

MRONJ: Medication-Related Osteonecrosis of the Jaw

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History

- 2004, new reports of difficult to treat jaw osteonecrosis associated with bisphosphonates.
 - Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ)**
- 2011, Antiresorptive-related Osteonecrosis of the Jaw (ARONJ)
 - associated with Denosumab
- 2014, **Medication-related Osteonecrosis of the Jaw (MRONJ)**
 - antiangiogenics implicated

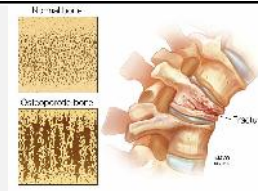
DIONJ- Drug Induced Osteonecrosis of Jaws

- DIONJ aka MRONJ
- ICD 10 code- 87.10
- Drug Osteonecrosis Articles (Marx)
 - Pre 2003: none
 - 2003-2014: ~2400+
- ~21,000 cases in literature (Marx)
- ~13,000 reported to FDA
 - Probably many thousands more unreported

MRONJ Diagnostic Criteria

- History of exposure to bisphosphonates, denosumab (RANKL), or antiangiogenic drugs
- No history of head/neck radiation
- Exposed jaw bone more than 8 weeks

Two Patient Groups



- 1) Osteopenia/osteoporosis, Paget's disease
 - To prevent hip + vertebral fractures
- 2) Primary bone cancer (multiple myeloma), or metastatic cancer to bones



Bisphosphonates

- Alters osteoclastic function
 - **may affect angiogenesis**
- **Life time affect, higher risk more doses**
- **Antineoplastic, HIGHEST RISK**
 - infused monthly for life of patient
- Osteoporosis, Lower dose PO or IV
- **Necrosis can follow minor trauma or infection**
- Necrosis very difficult to treat and exhibits similarities to severe osteoradionecrosis



Once-monthly BONIVA builds bone density to help keep my bones strong and healthy.

Boniva
ibandronate sodium tablets

RALLY WITH SALLY FOR BONE HEALTHSM

"I take BONIVA to help me manage my osteoporosis and strengthen my bones."

Like Sally Field, you, too, can help protect your bones with once-monthly BONIVA.

Bisphosphonates

Table 1. Different types of bisphosphonate in current usage.

Active ingredient	Trade name	Administered
Alendronate	Fosamax [®] , Fosavance [®]	Orally
Etidronate	Osteum [®] , Difosfen [®]	Orally
Risedronate	Actonel [®] , Acrel [®]	Orally
Tiludronate	Skelid [®]	Orally
Zoledronate	Zometa [®] , Aclasta [®]	Intravenously
Pamidronate	Aredia [®] , Linoten [®] , Pamifos [®] , Xinsidona [®]	Intravenously
Ibandronate	Bondronat [®]	Orally, Intravenously
Clodronate	Bonefos [®]	Orally, Intravenously


Bisphosphonates- Other severe issues




Femur Fracture

Lawsuits

Now accepting clients injured by the following Osteoporosis medications:

- ▶ Actonel
- ▶ Boniva
- ▶ Fosamax



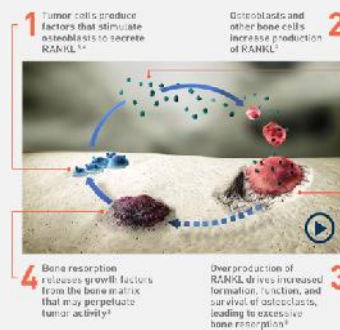
Did you suffer an atypical or low-energy Femur Fracture?

Actonel, Boniva, Fosamax, Prolia, and Reclast linked to injury.

[Click here](#) or call **(888) 633-5204**.

Denosumab (RANKL inhibitors)

- Monoclonal antibody disrupts maturation of osteoclasts
- Reduces osteoclastic activity by 85% in three days
- Half-life 25.4 days; ~4-5 months to clear completely
- **As levels diminish, the osteoclastic activity rebounds**
- Subcutaneous formulations;
 - XGEVA® monthly for cancer
 - Prolia® twice a year for osteoporosis



Half life

- Bisphosphonates- ~11 years
- Denosumab- ~26 days

Antiangiogenic Agents



- Treatment for many different cancers
- Tyrosine kinase inhibitors {Sunitinib (Sutent®); Sorafenib (Nexavar®)} and monoclonal antibodies directed against vascular endothelial growth factor {Bevacizumab (Avastin®)}.
- Association with osteonecrosis is **primarily case reports, low risk**



Disease caveats

- **Denosumab ideal for drug holiday** as body clears from system
 - effectively normal bone around 3-4 months for healing

BUT

- Denosumab cases can be more aggressive initially
- Bisphosphonate followed by Denosumab or Antiangiogenics can be more rapid/extensive disease even years later

MRONJ drugs

- Bisphosphonates
 - PO- Alendronate (Fosamax®), Residronate (Actonel, Atelvia®), Etidronate (Osteum®, Difosen®), Tiludronate (Skelid®)
 - PO or IV- Ibandronate (Boniva®), Clodronate (Bonefos®)
 - IV- Pamidronate (Aredia®)
 - IV- Zoledronate
 - Reclast® (low dose/yearly); **Zometa® (high dose/monthly)**
- Denosumab (RANKL inhibitors)
 - SC- Prolia® (low dose/6 months); **XGEVA® (high dose/monthly)**
- Antiangiogenics
 - IV- Bevacizumab (Avastin®),
 - PO- Sorafenib (Nexavar®), Sunitinib (Sutent®)

MRONJ Risk Factors



- Potency of drug risk
 - IV forms (~5%); 5 out of 100 patients
 - Oral forms (~0.04%); 4 out of 10,000 patients
- Duration of drug use
- Dentoalveolar surgery
 - Tooth extraction (~60% initiating event)

MRONJ Risk Factors



- Mandible > Maxilla
- Poor oral hygiene, heavy tobacco
- Medically compromised state
 - Diabetes, HIV, malnutrition, Steroids etc.
- **Increased risk any combination of bisphosphonates, denosumab, antiangiogenics**

Pertinent Medical History

- Do you now or have you in the past taken any steroids?
- Do you have a history of radiation to the head, neck or jaw areas?
- Do you smoke cigarettes or use tobacco products?
- Do you now or have you ever taken Alendronate (Fosamax®), Clodronate (Bonefos®), Etidronate (Osteum®, Difosen®), Ibandronate (Boniva®), Pamidronate (Aredia®), Residronate (Actonel®, Atelvia®), Tiludronate (Skelid®), Zoledronate (Reclast® or Zometa®), Denosumab (Prolia®, Xgeva®), Bevacizumab (Avastin®), Sorafenib (Nexavar®), Sunitinib (Sutent®) or any osteoporosis drugs?
- Do you now or have you ever had chemotherapy? Please list therapy _____
- Do you have osteoporosis, Paget's disease or ever been treated for any bone disease?
- Do you have a history of multiple myeloma, bone cancer, breast cancer, prostate cancer, colon cancer, or lung cancer?
- Do you have a history of any cancer, if so please list _____
- Any other medical problems that you would like to list _____
- Please list current medications _____

CTX (C-Terminal Telopeptide)

- Metabolite of bone degradation, marker of osteoclastic function
- Blood draw, costs ~\$200, 2 weeks for results
- Normal 300+ pg/ml
- **Below 150 thought to be at risk for osteonecrosis**
- **ADA/AAOMS validity of CTX not confirmed + not recommended**
- **CTX Testing - good thought, unproven, likely many other factors**

Drug Holiday?



- Marx- CTX over 150 and holiday ~3 months for Denosumab, ~9 months for bisphosphonates pre-surgery; 3 months off after surgery.
- AAOMS- 2009 Bisphosphonates (3 months before, 3 months after); 2014 probably no good evidence
- ADA- 2011, less than 2 years of Bisphosphonates or Denosumab, probably no need for drug holiday
- FDA- "no substantial data available to guide decisions regarding the initiation or duration of a drug holiday."
- Damm/Jones- No good evidence, but based on bone physiology theoretically ~ 2 months before and after procedure for PO medications.

Drug Holiday?



- **Very weak evidence for Bisphosphonates (long half life)**
- **Beneficial for Denosumab ~3-4 months before surgery, ~2+ months after**

Before therapy,
All MRONJ risk medications

- **Comprehensive dental workup** for all prior to initiation
- Ideally ~1 month prior for all bony procedures
- **DIFFICULT with new cancer; No excuse for osteoporosis!**

Before therapy,
IV bisphosphonates or XGEVA



- **Dental evaluation**, eliminate all oral infection
- Improve oral health to prevent invasive therapy
- Large tori should be removed
- No need to delay if only noninvasive dental therapy
- Ideally OMFS baseline exam for high risk

Active therapy, IV bisphosphonates or XGEVA



- **Invasive bony procedures should be avoided**
- Splint teeth with 1+ or 2+ mobility
- If non-restorable, root canal therapy with crown amputation is safer than extraction, unless 3+ mobility
- All elective bony procedures are contraindicated;
 - removal of impacted teeth and tori, implants, endo/perio surgery, active orthodontics
- Frequent recall every ~3 months

MRONJ Safe

Safe procedures

- 1) Restorative/prosthetic procedures
 - No evidence that malocclusion or masticatory forces increase MRONJ risk
 - close recall for any removable prostheses
 - **sore spots increase MRONJ risk**
- 2) Nonsurgical periodontal therapy
- 3) Root canal therapy within apex
- 4) Orthodontic retention

Prolia (low dose Denosumab)

- Consult PCP + Oncologist
- Drug Holiday for ~3-4 months, bony procedure, ~2-3 months healing then restart if needed



Active or history, PO Bisphosphonates (what I do)

- Consider drug holiday (~3 months pre/post)
 - except biopsy or incision/drainage
- Procedural prophylactic antibiotics, peridex/saline, close recall
- Thorough informed consent discussed

Active or history, PO Bisphosphonates

Invasive bony procedures **very low risk (BUT NOT ZERO);**

- Extract infected/3+ mobile teeth; Otherwise prefer endo/restorative
- Simple implants +/- (no major grafts, sinus lifts, etc.)
- Impacted teeth or exostosis +/-
- Surgical Endo/Perio +/-
- Active Orthodontics +/-
- Major bony procedures
 - Trauma +, Infection +, Pathology +, TMJ +/-
 - No elective- e.g. Orthognathic, Cosmetic implants



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MRONJ + Osteoradionecrosis of Jaws

- **Prevention is key, most important and only reliable treatment**

Osteoradionecrosis (ORN)



- Irradiated bone becomes exposed with persistent infections
- **Newer radiation (IMRT- Intensity Modulated Radiation Therapy)**
 - focused on tumor, less scatter/collateral damage
 - 4 weeks prior; extract all questionable teeth, especially in radiation fields
 - **NO LONGER STANDARD OF CARE TO EXTRACT ALL TEETH!!!**
- Marked reduction in salivary function very common
 - **FLOURIDE TRAYS FOR ALL**

Osteoradionecrosis (ORN)



- Risk factors
 - Mandible, > 60 Gy radiation, poor OH, medically compromised, Ethanol+, Tobacco+
- High risk MRONJ precautions apply
- **Ideally do not manipulate bone after radiation**
- Unlike MRONJ;
 - HBO some benefit, rarely covered by insurance
 - Reconstruct jaws with vascularized bone free flaps (fibula, hip, etc.)

MRONJ staging

- **At risk group:** History of antiresorptives or antiangiogenics
- **Stage 0:** No clinical evidence of necrotic bone, but non-specific symptoms and clinical or radiographic findings
- **Stage 1:** exposed bone, no infection, **asymptomatic**
- **Stage 2:** exposed bone with **infection, symptomatic**
- **Stage 3:** exposed bone with infection with;
 - Radiographic extension to inferior border of mandible or sinus floor of maxilla
 - Or presence of an **extra oral fistula or pathologic fracture**

Most Common Microorganisms in MRONJ- Marx

- Actinomyces
- Veillonella
- Eikenella
- Moraxella

MRONJ Treatment

- Amoxicillin 500mg TID
- OR
- Doxycycline 100mg QD to BID
- **Add Metronidazole 500mg TID for flareups**
- 0.12% Chlorhexidine TID + Saline rinse for all exposed bone
- May require long term IV antibiotics, multiple surgeries in refractory cases



Ineffective Therapies commonly recommended for MRONJ

- Clindamycin
 - doesn't cover most frequent bacteria
- Hyperbaric oxygen
- Ozone
- Laser


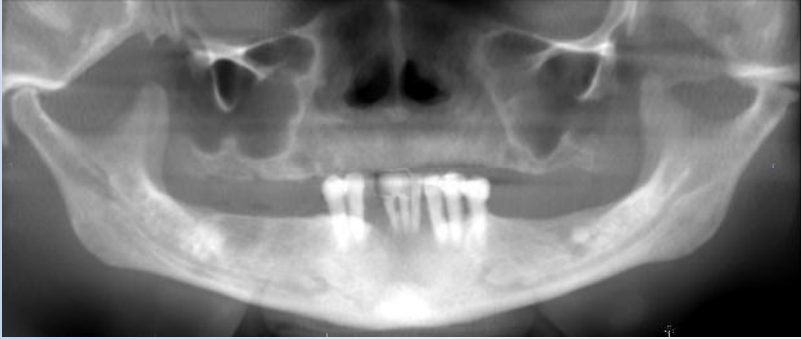
MRONJ Recommendations

At risk/Stage 0	Stage 1	Stage 2	Stage 3
<ul style="list-style-type: none"> Frequent recall Radiographs Pain control <ul style="list-style-type: none"> non-opiates preferred Lifelong follow-up 			
	<ul style="list-style-type: none"> Peridex + saline rinse for exposed bone Debridement or sequestrectomy 		
	(Experimental) <ul style="list-style-type: none"> Tocopherol (Vit E) Pentoxifylline 		
		<ul style="list-style-type: none"> PO advance to IV antibiotics 	
		<ul style="list-style-type: none"> Resection of jaw 	

Stage 1 + 2

88 yo F, Multiple Myeloma,
1.5 years of monthly Zometa

- Started as denture sore
- alternates symptomatic + asymptomatic with pain/purulence

Stage 3

64 yo F, Metastatic Breast Cancer, 9 months after extraction grossly mobile/purulent #14,
3 years XGEVA



Stage 3



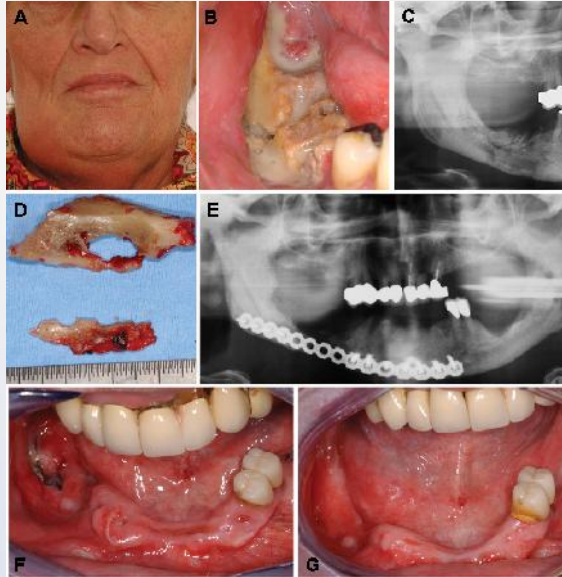
- alternates symptomatic/ asymptomatic with pain/purulence, no bone mobility
- Eventual sequestrectomy, buccal fat pad advancement closure

Stage 3

65 yo F Metastatic Breast Cancer, IV monthly Zometa

- (A) Right submandibular swelling, fluctuance, and skin erythema
 (B) Exposed mandible, purulent drainage
 (C) **Pathologic fracture right mandible**
 (D) Resected Bone
 (E) Immediate postop panoramic with reconstruction plate
 (F) 3 weeks postop with a late plate exposure
 (G) 4 months postop with local wound care

Craniomaxillofac Trauma Recon.
 2013 Sep; 6(3): 147-154.



Controversy

- **If develop MRONJ and have metastatic cancer, cannot stop therapy as this is life saving**
- Oncologists frequently stop therapy with MRONJ
- No real benefit with cessation
 - long half life of bisphosphonates, no tangible healing
 - XGEVA possible bony healing, but cancer spreads

MRONJ Summary

- **High Risk- Zometa, XGEVA**
 - No elective bony procedures
- More doses = more risk; On medication + switch classes, ↑↑ risk
- **Thorough medical history and consent**
- Preventative measures for all, **maintain teeth for lowest risk**
 - Ideally, bony procedures 1 month before any therapy

MRONJ Summary

- Advanced cases may require extensive surgery and hospitalization
- Removal of necrotic bone typically results in more necrosis
 - **Patients can and must live with exposed bone**
 - Goal is to eliminate pain
- No quick fixes, need lifelong follow-up by entire Dental Team

Articles

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Thank You