

MEDICATION-RELATED OSTEONECROSIS OF THE JAW

In 2004, a number of reports began to document a pattern of gnathic osteonecrosis that was difficult to treat and appeared to be associated with certain medications. An initial correlation to bisphosphonates led to the name Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ). In 2011, the name was modified to Antiresorptive-related Osteonecrosis of the Jaw (ARONJ) due to the discovery of an association with a monoclonal antibody designed to prevent osteoclastic maturation (denosumab). In 2014, the name was changed again to Medication-related Osteonecrosis of the Jaw (MRONJ) due to the discovery that antiangiogenic therapies also may be implicated. This last term is sufficiently generic and hopefully will stand the test of time.

The majority of this handout concentrates on bisphosphonates, but a brief description of denosumab and the antiangiogenic agents appear appropriate.

Denosumab is a monoclonal antibody that disrupts the maturation of osteoclasts. The medication is injected and reduces osteoclastic activity by 85% within three days. The half-life is 25.4 days; therefore, it takes 4-5 months to clear completely. As the levels diminish, the osteoclastic activity rebounds and it is not deposited within the bone. Two formulations are available. Xgeva® is injected monthly in cancer patients, while Prolia® is injected twice a year for patients with osteoporosis.

The antiangiogenic agents are prescribed for a variety of cancers and include tyrosine kinase inhibitors {Axitinib (Inlyta®), Cabozantinib (Cometriq®), Dasatinib (Sprycel®), Imatinib (Gleevec®), Pazopanib (Votrient®), Sunitinib (Sutent®); Sorafenib (Nexavar®)}, mTOR kinase inhibitors {Everolimus (Afinitor®), Temsirolimus (Torisel®)} and monoclonal antibodies directed against vascular endothelial growth factor {Bevacizumab (Avastin®); Ramucirumab (Cyramza®)}. The evidence supporting an association with osteonecrosis is based primarily on case reports, but a low risk does appear to exist. This risk is increased if these agents are combined with bisphosphonates.

Bisphosphonates represent a class of medications that appear to alter normal osteoclastic function and may affect angiogenesis. These drugs are utilized to decrease osteoporosis, slow the progression of Paget Disease and prevent osseous spread of neoplasms such as multiple myeloma, breast carcinoma and prostate carcinoma. When utilized as an antineoplastic, the medication typically is infused monthly for the life of the patient. In the other indications, the drug usually is given chronically by mouth or intravenously (annually or quarterly). Although the entire class of medications has been associated with an increased prevalence of gnathic osteonecrosis, the antineoplastics demonstrate the strongest association. The necrosis often follows minor trauma or infection. Once initiated, the process is very difficult to treat and exhibits similarities to severe osteoradionecrosis.

To provide an idea of the strength of the association between these medications and osteonecrosis, the following relative risks in cancer patients may be helpful.

Zoledronate: 100/10,000 (100X smaller risk in osteoporosis patients)

Denosumab: 70-90/10,000

Bevacizumab: 20/10,000

OSTEOPOROTIC MEDICATIONS BEYOND ESTROGEN

- Bisphosphonates
- Evista (raloxifene)
- Miacalcin (calcitonin)
- Prolia (denosumab)
- Forteo (teriparatide) or Tymlos (abaloparatide)

BISPHOSPHONATES

Antineoplastics are worse: Approximately 90% of reported cases

- Aredia (Pamidronate disodium): 100**
- Boniva (Ibandronate sodium): 10,000**
- Zometa (Zoledronic acid): 100,000**
- Bonfos (*Coldronate*): 10**

Therapeutic for Paget Disease, Osteogenesis Imperfecta, or Osteoporosis

- Actonel (Risedronate sodium): 5,000**
- Atelvia (Risedronate sodium): delayed release formulation 5,000**
- Boniva (Ibandronate sodium, PO or **IV 4/year**): 10,000**
- Fosamax (Alendronate sodium): 1,000**
- Reclast (Zoledronic acid, **IV 1/year**): 100,000**
- Bonfos (*Coldronate*): 10**
- Didronel (*Etidronate disodium*): 1**
- Skelid (*Tiludronate disodium*): 10**

Non-aminobisphosphonates are missing a nitrogen arm, are less potent, and have not been associated with osteonecrosis. ** refers to the relative potency.

Before initiating therapy with intravenous bisphosphonates

1. Thorough dental evaluation with elimination of all oral foci of infection.
2. Improve oral health to prevent future invasive therapy
3. All large tori should be removed.

The infusions need not be delayed if only noninvasive dental therapy is performed. If invasive dental procedures are necessary, the initiation of the infusions should be delayed one month; and the patients should receive prophylactic antibiotics associated with the dental therapy (penicillin; quinolones & metronidazole or erythromycin & metronidazole for those allergic). Once the infusions have begun, the patient should be recalled every four months.

Dental therapy in patients receiving intravenous bisphosphonates

1. Invasive procedures should be avoided.
2. Splint teeth with 1+ or 2+ mobility
3. If a tooth is nonrestorable and extraction is under consideration, endodontics and crown amputation are a better option unless the tooth demonstrates 3+ mobility.
4. All elective surgical procedures are contraindicated, including removal of impactions and tori, placing implants or performing periodontal surgery.

Similar guidelines for the PO bisphosphonates have not been solidified. The number of patients using these formulations are extremely high and the prevalence of complications extremely low. In spite of this, appropriate patient consent seems prudent and placement of implants is debatable.

Treatment of active osteonecrosis

1. Hyperbaric oxygen is minimally beneficial.
 2. Removal of necrotic bone typically results in more bone necrosis. Patients can and must live with exposed bone
 3. The goal of therapy becomes elimination of pain.
- Stage 0: No clinical evidence of necrotic bone but presents with nonspecific symptoms, clinical findings, or radiographic alterations which suggest potentially evolving osteonecrosis
Symptoms: Unexplained odontalgia, aching bone pain, sinus pain, altered neurosensory function
Clinical findings: unexplained loosening of teeth; sinus tract not associated with pulpal necrosis due to caries
Radiographic alterations: unexplained bone loss, altered trabecular pattern (patches of increased density, failure of remodeling in extraction sockets), thickening of lamina dura, decreased size of PDL, and narrowing of the inferior alveolar canal.
1. Provide symptomatic treatment and conservative management of local factors such as caries or periodontal disease
 2. Systemic management to reduce symptoms, including antibiotics and pain medications
 3. **Damm addition:** avoid any osseous procedure. Addition of bacteria to compromised bone risks progression of the process (active osteonecrosis)
- Stage 1: Necrotic exposed bone that is asymptomatic
1. Daily chlorhexidine rinse or irrigation
 2. Regular clinical follow-up
 3. If symptoms arise, reclassify as Stage 2
- Stage 2: Necrotic bone with pain and infection
1. Surgical removal of dead bone may lead to more dead bone
 2. Hyperbaric oxygen is of no benefit
 3. Treatment goal is to eliminate pain
 - ▶ Long-term pen V-K 500mg QID and Peridex.
 - ▶ Refractory cases: metronidazole 500mg TID added to the 1^o regimen.
 - ▶ Allergic patients: ciprofloxacin 500mg BID or erythromycin 400mg TID and metronidazole 500mg TID are recommended.
 4. Patients with severe cellulitis warrant hospitalization and IV antibiotics.
 5. Refractory cases: Operative therapy directed at reducing the volume of colonized necrotic bone may serve as a beneficial adjunct to antibiotic therapy.
- Stage 3: Necrotic exposed bone with pain, and infection combined with pathologic fracture, oroantral or oral-nasal fistula, extension to the inferior border, or extraoral sinus tract.
1. Large mass of necrotic bone overwhelms conservative measures
 2. Pain is refractory to PO and IV antibiotics
 3. Surgical debridement/resection
 - ▶ Pathologic fracture: reconstruction plate
 - Bone graft not advocated
 4. Following surgery, use Stage 2 antibiotic schedule

Dental therapy in patients receiving oral bisphosphonates

The ADA has convened an expert panel and provided a PDF related to the dental management of patients receiving oral bisphosphonate therapy. In addition, the ADA maintains a website link that provides updated information on a variety of oral health problems: <http://www.ada.org/professional.aspx> then click on Oral Health Topics. The PDF is very good, provides information relevant to every involved specialty and most likely represents the standard of care for the near future. The following comments are derived from this document.

Routine dental therapy should not be modified solely on the basis of bisphosphonate use. BON (bisphosphonate osteonecrosis) can occur spontaneously, due to dental disease or secondary to dental therapy. All dental patients using oral bisphosphonates should be informed that the risk of osteonecrosis is very low (0.7/100,000 patient-years), there are no diagnostic techniques to identify those at increased risk, and the best way to minimize the already low risk is good oral hygiene with regular professional dental care.

Situations associated with an increased risk of osteonecrosis include an age greater than 65 years, estrogen supplementation, use of glucocorticoids and prolonged use of bisphosphonates. It has been shown that bisphosphonates truly increase bone mass over time. There is a concern the prevalence of osteonecrosis may increase in patients who have significantly increased bone mass secondary to the medications. Hopefully, in the future, the medications will be used only for a limited period and stopped once an acceptable bone mass has been obtained.

For restorative dentistry and prosthodontics, all routine restorative procedures can be performed. There is no evidence that malocclusion or masticatory forces increase the risk of BON. All prosthodontic appliances should be adjusted for fit as needed.

To state the obvious, orthodontics is difficult in patients using these medications. Bisphosphonates preferentially are drawn to areas of high bone turnover, such as orthodontics. Therapy can be initiated with the proviso that a decision point will be made in 2-3 months when the success of tooth movement is evaluated. During therapy, chlorhexidine should be utilized twice daily. If the attending physician believes the bone mass has reached an acceptable level, a two-year drug holiday should be suggested until the orthodontics is completed. Orthognathic surgery and four-tooth extraction cases are not recommended.

When presented with patients that require periodontal therapy, all forms of non-surgical treatment are appropriate. When necessary, surgery should be minimized and aimed at obtaining access to root surfaces with modest bone recontouring. Use of guided bone regeneration or guided tissue regeneration should be reconsidered, since bisphosphonates decrease vascularity of the tissues and have a negative effect on grafted sites.

Conventional endodontics is not contraindicated, but manipulation beyond the apex is not recommended. If a tooth is salvageable, endodontics takes preference over extraction. Periapical surgical procedures are guided by the same recommendations as for any oral and maxillofacial surgical procedure.

If invasive surgical procedures become necessary, if possible, treat one sextant or tooth first and allow two month disease free follow-up while using chlorhexidine twice daily. After initial success, treatment may accelerate at a more normal multi-sextant and follow-up schedule. The sextant approach does not apply to emergency cases such as periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis or active abscesses. These pathoses already damage the medullary bone and can trigger BON. All sites should be treated immediately.

There is limited data regarding the effects of implant placement. Since implants require preparation of the osteotomy site, the use of implants should be considered carefully. Extensive implant placement or guided bone regeneration to augment deficient alveolar ridges are at increased risk for BON and is discouraged. Prior to any implant, the patient and dentist must thoroughly discuss the risks, benefits and treatment alternatives. This discussion and final consent should be documented in writing.

When considering oral and maxillofacial surgery, all invasive procedures should be preceded by written documentation and thorough discussion of the risks, benefits and alternative therapies. Endodontics is preferred over extractions. Bridges and partials represent a safer alternative to implants in many patients. Prophylactic antibiotics are not mandatory or even recommended except in patients in a high risk group. Post-surgical antibiotics are appropriate in patients who develop unexpected pain, purulence or active sequestration. Amoxicillin (500mg TID for 14 days) is recommended and may be combined with metronidazole (250mg, TID for 14 days). For those allergic to penicillin, clindamycin (300mg TID for 14 days) or azithromycin (250mg per day for 14 days) is appropriate.

CTX Testing

Marx incorporates use of a serum marker to assist in the timing of invasive procedures in patients utilizing oral bisphosphonates. This system is in its initial phases of evaluation and currently is not recommended by all authorities. C-Terminal Telopeptide is a metabolite of bone matrix degradation and is used as a marker of osteoclastic function. Evaluation for this metabolite is termed CTX testing and is performed by Quest Diagnostics Nichols East Lab in San Juan Capistrano, CA. Although the official reference range is wide, the CTX value in most normal individuals is over 300 and often between 400-500. Values below 150 are thought to be at risk for osteonecrosis. The current ADA and AAOMS position papers state the validity of CTX testing has not been confirmed and use of this test is not recommended.

When are bisphosphonates indicated?

Osteopenia is not an indication for bisphosphonate therapy. The North American Menopause Society updated their position statement in 2010 and utilizes the WHO's Fracture Risk Assessment tool (FRAX): www.shef.ac.uk/FRAX/index.htm.

Therapy is indicated if one of the following is present:

1. Previous osteoporotic vertebral or hip fracture
2. BMD T score of -2.5 or lower
3. BMD T score of -1 to -2.5 **AND** 10-year FRAX risk of 20% for major osteoporotic fracture or 3% risk of hip fracture

Long-term use of oral bisphosphonates harmful???

Long-term use of oral bisphosphonates is losing appeal but still commonplace. Extended studies have shown that the medications demonstrate significant osseous effects within the first three years, but slow increases in bone density continue to occur. A small number of reports have documented unexplained femur fractures occurring in patients who have been utilizing bisphosphonates for an extended period of time. In these publications, cessation of bisphosphonates is promoted after five years of continuous use.

In a large 10-year study, half of the participants stopped the meds at 5 years and were compared to those who continued use of bisphosphonates. The cessation group demonstrated only a small decrease in BMD over five years (<3%) and experienced no increase in nonvertebral fractures. A lower risk of vertebral fracture was noted in those who remained on bisphosphonates. The authors of this study concluded cessation of bisphosphonates was appropriate except in patients with extremely low BMD or clinical vertebral fractures.

BMD is measured by dual energy x-ray absorptiometry scan (DXA, DEXA scan). The results of this scan are compared to the average bone density of a 22 year old female. The following system is applied:

Normal: BMD within 1 standard deviation of normal

Osteopenia: BMD between 1-2.5 standard deviations below normal

Osteoporosis: BMD greater than 2.5 standard deviations below normal

Findings reported as T-score such as 0, -1, -2.5, etc.

Medicare pays for a DEXA scan every two years. In patients on oral bisphosphonates, it appears prudent to repeat this evaluation at this interval. After 5-6 years of active therapy, cessation seems appropriate except for those with very low BMD or clinical evidence of vertebral fractures. In these cases, bisphosphonates with regular bone scans could be continued or replaced with periodic Forteo, weight-bearing exercise, and calcium supplements.

DRUG HOLIDAY CONTROVERSY

In the original ADA position paper, a three month drug holiday before and after osseous surgery was suggested for any patient using bisphosphonates longer than three years. In the 2011 update, the ADA removed this suggestion with the following statement. *“No study results to date have confirmed that drug holidays are effective in prevention of ARONJ without increasing the skeletally related risks of low bone mass.”* In spite of this, the 2014 AAOMS update recommended use of a drug holiday for patients using bisphosphonates longer than four years or patients who also are utilizing systemic corticosteroids or antiangiogenic agents.

The following protocol can be used to resolve this controversy. With use of specific antiresorptive medications and appropriate surgical timing, the chance of osteonecrosis can be minimized while still protecting the patient from skeletally related risks of low bone mass.

DAMM'S CLINICAL APPROACH TO PATIENTS UTILIZING BISPHOSPHONATES BUT IN NEED OF OSSEOUS SURGERY

Patients utilizing bisphosphonates less than five years

1. Review results of the most recent bone scan
2. Osteopenic patients should utilize FRAX website to discover the necessity of continued therapy
3. Osteoporotic, Frax-recommended osteopenic, MD-mandated osteopenic
 - a. Reclast. Schedule surgery two months after infusion. This allows 10 months of healing prior to next infusion
 - b. Prolia. Schedule surgery two months after injection (79.9% degraded). Allows four months of healing prior to next injection

Patients utilizing bisphosphonates longer than five years

1. Evaluate for evidence of BRON Stage 0 (patchy radiodensity)
2. Review results of the most recent bone scan
3. Osteopenic patients should utilize FRAX website to discover the necessity of continued therapy
4. Alternative therapy should be suggested for osteoporotic patients and osteopenic patients (FRAX-recommended and MD-mandated)
 - a. Limited course of teriparatide (Forteo) or abaloparatide (Tymlos) combined with appropriate calcium and weight-bearing exercises. This therapy should be followed by re-evaluation of the osseous status with subsequent bone scan. Forteo or Tymlos would accelerate healing of the osseous surgical procedure.
 - b. Prolia administered in the patterns described above
 - c. Combination of Forteo or Tymlos with Prolia
 - d. Reclast administered in the pattern described above. This is the least acceptable alternative unless combined with Forteo. If nBP failed to resolve the osteoporosis after five years of therapy, continued Reclast most likely will be less than satisfactory

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ADA website that is meant to provide updated information
www.ada.org/prof/resources/topics/osteonecrosis.asp

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