Sixth Edition

Quality Resource Guide

Bisphosphonate and Other Medication-Related Jaw Necrosis

Part One - Background, Incidence and Risk Factors

Author Acknowledgement

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Educational Objectives

Following this unit of instruction, the practitioner should be able to:

1. Discuss the indications for the use of bisphosphonates and newer compounds in management of bone resorption.
2. Understand the underlying pathogenesis and mechanisms of alterations in bone metabolism induced by bisphosphonates and other medications.
3. Appreciate the level of risk in developing osteonecrosis of the jaws relative to the type of medication administered as well as the indications for the use of those agents in addition to bisphosphonates.
4. Understand why the jaws have a significantly increased risk of developing osteonecrosis versus other bones in association with administration of intravenous and oral forms of bisphosphonates and medications.
5. Place into perspective the relative potencies of anti-resorptive compounds and the relative degree of risk of developing jawbone osteonecrosis.
6. Increase awareness of management strategies of medication-related jaw necrosis beyond the use of bisphosphonates.

MetLife designates this activity for **1.5 continuing education credits** for the review of this Quality Resource Guide and successful completion of the post test.

The following commentary highlights fundamental and commonly accepted practices on the subject matter. The information is intended as a general overview and is for educational purposes only. This information does not constitute legal advice, which can only be provided by an attorney.

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The content of this Guide is subject to change as new scientific information becomes available.

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Introduction

The widespread use of bisphosphonates and other anti-resorptive agents as important drugs routinely used in the management of many primary bone diseases including osteopenia, osteoporosis, osteogenesis imperfecta of childhood, Paget's disease as well as multiple myeloma and metastatic cancer to bone is well established. Commonly, anti-resorptive therapy is employed for management of bony metastases from breast, lung and prostate cancer well as melanoma. They are also beneficial for treatment of tumor-related hypercalcemia. These agents may be administered orally (alendronate, ibandronate, risedronate), intravenously (pamidronate, zoledronate) or more recently, subcutaneously in relation to use of a monoclonal antibody (denosumab), a non-bisphosphonate compound (see below). Additionally, antiresorptive, non-bisphosphonate drugs have greatly reduced the complications of vertebral compression fracture, spinal cord compression and long bone fracture associated with benign osseous diseases, most notably osteoporosis. Significant improvements in the quality of life associated with the use of these agents have been reported, although there is no evidence to date demonstrating survival benefits in the cancer patient.[1,2] Attention to drug-related side effects associated with intravenously-administered forms of bisphosphonates was first noted in 2003 and subsequently confirmed by clinical studies of jaw-related morbidity and complications.[3,4] More recently, similar reports of jaw-related complications have been noted in relation to the use of denosumab, a monoclonal antibody directed toward modifying bone resorption by affecting an alternative metabolic messaging pathway at the osteoclast level.

Pathogenesis

Bisphosphonates act primarily by inhibiting osteoclastic function, thus stabilizing or inhibiting osteoclast-mediated bone resorption. More specifically, osteoclast structural integrity is disrupted secondary to interruption of critical intracellular biochemical pathways (prenylation of GTP-binding proteins). Bisphosphonates also inhibit osteoclast recruitment, development and migration, and decrease bone resorption in the absence of a significant effect on mineralization.[5] An associated antineoplastic and antiangiogenic effect of these agents has been stated to contribute to their overall clinical effectiveness in cancer patients. This benefit is considered to result from their long-lasting and significant effect on reduced serum levels of vascular endothelial growth factor secondary to bisphosphonate administration.[6,7] Bisphosphonates possess a high affinity for calcium and bind strongly to hydroxyapatite crystals; thus they are deposited into the bone matrix. When subsequently ingested by the osteoclast, there is a resultant inhibition of osteoclast function and ultimate apoptosis or cell death. This stabilizes bone resorption and liberates calcium and collagen-related peptide fragments (telopeptides). In this manner, these agents have greatly improved quality of life for those with primary bone disease (myeloma) or metastatic bone disease by decreasing the level of bone turnover secondary to decreased resorption, while allowing mineralization of bone matrix to continue.[8] Additionally, bisphosphonates can affect the immune system by impacting gamma-delta T lymphocytes, which in turn leads to macrophage dysfunction.

There is also a segment of the population using oral bisphosphonates for benign conditions including but not limited to Paget's disease of bone, osteopenia and osteoporosis, with over 150 million prescriptions written for bisphosphonates in the U.S. between 2005 and 2009 for management of osteopenia and osteoporosis.[9] (see **Table 1**)

More recently, the use of denosumab, a monoclonal antibody which binds to RANKL, an osteoclast and T-lymphocyte cell surface receptor involved with a signaling pathway that regulates osteoclast differentiation, activation, function and survival, thus preventing precursor osteoclasts to form, thus reducing bone resorption.[10] Indications for use of this agent are similar to those of bisphosphonates with the associated risk of osteonecrosis development well-documented. Recent studies concerning denosumab have called attention to a much-increased osteonecrosis risk of up to 10 times versus that with bone resorption inhibitors alone.[11]

Additionally, the use of newer classes of drugs designed to interfere with vascular supply to neoplasms not intended to manage bone resorption have also contributed to the incidence

Table 1 - Bisphosphonates, biologic agents (denosumab) and their indications

For Benign Bone Disease	
Alendronate (Fosamax®) Ibandronate (Boniva®) Residronate (Actonel®) Osteopenia/osteoporosis Etidronate (Didronel®) Tiludronate (Skelid®) Zoledronic acid (Zometa®) Denosumab (Prolia®; Xgeva®) Romosozumab (Evenity®)	**Indication:** Osteoporosis, Paget's disease
For Benign Bone Disease	
Clodronate (Biofos®)* Pamidronate (Aredia®) Zoledronic acid (Zometa®) Denosumab (Prolia®; Xgeva®)	**Indication:** Tumoral hypercalcemia, myeloma and metastatic cancer

* Available in Canada

of jawbone osteonecrosis lending credence to the notion that the pathogenesis of jawbone osteonecrosis also includes other agents as evidenced by this association. These agents include tyrosine kinase inhibitors as well as monoclonal antibodies which target vascular endothelial growth factor (VEGF), such as sorafenib, regorafinib and bevacizumab. It is this association, along with similar medication relationships, which has led to a modification of the term "bisphosphonate-related osteonecrosis of the jaws", or BRONJ, to "*medication-related osteonecrosis of the jaws*", or MRONJ, currently the preferred term.

Ruggiero and colleagues, in 2004, reported 63 cases of bisphosphonate-related osteonecrosis of the jaw (BRON); each patient had cancer and received bisphosphonate treatment as part of overall oncologic management.[4] This publication followed an earlier report by Marx noting the possible emergence of a growing clinical problem or "epidemic".[3] These reports have emphasized the seemingly unique association between the presence of jawbone necrosis or what has been known as BRONJ and the use of bisphosphonates, in particular, the potent intravenous forms, pamidronate and zoledronate, used predominantly in oncologic disease management on a frequency level beyond that used for benign conditions. Less potent orally administered bisphosphonates are available, but poorly absorbed, and are not effective in the management of tumor-related hypercalcemia/metastatic cancer or myeloma, thus the use of intravenous delivery. Intravenous bisphosphonates are over 300 to 10,000 times more potent than etidronate, the reference anti-hypercalcemia agent, in terms of osteoclast inhibition by virtue of their essentially 100% bioavailability and relative effective dose.[5] (see **Table 2**)

In addition to the osteoclast-related effect, the anti-angiogenic property of bisphosphonates contributes to the stated avascular component of the osteonecrosis process[8], further added to in many cases by the specific use of anti-angiogenic drugs in management of several forms of malignancy. These agents produce an associated reduction in direct tumor cell proliferation and invasive behavior, including diminishing rates of tumor cell migration and invasive characteristics, by inhibiting several classes of matrix metalloproteinases (MMP 3, 12,13, and 20),[12] and in the case of anti-angiogenic agents, reduce microvascular sprouting and growth in tumor systems.[13]

The predilection of the maxilla and mandible for osteonecrosis involves several factors. The most significant anatomic or physiologic factor relates to the particularly high rate of alveolar bone turnover, estimated to be up to 10 fold that of bone at other anatomic sites. Of greatest importance is the fact that the region adjacent to the periodontal membrane demonstrates the highest level of bone formation/resorption (especially after tooth extraction) versus other locations.[1] Additionally, recent studies have shown that jaw bone marrow-derived osteoclast precursors are capable of accumulating higher concentrations of bisphosphonates when compared to long-bone marrow osteoclast precursors,[15] Other predisposing issues that may increase the risk of developing BRON include local factors such as the presence of periodontal disease or other infections, performance of dentoalveolar surgery, prior trauma, corticosteroid therapy and immunocompromise, presence of vascular insufficiency or a neoplastically-mediated hypercoagulable state.[16] Other major risk factors reported include the type of bisphosphonate, potency of the agent and duration of administration.[17] The preferential deposition of bisphosphonates in areas of normally high bone turnover, coupled with the extremely high remodeling rate of the mandible and maxilla after tooth extraction and the possible increased osteoclast uptake by jawbone osteoclasts, make the jawbones primary risk sites following dentoalveolar surgery.[18]

Table 2 - Bisphosphonates and their relative potencies (after Zahrowski, JJ. J Oral Maxillofac Surg 2007; 65:1440-1441)

Agent	Relative Potency
ORAL	
Etidronate (Didronel®)	1:1
Tiludronate (Skelid®)	1:10
Alendronate (Fosamax®)	1:700
Risedronate (Actonel®)	1:2,000
Ibandronate (Boniva®)	1:4,000
INTRAVENOUS	
Etidronate (Skelid®)	1:1
Pamidronate (Aredia®)	1:325
Zoledronic acid (Zometa®)	1:10,000

* Available in Canada

Incidence

The overall incidence (number of cases within a defined population during a predetermined period) of MRONJ is difficult to determine, due to the pervasive use of bisphosphonates, and more recently denosumab, romosozumab, and more recently certain tyrosine kinase inhibitors with the likelihood that a general and significant degree of under-reporting occurs. The key to assessing population-based data regarding this widespread problem is development of a registry of cases where collection of systematic information and outcomes of care can be obtained.[19] There has been an increase in the reporting of this condition since the initial publications on bisphosphonate use and bone toxicity, though many cases are simply managed but such data is not collected or harvested. Data from a web-based survey of myeloma and breast cancer patients treated with intravenous bisphosphonates noted that 6.8% of myeloma patients reported being diagnosed with bisphosphonate-related bony alterations, while an additional 5.9% were told they demonstrated suspicious clinical features. Of the breast cancer patients, 4.3% developed jawbone osteonecrosis while 7.7% showed suspicious features. Seventy-one percent of the patients surveyed received zoledronate, and 29% received pamidronate.[20,21] Available data indicate that up to 27.5% of individuals exposed to antiresorptive agents can develop jawbone osteonecrosis.[22, 23]

The mean time of developing BRON varies overall time of exposure along with the effective potency of the bisphosphonate administered. An 18-month mean time of onset associated with zoledronate (monthly dose) therapy has been reported versus a 6-year onset with pamidronate (3-4 week dose) treatment.[23] Others report a 9.9% incidence of bisphosphonate-related osteonecrosis in myeloma patients and 2.9% in breast cancer patients over an eight year period.[24] In another study of 303 myeloma patients receiving zoledronate, a two year time span was stated as a threshold when an increased level of caution was advised.[25] Chronologic estimates for jawbone necrosis development in patients taking oral bisphosphonates have been significantly longer than those associated with intravenous agents. Suffice to say that the risk of developing MRONJ in relation to the use of oral bisphosphonates is very low in comparison the risk associated with intravenous bisphosphonate therapy in the oncologic setting.

On balance, the reported cases and emerging experience support the notion that MRONJ is not an unconfirmed phenomenon and must be dealt with effectively.[26] The evolution from initial discovery to sequestrum formation can be rapid, though several months are more characteristic for this to occur.

Clinical data and statistics concerning the overall impact of denosumab on osteonecrosis of the jaws is being gathered, though it is clear that this agent likewise also carries a small risk of MRONJ development. Of note is the confirmed increased risk of jaw osteonecrosis development with denosumab use versus bisphosphonates in osteoporosis patients.[29]

Risk Factors

Risk exists for developing MRONJ when any form of bisphosphonate or similar stabilizing agent is taken. However, the specific type of agent will help determine the degree of risk. Orally ingested bisphosphonate forms demonstrate a much lower risk potential than the intravenously administered agents. The most frequently prescribed oral agent, alendronate (Fosamax®), has the greatest established time on the market and number of doses administered. Stated estimates of risk or incidence of developing MRONJ in association with oral alendronate administration is 0.7 per 100,000 patient years exposure.[26] Of the intravenously administered forms, zoledronate/zoledronic acid (Zometa®) is the dominant drug associated with development of MRONJ. The frequency of MRONJ is associated more with monthly zoledronate administration (4mg) in cancer patients than with any other type of bisphosphonate. Patients with malignant skeletal lesions such as metastatic cancer and myeloma receive overall intravenous doses that are 12-fold higher than patients with benign skeletal conditions such as osteoporosis and osteopenia. See **Table 3** for Risk Factor tabulation.

The total duration of bisphosphonate administration is of great importance regarding risk potential. If, and when, the patient discontinued using bisphosphonates is also very important. Three years of routine alendronate administration is associated with an approximate complication risk of 2% for patients having office-based oral surgical procedures, with the level of risk rising to 4% when the patient has had 3-4 years of exposure to the drug, 6% at 4-5 years of exposure, 9% at 5-6 years of exposure and 11% with exposure beyond 6 years.[27] Given the long half-life of bisphosphonates (up to 10 years at sites of low bone turnover, but less in alveolar bone due to its known higher rate of turnover), the obtained medical history should be specific with regard to use of these agents. It should include current as well as former use, duration and type of bisphosphonate administered.

Ninety-five percent of MRONJ cases occur in patients with malignant skeletal disease. The general level of risk for development of MRONJ in patients taking oral bisphosphonates for management of osteopenia, osteoporosis and Paget's disease remains relatively low. The risk of developing MRONJ when oral bisphosphonates are used in the context of managing these non-neoplastic conditions is 0.01% to 0.04%. Tooth extraction elevates that risk to 0.09% to 0.34%. The risk of developing MRONJ in patients being managed for benign skeletal disease with typical oral bisphosphonate doses is so minimal that it has been suggested that systematic screening and prevention programs, including the withholding of dental procedures, is not justified.[27]

Other risk factors for developing MRONJ include: periodontal and dentoalveolar surgery; local anatomic factors including maxillary and mandibular tori, and the mylohyoid ridge; and pre-existing inflammatory dental disease and other conditions. (**Table 4**)

Finally, the possibility that genetic factors may influence overall risk for development of BRON has been raised, based on single nucleotide

Table 3 - MRONJ Risk Factors

1. Drug-related: Type, potency and duration of bisphosphonate used, concomitant corticosteroid therapy or chemotherapeutic drug therapy
2. Local risk factors: Dentoalveolar, periapical and osseous periodontal surgery, diabetes, alcohol use, smoking and poor oral hygiene
3. Systemic risk factors: hypercoagulability, diabetes, alcohol use, tobacco smoking
4. Local anatomic factors: Palatal and mandibular tori, exostoses and mylo- hyoid ridges that may require surgical correction in the future
5. Demographic factors: age, race, cancer type, concurrent osteopenia or osteoporosis in juxtaposition with a cancer diagnosis

polymorphisms. Reported is a 12.7-fold increased risk of myeloma patients developing MRONJ when they had a homozygous allele (the "T-allele") compared to patients heterozygous for this allele.[29]

Note: Osteonecrosis of the jaws may occur in the absence of antiresorptive drug use (so-called "background" osteonecrosis of the jaws) though these agents are responsible for the vast majority of pharmacologically-induced osteonecrosis.[18]

Bisphosphonate-Related Jaw Necrosis – Part 2 discusses clinical management of MRONJ.

Table 4 - General Causes of Osteonecrosis[31]

1. Invasive or metastatic cancer
2. Cancer therapy (chemotherapy; radiotherapy)
3. Osteomyelitis/periodontal infection

a. Infection: viral; mycotic; bacterial

4. Mandibular/maxillary tori
5. Advanced age
6. Glucocorticoid treatment
7. Dental trauma (*e.g.*, dental extractions)
8. Idiopathic aseptic osteonecrosis
9. Other etiologies: cocaine abuse; vasculitic disease (Wegener's granulomatosis) certain forms of lymphoma

The following manuscripts are suggested reading for individuals interested in more in-depth exploration of this topic:

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13. Pabst AM, Ziebart T, Ackermann M, et al. Bisphosphonate's antiangiogenic potency in the development of bisphosphonate-associated osteonecrosis of the jaws. Clin Oral Invest 2014; 18(3):1015-1022
14. Garant PR. Oral Cells and Tissues. Quintessence Books, Carol Stream, IL, 2003, p.219.
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16. Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaws. Hematology 2006; 356-360.
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POST-TEST

Internet Users: This page is intended to assist you in fast and accurate testing when completing the "Online Exam." We suggest reviewing the questions and then circling your answers on this page prior to completing the online exam.

(1.5 CE Credit Contact Hour) Please circle the correct answer. 70% equals passing grade.

1. **Bisphosphonates may be used to treat all of the following except:**
   a. Osteoarthritis
   b. Osseous metastasis of lung and breast cancer
   c. Paget's disease of bone
   d. Myeloma

2. **The particular predilection for the mandible and maxilla for bisphosphonate-related osteonecrosis in comparison to other skeletal sites relates in large part to:**
   a. the presence of a highly restored dentition and metallic restorations.
   b. the oral microbial environment and its and its local disease-causing possibility
   c. the rate of alveolar bone turnover and metabolism.
   d. frequency of performing restorative dental procedures.

3. **The primary metabolic action of bisphosphonate agents is:**
   a. creation of healthy bone.
   b. enhancement of calcium mobilization by osteoclasts.
   c. alteration of osteoclast GTP-binding proteins
   d. promotion of osteoblast differentiation and proliferation.

4. **When compared to bisphosphonates, the mode of action of denosumab relates to binding to specific receptors which in turn:**
   a. prevents adequate bone mineralization
   b. promotes osteoclast degeneration
   c. inhibits osteoclast apoptosis
   d. interfere with precursor osteoclast maturation and survival

5. **Bisphosphonates exert an antiangiogenic and antineoplastic effect in vivo by:**
   a. reducing serum levels of vascular endothelial growth factor.
   b. direct endothelial toxicity.
   c. acting as a weak cytotoxic agent.
   d. altering intracellular calcium transport.

6. **Which of the following factors is most likely to contribute to the development of MRONJ?**
   a. poor occlusal inter-relationship.
   b. maxillary and mandibular tori.
   c. duration of bone-stabilizing medication use
   d. the presence of removable dental appliances.

7. **The risk of MRONJ developing in patients being managed for benign skeletal disease with oral bisphosphonates ranges from:**
   a. 1% to 4%
   b. 0.4%
   c. 0.7%
   d. 0.001% to 0.004%

8. **Of the currently available forms of bisphosphonate compounds available, which is the most potent on a milligram per milligram basis?**
   a. Zoledronate (Zometa®)
   b. Pamidronate (Aredia®)
   c. Alendronate (Fosamax®)
   d. Risedronate (Actonel®)

9. **The turnover rate of alveolar bone may influence which characteristic of bisphosphonate metabolism?**
   a. half-life of drug retention
   b. amino group cleavage
   c. dissociation from bone matrix
   d. calcium chelation

10. **Which of the following conditions is not an indication for the use of bisphosphonates?**
    a. multiple myeloma
    b. Paget's disease of breast
    c. osteoporosis
    d. bony metastasis

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