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"MRONJ: Dentistry and Physician Events under Bisphosphonates, Denosumab and Antiangiogenic Drugs"

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) can be difficult to treat and causes significant morbidity but is largely preventable. Published guidelines strongly recommend dental assessment and necessary remedial treatment before such drugs are commenced. Specific guidance on who should provide or arrange this care is lacking, and it may often be delegated to the patient arranging it with their own dentist. However, numerous factors can make this difficult [1]. There exists a large and growing group at risk of MRONJ who have significant amounts of oral disease. However, the risk of the condition is largely preventable. Promise is shown in several methods to organize timely dental care before treatment [2].

Keywords: Bisphosphonates (BPs); Denosumab (DS); Antiangiogenic drugs; Medication Related Osteonecrosis of the Jaw (MRONJ)

Introduction

Antiresorptive drugs: Bisphosphonates (BPs) and Monoclonal Antibodies: Denosumab (DS) are known to suppress osteoclastic activity irreversibly in the case of BPs and reversibly in the case of DS [3]. The American Surgery of Bone Mineral Research (ASBMR) in 2007 defined MRONJ as "necrotic bone area exposed to the oral environment with more than eight weeks of permanence, in the presence of chronic treatment with BPs, in the absence of radiation therapy to the head and neck". In 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) divided the MRONJ into 4 stages from 0 to 3, according to the clinical and radiological aspect of the osteonecrotic lesion: stage 0: Osteonecrotic lesion without sign-pathognomonic evidence of osteonecrosis: stage 1: osteonecrotic lesion with clinical signs and absence of clinical symptoms; Stage 2: Osteonecrotic lesion with sign and evident clinical symptoms; Stage 3: Osteonecrotic lesion with signs and evident symptoms that involve noble structures: pathological fractures, anesthesia of the lower dental nerve, oral-nasal communication, oral-sinus communication, skin fistulas [4].

Some antiresorptives as BPs, DS or antiangiogenic drugs may cause MRONJ. BPs, synthesized in the mid-19th century by German chemists, were initially used in industry due to their capacity to prevent the deposits of calcium carbonate, which made them especially useful in avoiding the deposit of calcium

salt in pipes. Later it was shown that they had great affinity with osseous tissue, where they inhibited the conversion of amorphous calcium phosphate in hydroxyapatite and they reduced the dissolution speed or the later [5]. BPs are synthetics compounds used in the treatment of various metabolic and malignant bone diseases: Osteoporosis, Paget Disease, Hypercalcemia, Multiple Mieloma, Metastatic breast cancer and Metastatic prostate cancer, Osteogenesis Imperfecta, Fibrous Dysplasia [6,7]. Publications have been described some cases of MRONJ because of BPs, Ds and antiagiocenic treatment [8].

According to the 2010 Osteoporosis Canada Clinical Practice Guidelines, DS is a first-line option for the pharmacological management of postmenopausal osteoporosis [9]. The discovery of the RANKL–RANK pathway as the primary mediator of osteoclast differentiation, activation, and survival facilitated the design of molecules that specifically target this pathway for the treatment of osteoporosis. By mimicking the effect of endogenous osteoprotegerin, denosumab, a fully human monoclonal antibody to RANKL, inhibited bone resorption with a rapid onset of action and a sustained but reversible effect [10].

Historically, the first drugs associated with the condition were bisphosphonates, which led to coining of the term MRONJ. However, there was a need to include other drugs in the etiopathogeny of osteonecrosis, such as other antiresorptive and antiangiogenic agents. The cases reported of antiangiogenic agent-related osteonecrosis have been accumulating over the years and, therefore, the most appropriate term for the condition is MRONJ. Antiangiogenic drugs are indicated in the treatment of certain tumors, since they stop the formation of new blood vessels, controlling tumor growth and the chance of metastasis. The mechanism of action of antiangiogenic agents is, in simple terms, blocking the direct or indirect action of VEGF [11].

Discussion

Nowadays, some consensus has been publicated to established guidelines about MRONJ. Historically some Consensus were studied to stablish etiology, diagnosis and some resective or atraumatic treatments like Canada Consensus Marx, et al. 2007 [12]; SECOM Junquera M, et al. 2008 [13]; Task Force Yapanese Yoneda, et al. 2010 [14]; AAOMS Ruggiero SL, et al. 2009 [15], Ruggiero et al: 2014 [16]; Korean Society Consensus Kim KM, et al. 2015 [17], AOCMF ARONJ Fleisher KE, et al. 2016 [18], ASBMR Task Force Burr DB, 2007 [19], Adler RA, et al. 2016 [20], Task Force MRONJ Khan AA, et al. 2017 [21], Stavropoulos A, et al. 2018 [22], Limones, et al. 2020 [23]. For that reason, it is so important dentists and physicians ought to attend patients together.

Conclusion

According the publications cited, dental treatments are incomplete in most studies. Direct comparison is difficult. However, promising strategies to prevent MRONJ have been demonstrated [1,24]. It is essential that patients with MRONJ be treated in an interdisciplinary fashion. The patient's stomatognathic system should be examined preventatively prior to the initiation of BPs, DS or antiangiogenic treatment in order to avoid pathological buccal manifestations, following the same healthcare clinical protocols used for patients receiving head and neck radiotherapy. Additionally, patients should be informed of the precautions to be taken, including regular dental appointments for oral health assessment. The risk of developing MRONJ should be evaluated according to the type of BPs, DS or antiangiogenic administered and treatment duration [25,26].

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