

Update on Bisphosphonates

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1. History of Bisphosphonates

1890 – Used as anticorrosive and antiscaling agent

1960 – Feish et al reported in *Science* ability of diphosphonate to inhibit hydroxyapatite dissolution in vitro and bone resorption in vivo

Early 90's 1st generation of non nitrogen containing bisphosphonates: etidronate and clondronate

1995 – FDA approves use of Nitrogen containing Bps: more potent
- pamidronate (Aredia) and iv for treatment of osteolytic metastasis and hypercalcemia– MM, Breast Cancer, Prostate Cancer

- Alendronate (Fosamax) orally for treatment of osteoporosis

1998 – FDA approval of Risedronate (actonel) oral

2001 – FDA approves use of Zoledronic Acid (Zometa) iv

Generic Name	Brand Name	Delivery	Relative potency
Zoledronic Acid	Zometa Bonviva	IV	10000 +
Pamidronic Acid	Aredia	IV	1000 to 5000
Risedronate	Actonel	Oral	1000
Alendronic Acid	Fosamax Fosavance Osteomel Adrovanse Tevanate Fostepor Romax	Oral	1000
Clodronate	Bonephos	Oral	10
Etidronate	Didronel	Oral	1

1. History of BRONJ

2001, 2002 – First cases of Osteonecrosis reported from University of Miami and Long Island Medical Centre, NY to FDA

- Similar to osteoradionecrosis
- Non responsive to surgical debridement
- In cancer patients receiving different chemotherapy regimes
- common denominator – bisphosphonate therapy

2003 – first papers published by Marx R and Ruggiero in JOMS

2006 – first guidelines on how to provide safe dental treatment to patients on bisphosphonates published on Journal of Clinical Oncology Practice

2. Definition of BRONJ

Patients may be considered to have BRONJ if all of the following 3 characteristics are present:

- 1. Current or previous treatment with a bisphosphonate*
- 2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks*
- 3. No history of radiation therapy to the jaws*

BRONJ = BIONJ = BION = BON = ONJ

Table 4. CLINICAL STRATIFICATION AND STAGING GUIDELINES OF PATIENTS TAKING BISPHOSPHONATES AND THOSE WITH OSTEONECROSIS OF JAW

Stage	Description
At risk	No apparent exposed/necrotic bone in asymptomatic patients treated with either intravenous, injectable, or oral bisphosphonates
Stage 0	No clinical evidence of exposed/necrotic bone but nonspecific symptoms or clinical and radiographic findings suspicious for possible BRONJ
Stage 1	Exposed, necrotic bone that is asymptomatic and no evidence of inflammation or infection
Stage 2	Exposed, necrotic bone that is associated with pain, erythema, and inflammation or infection with or without purulent drainage
Stage 3	Exposed, necrotic bone in patients with pain, inflammation or infection, and 1 or more of the following: exposed and necrotic bone extending beyond the region of the alveolar bone resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor

Adapted from American Association of Oral and Maxillofacial Surgeons revised stratification and staging guidelines, with permission.

John E. Fantasia. Bisphosphonates: Practical Considerations. J Oral Maxillofac Surg 2009.

3. Pathogenesis

- Many hypothesis, few facts
 - Reduced bone turnover
 - Osteoclast inhibition. *Russell et al. Ann N Y Acad Sci. 2007*
 - Apoptosis of osteoclasts and osteocytes. *Idris et al. Calcif Tissue Int. 2008*
 - Soft tissue toxicity. *Reid et al. Bone, 2007*
 - Antiangiogenic effect. *Hansen et al. J Oral Pathol Med. 2006*
 - Bone necrosis associated with inflammation, preceding clinical onset (bone exposure).
Lesclous et al. Bone 2009

4. Epidemiology

High risk patients: (IV)

Multiple Myeloma, Breast Cancer, Solid tumor

1,8 to 12% of BRONJ

Bamias et al. J Clin Oncol. 2005

Low risk patients: (Oral)

Osteoporosis

Paget's disease

From **0,01%** to **0,001%**

Khosla et al. J Bone Miner Res. 2007

**BRONJ in oncologic patients is:
more common,
more extensive,
involves a greater soft tissue loss, more
difficult to treat,
more unlikely to resolve.**

Marx et al. J Oral Maxillofac Surg 2009

5. Risk factors

1. Time and type of Bisphosphonate used
 - IV bps
 - > 3 years on oral bps
2. Dental Treatment.
 - 60% of BRONJ cases after dental surgery. *Woo et al. Ann Intern Med. 2006*
 - Oncology pts on IV bps who undergo dentoalveolar procedures have a 5 to 21 fold increased risk of BRONJ. *Jadu et al. Ann Oncol. 2007*
 - Oncology pts on IV bps with Periodontal disease have a 7 fold increased risk of BRONJ. *Hoff et al. J Bone Mineral Research. 2006*
3. Disease/medication that compromise blood supply, oxygenation, cellular metabolism and immune response

Table 3 Historical risk factors for osteonecrosis

- Chemotherapy
- Cancer
- Immunotherapy
- Female sex/estrogen
- Coagulation abnormalities
- Infections
- Smoking
- Dental risk factors (edentulous regions, periodontal disease, dental abscesses, surgical procedures involving the bone, trauma from ill-fitting dentures)
- Sickle-cell disease
- Systemic lupus erythematosus
- Atmospheric pressure variations
- Hemodialysis
- Hypersensitivity reactions
- Hypothyroidism
- Storage diseases
- Corticosteroids
- Hypertension
- Arthritis
- Blood dyscrasias
- Vascular disorders
- Alcohol abuse
- Malnutrition
- Advanced age
- Gaucher disease
- Human immunodeficiency virus infection
- Chronic inactivity
- Hyperlipidemia and embolic fat
- Osteoporosis
- Neurologic damage

*From Silverman et al. Feb 2009.
American Journal of Medicine*

5. Other risk factors

- **Diabetes.** *Khamaisi et al. J Clin Endocrinol Metab, 2007*
- **Obesity.** *Wessel et al. J Oral Maxillofac Surg. 2008*
- **Race: White.** *Badros et al J Clin Oncol 2006*
- **Genetics:** Presence of T allele in the SNP rs1934951 located in the CYP2C8 gene increases risk of developing BRONJ by 12,5 fold. *Sarasquete et al. Blood. 2008*

17th June 2009
To All Clinical Dental Staff

Dear Colleague

**RE: GUIDELINES FOR BISPHOSPHONATE-ASSOCIATED
OSTEONECROSIS OF THE JAWS**

The following local guidelines have been based on the current literature and in particular the Canadian guidelines published in the Journal of Rheumatology 2008; 35:1391-1397. These were approved by the Dental Clinical Governance Committee of DSG for implementation and will be reviewed in one year's time.

6. Dental treatment in high risk patients

- Prevention
 - Stop smoking
 - Reduce alcohol
 - Improve OH
 - Frequent reviews
 - Inform pt of risk of developing BRONJ
 - Check up + any surgery needed prior to starting IV bisphosphonates treatment



BRITISH
Journal of
Oral and
Maxillofacial
Surgery

www.bjoms.com

A survey of consultant members of the British Association of Oral and Maxillofacial Surgeons regarding bisphosphonate-induced osteonecrosis of the jaws

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In the previous 3 months 26 of 177 consultants (15%) had screened at least one patient before starting intravenous bisphosphonates. Responses to the question “What would

Preventive dental treatment and surgical treatment prior to starting IV bisphosphonates reduced risk of BRONJ among patients with malignancy by 66% (from 3 to 1 %).

Dimopoulos et al, Ann Oncology 2009 and Ripamonti et al Ann Oncology 2009

6. Dental treatment in high risk patients

- Periodontal treatment
- Conservative treatment
- RCT instead of XLA's
- Soft lining in dentures + frequent relines
- No implants
- Avoid surgery: extractions, apicectomies, perio surgery

6. Dental treatment in high risk patients

- If surgery is unavoidable, refer to Hospital, Oral Surgery Department, where they might:
 - Stop bisphosphonates medications for 3 to 6 months prior to surgery
 - Informed consent about risk of BRONJ
 - Preoperative Chlorhexidine m/w and ABC (amox 3 g or clindamycin 600 mg)
 - Conservative surgical technique
 - Postoperative Chlorhexidine m/w and abs: Amox 250 TDS 7/7 + Metronidazole 200 mg TDS 7/7
 - Socket follow up

6. Dental treatment in high risk patients

- If the patient develops BRONJ or we diagnose it in a new patient, refer to Oral Surgery Dept :
 - Conservative management
 - Stop bisphosphonates
 - Postoperative Chlorhexidine m/w and abs: Amox 250 TDS 7/7 + Metronidazole 200 mg TDS 7/7
 - Socket follow up

7. BRONJ related to oral bisphosphonates

- Very rare (Between 1 in 10000 to 1 in 100000)
- Generally reverses with drug holiday
- Only stages I and II of BRONJ
- Assess patient's risks individually; the more risk factors present, the more conservative our approach
- Inform patient of their risk and involve them in the treatment plan decision

8. Future developments

1. Reduce dosis of iv bisphosphonates

Incidence of	Skeletal related events (ie. Fractures)	BRONJ
51 pt on 4 mg Zoledronic acid monthly	15,1 %	6,7 %
55 pt on 4 mg Zoledronic acid monthly for 1 year and quaterly thereafter	17,7 %	0,8 %

Corso et al. Leukemia. 2007

Retrospective cohort study in multiple myeloma patients

8. Future developments

2. Reduce dosis of iv bisphosphonates

New guidelines (Mayo clinic 2006 and American Society of Clinical Oncology 2007) advise on treatment of Multiple Myeloma patients with IV bisphosphonates for only 2 years.

Lacy et al. Mayo Clin Proc 2006 and Kyle et al. J Clin Oncol. 2007

London, 24 September 2009
Doc. Ref. EMEA/CHMP/292475/2009

Questions and answers on the review of bisphosphonates and the risk of osteonecrosis of the jaw

Finally, the Committee concluded that further data are needed to determine the precise measures that could minimise the risk of osteonecrosis of the jaw, including looking at how intravenous bisphosphonates should be given (such as their dose, how often they are given and for how long), and looking into the risk of osteonecrosis of the jaw in patients taking bisphosphonates by mouth for long periods. The CHMP noted that other possible risk factors for developing osteonecrosis of the jaw should be considered, such as gender, genetic factors, smoking and other treatments or diseases that the patient has, as well as the type of cancer a patient has and how long they have had it. Finally, the Committee concluded that information on the known and potential risks of osteonecrosis of the jaw with bisphosphonates should be clearly communicated to healthcare professionals and to patients.

8. Future developments

3. Serum CTX testing

Marx et al. J Oral Maxillofac Surg 2009

Bone turnover marker assay to determine risk of developing BRONJ in oral Bps pts:
Serum CTX (C-terminal telopeptide) testing > 150 pg/mL
- Indicates osteoclast activity
- Not reliable for oncologic or rheumatic patients (methotrexate, prednisolone)

Table 2 Summary of Marx's protocol¹⁷ and suggestions for patients on oral bisphosphonates who require oral surgery

Bisphosphonate use > 3 years

- Contact physician to discontinue bisphosphonate 3 months before surgery and for at least 3 months postoperatively, but preferably for 1 year.
- Determine serum CTx level at time of consultation and immediately before surgery. CTx must be ≥ 150 pg/mL before proceeding with surgery.
- Detail informed consent regarding risk of bisphosphonate-associated osteonecrosis (BON).
- Use an alternative to bisphosphonate for long-term treatment, if possible.

8. Future developments

4. Hyperbaric Oxygen

Prospective randomized controlled trial of 70 patients currently in progress

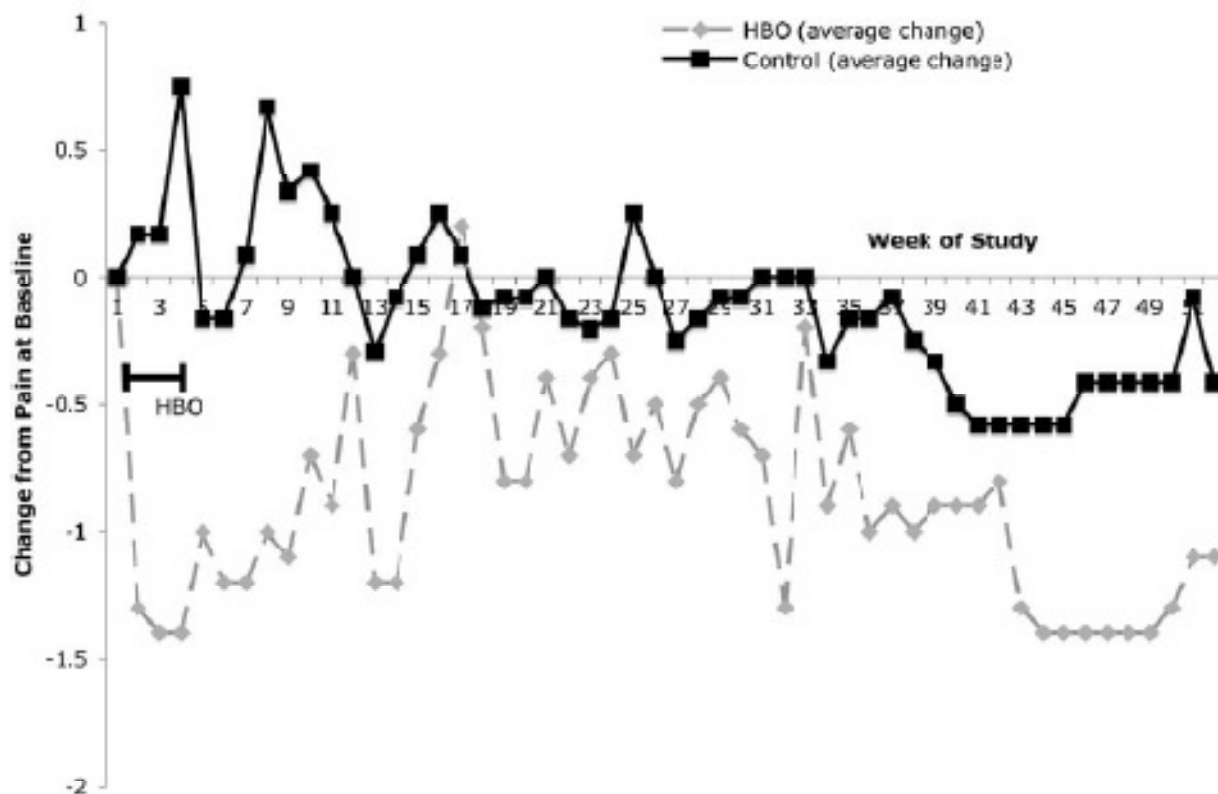


FIGURE 2. Change in average weekly pain score by treatment group. Pain decreased for both treatment groups relative to the level at first consultation. Average change in pain scores from week 0 to week 52 is shown. Pain was measured on 0 to 10 scale, with 10, maximum and 0, no pain. Pain scores were solicited on weekly basis by telephone interview or e-mail. To normalize the scale, the change in each individual's pain score was calculated by subtracting the previous week's score from the current week's value. Individual changes were averaged and plotted by the treatment groups. Censored observations were entered as the last available value in the calculations.

John J. Freiberger. Use of HBO in Treatment of BRONJ. J Oral Maxillofac Surg 2009.

8. Future developments

5. Alternatives to Bps: **Denosumab**

Monoclonal Anti-RANKL antibody currently in clinical trials for both osteoporosis and cancer populations, has been shown to suppress remodelling to an extent equal to or greater than bisphosphonates. No cases of BRONJ have been reported.

Lewiecki et al J Bone Miner Res. 2007

Lipton et al. J Clin Oncol. 2007

9. Recommendations

- Include in medical history form questions about:
 - Osteoporosis
 - Long term use of corticosteroids
 - Paget's disease
 - Multiple myeloma
 - Breast cancer
 - Prostate cancer
- Learn generic and brand name of bps
- Enquire about time that pt has been taking bps
- Communicate with: GP, oncologist, endocrinologist, gynecologist, rheumatologist and discuss risk of BRONJ. Do not assume that they are aware of it.

- 50 Questionnaires to GP's (44% Response)
- 58% stated they DO NOT advise patients to inform dentists of changes to their medical history
- 35% stated they DO NOT consider Bisphosphonate therapy a danger to dental care

Rob Isaac

Max Fax SHO @ Cardiff UDH

9. Recommendations

- Explain risks to patient and obtain informed consent
- Refer patients on IV bps requiring surgery to hospital
- Be professional:
 - do not panic
 - do not jump to the unknown
- Keep up to date:
 - www.ada.org/prof/resources/topics/osteonecrosis.asp
 - www.evidence.nhs.uk
 - www.sigwales.org

Many Thanks!