# Bisphosphonate-related osteonecrosis of the jaws

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## ABSTRACT

Bisphosphonates are potent inhibitors of bone resorption, and are 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. Since 2003, avascular osteonecrosis of the jaw has been associated with the use of bisphosphonates, mainly intravenous. According to the literature, the occurrence of osteonecrosis of the jaw has ranged from 0.8% to 12% of the patients on bisphosphonates, most of them on prolonged use. Physicians and odontologists should be aware of that potential complication in dental treatment.

**Keywords:** osteonecrosis; maxillary diseases; osteoporosis.

*[Rev Bras Reumatol 2011;51(4):401-7] ©Elsevier Editora Ltda*

## INTRODUCTION

Bisphosphonates (BFT) are potent inhibitors of bone resorption, and are 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] Bisphosphonates increase bone mass and mineralization, with an increase in bone mineral density and resistance, and a reduction in the risk of bone fracture.

Bisphosphonates show selectivity for areas of bone resorption and inhibit the action of osteoclasts. In molecular terms, one of the major actions of BFT 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.[1-3] In general, BFT are systemically well tolerated. Their adverse effects are rare and consist in low and transient fever, fatigue, arthralgia, nausea, esophagitis, renal failure, hypocalcemia, and bone pain.[4] The use of BFT, however, has been associated with cases of avascular osteonecrosis of the jaw (Figure 1). Other skeletal bones have not been involved. The general symptoms include difficulty in eating and speaking, swelling, pain, bleeding, paresthesia of the lower lip, and tooth mobility and loss. The radiographic findings are not specific, thus, such lesions might require biopsy to rule out metastases.[5]

This study aimed at reviewing the literature regarding the risk of BFT-related avascular osteonecrosis of the jaws, in addition to providing guidance for prevention and treatment according to the stage of the disease.

## REVIEW OF THE LITERATURE

Pamidronate and zoledronate belong to the drug class of bone resorption inhibitors, which have been used for years for the treatment of osteoporosis. The clinical efficacy of such drugs in the treatment of osteopenia/osteoporosis has been well established.[6] The presence of nitrogen in their formulation makes their metabolization difficult, leading to their accumulation in

Received on 05/21/2010. Approved on 04/30/2011. Authors declare no conflict of interest.
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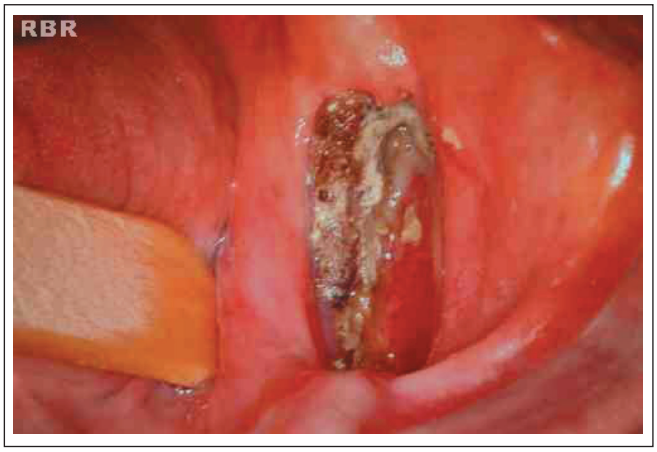


**Figure 1**
Bisphosphonate-related osteonecrosis. Left retromandibular region.

bones and prolonged action.[7] Oral BFT have been more often indicated for the treatment of osteoporosis and osteopenia. They have also been indicated in other less common conditions, such as Paget's disease and osteogenesis imperfecta. Table 1 shows the characteristics of the BFT indicated for treating osteoporosis available in the Brazilian market.

The association of BFT with osteonecrosis of the jaws was first reported in 2003 by Marx.[8] The author reported 36 cases of avascular osteonecrosis, 29 of which in the mandible, five in the maxilla, and two in both bones. Of the 36 patients, 24 were on intravenous (IV) pamidronate, 90 mg monthly; six used initially pamidronate at the same dosage, and then changed to IV zoledronate, 4 mg monthly; and six received only IV zoledronate, 4 mg monthly. The indications for the use of those drugs were multiple myeloma-related hypercalcemia (18 patients), metastatic breast carcinoma-related hypercalcemia (17 patients), and treatment of osteoporosis (one patient).

After the first report in 2003,[8] several studies by oral and maxillofacial surgeons have associated the use of BFT with avascular osteonecrosis of the jaws. In December 2004, Novartis, the manufacturer of pamidronate and zoledronate, called attention to the risk of osteonecrosis.[9] A search in the PubMed database (*U.S. National Library of Medicine and the National Institutes of Health*) (http://www.ncbi.nlm.nih.gov/sites/entrez) on February 2nd, 2011, with the descriptors (bisphosphonate) AND (osteonecrosis of the jaws) identified 928 articles.

To differentiate from other bone pathologies, the following working definition of avascular osteonecrosis of the jaw has been adopted by the American Association of Oral and Maxillofacial Surgeons (AAOMS):[10] Patients may be considered to have BFT-related osteonecrosis of the jaw in the presence of all the following three characteristics: 1) previous or current treatment with a BFT; 2) exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and 3) no history of radiation therapy in the region.

The cumulative incidence of avascular osteonecrosis of the jaw ranges from 0.8% to 12%. It is more often related to the intravenous, monthly administration and for a period longer than three years. The use of BFT in such conditions 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.[10-12]

The oral route is more common in the treatment of osteoporosis. Until 2006, according to IMS Health, over 190 million oral BFT prescriptions had been dispensed worldwide.[10] Patients under treatment with oral BFT are considered at low risk as compared with patients with cancer receiving intravenous monthly treatment with BFT, which significantly increases the risk of osteonecrosis.[11] However, cases of osteonecrosis of the jaws have been reported in patients on oral BFT.[13,14] An Australian control has estimated that the incidence for patients treated weekly with alendronate ranges from 0.01% to 0.04%.[15] Among 13 thousand patients of an American health

**Table 1**
Characteristics of the BFT indicated for treating osteoporosis in Brazil

| BFT | Primary indication | Dose | Route | Relative potency |
|---|---|---|---|---|
| Alendronate | Osteoporosis | 10 mg/day<br>70 mg/week | Oral | 1 |
| Ibandronate | Osteoporosis | 2.5 mg/day<br>150 mg/month<br>3 mg/3 months | Oral<br><br>IV | 1 |
| Risedronate | Osteoporosis | 5 mg/day<br>35 mg/week | Oral | 1 |
| Zoledronate | Bone metastases<br>Osteoporosis | 4 mg/3 weeks<br>5 mg/year | IV<br>IV | 10+ |

care insurance, receiving oral BFT for a long time, the prevalence was 0.06% or 1:1,700 patients.[16]

The occurrence of osteonecrosis of the jaw seems to be related to the use of intravenous BFT. However, data are inaccurate, and given the large number of patients being treated for osteoporosis, receiving oral BFT for a long period, it is likely that many cases may appear in that group of patients, since duration of therapy is one of the risk factors.[17,18]

Comorbidities, such as obesity and the chronic use of corticoids, can be associated, but that relation has not been clarified. The local risk factors include oral surgery, dental implant placement, extractions, and periodontal surgery involving bone lesions. Local factors also include the presence of bony exostoses (lingual and palatal tori) and poorly adapted prostheses. Regarding demographic and systemic risk factors, the studies are scarce. Gender does not seem to influence; however, the Caucasian race, advanced age and smoking seem to increase the risk, while alcohol consumption does not.[18-20]

Prior to treatment with intravenous BFT, the patient should have a thorough oral examination, all unsalvageable teeth should be removed, all invasive dental procedures should be completed, the prostheses should be well adapted, and optimal periodontal health should be achieved. Therefore, the risk for osteonecrosis of the jaw is reduced, but not eliminated.[18,19] Some instructions and protocols for patients at risk for osteoradionecrosis seem to be the same for patients under treatment with intravenous BFT. When previous surgery is needed, if systemic conditions permit, the beginning of the BFT therapy should be delayed until the operated area has mucosalized or until there is complete osseous healing.[10-12]

Table 2 shows staging of osteonecrosis of the jaw and the corresponding treatment strategies proposed by the AAOMS in 2009.[10]

The oral use of BFT is not that critical for the risk of avascular osteonecrosis of the jaw. Thus, elective oral surgeries are not contraindicated, but the patient should be aware of the risk. If systemic conditions permit, interruption of oral BFT should be considered for a period of three months before and three months after elective surgery to reduce the risk of osteonecrosis. That approach is justified based on extrapolated data, showing BFT-therapy-related fluctuations of osteoclast function, and on the conclusions of recent studies showing better results of the treatment of avascular osteonecrosis of the jaw with drug discontinuation.[21-23]

## CONCLUSIONS

There is evidence that the use of bisphosphonates is associated with avascular osteonecrosis of the jaw, which is rare and affects the quality of life of patients already physically impaired. Patients under the treatment of BFT or who are going to initiate that treatment, particularly if intravenous, but also oral, for long periods, should be carefully assessed by a physician and dental surgeon to avoid osteonecrosis.

**Table 2**
Staging and treatment strategies of osteonecrosis of the jaw

| Staging | Treatment strategy |
|---|---|
| At risk category<br>Patient under treatment with either oral or IV BFT, with no apparent necrotic bone | • No treatment indicated<br>• Patient education |
| Stage 0<br>No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms | • Systemic management, including the use of pain medication and antibiotics |
| Stage 1<br>Exposed necrotic bone in asymptomatic patients with no evidence of infection | • Oral antibacterial mouth rinse<br>• Clinical follow-up on a quarterly basis<br>• Patient education and review of indications for continued BFT use |
| Stage 2<br>Exposed necrotic bone with infection as evidenced by pain and erythema, with or without purulent drainage | • Symptomatic treatment with oral antibiotics<br>• Oral antibacterial mouth rinse<br>• Pain control<br>• Superficial debridement to relieve soft tissue irritation |
| Stage 3<br>Exposed necrotic bone in patients with pain and erythema and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, such as inferior border and ramus in the mandible, maxillary sinus or zygoma in the maxilla, resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or to the maxillary sinus floor | • Oral antibacterial mouth rinse<br>• Antibiotic therapy and pain control<br>• Debridement/surgical resection for prolonged relieve of pain and infection |

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