Medication-Related Osteonecrosis of the Jaw: What’s New and What Can You Do?

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Outline
- Bone metabolism
- Bisphosphonates (Anti-Resorptives, AR) in the treatment of:
  - Osteoporosis patients
  - Cancer patients
- ARs and other drugs in ONJ
- Staging of ONJ
- Case reviews
- Treatment guidelines for ONJ

Bone Metabolism

Robbins and Cotran, Pathologic Basis of Disease, 7th Ed

Bone Metabolism

Yorgan TA, Schinke T Mol Cell Ther 2014 Jul 14:2:22
Bisphosphonates (BPs)
- Analogues of inorganic pyrophosphates
- Potent inhibitors of bone metabolism, particularly osteoclast function
- Most common use: treating osteoporosis or other metabolic bone disorders (Paget disease of bone, hyperparathyroidism)
- Critical co-therapy for patients with cancers that target the skeleton

BP pharmacology
- BP adsorb to bone hydroxyapatite and become integrated into bone matrix
- Not readily metabolized, especially nitrogen forms
- Like bone, persistence of some BPs estimated at 10-12 years (10% skeletal turnover/yr)

Bone Metabolism

Bisphosphonates and ONJ: History of an association
- Fall 2003, Dr. Robert Marx, U. Miami
  - letter to editor, 36 patients
- Fall 2004, Dr. Sal Ruggiero, LIJMC
  - 63 patients
    - 56 (89%) cancer patients
    - 7 (11%) osteoporosis patients

Bisphosphonates and ONJ: History of an association
- May 2006, AIM;144:753-61
  - 368 patients
  - IV bisphosphonates: 94%
  - Post-oral surgery: 60%
  - Females > Males (3:2)
  - Mand (65%), Max (26%), both (9%)
ONJ in 2018

- Over 2000 scientific articles
- Tens of thousands of affected patients, most with more potent bisphosphonates (and higher doses) in cancer patients
- Evidence for cumulative dose effect (total mg X total time of use)
- Also seen with newer ARs and other meds

Osteoporosis and anti-resorptives

Osteoporosis

Disorder characterized by reduced bone strength and an increased risk of fracture.

Bone strength = “Quantity” (BMD) + “Quality” (micro-architecture)

Normal vs. Osteoporotic vertebrae

Osteoporosis in the US

- 10 million Americans over age 50 (9.5 million women, 2.5 million men) have osteoporosis and 44 million others have low bone mass (osteopenia)
- Affects ½ of US population over 50
- 1 in 2 women and 1 in 4 men over age 50 will have a fracture in their remaining lifetimes (hip, spine, wrist, ribs)

http://www.nof.org/osteofraxis/diseasefacts.htm

Bone fracture in Women: greater risk than for stroke, heart attack and breast Ca combined!

Permission from the American Society of Bone and Mineral Research


**Oral Bisphosphonates and ONJ**
- Long term use of oral bisphosphonates for osteoporosis is associated with an ONJ prevalence of ~ 0.1-0.2%
- Alendronate (Fosamax) most common
- Risk for ONJ related to cumulative dose:
  1) duration of BP use
  2) total BP dose (exposure)

**IV bisphosphonate for osteoporosis**
- **Reclast®** (zolendronate)
  - 5 mg IV infusion once yearly (compared to 4 mg Q 3-4 weeks in Ca pts, 10-12X higher dose)
  - Low risk of jaw complications, prevalence of 0.02%, equivalent to controls
  - 1 case in 5900 patients compared to 1 in 5100 controls, Grbic et al JADA 2010
  - Note: Osteoporosis patients may forget to list Reclast as a medication

**Bisphosphonates in osteoporosis**
- Compared to cancer patients, lower BP dosing and use of less potent forms is typical in the treatment of osteoporosis
- As a result, ONJ is less common among osteoporotic patients and severe presentations are rare

**Alternative anti-resorptive: IV denosumab (Prolia) for osteoporosis**
- RANK ligand inhibitor
  - 60 mg subQ every 6 months (120 mg/yr)
  - Cancer patients, 120 mg every month (Xgeva)
  - 6X higher dose
Robbins and Cotran, Pathologic Basis of Disease, 7th Ed.

Action of RANK ligand


Denosumab inhibition of RANK ligand

Skeletal malignancies and anti-resorptives


Cancers that target skeleton (annual prevalence in US)

- Multiple myeloma (120,000)
- Metastatic carcinomas
  - Breast cancer (3.1 million)
  - Prostate cancer (2.9 million)
  - Lung cancer (430,000)

http://www.cancer.org

Cancers that target skeleton

- IV BP/AR therapy for Ca patients is standard of care in most oncology treatment centers
  - Multiple myeloma: ~ 9 of 10 patients
  - Metastatic solid cancers
    - Breast: 2 of 3 patients
    - Prostate: 2 of 3 patients
    - Lung: 1 of 3 patients
Benefits of IV ARs in skeletal cancers

- Reduced skeletal fractures and infections
- Decreased pain and analgesic use
- Extended patient survival with improved quality of life

ARs and skeletal cancers

- Use of IV ARs increases median survival by years compared to weeks/months with anticancer agents alone
- In addition, quality of life measures are also significantly better for the families or caregivers of affected patients

Drug delivery and skeletal bioavailability

- With IV BP, up to 50% comes in contact with skeleton
- In contrast, GI absorption of oral BP is only ~1% and drug contact with skeleton is <0.5% of original dose
- 100X greater drug availability
- Prevalence of ONJ in Ca patients: 1-3%

Pathogenesis of MRONJ

Why the jaws?

- Harsh environment
  - Trauma-intense, microbial-rich region
  - Frequent minor injuries and infections (denture sores, traumatic ulcers, periapical disease, gingivitis, periodontitis, pericoronitis)
  - Tooth extraction is the most common surgical procedure involving bone

Pathogenesis of MRONJ

Why the jaws?

- High metabolic rate of jaw bones
  - Bone turnover in dog jaws is 3-6 fold greater than in their appendicular (long bones) skeleton
  - Relative bone turnover:
    - mandible > maxilla
    - alveolar processes > body of jaws

Pathogenesis of MRONJ

Why the jaws?

1. Osteoclast suppression by ARs likely has greatest impact at skeletal sites with highest metabolic demands (i.e., jaws/alveolar bone)
2. Ineffective bone remodeling/wound healing + colonization by a complex oral microfilm leads to prolonged bone exposure and bone necrosis (ONJ)
Newer anti-resorptives
- Anti-RANKL (Denosumab [Xgeva, Prolia])
  - ONJ seen in Ca patients, prevalence 1-2%, 0.06% in osteoporosis patients
- Anti-Cathepsin K (Odanacatib)
  - No cases of ONJ (up to 8 yrs of tx), off market Sept 2016, increased stroke risk
- Anti-Sclerostin (Romosozumab, Blosozumab)
  - 1 case of ONJ to date

Recent drugs associated with ONJ: Anti-angiogenics in cancer patients
- Bevacizumab* (Avastin, mAb to VEGF-A, vascular endothelial growth factor-A)
  - < 20 reported cases of ONJ
- Sunitinib* (mAb to RTK, receptor tyrosine kinase)
  - < 10 reported cases of ONJ
- * Patient risk for ONJ is increased when combined with anti-resorptive drugs

MRONJ Case Definition (AAOMS 2014)
- Current or previous AR or anti-angiogenic treatment
- Exposed, necrotic bone of the maxillofacial region that has persisted for > 8 weeks
- No history of radiation therapy or metastatic disease to the jaws

Additional considerations
- Increased Age
- Smoking (+/-)
- Obesity
- Corticosteroid therapy

Staging of MRONJ
- Stage 0 - "at-risk" patients, +/- symptoms
- Stage 1 - bone exposure, no pain
- Stage 2 - bone exposure + evidence of infection, often pain
- Stage 3 - bone exposure + infection plus:
  - Exposure extending beyond alveolar bone
  - Pathologic fracture
  - Extra-oral fistula or oronasal/orontral communication
  - Bone lysis extending to jaw border

Stage 0

- Hx of treatment with ARs or anti-angiogenics
- Most patients asymptomatic and no clinical or radiographic abnormalities
- Some patients may have non-specific clinical +/- radiographic findings or symptoms without an identifiable odontogenic or infectious/inflammatory cause

Stage 0 Clinical symptoms/signs

- Symptoms
  - Dull, aching pain of mandible, may radiate to the TMJ region
  - Sinus-like pain of maxilla
  - Dysthesia, altered sensations
- Findings
  - Loosening of teeth, unrelated to routine periodontal disease
  - Parulis/sinus tract/fistula in absence of caries and pulpal necrosis

Stage 0 Radiographic Changes

- Persistence of extraction sockets
- Thickened lamina dura, PDL alterations
- Unexplained alveolar bone loss
- Cortical thickening as well as fragmentation or splintering
- Thickening/narrowing of inferior alveolar canal
  - Yet recent review by Devlin et al.* found no distinctive early features of ONJ features, esp. in the presence of local infection


MRONJ Case Reviews
ONJ: Cancer patient

- 66 year old female
- History of hypertension, osteoporosis, multiple myeloma
- Long term IV bisphosphonate and steroid use

- June 2003
- July 2003
- September 2003
- April 2004
- May 2004
Torus palatinus: presentations of ONJ

92 yo female, alendronate

Lesion progression with sequestration

Following sequestrectomy
88 year-old woman with history of extraction (#21) months ago but now exposed bone bilaterally. Pain, purulence and sequestra noted

TX: amoxicillin, metronidazole and CHX

Alendronate: partial prosthesis
April 2007

June 2006

Han Solo in carbonite


Direct effect on osteoclast

Active

Osteoclast

Inactive

Bisphosphonate

Bone

Fleisch H, Bisphosphonates in Bone Disease, 2000, p. 43
Markers, drug holidays and dental care

Serologic markers and ONJ risk
- In patients on AR therapy who require oral surgery, a test or indicator of the patient risk for developing ONJ would be valuable for patient management
- Several serologic biochemical agents have been examined, including markers of both bone resorption and formation

Bone resorption marker
- C-terminal cross-linking telopeptide (CTX) results form osteoclast digestion of type I collagen, the predominant bone protein
- Serum (and urine) CTX levels reflect total bone resorption activity
- Since bisphosphonates reduce bone turnover, they result in lower CTX levels

Bone resorption marker
- Unfortunately, CTX levels show significant variability: both inter- and intrapatient
- Longitudinal studies of CTX levels have not always correlated with the results of bone mineral density studies
- Conclusion: No evidence that CTX levels can predict individual AR patient risk for ONJ (proposed risk level: 150 pg/ml)

Adult Serum Reference Ranges: CTX (βL Subtype)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>18 - 29 years</td>
<td>87 - 1200 pg/ml</td>
<td>64 - 640 pg/ml</td>
</tr>
<tr>
<td>30 - 39 years</td>
<td>70 - 780 pg/ml</td>
<td>60 - 650 pg/ml</td>
</tr>
<tr>
<td>40 - 49 years</td>
<td>60 - 700 pg/ml</td>
<td>40 - 465 pg/ml</td>
</tr>
<tr>
<td>50 - 68 years</td>
<td>87 - 345 pg/ml</td>
<td>100 -1000 pg/ml*</td>
</tr>
</tbody>
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*http://dx.doi.org/10.1038/bonekey.2014.68
Bone formation marker

- Bone-specific alkaline phosphatase (BAP) is found in osteoblasts; serum level reflects bone forming activity
- Some studies have found lower serum BAP levels in ONJ patients compared to AR patients without ONJ
- Conclusion: Despite encouraging results, BAP levels are not reliable predictors of risk for ONJ in AR patients (MGSAN)


Why have drug holidays been suggested for anti-resorptives (ARs), and particularly BPs?

Bone Metabolism

Robbins and Cotran, Pathologic Basis of Disease, 7th Ed

Concerns with long-term AR use

- Increasing cumulative AR treatment associated with increasing risk for
  - ONJ
  - Atypical femoral fractures (AFF)
    - Resulting from no or minimal trauma
    - 2X increased risk with >5 yr BP use

Drug holiday in osteoporosis

- Limited but consistent evidence that drug holiday can be used without increasing the risks of fractures, including AFF
- If > 3-5 years BP use, a holiday of 1-2 years can be considered for otherwise healthy patients with good bone density by DEXA scan
Drug holiday in osteoporosis

- Currently, there is *limited* evidence to support consideration of a “drug holiday” or waiting periods for *prevention* of ONJ
- *Accumulating* evidence suggests antiresorptive drug holidays may be useful in *treatment* of existing ONJ
- A possible option in skeletally-stable patients, at relatively low risk for fracture

Important note for dental patients:

- No fatal cases of ONJ reported to date with a non-fatal risk ratio of 1:1200 (Lo et al. 2010)
- AR significantly reduces risk of skeletal fractures and associated fatalities
  - The osteoporosis risks are considerable with a non-fatal risk ratio of 1:423 and a fatal risk ratio of 1:2,116 (Sambrook et al. 2010)

Hypothetical trade-off for stopping AR:

- ~2 cases of ONJ for 1 patient death
- ~1 cases of ONJ for 4 hip fractures
- Complications of hip fracture (loss of mobility, function, pain, susceptibility to serious infection, death) typically more serious than complications of ONJ

In patients with ONJ lesion(s), preliminary published evidence suggests that a drug holiday may promote normal healing as part of overall patient care

- Patient and managing physician should be involved in decisions regarding AR treatment

Treatment guidelines for patients on AR therapy

- Identify patients at risk through a comprehensive medical history
- Provide current information to “at risk” patients regarding risks/benefits of AR treatment including ONJ
- Encourage excellent oral hygiene and regular dental care to reduce ONJ risk
Antimicrobials
- Topical rinses
  - Chlorhexidine
  - Alcohol-free
  - Povidone-iodine

When is topical chlorhexidine not enough?
- Active suppuration is present
- Systemic symptoms are present
- When sequestrectomy is indicated

Systemic antibiotics
- Most 1st line recommendations involve penicillin or amoxicillin with substitution of similar spectrum drugs (clindamycin) in allergic patients
- Amoxicillin-metronidazole combination can be useful
- Month-on/month-off dosing preferable to continuous use (resistance)

Systemic antibiotics
- For limited cases, a 2-wk course is generally adequate
- For more severe cases, a 4 to 6-wk course may be warranted
- On/Off dosing (antibiotic holiday) is preferable to continuous use (resistance)
- IV antibiotics if oral agents exhausted
Alternative medications for ONJ

- Pentoxifylline (Trental) and Vit E first described for use with radiation-induced fibrosis in 1996, osteoradionecrosis in 2008, ONJ in 2010
- Pentoxifylline is a safe, xanthine derivative used to treat peripheral vascular disease. Vit E scavenges free radicals, decreasing inflammation and fibrosis
- Rx: Pentoxifylline extended-release tabs, 400mg, BID and Vit E 1000 IU daily
- No large trial data, but early studies are positive

Dental treatment for patients on AR therapy (Stage 0)

- Treatment plan to minimize the need for and extent of surgery
- Conservative, non-surgical therapy effective in 70-80% of 120 patients (Lerman, 2013)
- Surgery may be necessary, especially in sites of active infection
- Extraction, debridement and resection have been performed with successful outcomes

Choice B: "Orthodontic treatment for patients on AR therapy (Stage 0)"

- Orthodontic tooth movement is possible in low-risk patients
- Patients should be fully informed about the likelihood of longer treatment times and the need for impeccable oral hygiene
- Restorative options or hybrid treatment plans should be considered to meet patient objectives

Surgical Treatment for patients on AR therapy

- In advanced Stage 2/3 presentations, CT or cbCT recommended for Tx planning*
- Removal of all necrotic bone/involved teeth, smoothing vital bone edges and tension-free primary closure recommended
- Up to 90% success rate for segmental resections in stage 3 ONJ


Dental implants and ONJ

- In a total of three studies from 2008-10*, 690 implants placed in 212 BP users were associated with no ONJ lesions
- Implant survival also equivalent between users (95-100%) and non-users (96-99%)+

A frequent question...
What are the risks for ONJ with the placement of dental implants?

Currently, the risk for ONJ with intraosseous dental implants is extremely low.

*Sell and Bell J. Oral Maxillofac Surg 2008;66;1022
Grant BT et al., J Oral Maxillofac Surg 2008;66;223
Koka S et al., Prosthodontist 2010;54;108
*Kumar and Honne. Eur J Prosthodont Restor Dent 2012;20:159
Dental implants and ONJ

- Zahid et al found that implant success rate was nearly identical between controls (300) and BP users (26).
- Overall, low risk for ONJ probably reflects limited bone exposure and minimal bone remodeling associated with modern implants.
- For Ca patients, perioperative antibiotics may help further reduce the risk of failure or ONJ.


ONJ treatment: 2018

- Obtain informed consent
- Minimize patient smoking
- Minimize infection sites/risk
- Minimize trauma to osseous tissues
- Treatment plan to minimize extractions and osseous surgery in risk patients

ONJ treatment: 2018

- Use topical CHX for simple bone exposures
- Consider pentoxifylline/Vit E therapy
- Combine CHX with systemic antibiotics in areas of exposure + active infection
- Plan surgical management with CT/cbCT imaging to remove all necrotic bone and achieve primary closure

Reminders

- Don’t forget Reclast or Prolia; osteoporosis patients and their care-givers will.
- Anti-angiogenic treatment in Ca patients may further increase risk of ONJ

Final Reminder

- Patients should never be advised to withhold a medication without consulting the prescribing physician.
- Risks associated with osteoporosis will virtually always outweigh those of ONJ

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Thank You!