Bisphosphonate–Related Osteonecrosis: Where are we today and what the future holds?

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Bisphosphonate-Related Osteonecrosis

Bisphosphononates

- Synthetic analogs of naturally occurring pyrophosphate
- Potent inhibitors of bone resorption
  - Internalized by osteoclast, decrease their ability to resorb bone and their life expectancy.
  - Cause osteoclast apoptosis
- Incorporates into hydroxyapatite and changes bone micro architecture
Bisphosphonate-Related Osteonecrosis

R1 (Hydroxyl Group): Increase the affinity
R2 cause the anti-resorption
1st Generation (Non- Nitrogen Containing)  
:  R2 group is non-nitrogen  
Etidronate (Didronel) - CH3  
Clodronate (Benofos)- Cl
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2nd Generation: R2 group contains nitrogen in form of a primary amino group

- Alderonate (Fosamax)
- Pamidronate (Aredia)
- 10-1000 more potent than the 1st generations
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3rd Generations: R2 group contains nitrogen but within a heterocyclic group

- Risedronate (Actonel)
- Ibandronate (Boniva)
- Zoledronic Acid (Zometa)
- 10,000- 100,000 more potent than 1st generation
Pamidronate: $R^2=\text{(-CH}_2\text{)}_2\text{-NH}_2$

Alendronate: $R^2=\text{(-CH}_2\text{)}_3\text{-NH}_2$

Risedronate: $R^2=\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-NH}_2$

Zoledronic acid: $R^2=\text{-CH}_2\text{-N}\text{=CH}_2\text{-N}\text{=CH}_2$
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All the cases that have been reported so far were associated with the nitrogen-containing bisphosphonates (Zometa, Aredia, Boniva, Actonel, Fosamax).

There has not been any reported cases of BRONJ associated with non-nitrogen containing BPs (Didronel, Skelid and Bonefos).
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- WHY?
  1) Mevalonate pathway VS synthesis of ATP analogues ----→ Potency
  2) Effect of nitrogen containing on vascularization
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- **September 2003**
  - Dr. Robert Marx reported avascular necrosis of the jaws in 36 patients taking Aredia or Zometa
  - 50% of patients had Multiple Myeloma

- **December 2003**
  - Dr. Marx and Dr. Ruggiero: Presentation to Novartis board. San Antonio, TX

- **May 2004**
  - Dr. Ruggiero and colleagues reported 63 patients with BRON over 3 years span (2001-2003)
  - 28 patients had Multiple Myeloma
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TIMELINE

- September 2004
  - Novartis, manufacturer of Aredia and Zometa, notified healthcare professionals about addition of osteonecrosis of the jaws to warning labels
- 2005, warning label was added to oral BP
- June 2006
  - ADA released expert panel recommendation for management of patients on Oral Bisphosphonate therapy
- September 2006
  - American Association of Oral and Maxillofacial Surgeons released expert panel recommendation
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**TERMINOLOGY**

- **BRONJ**
  - Bisphosphonate-Related Osteonecrosis of the Jaw/AAOMS
- **BON**
  - Bisphosphonate-associated osteonecrosis/ADA
- **Osteochemonecrosis ??**
- **BRON**
  - Bisphosphonate-Related osteonecrosis
Bisphosphonate-Related Osteonecrosis

CAUSES

Why?

1. Defect in wound healing and jawbone remodeling

Osteoclast inhibition:

impaired osteoclast function interferes with normal bone turnover and resorption causing dense, poorly formed brittle bone
Why?

2. Compromised blood flow and lack of oxygenation:
   - Inhibition of endothelial cell function
   - Inhibition of blood vessels sprouting
   - Cells demonstrate decrease proliferation and Capillary tube formation
   - Anti-angiogenic properties due to decreased levels of VEGF, a potent angiogenic factor
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Why?

3. Combination of 1 and 2:
   Decreased blood flow and poor oxygenation in combination with poorly formed bone
Hypothetical mechanism of osteonecrosis induced by potent nitrogen-containing bisphosphonates. Through inhibition of osteoclast function (a) and angiogenesis (b) the regenerative capacity of the bone is impaired. After local trauma the non-healing wound can develop into osteonecrosis and is prone to surinfection by commensal flora (c) leading to osteomyelitis.

T. Van den Wyngaert¹²,*, M. T. Huizing¹ and J. B. Vermorken¹
Annals of Oncology 2006 17(8):1197-1204;
Bisphosphonate-Related Osteonecrosis

Why?

4. Hypocalcemia coupled with elevated PTH serum level

*Ardine et al: Ann Oncol 2006*
Bisphosphonate-Related Osteonecrosis

- Bisphosphonates:
  - IV
  - Oral
Bisphosphonate-Related Osteonecrosis

- IV Bisphosphonate:
  - Used in patients with breast, prostate, lung and other cancers with bone metastasis
  - Management of lytic lesions such as Multiple Myeloma
  - Osteoporosis? NEJM (Zometa 2mg/6months or 4mg/year)
  - Giant Cell Tumor ???
Staging

Stage 1

Characterized by exposed bone that is asymptomatic with no evidence of significant soft tissue infection.

Courtesy of Dr. Ruggiero
Bisphosphonate-Related Osteonecrosis

- IV Bisphosphonate:
  
  Impacts the quality of life in patients when cancer involves the skeletal system:
  - Prevents and/or reduces hypercalcemia
  - Stabilizes bony pathology
  - Prevents fractures
Bisphosphonate-Related Osteonecrosis

IV Bisphosphonate:

1. pamidronate (Aredia): 1991 Novartis
   - administered over a 2-24 hour period every 3-4 weeks/90mg

2. zoledronic acid (Zometa): 2001 Novartis
   - administered over a 15 minutes period at 4mg dosage

3. clodronate (Bonefos): Schering AG
   - used mainly in Canada both oral/IV
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More than 2.8 million patients have been treated with IV BP

Incidence:

- February 2005, Novartis was aware of 875 cases
- Fall of 2005, increased to 2,227 cases
- April 2006, AAOMS did an internet survey of 1,235 members and reported 4,737 cases
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*Durie et al (NEJM 2005)*:

1,203 patients with breast cancer and MM revealed 12.8%

Depending on studies incidence ranges from 0.8-12 % and is rising.
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- Oral Bisphosphonate:
  - Over 190 millions prescriptions
  - Used to treat osteoporosis and osteopenia
  - Used in patients with Paget’s Disease and Osteogenesis Imperfecta
Osteoporosis vs Osteopenia

- Osteoporosis is a disease that breaks down the tissue in our bones, making them fragile and more likely to break.
- Osteopenia is not a disease, but a term that describes low bone density.
- Both can lead to painful fractures.
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DEXA (Dual Energy X-ray Absorptiometry):
- Use to measure bone density
- Lower spine and hips
- Use to diagnose osteoporosis and osteopenia
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T Score:
T more than −1 is normal
-2.5 < T < -1.0 Osteopenia
T less than -2.5 is osteoporosis

Fosamax: Osteopenia 35mg/day
Fosamax: Osteoporosis 70mg/day
Bisphosphonate-Related Osteonecrosis

Oral Bisphosphonates

- Actonel (risedronate) Procter & Gamble
- Boniva (ibandronate) Roche laboratory
- Fosamax (alendronate) Merck & Co
- Fosamax Plus D Merck & Co
- Skelid (tiludronate) Sanofil Pharm
- Didronel (etidronate) Procter & Gamble
- Bonefos (clodronate) Schering AG
Bisphosphonate-Related Osteonecrosis

March 2006 (ADA):

- Fosomax (1997) 170 cases
- Actonel (1998) 20 cases
- Boniva (2005) 1 case

Translates into 0.7 cases per 100,000 people

Australian and Israeli reports (0.01-0.04%) with extraction (0.09-0.34%)
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According to AAOMS a case is considered to be BRONJ when all of the following characteristics are present:

1. Current or previous treatment with BP
2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks.
3. No history of radiation therapy to the jaw
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Diagnosis:
- Panorex and PA are poor radiographic screenings

How to Diagnose:

Clinical Presentation
Bisphosphonate-Related Osteonecrosis

- Symptoms: pain, soft tissue swelling and infection, loosening of teeth, drainage and exposed bone.
- Majority occur after dental treatment
- Rarely spontaneous
- May present with in weeks or months after dental treatment
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Risk factors for development of BRONJ:

1. Drug-related risk factors
   a. Potency:
      Zometa (100,000) > Boniva (10,000) > Actonel (10,000) > Fosamax (1,000) > Aredia (100) > Skelid (10) > Didronel (1)
   b. Duration and Dosage of therapy
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2. Local Risk Factors:
   a. Dentoalveolar surgery: Surgery increases risk by 7-9 times
   b. Local Anatomy: Man/Max (2:1), more in the area of tori, mylohyoid ridge, bony exostoses
Bisphosphonate-Related Osteonecrosis

Risk factors con’t

3. Demographic, Systemic and other factors
   - Age: with each decade 9% increase
   - Race: Caucasians
   - Cancer Diagnosis: MM>Breast>others
   - Osteoprosis, Diabetes, Smoking, Alcohol, **corticosteroid**, Chemotherapeutic Drugs, Poor oral hygiene
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Treatment Strategies:
A. Patients about to initiate IV bisphosphonate
   - Caries control
   - Extraction of Non-restorable and/or teeth with poor prognosis (14-21 days prior to IV)
   - Emphasis on hygiene/routine exam
Bisphosphonate-Related Osteonecrosis

B. Asymptomatic Patients on IV:
- Emphasis of oral hygiene/Check-up
- Avoid procedures that cause direct osseous injury
- Non-restorable teeth may be treated by removal of the crown and endo treatment of the remaining root
- Implants should be avoided in patients that had 4-12 times dose/year
Bisphosphonate-Related Osteonecrosis

c. Asymptomatic Patients on oral BPs:
   1. Patients taking oral BPs less than three years and no risk factors:
      - No alteration
      - Add risk in your informed consent for surgeries
CONSENT FOR ORAL SURGERY IN PATIENTS WHO HAVE RECEIVED ORAL BISPHOSPHONATE DRUGS

Page 1 of 2

Patient's Name  Date

Please initial each paragraph after reading. If you have any questions, please ask your doctor BEFORE initialing.

___ 1. You have been treated with oral Bisphosphonate drugs, and you should know that there is a risk of future severe complications that might happen with dental treatment. There is a small but real risk. Jaw bones usually heal themselves very well and maintain their normal health. In some patients, Bisphosphonate drugs seem to affect the ability of jaw bones to break down or remodel themselves, and this interferes with the jaw's ability to heal itself. This risk is increased after surgery, especially from extractions, gum surgery, implant placement or other "invasive" procedures that might cause even mild trauma to bone. Necrosis (dying cells) or Osteonecrosis (dying bone cells) may result, and an infection may occur in the soft tissue and/or inside the bone. This is a long-term process that destroys the jawbone that is often very hard or even impossible to get rid of.

___ 2. Your medical/dental history is very important. We must know the medications and drugs that you have received or taken before, and are receiving or taking now. A correct medical history, including names of physicians is important.

___ 3. The decision to stop oral Bisphosphonate drug therapy before dental treatment should be made by you in talking with your medical doctor.

___ 4. If a complication occurs, antibiotic therapy may be used to help control infection. For some patients, such therapy may cause allergic responses or have undesirable side effects such as stomach discomfort, diarrhea, swelling of the colon, etc.

___ 5. If osteonecrosis should occur, treatment may be long and difficult. You might need ongoing intensive therapy that could include hospitalization, taking antibiotics for a long time, and removal of dead bone. Reconstructive surgery may be needed, including bone grafting, metal plates and screws, and/or skin flaps and grafts.

___ 6. Even if there are no immediate complications from the proposed dental treatment, the area is always subject to breakdown by itself at any time and infection due to the unstable condition of the bone. Even the smallest trauma from a toothbrush, chewing hard food, or denture sores may set off a complication.
CONSENT FOR ORAL SURGERY TREATMENT IN PATIENTS WHO HAVE RECEIVED ORAL BISPHOSPHONATE DRUGS

Page 2 of 2

7. We may need to see you on a long-term basis after your surgery to check your condition. It is very important that you keep all of your scheduled appointments with us. Regular and frequent dental check-ups with your dentist are important to try to prevent breakdown in your oral health.

8. I have read the information above and understand the possible risks of having my planned treatment. I understand and agree to the following treatment plan:

________________________________________________________________________________________________________________________

________________________________________________________________________________________________________________________

________________________________________________________________________________________________________________________

9. I understand the importance of my health history and I have given you all information. I understand that if I don’t give you true health and complete information, it may be harmful to my care and lead to unwanted complications.

10. I realize that even though the doctors will take all precautions to avoid complications; the doctor can’t guarantee the result of the proposed treatment.

CONSENT

I certify that I speak, read and write English and have read and fully understand this consent for surgery and have had my questions answered. All of the blanks were filled in before I initialed or signed the form.

Patient’s (or Legal Guardian’s) Signature Date

Doctor’s Signature Date

Witness’ Signature Date
Bisphosphonate-Related Osteonecrosis

2. Patients taking oral BPs less than three years and also taking corticosteroids: contact the provider to stop BPs for three months prior to treatment and re-start after osseous healing

3. Patients taking oral BPs for more than 3 years with/without steroids: Same as above
Dear Dr. ____________________________

Date ______________________

Re: _____________________________

I am currently seeing your patient, __________________. Your patient informs me that she/he has been taking an intravenous or oral bisphosphonate (Fosamax, Actonel, Boniva, Didronel, Skelid). As you know, a number of patients have developed osteonecrosis of the jaws (ONJ) after taking bisphosphonates, particularly IV bisphosphonates.

The American Association of Oral and Maxillofacial Surgeons has recently issued a “Position Paper” on “Bisphosphonate-Related Osteonecrosis of the Jaws”. While oral bisphosphonates are associated with only a small number of osteonecrosis cases at this time, it appears that the risk of developing Bisphosphonate-Related Osteonecrosis of the Jaws (BRON) associated with oral bisphosphonates may be increased when duration of therapy exceeds three years, and/or when oral bisphosphonates are given concomitantly with long-term corticosteroids or chemotherapy, the patient has diabetes, smokes, uses excessive alcohol, or has poor oral hygiene. Your patient meets one of these criteria.

For patients who have been on oral bisphosphonates more than 3 years, or have taken oral bisphosphonates and have one of the additional risk factors listed above, the AAOMS Position Paper recommends the following for patient management prior to any elective dentoalveolar surgery:

“…the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least three months prior to oral surgery, if systemic conditions permit. The bisphosphonate should not be restarted until osseous healing has occurred (approximately three more months).”

Please advise our office by return fax (___________) if you would:

CHECK ONE

■ recommend a drug holiday as described above __________

■ not recommend a drug holiday as discussed above __________

Signature __________________________________________

Once we have your recommendation, we will contact your patient with your recommendation and schedule our surgery in compliance with it. Thank you for your help with this patient. Working together, we can provide good care for your patient.

Cordially,
Bisphosphonate-Related Osteonecrosis

- June, 2006, ADA, Expert panel recommendation:
  - Not allergic to penicillin
  - Amoxicillin: 500mg / q8h/ 14 days
  - Metronidazole: 250mg/ q8h/ 14 days
  - Allergic to penicillin
  - Clindamycin 300mg/ q8h/ 14 days
  - Azithromycin 250mg/ q24h/ 10 days
  - Start antibiotic 1-2 days prior the procedure
  - Chlorhexidine/ 2x/ day/ two months post surgery
Bisphosphonate-Related Osteonecrosis

Patients with established BRONJ:

Stage 1:
Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection

Treatment: Use of oral antimicrobial rinses, such as chlorhexidine 0.12%
Staging

Stage 1

Characterized by exposed bone that is asymptomatic with no evidence significant soft tissue infection

Courtesy of Dr. Sal Ruggiero
Bisphosphonate-Related Osteonecrosis

- **Stage 2:**
  Exposed/necrotic bone in patients with pain and clinical evidence of infection:
  
  Treatment: oral antimicrobial rinses in combination of antibiotic therapy
  
  i.e Penicillin group, quinolones, metranidazloe, clindamycin, doxycycline, erythromycin
  
  Sometimes combination/ IV antibiotics
Stage 2

- Exposed bone associated with pain, soft tissue and/or bone infection

Courtesy of Dr. Sal Ruggiero
Bisphosphonate-Related Osteonecrosis

Stage 3:
Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathological fractures, extra-oral fistulas, or osteolysis extending to the inferior border

Treatment:
Surgical debridement/resection
Antibiotic/oral microbial rinses
Removal of mobile segments and extraction of symptomatic teeth within exposed bone
Discontinuation of BP (oral 6-12 months)
Stage 3

- Pathologic fracture
- Exposed bone associated with soft tissue infection that is not manageable with antibiotics due to the volume of necrotic bone.

Courtesy of Dr. Sal Ruggiero
Bisphosphonate-Related Osteonecrosis

CTX (C-terminal telopeptide):
- Fragments of type I collagen
- Is a bone marker that is sensitive to bone turn-over and is used for assessment of bone resorption
Bisphosphonate-Related Osteonecrosis

CTX (Carboxy-Terminal Telopeptide):
- Blood test/morning/fasting
- Has been used by Rheumatologists
- CA (San Juan Capistrano)

Quest Diagnostic 1800-642-4657
- Only for Oral-Bisphosphonate
- No value for IV-Bisphosphonate
- Not necessary in patients with less than 3 years on BPs
Bisphosphonate-Related Osteonecrosis

- The lower the CTX the less chances of osteoporosis

Does this mean the higher chances of osteonecrosis ?

- Normal Range
  F= 60-600 (pre-menopause)
  M= 60-800
Bisphosphonate-Related Osteonecrosis

BRONJ Risk
High Risk:
  CTX less or equal 100 pg/ml
Moderate Risk:
  CTX between 101-150pg/ml
Low Risk:
  CTX equal or more than 151

CTX value will increase with discontinuation of Oral Bisphosphonates
Bisphosphonate-Related Osteonecrosis

Suggestion:
- Stop bisphosphonate in patients with CTX below 151 for 3-4 months
- Another blood test if value above 150 continue with the procedure
- Restart Oral BPs 3 months after procedure
Bisphosphonate-Related Osteonecrosis

- **Bisphosphonate**
  - **Oral Form**
    - Less than 3 years
      - No Concern AB? add to consent
    - less than 3 years + Corticosteroids
      - More than 3 Years
      - CTX ????
      - less than 151
      - stop BPS for 3-4 months
      - New CTX/AB? add to consent
  - **IV Form**
    - Not started yet
      - Extract Hopeless teeth
      - wait 14-21 days recalls
    - Currently on IV BPs
      - No Surgeries
      - RCT on roots
      - Hygiene
Bisphosphonate-Related Osteonecrosis

- Why CTX (not NTx, alkaline phosphatase, osteocalcin)
- Why 151? (Lab is not aware of any correlation)
- Bone et al: The effects of prolonged use of 10mg of Aredia are sustained even 5 years after discontinuation.
- Oral Bisphosphonate use for more than three years will have effect on bone morphology for years.
Bisphosphonate-Related Osteonecrosis

- Alternatives to current oral BPs (Are they Practical?):
  1. Exercise and calcium
  2. Alternating oral BPs 6 months on/off
  3. Reloxifene (Evista): designer estrogen 1/10,000 will develop blood clot
  4. Rh PTH 1-34 (forteo): increase bone formation 100-300% within 3 months. Peaking at 9 months. What if Ardine is right?
Your husband is suffering from a very severe stress disorder. If you don’t do the following he will surely die. Each morning fix him a healthy breakfast. Be pleasant at all times. For lunch make him a nutritious meal. For dinner prepare an especially nice meal.

No chores. No nagging. Oh yes, and make love several times a week. Do this for the next year and he’ll regain his health completely!

What did the doctor say?

You’re going to die!
Bisphosphonate – Related Osteonecrosis

- Osteoprototic fractures in 1995:
  Half million fractures
  800,000 emergency visits
  2.6 million office visit
  180,000 individuals in nursing home
- 2006: 1.5 million fractures per year at cost of 14 Billion (Life time cost of a hip fracture is $81,300)
- 300,000 hip 700,000 vertebral
  250,000 wrist 300,000 other
- 10 years: estimated 5.2 million fractures a year in U.S
Bisphosphonate-Related Osteonecrosis

- 44 million American have osteoporosis:
- 1 in 2 men and 1 in 4 female with history of osteoporosis will have fractures.
- 24% of hip fracture patients will die within a year and another 20% end up in nursing homes.
Fosamax:
- Decreases the risk of hip fracture by 33%
- Decreases the hip fracture by 100,000 and death associated with fractures by 25,000 a year.
Bisphosphonate-Related Osteonecrosis

Case 1:

65 year male referred to O.S. at VA Northport for evaluation, prior to radiation to the jaw

PMH: History of prostate cancer

Meds: Treatment with Aredia and Zometa

- Patient has not worn his partial denture for more than a year
- No recent history of dental treatment

Case and Slides Courtesy of Dr. David Salehani
Bisphosphonate-Related Osteonecrosis

Nuclear Bone Scan:
- 3 stage scan, the tracer will be injected in the arm
- First scan right after the injection, 2nd scan 3-4 hours after
- Christmas tree picture
- The area that absorbs the most gamma radiation appears dark or “Hot Spots”
- These areas indicate a fracture, an infection or metastasis (usually more than one area of hot spot is an indication of metastasis)
Bisphosphonate-Related Osteonecrosis

Case 2:

58 YO Middle Eastern female presented for implant placement to private practice in January 2006

PMH: Non-significant

Meds: Fosamax for two years
Bisphosphonate-Related Osteonecrosis

Case 3:

78 YO Hispanic female
PMH: HBP
Meds: Fosamax for past 10 years
CC: Pain on lower left to hot and biting
Premier IntegraPost X-ray Overlay

3  4  4.5  4.5L  5  6

0mm  5mm  10mm  15mm  17mm

Unit of measure indicated by dotted line: 1mm
Bisphosphonate-Related Osteonecrosis

Most common commonly prescribed medication on patient > 50 (Dose Dependent)

1. Lipitor 10 mg
2. Norvasc 5mg
3. Fosamax 70mg
4. Plavix 75mg
10. Norvasc 10mg
11. Lipitor 20 mg
Bisphosphonate-Related Osteonecrosis

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