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Medication-Related Osteonecrosis of the Jaw: a Brief Review, Treatment and Practical Guidelines for Dentists

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ABSTRACT

Osteonecrosis of the jaws is a complication after treatment with antiresorptive drugs. Bisphosphonates (BPs) are widely used to treat conditions with bone metastases of malignant tumors such as multiple myeloma, breast cancer, prostatic cancer, as well as hypercalcemia of malignancy, osteoporosis, Paget's disease, and osteogenesis imperfecta. Denosumab is an antiresorptive agent that is used for the treatment of osteoporosis or metastatic bone diseases. These antiresorptive agents improve the quality of life of patients by increasing strength and bone mineral density, and reducing the risk of bone fractures. More than a decade had passed since the first publication of this pathology, and the occurrence of the disease, its pathophysiology, and proper treatment methods are still not fully elucidated. Prevention is critical in medication-related osteonecrosis of the jaw, because the treatment is difficult, and there are no universally accepted treatment protocols. There is an accepted approach of palliation of symptoms and controlling the associated infections. Treatment may follow one of three procedures: conservative management of pain, conservative or extensive (segmental) surgery, depending on the disease stage.

Keywords: osteonecrosis, bisphosphonates, antiresorptive drugs, surgery, quality of life

INTRODUCTION

The aim of this paper is to offer an update on the medication-related osteonecrosis of the jaw (MRONJ) and the preventive measures and management strategies that can be applied in osteonecrosis of the jaw (ONJ) due to antiresorptive drugs, and appraise their effectiveness according to the stage of the disease in which they are applied.

It has been more than a decade since the first publication of this pathology, and the occurrence of the disease, its pathophysiology, and proper treatment methods are still not fully elucidated.[1] Osteonecrosis of the jaw appearing after

bisphosphonate treatment was first described as a pathological condition by Marx, in 2003, in the USA. He described 36 cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in patients affected by malignant tumors.[1]

In 2009, the American Association of Oral and Maxillofacial Surgeons (AAOMS) established the criteria that define BRONJ as exposed bone in the oral cavities that is attributable to bisphosphonates, no history of radiation therapy, and the exposed bone persisting at least eight weeks without signs of healing.[2]

The AAOMS has reconvened in September 2013 to debate the current literature and the guidelines on this issue with so many unknowns. As a result, the AAOMS recommended changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw to medication-related osteonecrosis of the jaw (MRONJ). The motivation for changing the name was the significant number of cases of osteonecrosis that occurred in patients treated with other antiresorptive drugs, such as denosumab, and antiangiogenic agents.[3] The association proposed the following characteristics for MRONJ: treatment with antiresorptive or antiangiogenic medication currently or in the past, the bone remains exposed in the oral cavity for at least eight weeks with no healing, and the patient was not exposed to radiation therapy of the jaw in the past.[3]

Intravenous (IV) BPs are widely used to treat bone metastases of malignant tumors such as multiple myeloma, breast cancer, prostatic cancer, as well as hypercalcemia of malignancy.[4–7] Oral BPs are used to treat osteoporosis, osteopenia, Paget's disease, or osteogenesis imperfecta.[8–10]

Denosumab, a RANK ligand inhibitor, is an antiresorptive agent used for the treatment of osteoporosis or metastatic bone diseases, decreasing bone resorption and increasing bone density.[11,12] These antiresorptive agents improve the quality of life of patients by increasing strength and bone mineral density and reducing the risk of bone fractures.

Antiangiogenic agents prevent the development of new blood vessels, which leads to the cessation of angiogenesis.[13]

The risk factors for the development of ONJ in oncology patients, in the order of importance, include: intravenous BPs, zoledronic acid, pamidronate, radiation therapy, dental extraction, chemotherapy, periodontal disease, oral BP use, local suppuration, and denture use.[14–22] Demographic and systemic factors include: osteoporosis, glucocorticoid therapy, diabetes, erythropoietin therapy, tobacco use, hyperthyroidism, renal dialysis, and increasing age.[16–18,23,24] Significant risk factors for the development of ONJ in the osteoporotic population, in declining order of importance, include suppuration, BP use, dental extraction, and anemia.[14]

MRONJ appears more frequently in the mandible (73%) compared to maxilla (22.5%), and it involves both jaws in 4.5% of the cases.[25]

The pathophysiology of the disease is not entirely understood, as it was discovered that not only bisphosphonates increases the risk of jaw osteonecrosis. Another antiresorptive drug, denosumab, has similar effects, which stresses the need to explore mechanisms common to both drugs.[26,27]

Several hypotheses have tried to demonstrate the mechanisms of developing the disease. Given that the disease is multifactorial, it is unlikely that a single theory can explain its occurrence, and it is also unlikely that treatment is effective in all patients. The occurrence of numerous clinical and preclinical studies that reveal more evidence causes our hypotheses and treatment modalities to be in permanent change.

The first theory refers to bone remodeling inhibition. Antiresorptive drugs significantly decrease skeletal-related complications and relieve severe bone pain due to their direct effects on osteoclasts.[28–32] The primary mechanism of BPs and denosumab is to inhibit osteoclast function and increase apoptosis by different mechanisms, and this leads to altered bone remodeling, which is the leading hypothesis for ONJ development.[33–36]

Another important theory refers to inflammation and infection, which have been considered an important component of ONJ. Adults' teeth are almost always extracted because they have periapical or periodontal inflammation, and it is well known that extraction is a high-risk factor for developing ONJ.[3,37,38] Studies identified bacteria, especially Actinomyces species associated with active osteoclastic resorption on the necrotic bone surface.[39]

Angiogenesis inhibition is another major hypothesis attempting to explain the occurrence of ONJ. Bisphosphonates, especially nitrogen-containing BPs, induce a significant decrease in microvessel density in vivo, e.g. zoledronic acid inhibits proliferation and reduces the number and adhesion of circulating human endothelial cells.[40,41]

Other hypotheses in the pathophysiology of ONJ incriminate a direct soft-tissue toxicity of BPs, or an immune dysfunction pointed with the significant contribution of immunomodulators in the pathophysiology of the disease, in treatment with oral BPs and steroids.[3,38,42]

PREVENTIVE MEASURES

Prevention is crucial in MRONJ because the treatment is difficult, and there are no universally accepted treatment protocols for ONJ. There is an accepted approach of pal-

TABLE 1. Staging of Medication-Related Osteonecrosis of the Jaw (based on the American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw — 2014 Update).

At risk	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms
Stage 1	Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor

liation of symptoms and controlling the associated infections. Full dental screening and appropriate treatment are needed before treatment with antiresorptive or antiangiogenic drugs. All invasive treatments, especially dentoalveolar procedures, should be performed before starting treatment for ONJ.[25,43,44]

The dental protocol for cancer patients requiring oncology doses of intravenous antiresorptive drugs should include dental examination with dental radiographs to identify dental diseases before the initiation of oncology therapy. At this point, the dental practitioner should perform all necessary invasive treatments such as extractions or dental implants, and non-urgent procedures should be evaluated and treated only when necessary, potentially including a drug holiday if the condition of the patient allows it. The decision to discontinue therapy with bone-active agents must also consider the risk of fracture and implications for skeletal health.[45]

MANAGEMENT STRATEGIES

There are no universally accepted protocols for ONJ, but there is an accepted approach of palliation of symptoms and controlling the associated infections. Treatment strategies are a difficult challenge for clinicians, ranging from conservative nonsurgical intervention to extensive surgery. It is necessary to establish an appropriate and efficient treatment for patients undergoing therapy for ONJ. A multidisciplinary team approach, formed by an oncologist, a maxillofacial surgeon, and a dentist, is advised for evaluating and proposing an efficient and appropriate ONJ therapy. It should start with conservative treatment because the primary goals of treatment are the preservation of quality of life through control of necrosis progression, secondary infection, and pain.[3]

Treatment may follow one of the three procedures: conservative management of pain, conservative surgery or extensive (segmental) surgery, depending on the disease stage. Table 1 presents the staging system proposed by the AAOMS.[3]

Patients suitable for conservative management would be those considered to be at risk and/or in stage 0 and I.[3] Conservative management includes a rigorous oral hygiene, periodic dental checks on a quarterly basis, elimination of oral dental and periodontal disease, oral daily rinses, and antibiotic treatment. In most studies, these measures resulted in improvement of symptoms, osteonecrosis stabilization, and, consequently, increased quality of life. Chlorhexidine-based mouth rinses are of choice, as this antimicrobial substance is the "gold standard" in oral dental surgical procedures. The most widely used antibiotics are amoxicillin with or without clavulanic acid, clindamycin, and azithromycin.[46,47] Other therapies, such as hyperbaric oxygen, ozone therapy, and low-power laser therapy, complete the success rates of conservative treatment.[48] In this category, we could also include patients who, for health reasons, are not candidates for surgical treatment. This therapy continues indefinitely or until there is a progression of the disease.

In stage I, if exposed and necrotic bone or fistulae are present, they are rinsed with an antiseptic liquid and covered with an adhesive paste, three times a day. It is possible to proceed to surgical debridement in the absence of healing after eight weeks.[49]

As described in Table 1, surgical management is indicated in stage II and III when the exposed and necrotic bone is accompanied by pain, infection, or pathologic fractures. According to the severity of the lesions, the surgical procedures are different.

In stage II conservative surgery is recommended, which involves the removal of dead bone (sequestrectomy) and/or superficial surgical debridement of necrotic bone associated with oral antibiotics and daily rinses with chlorhexidine. The intervention should be as conservative as possible, but extended to reach healthy-appearing, bleeding bone.[49] In 2008, Wutzl *et al.* described the first prospective study reporting the outcome of treatment in a cohort of patients with BRONJ six months after the surgical treatment.[50] They concluded that minimal resection of the necrotic bone and local soft tissue closure might provide a satisfactory result for patients with established BRONJ.[50] Vescovi *et al.* obtained good results in MRONJ by combining surgical debridement with laser therapy.[51] In 2012, a study conducted by Martins *et al.* revealed that healing rates were higher among patients treated with low-intensity laser therapy and platelet-rich plasma applied to the surgical wound compared with those who did not receive this kind of treatment.[52]

In stage III, marginal or extensive (segmental) surgery is indicated for eliminating all the necrotic tissue, leaving only healthy bone with resection margins that extend into adjacent normal-appearing bone.[53–57] The closure of the soft tissue should be tension-free, with no underlying sharp edges of bone.

Extensive surgery is only indicated if it could improve the patient's quality of life, since in many cases there are no guarantees in obtaining healthy bone margins. Otherwise, a conservative approach to control symptoms and to prevent the progression of osteonecrosis is required.[53]

Additional measures, such as the combination of surgery with other therapies such as ozone, laser therapy, the use of stem cells, platelet-rich plasma, or the administration of parathyroid hormone, are also promising therapy strategies, but further clinical studies are needed to confirm their efficacy.[48,49,58–63]

CONCLUSION

A multidisciplinary team including oncologists, maxillofacial surgeons, dentist specialists should be involved in the therapeutic algorithm of medication-related osteonecrosis of the jaw in order to provide a proper management and informing the patients on the involved oral cavity risks. All patients should be evaluated by a dentist before antiresorptive drug administration begins. They should receive treatment for any pathology in the orodental area, and the patients' oral hygiene status, tooth decay, and active periodontitis should be evaluated. Dental practitioners should document bisphosphonate use in the patient's clinical history. The patients at risk for MRONJ should be monitored and examined after any surgical intervention in the orodental area in the next 12 months at least. The situation could be improved by increasing the number of studies conducted both in vitro and in vivo. The scientific community could help to expand and improve our knowledge about MRONJ and develop better strategies for patient care.

CONFLICT OF INTEREST

Nothing to declare.

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