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BISPHOSPHONATES : CAN THESE BE THE BONE EATERS ?

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ABSTRACT:

Bisphosphonates are a group of synthetic analogs of inorganic pyrophosphate (an endogenous regulator of bone mineralization) Bisphosphonates are a family of drugs used to prevent and treat osteoporosis, multiple myeloma, Paget's disease (bone cancers), and bone metastasis from other cancers. These drugs can bond to bone surfaces and prevent osteoclasts (cells that breakdown bone) from doing their job.

KEYWORDS: Bisphosphonates ,BRONJ, osteonecrosis,BON

INTRODUCTION

First report of bisphosphonate-associated osteonecrosis of the jaw (BRONJ) associated with the use of Zometa (zolendronic acid) and Aredia (pamidronate) was published in 2003[1,2]. An association with dental procedures such as tooth extraction was found in majority of the reported cases; however, less commonly BRONJ appears to occur spontaneously in patients taking these drugs.

BRONJ Case Definition:

Definition of BRONJ was given by AAOMS [3]:

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

1. Current or previous treatment with a bisphosphonate;
2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws.
4.

Risk Factors

The original position paper categorized the risk factors for BRONJ as drug-related, local, and demographic or systemic factors. Other medications, such as steroids and thalidomide, and other chemotherapeutic agents were thought to be risk factors, but no measurable associations were identified. Subsequently, 2 new sets of factors, genetic and preventative, were also included [4] .

I. Drug-related risk factors include

A. **Bisphosphonate potency:** zoledronate (Zometa) is more potent than pamidronate (Aredia), and pamidronate (Aredia) is more potent than the oral bisphosphonates; the IV route of administration results in greater drug exposure than the oral route[5,6,7,8] . Using a number of different risk measures, the BRONJ risk among cancer patients given IV bisphosphonate exposure ranged from 2.7 to 4.2, suggesting that cancer patients receiving IV bisphosphonates have a 2.7- to 4.2-fold increased risk of BRONJ than cancer patients not exposed to IV bisphosphonates [5,9] .

B. **Duration of therapy**: a longer duration appears to be associated with increased risk[6,7] .

II . **Local risk factors include**

A. Dentoalveolar surgery, including, but not limited to [5,7,8.]

- Extractions
- Dental implant placement
- Periapical surgery
- Periodontal surgery involving osseous injury

Four studies reported that dentoalveolar procedures or concomitant dental disease increased the risk of BRONJ between 5.3 (odds ratio) and 21 (relative risk)[5,8,10,11]. Thus, cancer patients treated with IV bisphosphonates who undergo dentoalveolar procedures have a 5- to 21-fold increased risk of BRONJ compared with cancer patients treated with IV bisphosphonates who do not undergo dentoalveolar procedures.

B. Local anatomy

1- Mandible - Lingual tori , Mylohyoid ridge

2- Maxilla- Palatal tori

It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses, and the mylohyoid ridge [12,13,14].

C. Concomitant oral disease:

Risk of BRONJ is 7 fold increased in cancer patients exposed to IV bisphosphonates with history of inflammatory dental disease like periodontal and dental abscesses [7].

III. Demographic and systemic factors

Seven studies reported increasing age as consistently associated with BRONJ[6],[15,8,10,11,16,17]. Sex was not significantly associated statistically with BRONJ.[6,15,8,10,11,16.] One study reported race to be a risk factor, with whites having an increased risk of BRONJ compared with blacks [8]. Other systemic factors or conditions (ie, renal dialysis, low hemoglobin, obesity, and diabetes) were variably reported to increase the risk of BRONJ.[9,10] Malignancy type was not significantly associated statistically with an increased risk of BRONJ, [6] although the presence of metastatic disease reached near statistical significance (*P* = .051) in the report by Wessel et al. [9] In contrast to the original *Position Paper*, a few current studies have noted an increased risk of BRONJ among patients exposed to chemotherapeutic agents (ie, cyclophosphamide, erythropoietin, and steroids) [10,16] . Others, however, have failed to confirm the association between chemotherapeutic agents and BRONJ risk.[5,15,8,9,17]According to Wessel et al [9] there is an increased risk of BRONJ among tobacco users, however no increased risk was associated with alcohol exposure.

IV. Genetic factors

Sarasquete et al [18]demonstrated that genetic perturbations (ie, single nucleotide polymorphisms, in the cytochrome P450-2C gene [CYP2C8]) were associated with an increased risk of BRONJ among multiple myeloma patients treated with IV bisphosphonates.

V.Preventive factors

Patients should undergo dental evaluations and receive necessary treatment before initiating IV bisphosphonate therapy. Also as IV bisphosphonates have long-term biologic activity , one could hypothesize that different dosing regimens might be equally effective and decrease the risk of BRONJ. Recent studies have suggested that manipulation of IV bisphosphonate dosing might be effective in reducing skeletal-related events and minimizing BRONJ risk. [17] In addition, preventive dental interventions before initiating IV bisphosphonate treatment can also effectively reduce, but not eliminate, the risk of BRONJ.

Pathogenesis of BRONJ

The exact pathogenesis remains obscure but four main theories regarding BRONJ prevail. Acording to Mcdonald, BRONJ is induced by an oversuppression of bone turnover. Due to their high affinity, bisphosphonates accumulate in bone and subsequently in cells involved in bone resorption, namely osteoclasts. Osteoclast function is inhibited and consequently bone remodeling is suppressed[19]. An oversuppression of bone turnover by a localized toxic BP level may induce an osteonecrosis[20, 21]. Although the bone turnover in the jaws is higher [22,23,24] , there is no evidence that BPs accumulate at higher concentrations in the jaw (compared with other sites) or that bone remodeling of the jaw bone is affected to a higher degree. A recent study has confirmed that uptake of BP is not increased in the jaw compared with other bones[25].

Second theory suggests that, BRONJ could be a response to infection. BPs are known to modulate the immune response of different cell types. [26,27] This may alleviate the immune response toward particular pathogens in biofilms such as *Actinomyces* species, which were found to be present in most cases of BRONJ. [28,29]

According to the third theory, BRONJ may occur due to the antiangiogenic effect of bisphosphonates leading to ischemia. Although the description of BRONJ as avascular necrosis and the antiangiogenetic effect in BPs in tumor tissues suggest a role in the pathogenesis of BRONJ [28, 30,] the angiogenesis during bone formation seems to be unaltered by bisphosphonates. [31,32]

Fourth theory suggests that, soft tissue toxicity may be a mediator of BRONJ by BP's toxicity toward different cell types, including mucosal tissue. It has been argued that localized accumulation of BPs may, in combination with other cancer therapy medications, lead to mucosal injury followed by exposed bone and BRONJ. [33,34,35] However, exposed bone is not present in all cases of histologically proved necrosis and some clinical symptoms, such as pain, abscess or fistula formation, and even impairment of nerve function, can emerge during the onset of BRONJ,[12,36] even when the mucosa is still intact.

All theories could play a role in the pathogenesis of BRONJ; however, none of them (in isolation or combination) is able to explain why the jawbone is the exclusive target. Also the current theories do not offer a plausible explanation as to why nitrogen-containing BPs, which do not overly accumulate in the jawbone compared with other bones, [19] result in an increased risk of developing BRONJ. It was demonstrated by Sato et al [37] in rats that bone-bound alendronate is released at acidic pH. In humans, acidic milieus are common in infections and wound healing after surgical procedures. Indeed, pH values in the range of 6.2 are not uncommon during infections. [38,39,40]

The jawbones are frequently exposed to marginal or apical periodontitis, extended caries with endodontic involvement, and surgical procedures such as tooth

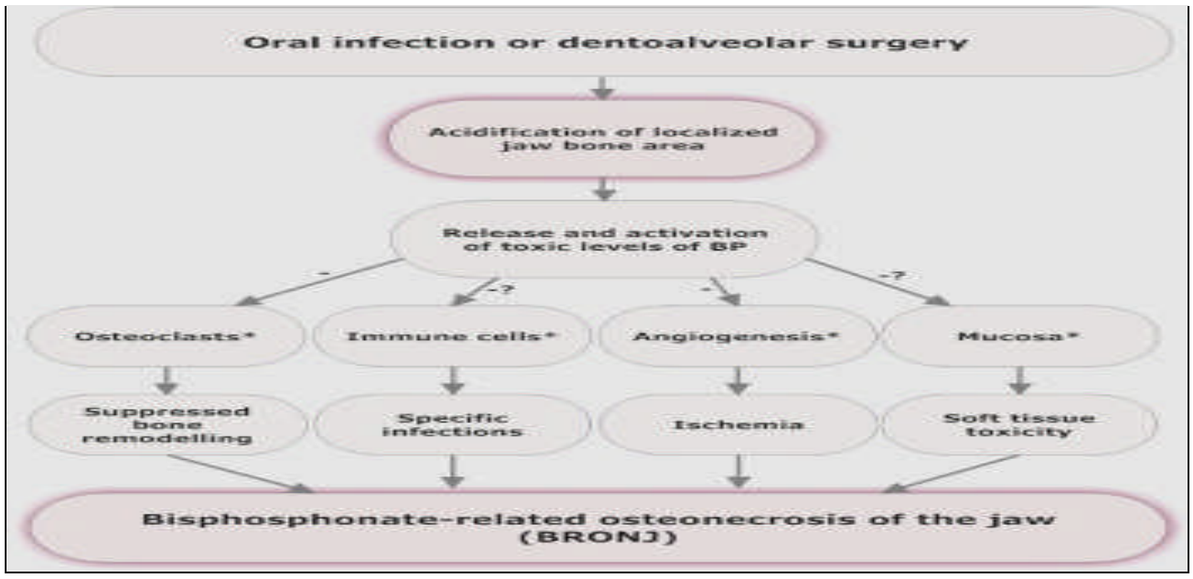

Fig.1. Schematic diagram of the potential pathogenesis of BRONJ

extractions or implant insertions. Resultant infections can herefore lead to localized tissue acidification (pH reduction) and subsequent increased BP release. Furthermore, pH reduction results in a protonated activation of nitrogen-containing groups (eg, NH_2 to NH^{3+}), thereby increasing the transformation of respective derivates to potentially toxic levels[41,42,43] . Based on this study Sven Otto et al[44] highlighted that a localized change in pH caused by dentoalveolar infections or surgeries is to date a neglected, primary factor that may elicit the onset of BRONJ. Schematic diagram **(Fig.1)** of the potential pathogenesis of BRONJ with decreased pH value as a crucial activator depicts inhibition of the listed processes or tissues (−), identify cursorily investigated pathogenesis theories (?), and identify the points at which risk factors (smoking, diabetes, steroids, chemotherapy, poor oral hygiene, comorbidity) might aggravate the BRONJ pathogenesis (*)[44].

Management Strategies for Patients Treated With Bisphosphonates [4]

Prevention of BRONJ

Before treatment with monthly IV bisphosphonates, the patient should undergo a thorough oral examination, any tooth that cannot be saved should be removed, all invasive dental procedures should be completed, and optimal periodontal health should be achieved. The risk of developing BRONJ associated with oral bisphosphonates, although exceedingly small, appears to increase when the duration of therapy exceeds 3 years. This period can be shortened in the presence of certain comorbidities, such as chronic corticosteroid use. If systemic conditions permit, the clinician might consider discontinuation of oral bisphosphonates for a 3-month period before and 3-month period after elective invasive dental surgery to lower the risk of BRONJ. The rationale for this approach is based on extrapolated data demonstrating fluctuations in osteoclast function related to bisphosphonate therapy and recent outcomes studies that have shown improved outcomes of BRONJ treatment with drug cessation. However long-term, prospective studies are required to establish the efficacy of drug “holidays” in reducing the risk of BRONJ for patients receiving oral bisphosphonates. The risk reduction could vary depending on the duration of bisphosphonate exposure. Modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Treatment Goals

- The major goals of treatment for patients at risk of developing or who have BRONJ are[4]:
- Prioritization and support of continued oncologic treatment in patients receiving IV bisphosphonates.
- Oncology patients can benefit greatly from the therapeutic effect of bisphosphonates by controlling bone pain and reducing the incidence of other skeletal complications.
- Preservation of quality of life through:
- Patient education and reassurance
- Control of pain
- Control of secondary infection
- Prevention of extension of lesion and development of new areas of necrosis

Exposed bone in maxillofacial region without resolution within 8-12 weeks in persons treated with bisphosphonate who have not undergone radiotherapy to jaws.

Staging and Treatment Strategies[4]

BRONJStage	Description	Treatment Strategies†‡§
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment indicated Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic management, including use of pain medication and antibiotics
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection	• Antibacterial mouth rinse • Clinical follow-up on quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage	• Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Superficial debridement to relieve soft tissue irritation
Stage 3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

Abbreviations: BRONJ-Bisphosphonate-related osteonecrosis of the jaw; IV- intravenous.

† *Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone; extraction of symptomatic teeth within exposed, necrotic bone should be considered because it is unlikely that extraction will exacerbate established necrotic process.*

‡ *Discontinuation of IV bisphosphonates has shown no short-term benefit. However, if systemic conditions permit, long-term discontinuation might be beneficial in stabilizing established sites of BRONJ, reducing risk of new site development, and reducing clinical symptoms. Risks and benefits of continuing bisphosphonate therapy should be made only by treating oncologist in consultation with oral and maxillofacial surgeon and patient.*

§ *Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution after debridement surgery. If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with treating physician and patient.*

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