REVIEW ARTICLE

Bisphosphonate related osteonecrosis of the jaws: An update

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ABSTRACT

Bisphosphonates (BPs) have been recommended for the use in patients with various bony lesions such as Paget's disease, hypercalcemia, osteoporosis, and multiple myeloma. Despite the increasing use and various benefits, bisphosphonate related osteonecrosis of the jaw (BRONJ) is a significant complication with significant morbidity. A search of PUBMED journal databases from January 2000 to April 2012 was conducted with the objective of identifying publications regarding BRONJ. Based on the available data current concepts in the diagnosis and management of BRONJ are discussed in this article.

Key words
Bisphosphonates, jaw, osteonecrosis

INTRODUCTION

Bisphosphonates (BPs) are a class of agents that have been increasingly recommended for patients with osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, osteolytic bone metastasis, and osteolytic lesions of multiple myeloma.

Despite the various benefits, bisphosphonate related osteonecrosis of the jaws (BRONJ) is a significant complication in a group of patients receiving these drugs which also adversely affects the quality of life and produces significant morbidity in the these patients.

A few years after their approval for use, the phenomenon of BRONJ was first recognized and reported in 2003 with the demonstration of bony lesions of the mandible and/or maxilla in patients treated with pamidronate or zoledronate.[1-4] It was also recognized in all countries where BPs were prescribed. Starck and Epker[5] in 1995 reported failure of osseointegrated implants in patients treated with BP for osteoporosis. However, due to limitation of a single case report a direct cause and effect of BP use and implant failure could not be established. The other related complications associated with BPs include decreased bone healing and inhibition of orthodontic tooth movement. Inhibition of tooth movement is due to decreased osteoclastic activity limiting bone turnover and repair.[6]

There is increasing concern that the oral BPs are implicated in osteonecrosis of the jaws, however, the incidence is low as compare with more potent intravenously administered BPs. Uniquely, bisphosphonate related osteonecrosis is only seen in the jaws and has not been reported in long bones. The extensive blood supply and a faster bone turnover rate of jaw structures compared with other bones, resulting in higher concentrations of bisphophonates in jaw bone is the possible reason for it.[7] However, some authors have even questioned the association of BPs and osteonecrosis of the jaw, suggesting that a causal relationship has not been definitely proven.[8,9]

Method of selection of articles: An online search was performed using a full-text electronic journal database (PubMed). All the papers published in English from January 2000 to April 2012 were considered for the review. The following keyword combinations were used for online search: BPs, jaw osteonecrosis, diphosphonates, and BP-related osteonecrosis. Full text articles, case series, retrospective/prospective studies, short communications, abstracts were included for the review. The primary objective was to identify all articles describing following characteristics of BRONJ:

1. Demographic characteristics of BRONJ

Access this article online	
Quick Response Code:	Website: www.ejgd.org
	DOI: 10.4103/2278-9626.105351

2. Risk, prognosis, treatment selection for BRONJ
3. Therapeutic uses of BP therapy
4. Dental aspects of BRONJ

All the papers from the online search results of the literature search were analyzed by the authors for potential inclusion in this review.

Based on the available data and extensive review of the literature by the authors, the current concepts in the diagnosis and management of BRONJ are discussed in this article. We also emphasize the important role of dental and medical specialties in the diagnosis and management of affected patients. As the knowledge base and experience in addressing BRONJ evolves, further modifications and refinements of the current strategies will be required.

BACKGROUND

Indications and benefits of bisphosphonate therapy

Use of intravenous bisphosphonates (IVBPs) is standard of care in cancer patients for the treatment of hypercalcemia of malignancy[10,11] as well as the prevention of skeletal related events (SRE).[12] The most common malignancies include multiple myeloma, breast, prostate and lung cancers. The IVBPs are also effective in the prevention of SRE such as bony pathology and fractures.[13] While the IVBPs have not been shown to improve cancer specific survival, they have had a significant impact on the quality of life for patients with advanced cancer and SRE. The risk of SRE was reduced to 47% in breast cancer and multiple myeloma patients treated with zoledronic acid for 25 months.[14] The risk of SRE in patients with these malignancies who do not receive IVBP therapy appeared to be between 48% and 68%.[15] Zoledronic acid was shown to reduce the risk of SRE from 49% to 38% in hormone refractory prostate cancer patients.[16] It was also shown to reduce the risk of SRE in patients with lung cancer after 21 months of intravenous therapy.[17]

Oral BPs are indicated for the treatment of osteoporosis and osteopenia.[18] They are also used for a variety of less common conditions such as Paget's disease of bone and osteogenesis imperfecta of childhood.[19,20] By far the most prevalent and common indication is osteoporosis.[21,22] Osteoporosis may arise in the context of other disease such as inflammatory bowel disease or primary biliary cirrhosis, use of steroids or as a consequence of post-menopausal aging.[23-25] Whatever the underlying etiology of osteoporosis, BPs in conjunction with calcium and vitamin D may play a vital role in its management.

Risks of bisphosphonate therapy

In 2003 and 2004, oral and maxillofacial surgeons were the first clinicians to recognize and report cases of non-healing exposed, necrotic bone in the maxillofacial region in patients treated with IVBPs.[3,26] Several case series and reviews have been published since these initial reports.

In September 2004, Novartis Pharmaceuticals Corporation, NJ, USA, the manufacturer of the IVBPs Pamidronate (Aredia) and Zoledronic acid (Zometa), notified health care professionals and provided cautionary language related to the development of osteonecrosis of the jaws.[27] This was followed in 2005 by a drug class warning of this complication for all BPs including the oral preparations.

Definition and estimated incidence

To distinguish BRONJ from other delayed healing conditions of the bone the following working definition was adapted by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007.[28] Patients may be considered to have BRONJ if all of the following three characteristics are present:

1. Current or previous treatment with a BP
2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and
3. No history of radiation therapy to the jaws.

Estimated incidence

IVBPs and incidence of BRONJ

More than 90% of cases of osteonecrosis of the jaw have been seen in patients with cancer who received IVBPs.[29] Currently available published incidence data for BRONJ are limited to retrospective studies with limited sample sizes. Based on these studies, estimates of the cumulative incidence of BRONJ range from 0.8% to 12%,[30,31] however, some authors have reported its incidence ranging from 0.8% to 18.6%.[32,33] With increased recognition, duration of exposure and follow up it is likely that the incidence will rise.

Oral bisphosphonates and incidence of BRONJ

Based on data from the manufacturers of Alendronate (Merck, White House Station, NJ, USA) the incidence of BRONJ was calculated to be 0.7/1,00,000 persons/years of exposure.[28] Another study based on prescription data in Australia reported that the estimated incidence of BRONJ for patients treated weekly with Alendronate is 0.001-0.04%. After dental extractions the rate increased to 0.09-0.34%.[28] Although these are the best data available to date, there may be serious under reporting.

Risk factors

Risk factors for the development of BRONJ can be grouped as drug related, local, and systemic factors.

1. Drug related risk factors include
   A. Potency of the particular BP: Zoledronate is more potent than Pamidronate and Pamidronate is more potent than oral BPs, the intravenous route used with these potent nitrogen containing BPs

(NBPs) results in a greater drug exposure than the oral route.[34]

B. Duration of therapy: Longer durations appear to be associated with increased risk.[35]

2. Local risk factors include
   A. Dentoalveolar surgery including but not limited to extractions, dental implant placement, periapical surgery, periodontal surgery involving osseous injury, and denture wearers. Patients receiving IVBPs and undergoing dentoalveolar surgery are at least seven times more likely to develop BRONJ than patients who are not having dentoalveolar surgery. Recent studies demonstrated 16- to 44-fold increased risk of BRONJ in patients receiving BPs who underwent dental extractions. One study reported 5-fold increased risk of BRONJ development in breast cancer patients treated with Zoledronate who were also wearing dentures.[34,35] Rinchuse *et al.*[36] reported failure of orthodontic extraction space closure in a patient on IV zoledronic acid (Zometa, 500 mg infusion once per month) for 11 months.
   B. Local anatomy: It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio). The possible explanation for higher incidence lesion in mandible than in maxilla is that mandibular bone has a higher composition of cortical bone, whereas maxillary bone has a higher composition of medullary bone; the difference in microcirculation between mandible and maxilla is the other reason for it.[6] The lesion is more commonly found in areas with thin mucosa overlying bony prominences such as torii, bony exostosis, and the mylohyoid ridge.[37]
   C. Concomitant oral disease: Hoff *et al.*[38] found that cancer patients exposed to IVBPs with a history of inflammatory dental disease (e.g., periodontal and dental abcesses) are at a 7-fold increased risk of developing BRONJ.

3. Systemic risk factors include
   A. Age: With each passing decade there is a 9% increased risk for BRONJ in multiple myeloma patients treated with IVBPs.[35]
   B. Race: Caucasians were found to be at a higher risk.[35]
   C. Cancer diagnosis: Risk is greater for patients with multiple myeloma than for patients with breast cancer and patients with breast cancer have a greater risk than those with other cancers. Sarasquete *et al.*,[39] recently demonstrated that CYP2C8 gene diversity influences the likelihood of the development of BRONJ in multiple myeloma patients receiving BP therapy.
   D. Osteopenia/osteoporosis along with other cancer increase the risk of BRONJ.

Apart from the above mentioned factors corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs are also thought to be risk factors for BRONJ. Further studies are required to accurately determine whether these factors are associated with BRONJ risk.[38]

PATHOGENESIS

Yamaguchi *et al.*,[40] in 2010 presented a working hypothesis for the mechanism underlying BRONJ. They stated that in patients treated with NBPs, infection, and/or tooth extraction induced inflammation was augmented, facilitating a local accumulation of NBPs within the jaw bone. Infection also induces lipopolysaccharide (LPS) release and hence, the production of the inflammatory cytokine interleukin 1 and/or tumor necrosis factor and infiltration of granulocytes and/or macrophages. Destruction of bone by these inflammatory cells can result in the release of accumulated NBPs. The released LPS, NBPs, and inflammatory cytokines might mutually augment their inflammatory actions. The augmented inflammation would then promote additional accumulation of NBPs within the jaw bones and further infiltration of granulocytes, leading to bone destruction with a consequent additional release of NBPs from the jaw bones. This vicious cycle could further aggravate the inflammation, resulting in necrosis and exposure of the jaw bones. In brief local and sustained (or repeated) release of a high concentration of NBPs from the jaw bones might be an important cause of BRONJ.

Another etiological model proposed by Wehrhan *et al.*[41] states that suppressed expression levels of Muscle Segment Box Msx-1 and Receptor activator of nuclear factor kappa-B ligand (RANKL) along with elevated level of Bone morphogenetic proteins (BMP)-2/4 is seen in BROJ tissues. Msx-1 is a cellular plasticity and proliferation mediating transcription factor which prevent terminal differentiation and stimulates proliferation of progenitor cells. It is co-expressed with RANKL on cranial neural crest cells derived jaws hard and soft tissue progenitor cells. Msx-1 suppression in ONJ-adjacent periodontal tissue suggested a BP related impairment in cellular differentiation that occurred exclusively in jaw remodeling.

TOOLS FOR DIAGNOSIS

Imaging

The radiographic features of BRONJ are not specific. Periapical and panoramic radiographs serve as an initial screening modality. CT and MRI provide a more comprehensive evaluation of the jaws and help to delineate the extent of the disease. Three phase bone scans are used as screening modality for patients with symptomatic or asymptomatic osteonecrosis. Bone scan can show abnormal radionuclide uptake 10-14 days

before bone mineral loss, significant for radiographic changes seen on conventional films. This could make them more sensitive in detecting early sub-clinical BRONJ. Tetracycline bone fluorescence has recently been used to visualize margins of the osteonecrosis more precisely, given that only viable, but not necrotic, bone fluoresces. Fluorescence-guided bone resection might improve the surgical therapy of osteonecrosis.[42]

Serum collagen telopeptide

Biochemical bone turnover markers are released during bone remodeling and can provide a measure of the rate of bone metabolism. One of these bone turnover markers is serum C-terminal telopeptide (CTX). Serum CTX measures the serum level of the C-terminal telopeptide-related fragment from a cross-linking chain in type I collagen, which is cleaved by the osteoclast in bone resorption. This is a reliable index for evaluating the bone turnover rate and the anti-resorptive therapy.[43] Whether the serum CTX value is as a good index to predict the risk of BRONJ is controversial. Marx *et al.*,[44] found lower serum CTX values in patients with BRONJ. A study by Kwon *et al.*[45] displayed the same pattern. Bagan *et al.*[46] attempted to find a correlation between CTX value and the number of lesions but they could not identify and correlate. In any event CTX monitoring could help determine healing capacity and improving the predictive outcome of BRONJ.

STAGING AND TREATMENT STRATEGIES

Stage 1

Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.

Treatment strategy

Anti-bacterial mouth rinse, clinical follow up on a quarterly basis, patient education and review of indications for continued BP therapy.[37]

Stage 2

Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage.

Treatment strategy

Symptomatic treatment with broad spectrum oral antibiotics e.g., penicillin V, cephalexin, clindamycin, or first generation fluoroquinolone, oral anti-bacterial mouth rinse, pain control, only superficial debridements to relieve soft tissue irritation.

Stage 3

Exposed/necrotic bone in patients with pain, infection and one or more of the following – pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border of the mandible.

Treatment strategy

Anti-bacterial mouth rinse, antibiotic therapy and pain control, surgical debridement/resection for long term palliation of infection and pain.
*Adapted by the AAOMS in 2007.[28]

In 2007 the AAOMS[28] modified the original staging by Ruggiero *et al.*,[37] to include at risk category which includes patients with no apparent exposed/necrotic bone who have been treated with either oral or IVBPs, no treatment is indicated for these sub-set of patients. Teriparatide therapy was recently used in osteonecrosis of jaw caused by Alderonate and it resulted in satisfactory healing of the lesion. Teriparatide action is believed to be due increased number of remodeling units and increased bone formation within each unit which may have promoted healing.[47]

DISCUSSION

Intravenous and oral BPs are used as standard of care in cancer patients for the treatment of hypercalcemia of malignancy, prevention of skeletal of related events, osteoporosis, osteopenia, Paget's disease as well as osteogenesis imperfectii of childhood.

The incidence of BRONJ worldwide with IVPB'S has been reported as 0.8-18.6%[32,33] and 0.09-0.34%.[28] The main drawback for the above mentioned data is that it is only limited to a few retrospective studies with few sample sizes. However, the authors are of the opinion that there might be a serious under reporting in the Indian subcontinent as there is not much published data available regarding the incidence of BRONJ.

The diagnosis of BRONJ clinically is based on three characteristics namely current or previous treatment with a BP, exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks, and no history of radiation therapy to the jaws. Regarding radiographic diagnosis of BRONJ though peri-apical and panoramic radiographs are the initial screening modality, CT and MRI help in delineating the extent of the disease. Bone scans are more sensitive in detecting early subclinical BRONJ. Recently tetracycline bone fluorescence has been used to visualize the margins of the osteonecrotic bone more precisely. Serum collagen telopeptide values are a good index to predict the risk of BRONJ. Lower serum CTX values were noted in patients with BRONJ in studies done by Marx *et al.*,[44] and Kwan *et al.*,[45] however, Bagan *et al.*[46] could not find a correlation between CTX value and the number of lesions.

Management of BRONJ depends on early recognition and staging. Treatment strategies vary from patient education, anti-bacterial mouth rinses, antibiotic therapy, and

pain control to resection.[48] The drug holiday should be considered but its benefits are doubtful in cases of IVBPs as the half-life of the drug is about 10 year and their prolonged use results in the substantial accumulation of this drug in the skeleton. Thus, a long "drug holiday" would be required to eliminate the drug from the body which is not possible in many cases.[49] Thus, a fact which has to be emphasized is the importance of early diagnosis of BRON and the role and effective communication between the dental and medical specialties for better management of the affected patients.

The dental treatment of patients receiving intravenous BPs should be focused on reducing the risk for BRONJ and minimizing the need for surgical procedures. Thus, whenever possible the tooth extractions, periodontal treatment with flap raising, dental implants are to be avoided in patients receiving IVBPs.[46] However, there are certain cases where extraction is unavoidable, patient should be carefully informed of the risks of BRONJ, with signing of the corresponding consent document. The extraction should be performed in a minimally traumatic manner, with curettage of the socket, cleansing of the surgical bed, and suturing of the wound margins. Antibiotic prophylaxis is to be provided before and after extraction.

CONCLUSION

The evidence-based literature on BRONJ is growing but there are still many controversial aspects. Prospective clinical trials are required so that a more comprehensive staging system can evolve, which would enable clinicians to make accurate judgments about risk, prognosis, treatment selection, and outcome for patients with BRONJ.

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How to cite this article: Kumar RA, Sawhney C, Kumar S, Dhingra M. Bisphosphonate related osteonecrosis of the jaws: An update. Eur J Gen Dent 2012;1:131-6.

Source of Support: Nil, **Conflict of Interest:** None declared.