osteoporosis. A 2004 panoramic radiograph revealed a normal trabecular pattern (Fig. 2).

In February of 2007, she presented with root decay and pulpal involvement of the right mandibular second bicuspid, and was referred to an endodontist for therapy. Despite attempts at conservative therapy, serious periapical inflammatory disease developed and led to extraction of the tooth, an associated hospitalization, and extended antibiotic therapy. A panoramic radiograph taken shortly after the extraction in March 2007 continued to demonstrate an appropriate trabecular pattern (Fig. 3). The right mandibular first molar was slightly mobile and tender. Following removal of the second molar pontic, the mobility and sensitivity of the first molar resolved. In late August and early September, a new 3-unit bridge was delivered to replace the right mandibular second bicuspid.

In October 2007, the patient returned with a complaint of significant pain in the mandible, which extended from the anterior dentition all the way around to the newly placed prosthesis. A night guard was constructed, but failed to reduce the associated dental discomfort. In January of 2008, the pain continued to be problematic. The clinical presentation and vitality testing of the entire anterior dentition were within normal limits, despite the significant sensitivity of these teeth. A return trip to the endodontist was recommended in an attempt to rule out the mandibular first molar as the primary focus of infection. Although no obvious periapical inflammatory disease was noted, the constant pain led to a second referral to an oral and maxillofacial surgeon, who extracted the mandibular first molar in March of 2008. In spite of this intervention, the dental discomfort continued, involving the entire anterior and right body of the mandible.

In June 2008, an additional follow-up panoramic radiograph was obtained (Fig. 4). In this radiograph, the explanation of the chronic oral discomfort was obvious. The trabecular pattern of the medullary areas of the mandible was atypical, with a diffuse patchy radiopacity which extended from the left mandibular cuspid to the right posterior body of the mandible. In addition, the remodeling of the extraction site of the second bicuspid was incomplete after a period of 15 months. When the radiographic pattern was combined with the 8-month history of unexplained odontalgia, the diagnosis of BRON, Stage 0, was made. Following the BRON diagnosis, the risedronate was discontinued by the patient's attending physician in July 2008. Over the next few months, the widespread dental discomfort slowly resolved.

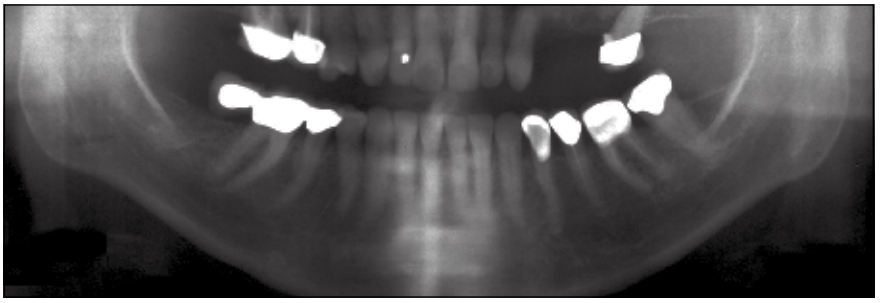

Fig. 2. 2004 panoramic radiograph. Note the normal trabecular pattern.

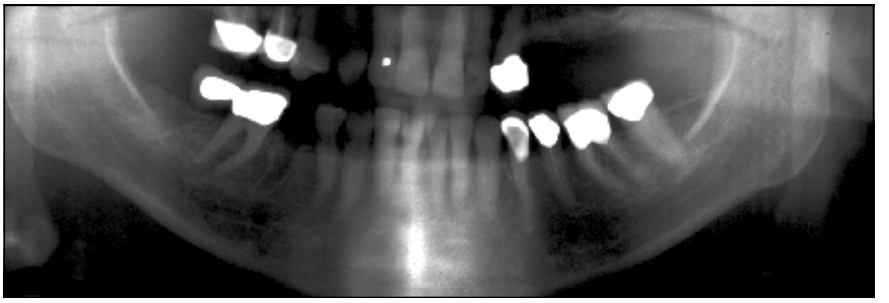

Fig. 3. 2007 panoramic radiograph taken shortly after extraction of the right mandibular second bicuspid. Note the trabecular pattern remains largely unaltered.

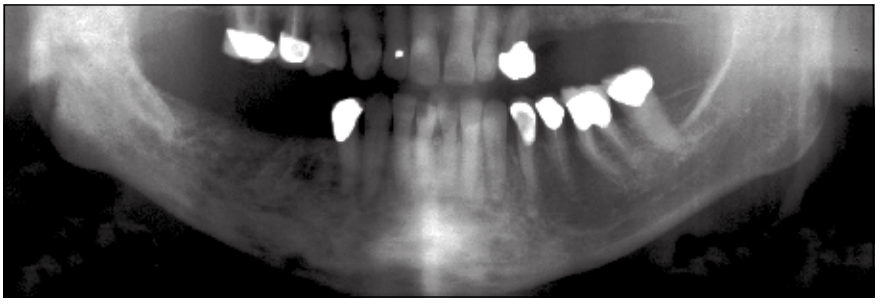

Fig. 4. 2008 panoramic radiograph. Note the diffuse patchy radiopacity of the anterior and right body of the mandible, with incomplete remodeling of the previous extraction site of the second bicuspid.

Discussion

In the 2008 panoramic radiograph, the patchy radiodensity supported the diagnosis of osteonecrosis, even though exposed necrotic bone was not evident. In ischemic-damaged bone, where dead bone abuts living marrow, layers of new bone are applied to the surface of the dead bone. This double layering of bone is responsible for the patchy radiodensity noted in the current patient. One must question how extraction of the right second bicuspid and first molar can lead to an altered bone pattern that extends from the left mandibular

cuspid to the right posterior body of the mandible. The osteocytes within this bone have the potential to live for decades, and should not have undergone necrosis without provocation. As mentioned in the discussion of bone remodeling, the vascular supply is a critical component of bone homeostasis. In all likelihood, the extraction led to increased mandibular concentrations of nBP, which are known to block appropriate angiogenesis. Without the ability to maintain an appropriate vascular supply, ischemic damage occurred, leading to extensive loss of bone vitality. As described in the discussion of nBP pharmacokinetics, the medications are concentrated into sites of active bone remodeling. It is proposed that this adverse outcome could have been avoided if the serum was clear of nBP at the time of the extractions. If no drug was present in the serum, then none could be concentrated into the bone during the period of bone remodeling associated with healing of the surgical site.

What is an appropriate presurgical and postsurgical period for the serum to be free of nBP? A 6-month drug holiday (3 months presurgical and 3 months postsurgical) has been suggested in previous position papers, but the nBP pharmacokinetics and basic bone remodeling process do not support these time frames.[13] Once nBP reaches the serum, renal excretion quickly eliminates 50%, with the remainder deposited in the skeleton. The osteocytes have a low affinity and quickly release the medication. Osteoblasts incorporate the drug into the bone, where it is inert until released by future remodeling. The only reservoir for the medication is the osteoclasts, and they continue to release the drug for a few weeks. Since the life span of an osteoclast is 2 weeks, the only nBP available for release after 2 weeks would be the nBP passed from the original osteoclast to the subsequent generation, along with a small amount released from the bone. With this knowledge, it would be expected that the majority of free nBP within the serum would be minimal at 2 weeks, and extremely low at 2 months (equal to 4 times the life span of an osteoclast). Therefore, a 2-month drug free period prior to an oral surgical procedure seems more than adequate.

Since nBP concentrates in areas of active remodeling, an appropriate postsurgical drug-free period also is critical. This period should be extended until the bone has returned to a normal lamellar pattern, without an increased number of osteoclasts and osteoblasts. As described previously, the bone remodeling period varies from 2 to 8 months, with 4 months being typical. With this knowledge, the recommended postsurgical drug-free period should be at least 4 months, with 8 months being even safer. However, an osteoporotic patient cannot be removed from their protective therapy for 8 months while the bone heals. The risks of hip and vertebral fracture outweigh the concerns related to BRON; fortunately, safe alternatives exist, and will be discussed later in the article.

A review of bone mineral density (BMD), as it relates to osteoporosis would help all dentists as they discuss the possibility of surgery with their patients.[14] The World Health Organization (WHO) utilizes the dual energy X-ray absorptiometry scan (DXA, or DEXA), to define osteoporosis.[15] The results are compared to an arbitrary norm and reported as *T-scores.* Bone densities between -1.0 to -2.5 standard deviations below the norm are classified as *osteopenic,* while those that are ≤-2.5 are diagnosed as *osteoporotic.*[15]

Due to the significant morbidity and mortality associated with osteoporotic hip and vertebral fractures, antiresorptive therapy is strongly recommended for patients with confirmed osteoporosis. The therapy for patients with osteopenia is less well-defined. To lessen the confusion, the WHO established an online *Fracture Risk Assessment* tool (FRAX) (www.shef.ac.uk/frax), through the University of Sheffield, England. This short online assessment calculates a patient's 10-year risk of a major osteoporotic fracture. Therapy is recommended in patients with osteopenia only if the calculation tool predicts a 20% risk of major osteoporotic fracture (hip, shoulder, wrist, and spine), or at least a 3% risk of hip fracture. Use of this tool should be strongly encouraged for all osteopenic patients.

An additional controversy continues for patients who remain osteoporotic after 5 years of nBP therapy. The positive effects of nBP are most noticeable when skeletal concentrations of the drug are low, with greatest gains in bone density occurring during the first few years of use. As the skeletal concentrations of nBP rise, reduced osteoclastic differentiation and increased osteoclastic apoptosis begin to negatively impact the skeleton. In addition to problems encountered within the jaws, physicians are increasingly reporting unusual subtrochanteric and femoral shaft fractures occurring in long-term users of nBP.[16] Such fractures led some physicians to state that current evidence suggests an extended drug holiday should be instituted after 5 years of nBP use.[17] Patients who remain at high risk for fracture should be considered for treatment with alternative therapies, such as teriparatide or raloxifene.[18]

Before presenting a specific pattern for managing osteoporotic patients in need of an oral surgical procedure, a short discussion of 2 medical alternatives to nBP is necessary. Denosumab (Prolia, Amgen, Inc.) is a monoclonal antibody that targets and binds to RANK ligand, which is necessary to allow maturation of osteoclastic precursors into differentiated osteoclasts.[19] This therapy not only inhibits formation of differentiated osteoclasts, but also inhibits the function and survival of previously formed osteoclasts. Denosumab reduces osteoclastic function by 85% within 3 days of administration and obtains maximal reduction within 1 month. After that time, the effect on osteoclasts drops as the concentration of the medication wanes. The half-life is 25.4 days, which means the drug takes 4-5 months to drop to insignificant levels.[19] Although the medication is not incorporated into bone as is nBP, denosumab is known to be associated with osteonecrosis. However, the process tends to respond more readily to intervention than the osteonecrosis that is associated with nBP use.[20,21] Denosumab is available in 2 formulations: Prolia, for osteoporosis that is injected at 6-month intervals, or Xgeva (Amgen, Inc.), which is administered every 4 weeks for cancer patients.[19,22]

Both nBP and denosumab are antiresorptive agents that work by reducing osteoclast formation, increasing osteoclastic apoptosis, and slowing the rate of bone remodeling. Since bone formation only occurs at sites of active bone remodeling, an anabolic agent that increases the number of BMUs would be a much more powerful agent against osteoporosis. Teriparatide (Forteo, Eli Lilly and Company) is an anabolic parathyroid hormone that, when given intermittently, does not decrease the number of BMUs and promotes both an increased number and

increased survival of osteoblasts.[23] This anabolic approach has a much greater ability to increase bone density than the antiresorptive agents that inhibit bone remodeling (and ultimately new bone formation).[24] Forteo is not associated with osteonecrosis, and has been shown to dramatically reduce the healing time in BRON.[25,26]

With the knowledge of the nBP pharmacokinetics, bone remodeling, and the medical alternatives, it is possible to design a pattern of patient care which clears the serum of nBP at the time of bone remodeling and prevents concentration of the drug in surgical sites, but also continues to protect the osteoporotic patient from fracture.

For patients who need or desire an oral surgical procedure and are utilizing nBP, the first step should be review of a recent bone mineral density evaluation. If the results suggest osteopenia rather than osteoporosis, the FRAX website should be utilized to judge the necessity for continued antiresorptive therapy. For patients with osteoporosis or osteopenia that is recommended for continued therapy by FRAX, the following are options which can avoid concentration of nBP into surgical sites without placing the patient's skeleton at risk for fracture.

1. The nBP could be discontinued and replaced with Prolia (denosumab). Once the denosumab therapy is initiated, any elective surgery could be timed to occur 2 months after an injection with Prolia. At this time, 79.9% of the medication would have been degraded. This timing would allow 4 months of healing prior to the next injection. Although some degree of delayed healing would be expected, the effect would be minimal, and unlike nBP, no drug is concentrated into sites of remodeling.
2. The nBP therapy could be replaced with Forteo (teriparatide). This anabolic therapy results in significant new bone growth and most likely would not only eliminate the chance of osteonecrosis but also would shorten the healing time of the surgical site.
3. The oral nBP could be replaced with zoledronic acid (Reclast, Novartis Pharmaceuticals Corporation), administered intravenously on an annual basis.[27] The surgery could be scheduled 2 months after the annual infusion. As mentioned previously in the pharmacokinetics of nBPs and the second paragraph of the Discussion, the serum would be essentially clear of the medication at that point in time and none would be available to concentrate into the sites of osseous remodeling associated with the surgical sites. Once again, such timing would provide adequate time for the serum to clear of nBP prior to the surgery with 10 months of healing prior to the next infusion.

Conclusion

The management strategies described in this article are based on a therapeutic hypothesis, and should not be considered an approved approach to patient care without further studies. In spite of this, the drug pharmacokinetics and physiology of bone remodeling strongly suggest that these alternatives may have the ability to reduce the prevalence of osteonecrosis while consequently continuing to protect the skeleton of the osteoporotic patient. Hopefully, future clinical studies will shed more light on this difficult area of patient care.

Author information

Dr. Damm is a professor, Department of Oral Health Sciences, Division of Oral Pathology, College of Dentistry, University of Kentucky, Lexington. Dr. Jones is in private practice in Chanute, Kansas.

References

1. Hellstein JW, Adler RA, Edwards, E, et al. Managing the care of patients receiving antiresorptive therapy for the prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc.* 2011;142(11):1243-1251.
2. Hellstein JW, Adler RA, Edwards B, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: recommendations from the American Dental Association Council on Scientific Affairs. Available at: http://www.aae.org/uploadedFiles/Publications_and_Research/Endodontics_Colleagues_for_Excellence_Newsletter/BONJ_ADA_Report.pdf. Accessed May 6, 2011.
3. 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(5):527-534.
4. 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(11):1567-1575.
5. Palmer RM, Saywell RM Jr, Zollinger TW, et al. The impact of the prospective payment system on the treatment of hip fractures in the elderly. *Arch Intern Med.* 1989;149(10):2237-2241.
6. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet.* 2002;359(9319):1761-1767.
7. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. *J Dent Res.* 2007;86(11):1022-1033.
8. Doll B, Aleef M, Hollinger JO. Overview of fracture repair. In: Pietrzak WS, ed. *Orthopedic Biology and Medicine: Musculoskeletal Tissue Regeneration, Biological Materials and Methods.* Totowa, NJ: Humana Press; 2008:39-61.
9. Parfitt AM. Osteonal and hemi-osteonal remodeling: the spatial and temporal framework for signal traffic in adult human bone. *J Cell Biochem.* 1994;55(3):273-286.
10. Knothe Tate ML, Adamson JR, Tami AE, Bauer TW. The osteocyte. *Int J Biochem Cell Biol.* 2004;36(1):1-8.
11. Frost HM. Tetracycline-based histological analysis of bone remodeling. *Calcif Tissue Res.* 1969;3(3):211-237.
12. Martin RB, Burr DB, Sharkey NA. *Skeletal Tissue Mechanics.* New York, NY: Springer-Verlag Inc; 1998:84.
13. Ruggiero SL, Dodson TB, Assael LA, et al. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws–2009 update. *J Oral Maxillofac Surg.* 2009;67(5 Suppl):2-12.
14. Marx RE, Cillo JE, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofacial Surg.* 2007;65(12):2397-2410.
15. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser.* 1994;843:1-129.
16. Park-Wyllie LY, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures. *JAMA.* 2011;305(8):783-789.
17. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. *Geriatrics.* 2006;61(1):31-33.
18. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab.* 2010;95(4):1555-1565.
19. Amgen, Inc. Prolia [prescribing information]. Available at: http://pi.amgen.com/united_states/prolia/prolia_pi.pdf. Accessed May 6, 2013.
20. Diz P, Lopez-Cedrun JL, Arenaz J, Scully C. Denosumab-related osteonecrosis of the jaw. *J Am Dent Assoc.* 2012;143(9):981-984.

Published with permission by the Academy of General Dentistry. © Copyright 2013 by the Academy of General Dentistry. All rights reserved. For printed and electronic reprints of this article for distribution, please contact rhondab@fosterprinting.com.

21. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet.* 2012; 379(9810):39-46. Comment in: Kyrgidis A, Tzellos TG. Denosumab in castration-resistant prostate cancer. *Lancet.* 2012;379(9828):e50, Author reply: e50-e51.
22. Amgen Inc. Xgeva [prescribing information]. Available at: http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf. Accessed May 6, 2013.
23 Eli Lilly and Company. Forteo [prescribing information]. Available at: http://pi.lilly.com/us/forteo-pi.pdf. Accessed May 6, 2013.
24. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev.* 2000;21(2):115-137.
25. 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(3): 573-580.
26. Cheung A, Seeman E. Teriparatide therapy for alendronate-associated osteonecrosis of the jaw. *N Engl J Med.* 2010;363(25):2473-2474.
27. Novartis Pharmaceuticals Corporation. Reclast [prescribing information]. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/reclast.pdf. Accessed May 6, 2013.

Manufacturers

Amgen, Inc., Thousand Oaks, CA
800.772.6436, www.amgen.com

Eli Lilly and Company, Indianapolis, IN
800.545.5979, www.lilly.com

Novartis Pharmaceuticals Corporation, New York, NY
888.669.6682, www.us.novartis.com