Review Article

Bisphophonates related osteonecrosis of the jaw

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ABSTRACT

Objective: With sporadic reporting of BPs related osteonecrosis of jaw and in absence of definitive guidelines regarding the management of such patients, the dentists and the oral and maxillofacial surgeons need to be updated about this issue. The objective of this article was to produce an updated bibliographic review of BPs related ONJ. This paper reviews the literature regarding the same for better understanding of the problem and its management. **Background:** Bisphosphonates (BPs) are potent inhibitors of bone resorption and are widely used in the treatment of osteoporosis and other diseases that cause bone mass loss, such as Paget's disease, bone metastases, and multiple myeloma, to prevent pathological fractures. With increasing use, evidence is emerging that patients taking BP drugs are at risk of developing osteonecrosis of the jaws (ONJs), sometimes occurring spontaneously, but more commonly following dental extractions or oral bone surgery. **Materials and Methods:** A bibliographic search was carried out using PubMed, Medline, and search engines ending in April, 2013. The search terms used were: Oral BPs, dental implants, and osteonecrosis. **Conclusion:** On the basis of available literature, the management of patients on bisphosphonates requiring dental treatment is classified according to the duration of BPs treatment, method of administration of BPs etc. Dental treatments when planned carefully in such patients have a fair to good prognosis.

Key words: Bisphosphonate, implants, osteonecrosis of jaw

Introduction

Bisphosphonates (BPs) are potent inhibitors of bone resorption and are widely used in the treatment of osteoporosis and other diseases that cause bone mass loss; such as Paget's disease, bone metastases, and multiple myeloma to prevent pathological fractures.[1] The clinical efficacy of such drugs in the treatment of osteopenia/osteoporosis has been well-established.[2] But with increasing use, evidence is emerging that patients taking BP drugs are at risk of developing osteonecrosis of the jaws (ONJs), sometimes occurring spontaneously, but more usually following dental extractions or oral bone surgery. For example in Australia, there were 2.3 million BP prescriptions in 2003 which were equal to the number of amoxycillin prescriptions in the same year.[1] In 2004, this had increased to 2.5 million BP prescriptions.[3]

The association of BPs, that is, Zometa (zolendronic acid) and Aredia (pamidronate) with ONJs of 36 cases was first reported in 2003 by Marx.[4] In December 2004, Novartis, the manufacturer of pamidronate and zoledronate, called attention to the risk of osteonecrosis.[5]

This article aims to review the available literature about the possible association between dental treatment and BPs as the dental management plan for these patients needs to be carefully formulated to minimize the risk of avascular necrosis of the jaws and allow for the maintenance of overall health care of the patient.

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Nomenclature

The term BP-associated osteonecrosis (BON) originated in a paper published in the Journal of the American Dental Association.[6] Different nomenclatures are used to identify osteonecrosis associated with a BP include ONJ, BP related ONJ (BRONJ), BP induced ONJ (BIONJ), and BP associated ONJ (BONJ). The term BRONJ will be used in this article as the pathogenesis behind the disease is still inconclusive.

Definition

Various medical associations and research societies have defined ONJ. To differentiate from other bone pathologies, the following working definition of avascular ONJ has been adopted by the American Association of Oral and Maxillofacial Surgeons (AAOMS).[5] Patients may be considered to have BRONJ in the presence of all the following three characteristics: 1) Previous or current 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 in the region.

Chemistry and Mechanism of Action

BPs are synthetic compounds with a chemical structure similar to that of inorganic pyrophosphate, an endogenous regulator of bone mineralization.[7]

While pyrophosphate is comprised of two phosphate groups linked by phosphoanhydride bonds (P-O-P structure), BPs are comprised of two phosphonate groups linked by phosphoether bonds (P-C-P structure). There are two main types of BPs: Nitrogen containing (alendronate (ALN), risedronate, pamidronate) and non-nitrogen containing (etidronate, tiludronate).[7]

BPs act almost exclusively on bone when administered at physiological doses because of specific affinity to bone, where they deposit both in newly formed bone and in proximity to the osteoclasts. BPs act on bone through several mechanisms simultaneously. They can both decrease osteoclast activity and decrease osteoclast numbers. The first is exemplified by internalization by osteoclasts, causing disruption of osteoclast-mediated bone resorption,[1,7] the second by inhibiting osteoclast recruitment and accelerating programmed cell death (apoptosis) of osteoclasts, thus reducing osteoclast numbers. Both mechanisms lead to reduction of bone resorption and to a decrease in bone turnover.[7,8]

At the tissue level, BPs (i) inhibit bone resorption (extensively documented for nitrogen containing BPs ALN and consequently, (ii) bone turnover and (iii) increase bone density (up to 11% over 7 years in the spine), and (iv) bone strength, assessed by a reduction in fractures and by *ex vivo* mechanical testing in animals.[1]

In molecular terms, one of the major actions of BPs is the inhibition of the enzyme farnesyl diphosphate synthase, causing several cytoskeletal alterations, reducing the bone resorption capacity of the osteoclasts and inducing apoptosis of those cells.[1,9,10]

The half-life of BPs in the circulation is quite short, ranging from 30 min to 2 h.[11] The presence of nitrogen in their formulation makes their metabolization difficult, therefore, once incorporated into bone tissue, they can persist for up to 10 years, depending on the skeletal turnover time[11,12] and hence, prolonged action.[13] This explains why single or short courses of intravenous (IV) injections can be effective for a long time in the management of Paget's disease[11] and the cumulative effects are visible even when the patient is not using BP therapy.

Incidence

A Europe-wide review in 2009 on the risk of ONJ in association with the use of BPs concluded that the risk is greater for patients receiving IV BPs for cancer, than for patients receiving oral BPs for osteoporosis or Paget's disease of bone. The risk appears to be low in patients taking BPs by mouth.[7]

The cumulative incidence of avascular ONJ ranges from 0.8 to 12%. It is more often related to the IV monthly administration, and for a period longer than 3 years; which is more common in the treatment of hypercalcemia secondary to malignant tumors; to bone metastases from breast, prostate, and lung cancer; and to osteolytic diseases, such as multiple myeloma.[5,14,15] The risk of developing BON appears to be very low and is estimated to occur in approximately 0.7 per 100,000 person-years' exposure to ALN.[16]

The osteonecrosis of other skeletal bones due to BPs usage has not been reported. The unique environment of the oral cavity could explain why the maxilla and mandible are solely involved. The jaws have a greater blood supply than other bones and a faster turnover rate related to their daily activity and presence of teeth, therefore, BPs are highly concentrated in jaws.[17] It can be hypothesized that patients who have received long-term BP therapy may have a compromised blood supply to their maxilla and mandible. When dental extractions are performed on this group of patients, the open bony wound with a compromised healing ability cannot cope with the presence of oral microflora[18] due to which the extraction wound, then, becomes infected and progresses into osteomyelitis. It then develops into osteonecrosis.[18]

It should be noted that all other bones in the skeleton are well enclosed in the soft tissue and thus protected from a resident microflora.[7]

The limited data in the literature show that ONJ is much less common among patients administered oral BPs at the lower doses used for osteoporosis compared with patients who receive higher doses used for metastatic cancer.[19] The type of study (retrospective vs. prospective), no specific diagnostic code for this condition,[19] inconsistent definition of ONJ, as well as a possible lack of adjudication can contribute to the large range of incidence estimates.

Pathogenesis

The relationship between BPs and BRONJ has not been well understood[20,21] and current information on incidence and prevalence is inconclusive.[22] Several possible mechanisms of BRONJ pathogenesis have been suggested which includes ischemia, reduced bone turnover, inhibition of angiogenesis, toxicity to bone, toxicity to soft tissue, microcracks, inflammation and infection.[23-26]

One of the proposed mechanisms suggests that BRONJ can be caused by BP induced low bone turnover, which leads to decreased blood flow, bone cell necrosis, and apoptosis.[4,27] In conjunction with infection, this leads to the development of exposed, nonhealing bone areas in the mouth,[4,17] which may be thought of as an 'inside-out' process. However, the available data would suggest an 'outside-in' process as more likely, in which mucosal damage is the event preceding infection and subsequent bone necrosis.[28]

It is suggested that a multifactorial model is required to explain the pathogenesis of BRONJ as the combination of compromised immunity, that is, diabetes, human immunodeficiency virus infection; and medications like steroids and cytostatic agents can affect wound healing and interfere with wound epithelialization.[19]

Various researchers have reported that microbial biofilms may play a role in the etiopathogenesis of 65-80% of the chronic human infections.[26,29] Specific staining for bacteria typically reveals Actinomyces,[30] although this common oral organism may be found as a consequence of the lesion rather than as an initiating factor. Bacterial analysis of ONJ is limited, however, and more studies are needed to determine whether anaerobic bacteria, such as those involved in periodontal disease, are concerned.

Risk Factors for Bronj

Several retrospective clinical studies have identified potential risk factors associated with the development of BRONJ.

History of dentoalveolar trauma

In the majority of BRONJ cases, recent dentoalveolar trauma was the most prevalent and consistent risk factor.[17,31,32] Patients with a history of inflammatory dental disease, for example, periodontal and dental abscesses, are at a seven-fold increased risk for developing BRONJ.[33]

Systemic situations

Residual multiple myeloma or another malignancy; hypoproteinemia; renal impairment from disease or drugs; and/or chemotherapy are some of the systemic predisposing factors.[5,7,34,35] Other co-morbid conditions like hypertension, hyperlipidemia, hypercholesterolemia, rheumatoid arthritis, and diabetes may also possibly contribute to risk of developing BRONJ in patients receiving BPs for noncancer indications.[17]

Duration of bisphosphonate exposure

This appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a greater risk of developing disease.[17,31,33]

Type of bisphosphonate

The more potent IV BPs, such as pamidronate and especially zolendronate, appear to be significantly more problematic as compared with the oral BP medications. Initially, BRONJ was seen only with the use of the more potent IV forms of the drug, however, there have been reports of osteonecrosis in patients on the less potent oral forms.[7,17,27]

Gender of the patient

The literature reports more cases of BRONJ in females than males, which is likely a reflection of the large number of cases reported in breast cancer patients. With postmenopausal osteoporosis as an indication for BP use, a large percentage of the female population may also be at risk for developing BRONJ. Patients receiving oral BP therapy for osteoporosis that develop BRONJ have typically been exposed to these agents for a longer period of time (greater than 3 years) or were also exposed to steroid therapy.[5]

Jaw anatomy

ONJ occurs twice as frequently in mandible than in maxilla and areas with thin mucosa such as torus mandibularis, bony exostosis, and mylohyoid ridge.[17,36,37]

Genetic factors

It has been demonstrated that genetic perturbations, that is, single nucleotide polymorphisms (SNPs) in the cytochrome P450-2C gene (CYP2C8) gene were associated with an increased risk for BRONJ among multiple myeloma patients treated with IV BPs.[38]

The general risk factors may also be classified as local (e.g., poor oral hygiene, dental extraction, and infection), systemic (e.g., cancer, metastasis, chemotherapy, smoking, obesity, and malnutrition), and drug-related (e.g., duration of BP therapy and steroid use).[4,34,35]

Clinical Features of BRONJ

Patients with no clinical evidence of necrotic bone, but present with nonspecific symptoms or clinical and radiographic findings, such as

Symptoms

- Odontalgia not explained by an odontogenic cause.
- Dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region.
- Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall.
- Altered neurosensory function.

Clinical findings

- Loosening of teeth not explained by chronic periodontal disease.
- Periapical/periodontal fistula that is not associated with pulpal necrosis due to caries.

Radiographic findings

- Alveolar bone loss or resorption not attributable to chronic periodontal disease.
- Changes to trabecular pattern—dense woven bone and persistence of unremodeled bone in extraction sockets.
- Thickening/obscuring of periodontal ligament (thickening of the lamina dura and decreased size of the periodontal ligament space).
- Inferior alveolar canal narrowing.

These nonspecific findings, which characterize stage 0, may occur in patients with a prior history of stage 1, 2, or 3 disease who have healed and have no clinical evidence of exposed bone.[5]

Diagnostic Assessment of Osteonecrosis of the Jaw

Lesions following AAMOS criteria should be further assessed through bone morphology, soft tissue (gingiva), and bone function using various scanning techniques.

Assessment of bone function (metabolic activity)

Bone scintigraphy

A useful screening tool for detecting local bone remodeling/modeling activity is bone scintigraphy with Tc-99 methylene diphosphonate (MDP), which has high sensitivity but low specificity.[39] This technique aims to detect high bone turnover sites.

Positron emission tomography

Positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (FDG) is capable of noninvasively detecting osteomyelitis (acute and chronic) with a high degree of accuracy. Inflammatory cells, such as neutrophils and activated macrophages, present in areas of acute or chronic inflammation take up FDG as a result of increased glycolytic activity[40-42] and accumulation of FDG in this way is a useful indicator of inflammatory processes.[43]

Assessment of bone morphology (noninvasive imaging)

Panoramic radiography

Panoramic radiographs orthopantomography (OPG) cannot adequately distinguish between osteonecrosis and metastatic osteoblastic lesions, but is useful when a combination of osteolysis and osteosclerosis is present (osteosclerosis is found in chronic osteomyelitis). The two-dimensional image quality renders difficulty in differentiating the margins between necrotic and healthy bone, with the result that early lesions can be missed. However, consensus suggests conventional radiographs should be used first-line as part of routine radiologic investigation.[36]

Dental computed tomography

Computed tomography (CT) accurately detects alterations inside the bone, periosteal reactions, and soft tissue alterations. In patients with BRONJ, CT can diagnose osteolytic and osteosclerotic regions, depending on the stage of the disease. More dense bone characterizes the necrotic area and more lytic areas illustrate the infected regions with pus and soft tissue swelling. The differentiation between malignant metastatic osteolysis and benign osteolysis may be difficult with CT.

Cone beam computed tomography

An alternative to CT, Cone beam computed tomography (CBCT) has gained increased acceptance as a three dimensional imaging modality[44,45] particularly in the maxillofacial bone area.[46,47] This is a relatively new technique that uses lower radiation dosages, and has a higher spatial resolution than conventional CT, providing improved image quality (especially for cancellous bone).[48,49] CBCT is optimized for planning the placement of oral implants, but not for diagnosis of BRONJ.

Magnetic resonance imaging

In patients with complicating clinical factors, fat-suppressed contrast-enhanced T1-weighted Magnetic resonance imaging (MRI) has been shown to be significantly more sensitive than scintigraphy and significantly more specific than nonenhanced MRI or scintigraphy in diagnosing osteomyelitis.[50]

Serum markers

The use of serum levels of the collagen breakdown product, C-terminal cross-linking telopeptide of type I collagen (CTX), has been advocated as a risk predictor for developing BON. Serum CTX and urinary N telopeptide of type I collagen (NTX) are considered markers for bone resorption. Higher levels of these markers are associated with active bone turnover.

But further research, is required to substantiate the findings by well-controlled, randomized clinical trials.[51-53]

Recommended assessment procedure for osteonecrosis of the jaw

The diagnosis of BRONJ is made clinically if an oral lesion with exposed bone persists for more than 8 weeks. Lesions in patients who have had radiation therapy to the head and neck, or who have malignant disease within the jaw should be excluded from the diagnosis of BRONJ. Radiological assessment should be used to confirm the diagnosis and its extent. The radiologic assessment of BRONJ should incorporate the use of OPG or scintigraphy with MDP as first-line, with dental MRI or spiral dental CT, or CBCT (for bone only) used as more advanced approaches in cases that require further differential diagnosis

The staging and associated treatment strategies are tabulated in Table 1.

The use of oral antimicrobial rinses in combination with oral systemic antibiotic therapy; penicillin, metronidazole, quinolones, clindamycin, doxycycline, and erythromycin is indicated for stages I and II of BRONJ.[5,55]

Table 1: Staging and treatment strategies

BRONJ staging[54]	Treatment strategies[54]
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 the use of pain medication and antibiotics
Stage 1	
Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse Clinical follow-up on a 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 the region of the 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, (i.e., 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 of sinus floor	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/ resection for longer term palliation of infection and pain

BRONJ: BP related ONJ

Treatment goals

The major goals of treatment for patients at risk of developing or who have BRONJ are

1. Prioritization and support of continued oncologic treatment in patients receiving IV BPs.
2. Preservation of quality of life through:
   a. Patient education and reassurance,
   b. control of pain, and
   c. control of secondary infection.
   d. Prevention of extension of lesion and development of new areas of necrosis.

Treatment strategies

The proposed treatment strategies[5,6,17,36,50,56] for patients of BP therapy is as follows

I. Patients about to initiate IV BP treatment
   1. The treatment objective for this group of patients is to minimize the risk of developing BRONJ.[1] Initiation of BP therapy should be delayed until dental health is optimized.[57]
   2. Nonrestorable teeth and those with a poor prognosis should be extracted.
   3. Necessary elective dentoalveolar surgery should also be completed at this time and it appears advisable that BP therapy should be delayed, if systemic conditions permit, until the extraction site has mucosalized (14-21 days) or until there is adequate osseous healing.
   4. Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region and the cause should be removed.
   5. Educate the patients about the importance of dental hygiene and regular dental evaluations, and specifically instructed to report any pain, swelling, or exposed bone.

II. Asymptomatic patients receiving IV BPs
   1. Maintain good oral hygiene and dental care to prevent dental disease that may require dentoalveolar surgery.
   2. Procedures that involve direct osseous injury should be avoided.
   3. Nonrestorable teeth may be treated by removal

of the crown and endodontic treatment of the remaining roots.[50]

4. Placement of dental implants should be avoided in the oncology patient exposed to the more potent IV BP medications (zoledronic acid and pamidronate) on a frequent dosing schedule (four to 12 times per year).

III. Asymptomatic patients receiving oral BP therapy
Patients receiving oral BPs are at much lesser risk for developing BRONJ than those treated with IV BPs.[17,27,58] Elective dentoalveolar surgery does not appear to be contraindicated in this group. It is recommended that patients be adequately informed of the small risk of compromised bone healing. Sound recommendations based on strong clinical research designs are still lacking for patients taking oral BPs.

IV. Patients with BRONJ
The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis.
Patients with established BRONJ should avoid elective dentoalveolar surgical procedures, since these surgical sites may result in additional areas of exposed necrotic bone. These patients respond less predictably to the established surgical treatment algorithms for osteomyelitis or osteoradionecrosis.

Surgical debridement

Surgical debridement has been variably effective in eradicating the necrotic bone.[4,24,59,60] It may be difficult to obtain a surgical margin with viable bleeding bone due to the pharmacologic influence of the BP. Therefore, surgical treatment should be delayed if possible and reserved for those patients with stage 3 disease or in those cases with well-defined sequestrum. Loose segments of bony sequestrum should be removed without exposing uninvolved bone.[61]

The extraction of symptomatic teeth within exposed, necrotic bone should be considered, since it appears unlikely that the extraction will exacerbate the established necrotic process.

Case reports with small sample sizes have documented the use of other nonsurgical treatment strategies, such as, platelet rich plasma, parathyroid hormone, and bone morphogenic protein.[62]

The efficacy of these treatment modalities needs to be established through additional research and controlled studies.

Implant placement and BPs

There is a paucity of data on the effects of implant placement in patients taking oral BPs.[63-65] Out of the five published papers on implant and BPs, only one case of osteonecrosis around implant has been reported from more than 845 implants placement.[63,64,66-68] in patients on IV. BPs and oral BPs for approximately 3 years.

Because implant placement requires the preparation of the osteotomy site, treatment plans should be carefully considered. Recommendations published by the American Dental Association warn that the placement of dental implants or guided bone regeneration involves an increased risk of osteonecrosis in patients undergoing treatment with oral BPs.[16] The AAOMS do not contraindicate dental implant placement in patients who have been taking BPs orally for under 3 years prior to surgery providing they do not present other risk factors such as medication with corticosteroids or advanced age (over 70 years).[69]

Due to the lack of research and the controversy surrounding dental implants for these patients, it is better to avoid them altogether along with all other types of oral surgery.[70] Before implant placement, the dentist and the patient should discuss the risks, benefits, and treatment alternatives, which may include, but are not limited to, periodontal, endodontic, or non-implant prosthetic treatments.

A randomized clinical trial conducted at Linköping University Hospital in Sweden has shown that dental implants with a BP nano layer have improved stability. A nanometer-thin protein layer is attached to the metal surface and a BP is attached to the protein. When the BP is released, a local effect is obtained, which improves implant stability.[71,72]

Conclusion

At present there are no studies that adequately address the incidence of BONJ. The few studies to date use a wide range of methods, all with potential shortcomings, and have reported varied conclusions. Without good information on the incidence of BON it is difficult to predict a patient's risk. Conservative surgical procedures, proper sterile environment, appropriate use of oral disinfectants, and the principles of effective antibiotics are the suggested recommendations to be followed when treating patient on/with history of BP use.

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