MRONJ: Dentistry and physician events under bisphosphonates, denosumab and antiangiogenic drugs

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ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) has been shown to be difficult to treat and can cause significant morbidity, but it can be prevented. Published guidelines strongly recommend dental assessment and critical treatment as the best option. It is known that these patients have no idea where to go. However, there are factors that make referral difficult. Patients at risk of MRONJ present significant oral manifestations. Moreover, the risk of the condition is largely preventable. Promise is shown in several methods to organize timely dental care before treatment. Therefore, it is necessary to be aware of this.

Key words: 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 (Wan et al., 2020). 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, American Association of Oral and Maxillofacial surgeons (AAOMS) divided 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 (Khan et al., 2015). 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. According to Gámez et al. 2008, 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 (Abu-Id et al., 2008;Bensadoun et al., 2008). Publications have described some cases of MRONJ because of BPs, DS and antiangiogenic treatment (Dimitrikopoulos et al., 2006). According to the 2010 Osteoporosis Canada Clinical Practice Guidelines, DS is a first-line option for the pharmacological management of post menopausal osteoporosis (Josse et al., 2013). 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 (McClung, et al., 2006). 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 etiopathogenesis 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 (Caminha et al., 2019).

**DISCUSSION**

Nowadays, some consensus has been published in order to establish guidelines about MRONJ. Historically some consensus was studied in order to establish etiology, diagnosis and some resective or atraumatic treatments like Canada consensus (Marx et al., 2007), SECOM (Junquera et al., 2008), Task Force Japanese (Yoneda et al., 2010), AAOMS (Ruggiero et al., 2009; Ruggiero et al., 2014) Korean society consensus (Kim et al., 2015) AOCMF ARONJ (Fleisher et al., 2016) ASBMR (Task Force Burr DB, 2007; Adler et al., 2016) Task Force MRONJ (Khan et al., 2017; Stavropoulos et al., 2018; Limones et al., 2020). For that reason, it is so important dentists and physicians ought to attend to patients together.

**CONCLUSION**

According to the publications cited, dental treatments are incomplete in most studies. Direct comparison is difficult. However, promising strategies to prevent MRONJ have been demonstrated (Steel, 2019; Picardo and Rey 2017; Wan et al., 2020; Khan et al., 2015; Gámez et al., 2008; Abu-Id et al., 2008; Bensadoun et al., 2008; Dimitrikopoulos et al., 2006; Josse et al., 2013; McClung, et al., 2006; Caminha et al., 2019; Marx and Robert 2007; Junquera et al., 2008; Yoneda et al., 2010; Ruggiero et al., 2009; Ruggiero et al., 2014; Kim, et al., 2015; Fleisher et al., 2016; Burr, 2007; Adler et al., 2016; Khan et al., 2017; Stavropoulos et al., 2018; Limones et al., 2020; Picardo et al., 2015). 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 (Picardo and Rey 2007; Ghidini et al., 2017).

**REFERENCES**


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