

Bisphosphonate Related Osteonecrosis of the Jaws: A Review and Update

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Introduction

The intravenous bisphosphonate drugs, Pamidronate (Aredia) and Zoledronate (Zometa), were approved for use in metastatic cancer therapy in 2001 and 2002, respectively. In 2003, Marx first reported painful exposure of bone in the mandible and maxilla in patients receiving intravenous bisphosphonates.¹ In the years that have followed, many more cases of jaw necrosis have been reported in the U.S. and abroad.^{2,3} Oral bisphosphonate medications like Alendronate (Fosamax), which are used for osteoporosis therapy, have also been linked to the process, but much less frequently. This condition which was formerly known as avascular necrosis of the jaws is now referred to as bisphosphonate related osteonecrosis of the jaws (BRONJ).⁴ Expert panels, consisting of representatives of the pharmaceutical industry, dental specialists, oncologists, and bone physiologists have assembled to examine risk factors, recognition, prevention, and treatment of BRONJ. The American Association of Oral and Maxillofacial Surgeons (AAOMS) established a BRONJ Task Force which released a position paper concerning BRONJ in September, 2006. Using information gathered over the last two and one-half years, this position paper was updated in January 2009. This update reflects the

most current research and thought on this condition.

In the spring of 2005, this author published an article which described BRONJ and presented information about the process, which was available at that time. In light of the research and experience gained in treating BRONJ since that time, this review and update is offered.

Bone Metabolism

Calcium homeostasis in the body is a coordinated effort of the kidneys, parathyroid glands, and intestines, in consort with the skeleton. Precursor cells within the bone marrow are capable of differentiating into osteoclasts or osteoblasts. Osteoblasts mature into osteocytes, the most numerous cells in the mineralized bone matrix. The mineralized matrix is a rich source of growth factors, including insulin-like growth factors 1 and 2 and bone morphogenic protein. Decreases in serum calcium stimulate parathyroid hormone production which stimulates osteoclastic bone resorption in an effort to release calcium from the bone into the blood stream. Acid secretion into the mineral matrix by the osteoclasts releases growth factors resulting in differentiation, stimulation, and maturation in osteoblasts, which are responsible for bone formation. Thus, the appropriate balance of osteoblastic and osteoclastic activity is maintained. In cancer patients, hormonal and cellular regulation is disrupted. Multiple tumor factors are secreted, including parathyroid related hormone (PTH)-related protein, which results in an exaggerated PTH-like function. Certain cancers, for example: lung, breast, prostate, and multiple myeloma commonly metastasize to the axial skeleton, particularly the long bones, pelvis, and vertebrae. The osteoclastic processes associated with metastasis result in hypercalcemia,

pathologic fractures and compression of the spinal cord.⁵

Osteoporosis also represents a bone remodeling imbalance, but to a lesser extent. In osteoporosis, resorption exceeds formation due to increased osteoclastic activity. This decrease in bone formation is often debilitating and sometimes lethal. Twenty percent of patients who sustain a hip fracture secondary to osteoporosis die in the ensuing three months, and fifty percent never walk again.⁶ Other processes with abnormal osteoclastic activity include osteopetrosis (genetic loss of osteoclasts), Paget's disease, and fibrous dysplasia.

Bisphosphonates

Bisphosphonates are non-metabolized analogues of pyrophosphate that avidly bind to bone mineral around resorbing osteoclasts and inhibit their function. Since they are not metabolized, high concentrations are maintained in the bone for long periods of time actively disrupting osteoclast-mediated bone resorption, thus maintaining bone density. Bisphosphonates are most commonly used in the treatment of osteoporosis and the complications associated with bone metastases. Bisphosphonates are available in injectable and oral preparations. The injectables are used primarily in the treatment of metastatic bone disease, although recent protocols for osteoporosis and Paget's disease have been approved by the FDA.⁴ Use of the intravenous bisphosphonates is considered the standard of care in the treatment of the hypercalcemia and osteopenia associated with metastatic malignancies. The oral bisphosphonates are most commonly used in the treatment of osteoporosis. The intravenous preparations are thirty to forty times more potent than the oral, and are statistically more likely to be associated with BRONJ.⁷

Intravenous Preparations

Pamidronate (Aredia) and Zoledronate (Zometa) are the two drugs utilized intravenously for metastatic cancer therapy. They are credited with decreasing the skeletal complications of metastatic cancers by up to one third. If tolerated, the cancer patient may be maintained on the drug indefinitely. One source estimates that there are currently three million patients on intravenous bisphosphonate therapy in the United States. Zometa has recently been approved for use in osteoporosis. Marketed under the name Reclast, it is injected once a year, compared to the four to twelve treatments per year protocol used in metastatic cancer therapy.

Oral Preparations

Oral bisphosphonate preparations are most commonly utilized in treating osteoporosis, especially in the postmenopausal female. The most common drugs are Alendronate (Fosamax), Risedronate (Actonel) and Ibandronate (Boniva). It is estimated that 14 million women in the United States are taking an oral bisphosphonate. In 2003, seventeen million prescriptions were written for Fosamax and six million for Actonel. Worldwide more than 190 million prescriptions for the oral bisphosphonates have been written. There have been rare reports of cases of esophageal cancer associated with oral bisphosphonate use.⁸

Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ)

Since first being reported by Marx and Ruggiero in 2003, more than 2000 cases of BRONJ have been reported. The number of cases is most likely significantly greater, since many cases go unreported. The bulk of the reported cases continue to be related to patients being treated with intravenous therapy for metastatic malignancy. Oral preparations represent less than 10 percent of reported cases.

The mechanism of BRONJ is the vascular insufficiency from the excessive inhibition of osteoclastic activity produced by the bisphosphonates. Bisphosphonates directly inhibit endothelial cell function, depress bone blood flow and display potent anti-angiogenic properties.⁹

All reported cases of BRONJ involve the jaws. The rapid remodeling that occurs in the jaws compared to the rest of the skeleton (the alveolar crest remodels at a rate ten-fold that of long bones), the added potential for inflammation due to the dentition and the bacterial rich oral environment provide a reasonable explanation for this.¹⁰ A number of cofactors have also been identified with increasing risk of BRONJ (see **Table 1**).¹¹ Local factors such as periodontitis, caries, abscessed teeth, failing endodontic therapy and tori may also impact occurrence rates. A history of inflammatory dental disease increases the risk of BRONJ at least seven-fold. Other potential risk factors include age, (multiple myeloma patients face a nine percent increased risk of developing BRONJ with each passing decade), and the concurrent diagnosis of osteopenia or osteoporosis in combination with a cancer diagnosis. Because only a small number of bisphosphonate patients develop bone necrosis, individual genetic variations in drug metabolism or skeletal homeostasis may confer susceptibility or resistance to developing BRONJ.¹²

Cases reported in patients taking intravenous preparations have seldom received therapy for less than a year. To date, no case of BRONJ has been reported in a patient taking an oral form for less than three years (in the absence of co-morbidities). Seventy-five percent (75%) of reported cases of BRONJ have been initiated by an invasive dental procedure with only twenty-five percent (25%) occurring spontaneously. The process is twice as likely to occur in the mandible as in the maxilla. The overall prevalence of BRONJ in the intravenous therapy population is three to eight percent (3-8%). The prevalence in patients taking an oral preparation is .09-.34% following an invasive procedure or incident of dental trauma and an incidence of .01-.04% in the absence of trauma.

Clinical Presentation of BRONJ

The clinical definition of BRONJ developed by the AAOMS BRONJ Task Force is: an osteonecrosis of the jaws that refers to a condition of exposed necrotic bone in the mandible or maxilla that persists for more than eight weeks in a patient who has taken or is

currently taking a bisphosphonate and has no history of radiation therapy to the jaws.¹¹ The most common presentation is exposed bone and pain, although the patient may be asymptomatic for months unless the area becomes infected or traumatized. Tooth mobility and deep bone pain may present before bone exposure. The process always begins in the alveolus, usually in the molar region. Dead bone is painless, unless infection is present. Progression to sequestrum formation is common. Unlike osteoradionecrosis, the maxilla is commonly affected. Early radiographic findings include widening of the periodontal ligament space and sclerosis of the lamina dura. Later radiographs may demonstrate regions of mottled bone and sequestrum formation. Cultures from affected areas reveal normal oral flora, commonly actinomyces, eikenella and moraxella. Microscopy shows dead bone with bacterial debris and granulation tissue. Potentially confusing clinical conditions which may have symptoms that resemble BRONJ include alveolar osteitis, sinusitis, periodontal disease, caries, periapical pathology, and TMJ disorders.

Management Strategies for the Bisphosphonate Patient: Management Prior to Beginning Therapy

Prior to beginning bisphosphonate therapy, the patient should have a thorough dental examination. Extraction of hopeless teeth and all invasive dental procedures should be performed, and optimal periodontal health should be achieved. Special attention should be directed to the lingual flange area of removable prosthetic appliances where mucosal irritation may be an issue. Removal of tori and other bony exostoses should be considered to eliminate potential areas of mucosal breakdown. If possible, surgical sites should be allowed to heal for at least 14 to 21 days before bisphosphonate therapy is begun. It is important to educate the patient regarding the absolute necessity of maintaining optimal oral health once therapy has begun.

Management of the Asymptomatic Bisphosphonate Patient

Maintaining good oral hygiene

and dental care is of the utmost importance. In the oncology patient receiving bisphosphonate therapy, procedures that involve direct osseous injury should be avoided. Non-restorable teeth should be treated by removal of the crown and endodontic treatment of the remaining roots. Placement of dental implants should be avoided. Patients taking Zoledronic acid (Reclast) via injection once annually for treatment of osteoporosis are at a much lower level of risk for developing BRONJ. Appropriate timing for dentoalveolar surgery in these patients is unknown and requires further study. Treatment considerations for the annual injection Zoledronic acid patient are the same as the asymptomatic oral bisphosphonate patient.^{13,14}

Elective dentoalveolar surgery, including implants, does not appear to be contraindicated in the patient taking an oral bisphosphonate for a period of less than three years and with no other risk factors (**Table 1**);¹⁵ however, patients need to be adequately informed of the small risk of compromised bone healing. This should be part of the informed consent process and also be appropriately annotated in the dental record. In patients with a three or more year history of oral bisphosphonate use or with other risk factors, it is recommended that their prescribing provider be consulted concerning a drug holiday. If the patient's systemic conditions permit, the drug should be stopped at least three months before oral surgery and should not be resumed until osseous healing has occurred. This strategy is based on the opinion of experts and observational studies. Long-term prospective studies are required to establish the efficacy of this practice. Use of a systemic marker of bone turnover (CTX) to determine risk of developing necrosis of the jaws is another strategy requiring further research.

Treatment of BRONJ

Treatment goals should include patient education and reassurance, control of pain and secondary infection, and the prevention of extension of lesions and development of new areas of necrosis. Staging of the disease process and treatment options

Table 1. Cofactors that Increase the Risk of BRONJ

1. Corticosteroid therapy
2. Diabetes and obesity
3. Smoking
4. Alcohol use
5. Poor oral hygiene
6. Chemotherapeutic drugs
7. Age
8. Renal dialysis
9. Low hemoglobin

for each stage have been developed (see **Table 2**).¹¹ It should be noted that these guidelines come from experience in treating BRONJ patients. No evidence from longitudinal prospective studies is available at this time.

There is less predictability than the accepted surgical treatment guidelines for osteomyelitis or osteoradionecrosis in dealing with BRONJ. Surgical debridement is variably effective and identifying viable peripheral bleeding bone may be difficult. Surgical treatment should be delayed and reserved for

patients with Stage 3 disease or well-defined sequestrum. Areas of necrotic bone that irritate the adjacent tissues should be removed and recontoured without the exposure of additional bone. Extraction of symptomatic teeth within exposed, necrotic bone should be considered since it appears unlikely that the extraction will exacerbate the established necrotic process. Elective dentoalveolar surgical procedures should be avoided. Acceptable outcomes for surgical therapy using resection and reconstruction with a reconstruction plate or obturator in patients with Stage 2 and Stage 3 disease have been described. The patient and clinician need to be aware of the potential for reconstruction plate failure due to the quality of the diseased bone. Immediate reconstruction with non-vascularized or vascularized bone is still considered problematic due to the continued potential for development of necrotic bone at the recipient site.

There are presently two studies evaluating the efficacy of hyperbaric oxygen therapy in the BRONJ patient. Preliminary reports have shown some improvement in wound healing, but its use as a sole treatment modality cannot be supported at this time. Other non-surgical strategies have been documented using platelet rich plasma, parathyroid hormone, and bone morphogenic protein, but these were case reports with small sample sizes. Additional research using controlled studies will be required to assess the effectiveness of these modalities.

Table 2. BRONJ Staging

Stage 0 (at risk)- taking a bisphosphonate with no exposed bone or symptoms; or non-specific symptoms or clinical and radiographic abnormalities

Stage I- exposed bone, no pain or infection

Stage II- exposed bone with infection and pain

Stage III- pathological fracture, large volume of necrotic bone, no response to antibiotics

Staging and Treatment Strategies: Stage 0

These patients have no clinical evidence of necrotic bone, but present with non-specific symptoms or clinical and radiographic findings. These symptoms include unexplained tooth or bone pain, loosening of teeth without periodontal disease or fistula formation without pulpal necrosis due to caries, and periodontal ligament changes or alveolar bone loss in the absence of periodontal disease. Treatment should include symptomatic treatment and conservative management of caries and periodontal disease. Systemic management may include medications for chronic pain management and control of infection with antibiotics as needed.

Stage 1

There is exposed and necrotic bone, but the patient is asymptomatic with no evidence of infection. No surgical treatment is indicated in these patients. The importance of oral hygiene should be emphasized and oral antimicrobial rinses should be utilized.

Stage 2

The manifestations in this stage are exposed necrotic bone with pain and clinical evidence of infection. Antibiotic therapy combined with oral antimicrobial rinses should be employed. Penicillin has proven effective against most of the isolated microbes. Quinolones, metronidazole, clindamycin, doxycycline, and erythromycin have been used with success in the penicillin allergic patient. Presence of *Actinomyces* may require adjustment of the antibiotic regimen. Patients may require combination antibiotic therapy in resistant cases. Patients may benefit from long-term low-dose antibiotic therapy with larger doses reserved for acute exacerbations.

Stage 3

These patients present with exposed and necrotic bone, pain, infection, and one or more of the following:

1. Exposed necrotic bone extending beyond the region of alveolar bone
2. Pathologic fracture
3. Extra-oral fistula
4. Oral antral/oral nasal communication
5. Osteolysis extending to the inferior border of the mandible or sinus floor

These patients benefit from debridement, including resection, in combination with antibiotic therapy, which may offer long-term resolution of acute infection and palliation of pain. Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within necrotic, exposed bone should be considered, since it is unlikely that the extraction will exacerbate the established necrotic process.

Discontinuation of Bisphosphonate Therapy

Discontinuation of IV bisphosphonates offers no short-term

benefit. However, if systemic conditions permit, discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development and reducing clinical symptoms. The risks and benefits of discontinuing therapy should be made only by the treating oncologist in consultation with the dentist/oral surgeon and the patient.

Discontinuation of oral bisphosphonate therapy has been associated with gradual improvement in clinical disease in patients with BRONJ. Six to twelve months after discontinuing the drug there may be either spontaneous sequestration or resolution following debridement surgery. Cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Conclusion

Bisphosphonates have received considerable attention in the dental literature since the first cases of what we now call BRONJ were reported in 2003. In the five years that have followed, new bisphosphonate drugs have been introduced (Boniva), new uses for existing drugs (Reclast) have been approved, and some 2000 cases of BRONJ have been reported. Although longitudinal prospective studies are currently in progress, up to now most of our knowledge concerning BRONJ comes from the treatment experiences of clinicians, retrospective studies of medical claims and patient records, and the extrapolation of bone physiology and pharmaceutical research. Until long-term prospective studies and evidence-based results validate the current therapies and protocols, we will continue to rely on the experiences of clinicians treating BRONJ patients to provide the information for furthering our understanding of the process. This paper was undertaken with the intent of reviewing BRONJ as we know it today.

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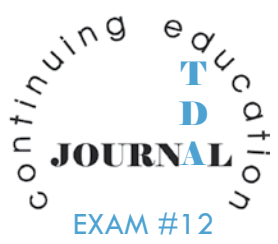
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Questions for Continuing Education Article - CE Exam #12

1. Who first reported bisphosphonate-related osteonecrosis of the jaws?
 - a. R E Marx
 - b. Groucho Marx
 - c. Schluger
 - d. Fox News
2. Oral bisphosphonates are used for:
 - a. Osteoporosis therapy
 - b. Melanoma
 - c. Enamel hypoplasia
 - d. Acromegaly
3. Certain cancers that metastasize to the axial skeleton may result in:
 - a. Hypercalcemia
 - b. Hypocalcemia
 - c. Increased high-density lipoproteins
 - d. Increased cholesterol
4. Decreases in serum calcium stimulate:
 - a. Intense thirst
 - b. Production of insulin-like growth factors
 - c. Parathyroid hormone production
 - d. Hyperthyroid disease
5. Bisphosphonates are non-metabolized analogues of:
 - a. Pyromania
 - b. Phosphoric acid
 - c. Pyrophosphate
 - d. Phenylketone
6. BRONJ is twice as likely to occur in:
 - a. Men
 - b. The maxilla
 - c. The mandible
 - d. All the above
7. The genetic loss of osteoclasts is:
 - a. Osteomyelitis
 - b. Osteopetrosis
 - c. Osteoblastosis
 - d. Trisomy of chromosome 21
8. The mechanism of BRONJ is:
 - a. Valvular insufficiency
 - b. Vascular insufficiency
 - c. Bone marrow dyscrasia
 - d. Unknown
9. All reported cases of BRONJ involve the:
 - a. Femurs
 - b. Jaws.
 - c. Pelvis
 - d. Humerus
10. Prior to beginning bisphosphonate therapy the patient should:
 - a. Have a thorough dental examination
 - b. Have all teeth extracted
 - c. Have a colonoscopy
 - d. A CBC and chest xray

Answer Form for TDA CE Credit Exam #12: *Bisphosphonate Related Osteonecrosis of the Jaws: A Review and Update*

Circle the correct letter answer for each CE Exam question:



1. a b c d	6. a b c d
2. a b c d	7. a b c d
3. a b c d	8. a b c d
4. a b c d	9. a b c d
5. a b c d	10. a b c d

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