STAGES AND PATHOPHYSIOLOGICAL MECHANISMS OF ACTION OF MRONJ

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Abstract: Medication-related osteonecrosis of the jaw (MRONJ) is a rare but severe disabling condition. The first case of MRONJ was reported by Marx in the early 2000s in a study of non-healing open bone in the maxillofacial area of a patient treated with bisphosphonate. The MRONJ placement system was developed in 2006 by Ruggiero et al. and subsequently adopted by American Association of Oral and Maxillofacial Surgeons (AAOMS) and updated in 2014. In at-risk asymptomatic patients without visible necrotic bone with a history of previous antiresorptive or antiangiogenic therapy, no treatment is recommended but only patient information on the risk of developing osteonecrosis and clinical signs and symptoms of this disease. Patients with established MRONJ are treated differently; the goals of treatment are mainly to control pain, infection and the progression of bone necrosis. Despite the strong association between jaw necrosis and bisphosphonates and other antiresorptive and antiangiogenic drugs, the pathophysiology of MRONJ is not fully understood.
Keywords: MRONJ, diagnostic criteria, pathophysiological mechanisms, Stages of MRONJ

1. INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but severe disabling condition, the exact cause of which has not yet been determined [12,9]. MRONJ is characterized by non-healing exposed bone in patients with a history or continued use of an antiresorptive or antiangiogenic agent and no history of radiation exposure to the head and neck [9,1].

The first case of MRONJ was reported by Marx in the early 2000s in a study of non-healing open bone in the maxillofacial area of a patient treated with bisphosphonate, an antiresorptive drug that affects the dissolution of mineral content in bone [12]. The incidence of this bone disease among antiresorptive users varies from 0.7% to 18% [12].

In the treatment of malignancies with an increased incidence of bone necrosis associated with these drugs, an association has been established between osteonecrosis of the jaw (ONJ) and drugs other than bisphosphonates, such as denosumab and antiangiogenic drugs [2]. To include all causative agents in ONJ-related diagnostic discourse, the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed that the nomenclature be changed from ONJ (BRONJ)-related bisphosphonates to MRONJ [2]. This review aims to identify all the causes and to summarize the preventive measures, diagnostic criteria and treatment strategies related to MRONJ.

After the first reported cases describing a possible link between bisphosphonate therapy and osteonecrosis of the jaw were reported in the Journal of Endodontics and the Journal of the American Dental Association, they named the phenomenon as bisphosphonate-related osteonecrosis of the jawor (BRONJ). Shortly afterwards, other communities and dental authors referred to the condition by various other names, including bisphosphonate-related osteonecrosis of the jaw (BRONJ). With the advent of other antiresorptive and antiangiogenic agents involved in this disease, in 2014 the American Association of Maxillofacial Surgeons (AAOMS) proposed the use of the term associated with medical osteonecrosis of the jaw or MRONJ. In 2019, the ADA's Scientific Council, a scientific information department, also proposed that the organization be renamed MRONJ. With this merger, the AAE Special Committee on Bisphosphonates recommends the use of the term associated with medicated osteonecrosis of the jaw (MRONJ).

2. DIAGNOSIS OF MRONJ

The diagnostic criteria for MRONJ developed by AAOMS are based on pharmacological history as well as clinical and radiographic features [10]. The patient may be diagnosed with MRONJ if both of the following criteria are met: history or continued treatment with antiangiogenic agents or antiresorptives such as bisphosphonate and denosumab; open or non-healing bone that can be seen through a fistula in the maxillofacial area that persists for more than eight weeks and has no history of head and neck radiation therapy or obvious metastatic jaw disease [12,9,10].

3. PATHOPHYSIOLOGICAL MECHANISMS OF MRONJ

The exact mechanism of exposed bone in the jaw is not known [4] but the most widely accepted theory is that exposed bone is the result of destruction of the osteoblast-osteoclast homeostatic cycle due to BP [8]. This homeostatic cycle is also referred to as the osteoclast-osteoblast axis by Hellstein and Marek [6]. Changes in this axis may be the most important risk factor for the development of osteonecrosis of the jaw. Biophosphonates have an affinity for binding to the bone mineral matrix and their primary pharmacological effect is the inhibition of bone resorption by reducing osteoclast function [8]. Due to this specific pharmacological effect, the number of osteoclasts increases in osteolytic lesions. With increased osteoclastic activity, the cellular activity of bone remodeling and resorption is impaired. BPs prevent the differentiation of osteoclasts from monocytes and macrophages and stimulate apoptosis of osteoclasts.

When the homeostatic cycle of osteoblasts-osteoclasts is destroyed, the activity of osteoblasts remains unaffected, which leads to increased bone mass and density [7]. Biophosphonate drugs are not metabolized and can remain in the bones for many years, disrupting the homeostatic cycle of bone remodeling and regeneration [8].

BP has also been shown to affect vascularization and inhibit angiogenesis. In a rat model, Fournier et al. [5] demonstrated that biophosphonate agents are able to inhibit angiogenesis and vascular endothelial growth factor (VEGF). In another study demonstrating the effects of BP drugs on vasculature, Wood et al. [13] showed that BP inhibited vascular endothelial cell proliferation. Therefore, an alternative mechanism leading to ONJ may be responsible for the antiangiogenic effects of BP.

The MRONJ placement system was developed in 2006 by Ruggiero, S. L., Fantasia, J. & Carlson and subsequently adopted by AAOMS and updated in 2014.

4. STAGES OF MRONJ

AAOMS offers the following strategies for diagnosis and treatment (according to the statement of MRONJ):

In at-risk asymptomatic patients without visible necrotic bone with a history of previous antiresorptive or antiangiogenic therapy, no treatment is recommended, but only patient information on the risk of developing osteonecrosis and the clinical signs and symptoms of the disease.

Stage 0 (unexposed variant of osteonecrosis of the jaw) - In the initial stage, an unexposed variant of osteonecrosis of the jaw occurred. It consisted of non-specific symptoms, clinical and radiological findings, but no clinical evidence of a necrotic bone. Symptomatic treatment was chosen, including analgesics for chronic pain and antibiotics to control infection. Control was issued by a conservative-affiliated treatment of some local factors, such as caries and periodontitis. Patient information and training is also discussed in the article[3].

Stage 1 - Asymptomatic patients with no evidence of infection, but with exposed and necrotic bone or a fistula that pierces the bone. Antimicrobial mouthwashes (chlorhexidine 0.12%), frequent clinical follow-up and patient training are recommended. No surgical therapy is indicated [3].

Stage 2 - Symptomatic patients - Pain and clinical evidence of infection (erythema in the area of exposed bone with or without purulent drainage) in patients with exposed and necrotic bone or fistula that pierces the bone. Symptomatic treatment with antibacterial mouthwashes, analgesics to control pain, and antibiotics to control infection and superficial deblocking is recommended to relieve soft tissue irritation and to control infections [3].

Stage 3 - Pain and clinical evidence of infection in patients with exposed and necrotic bone or fistula that penetrates bone and one or more of the following: exposed necrotic bone outside the alveolar bone leading to pathological fracture, extensive osteolysis to the lower limit of lower jaw or up to the maxillary sinus, external fistula, oral antral or oral communication of the oral cavity. The same recommendations as those of Stage 2 are given here, but surgical debridement / resection of the necrotic bone is also indicated [3].

Stage 0 was added to the updated version of AAOMS, representing the prodromal period and non-specific clinical or radiographic symptoms prior to any evidence of bone exposure [11]. These symptoms may present clinically as a toothache of a neodontogenic cause, radiating pain, unexplained pain or thickening of the sinus wall, and altered sensation. Radiologically, this may be unexplained bone loss that is not due to periodontal inflammation with a change in the trabecular bone model [11].

The formulation of MRONJ remains controversial - in particular the non-specific nature of stage 0 MRONJ and the definition of the disease itself. The dynamic nature of the staging system is also a matter of debate.

For example, stage 1 MRONJ may become stage 2 after infection, and stage 2 disease may be reduced to stage 1 after a short course of antibiotics.

The dentist may be the first to identify signs and symptoms of MRONJ. In such cases, the patient should be referred to oral and maxillofacial surgery or an oral oncology center experienced in the treatment of patients with MRONJ [11], and the physician should be informed of the patient's symptoms and possible treatments for and results of MRONJ. Ideally, your doctor will be able to recommend oral and maxillofacial surgery or an oral oncologist who

works at the same hospital to facilitate communication between care providers. The dentist will need to decide if and when to start treatment with chlorhexidine or broad-spectrum antibiotics. During the interval between diagnosis and appointment with OMFS, antibacterial lavage may be started as soon as MRONJ is suspected, but antibiotics should only be prescribed when signs of infection are observed.

5. CONCLUSION

Despite the strong association between jaw necrosis and bisphosphonates and other antiresorptive and antiangiogenic drugs, the pathophysiology of MRONJ is not fully understood. Therefore, effective and appropriate therapy for the condition has yet to be addressed. A collaborative approach involving dentists, prescribing doctors and pharmacists is crucial to prevent the development of MRONJ.

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