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Medication-related osteonecrosis of the jaw: Clinical and practical guidelines

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region of patients. ONJ can be caused by two pharmacological agents: Antiresorptive (including bisphosphonates (BPs) and receptor activator of nuclear factor kappa-B ligand inhibitors) and antiangiogenic. MRONJ pathophysiology is not completely elucidated. There are several suggested hypothesis that could explain its unique localization to the jaws: Inflammation or infection, microtrauma, altered bone remodeling or over suppression of bone resorption, angiogenesis inhibition, soft tissue BPs toxicity, peculiar biofilm of the oral cavity, terminal vascularization of the mandible, suppression of immunity, or Vitamin D deficiency. Dental screening and adequate treatment are fundamental to reduce the risk of osteonecrosis in patients under antiresorptive or antiangiogenic therapy, or before initiating the administration. The treatment of MRONJ is generally difficult and the optimal therapy strategy is still to be established. For this reason, prevention is even more important. It is suggested that a multidisciplinary team approach including a dentist, an oncologist, and a maxillofacial surgeon to evaluate and decide the best therapy for the patient. The choice between a conservative treatment and surgery is not easy, and it should be made on a case by case basis. However, the initial approach should be as conservative as possible. The most important goals of treatment for patients with established MRONJ are primarily the control of infection, bone necrosis progression, and pain. The aim of this paper is to represent the current knowledge about MRONJ, its preventive measures and management strategies.

Keywords: *Bisphosphonate-associated osteonecrosis of the jaw*, *bone metastases*, *drug therapy*, *medication-related osteonecrosis of the jaw*, *osteoporosis*

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region of patients.

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMSs) suggested to change the nomenclature from bisphosphonate- related osteonecrosis of the jaw (BRONJ) to MRONJ to

accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies.[1,2] The aim of this paper is to represent the current knowledge about MRONJ, its preventive measures and management strategies.

MEDICATION-RELATED OSTEONECROSIS OF THE JAW RELATED MEDICATION

Osteonecrosis of the jaw (ONJ) can be caused by two pharmacological agents: Antiresorptive (including bisphosphonates (BPs) and receptor activator of nuclear factor kappa-B ligand [RANK-L] inhibitors) and antiangiogenic.

BPs can be divided into aminobisphosphonates (NBPs) and non-NBPs on the basis of an amino functional group presence in the molecule. NBPs are the one involved in the ONJ [Table 1].

Intravenous (IV) BPs are utilized to treat conditions associated with cancer as well as hypercalcemia of malignancy, skeletal-related events connected with bone metastases from solid tumor and for the management of lytic lesion related to multiple myeloma.[3,4,5,6]

Oral BPs are used to treat osteoporosis,[7] osteopenia,[8] or other less common conditions such as Paget's disease and osteogenesis imperfecta.[9]

RANK ligand inhibitor (denosumab) is an antiresorptive medication that inhibits osteoclast function, decreases bone resorption, and increases bone density.[10,11] It is used in patients affected by osteoporosis or metastatic bone diseases.

Antiangiogenic medications hinder the development of novel blood vessels, blocking the angiogenesis-signaling cascade. They are basically divided into two types of drugs: Monoclonal antibodies that stop the receptor or growth factor (bevacizumab) and small molecules, which determine the block by binding the tyrosine kinase receptor (sunitinib and sorafenib). It has been hypothesized that they facilitate the other anticancer agents delivery.[12]

MRONJ pathophysiology is not completely elucidated.[13,14] There are several suggested hypothesis that could explain its unique localization to the jaws: Inflammation or infection, microtrauma, altered bone remodeling or over suppression of bone resorption, angiogenesis inhibition, soft tissue BPs toxicity, peculiar biofilm of the oral cavity, terminal vascularization of the mandible, suppression of immunity, or Vitamin D deficiency.[13,15,16,17,18]

Three risk factors such as local factors, underlying disease, and kind of medication [Table 2] should be considered. To explain the MRONJ disease frequency value, we have to consider two criteria: Therapeutic indications (osteoporosis/osteopenia and malignancy) and type of medication (BP and non-BP). The ONJ risk in patients treated with zolendronate is 50–100 times superior to individuals treated by placebo. The MRONJ risk in cancer patients treated by denosumab is similar to the possibility of ONJ in patients exposed to zolendronate.[13,19] As reported in Table 3, the risk of MRONJ is different on the basis of the medications and the administrations.[21,22,23,24,25,26,27] Even if the ONJ risk is similar, it is important to underline a substantial difference between BRONJ and DRONJ (denosumab-related ONJ). BRONJ occurs after a mean administration of 33 months (IV administration in cancer patients) or 48 months (oral administration in osteoporotic patients). DRONJ occurs early after treatment, independently of the number of previous administrations. Hence, ONJ risk after the use of RANK-L inhibitors decreases monthly while BP drugs remain stable for years. Risk of BRONJ is directly related to the duration of the therapy and total amount of the medication. Risk factors for MRONJ are reported in Table 2. Oral surgery is one of the greatest risk factors for MRONJ: According to several authors, 52–61% of patients reported tooth extraction as a precipitating event.[20,28] The risk of ONJ in patients treated by oral-BPs after a tooth

extraction is 0.5%; ONJ risk in patients with cancer treated with IV BPs ranges from 1.6% to 14.8%.[29] MRONJ appears more frequently in the mandible (73%) compared to maxilla (22.5%); it involves both jaws in 4.5% of the cases.[28]

DEFINITION AND STAGING SYSTEMS

Patients are affected by MRONJ if all the following clinical manifestations are demonstrated:

- Ongoing or antecedent treatment with antiangiogenic or antiresorptive drugs
- No patient history of radiation therapy or manifest metastasis to the jaw
- Exposed bone or presence of an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks.[1]

However, many authors disagree with the last definition. Hence, the exposed necrotic bone in the oral cavity is just one of the possible manifestations of BRONJ, and it is not found in all patients. In 2012, the SICMF (Italian Society for Maxillofacial Surgery) and the SIPMO (Italian Society of Oral Pathology and Medicine) proposed a new definition:[30] "BRONJ is an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible or maxilla of patients exposed to the treatment with nitrogen-containing BPs, in the absence of a previous radiation treatment." It was supported by a study[31] on a large population of European patients. According to the AAOMS definition, just the 76% of the BRONJ were diagnosed; 24% remaining ONJ could not be diagnosed because of nonvisible necrotic bone.

BRONJ staging systems are copious, and most of them are based on clinical findings: In 2006, Ruggiero *et al*.[16] proposed a clinical staging system with three different clinical levels based on signs and symptoms; in 2009, the AAOMSs implemented it with Stage 0.[2] Marx,[32] in 2007, was the only one who divided the stages on the basis of the lesion's size. Bedogni *et al*.,[30] in 2012, proposed a clinical-radiological staging system. Different BRONJ staging systems are given in Table 4.

PREVENTION OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW

Dental screening and adequate treatment are fundamental to reduce the risk of ONJ in patients under antiresorptive or antiangiogenic therapy or before initiating the administration.[28,33,34,35] The treatment of MRONJ is generally difficult, and the optimal therapy strategy is still to be established. For this reason, prevention is even more important. Several authors suggested a "drug holiday" before teeth extractions or other invasive procedures. However, there is no unanimous consensus on this treatment and not enough data to support the cessation of medical treatment in patients with osteoporosis. Currently, AAOMS considers appropriate drug holiday procedure as reported by Damm and Jones in "at risk" patients with extended exposure history (>4 years).[36] Even in cancer, individuals receiving IV therapy, there are limited data about the consequence of interrupting BPs IV administration before surgical procedures. If is allowed by patient conditions, the oncologist should consider to stop the therapy until the healing of soft tissue has occurred.[36] As part of a preventive approach, a distinction needs to be made between IV and oral therapy in patients under medical treatment or about to initiate it.

Cancer patients about to initiate intravenous medical treatment

Prior to the beginning of an IV medical treatment, the patient should always be carefully evaluated by a dentist. The main goals of preventive dental measures are to remove any oral infection, pathology, or risk factors in order to obtain a stable oral health situation, preventing the necessity for invasive dental procedures in the near or intermediate future.[37] Extraction of partially embedded teeth should be

performed at this time. Embedded teeth completely covered by bone and soft tissue without any communication with the oral cavity should be left undisturbed.[38] Conservative endodontic and prosthodontic therapies of teeth with good prognosis should be completed. Periodontal stabilization splints for teeth with Grades 1–2 mobility in patients with good dental hygiene and extraction in patients with poor dental hygiene are necessary.[35,37] If allowed by general health conditions, the beginning of antiangiogenic or antiresorptive treatment should be deferred as far as oral status is stable or, at least, until the surgical site has mucosalized (2–3 weeks).[1]

Inadequate dentures should be modified, rebased, or replaced to decrease the oral tissue pressure and to prevent sore spots, especially along the lingual flange region or at the mandibular tori. Patients should achieve a proper oral hygiene and be educated to report any grief, inflammation, or bone exposure. Patients should be included in a periodic clinical-radiological follow-up, the frequency of which is based on the medical administration, the number of risk factors, and oral health status.

Asymptomatic cancer patients receiving intravenous medical treatment

It is essential that a detailed oral evaluation with regular check-ups every 4–6 months for exposed bone and "early stage" MRONJ diagnosis. An orthopantomography every 6–12 months for radiographic evidence of osteosclerosis or osteolysis, widened periodontal ligament spaces, or furcation involvements should be performed.[37] A good oral hygiene is essential to prevent dental infections that may require dentoalveolar surgery. Indeed, every invasive procedure that involves bone injury should be avoided. Nonrestorable teeth should be treated by removal of the crown and endodontic treatment of the remaining roots.[39] Teeth with mobility Grades 1–2 should be splinted rather than removed only in the absence of dental/periodontal lesions; extraction of teeth with mobility Grade 3 and/or endodontal-periodontal lesion it should be completed with the minimum bone injury and providing antibiotic treatment. An antibiotic prophylaxis for surgery procedures is necessary: Penicillin remains the first choice, in case of penicillin allergy, a combination of quinolones-metronidazole or erythromycin-metronidazole is a valuable alternative. Inadequate dentures should be modified, rebased, or replaced and in case of fixed prosthodontics, the biological width should be respected. Elective surgery and dental implants placement should be avoided.

Osteoporotic patients about to start oral medical treatment

Starting the therapy, patients should be instructed to the risk of developing MRONJ, especially if the treatment exceed beyond 4 years.[23] Informative and educational documents about the current knowledge of MRONJ as well as the instruction to quickly report every signs and symptoms should be given to patients. Periodic clinical-radiological follow-ups are recommended. The importance of oral hygiene and dental health should be underlined.[1] Implant placement is possible but a cautious approach is suggested. Data are limited, so an informed consent for a nonquantifiable risk of long term developing of MRONJ should be obtained.

Osteoporotic patients receiving oral medical treatment

The risk of developing MRONJ associated with oral BPs is very low, and it increases when the duration of therapy exceeded 4 years.[23] This period should be decreased in the case of comorbidities as well as antiangiogenic or chronic corticosteroid drugs.[28,35] However, the risk of MRONJ in patients treated with oral BPs is lower compared to subjects treated with IV medications. Elective dentoalveolar surgery is not contraindicated in these patients.

Patients treated with oral-aminobisphosphonate for <4 years without risk factors No modification or

delay of surgery is necessary, and all dental procedures are possible in this group. The importance of oral hygiene and dental health should be underlined.[1] Informative and educational documents about the current knowledge of MRONJ as well as the instruction to quickly report every signs and symptoms should be given to the patient.

Patients treated with oral-aminobisphosphonate for <4 years with risk factors or for >4 years The patient should be motivated to achieve and maintain an optimal level of oral health.[1] A detailed oral evaluation with regular check-ups for exposed bone and "early stage" MRONJ diagnosis is suggested. An orthopantomography every 6–12 months for radiographic evidence of osteonecrosis should be performed. Teeth with mobility Grades 1–2 should be splinted whereas teeth with mobility Grade 3 should be extracted with minimum bone injury. An antibiotic prophylaxis for surgery procedures is necessary.[38] Inadequate dentures should be modified, rebased, or replaced and in case of fixed prosthodontics, the biological width should be respected. Endodontic procedures should be preferred to dental surgery. Implant placement is possible, but the patient should be informed about the possibility of short and long term loss of dental implants and ONJ risk.

TREATMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW

Treatment of ONJs is a demanding challenge for clinicians, and an effective and appropriate MRONJ therapy is still to be decided. It is suggested a multidisciplinary team approach including a dentist, an oncologist, and a maxillofacial surgeon to evaluate and decide the best therapy for patient. The choice between a conservative treatment and surgery is not easy, and it should be made on a case by case basis. However, the initial approach should be as conservative as possible. The most important goals of treatment for patients with established MRONJ are primarily the control of infection, bone necrosis progression and pain.[1]

At risk category

Patients are in this group if they have a treatment history with antiresorptive or antiangiogenic drugs. They do not need any treatment.[1] Anyway, they should be educated to the risk of developing MRONJ such as instructed to quickly report every signs and symptoms. Local risk factors management and periodical clinical and radiological check-ups are suggested.

Stage 0 A medical treatment (antiseptic, analgesic, antibiotic, and antiphlogistic therapy) and management of local risk factors are indicated.[1] Low-level laser therapy is a possible choice for treatment of osteonecrosis by helping reparative process, improving osteoblastic index, and stimulating lymphatic and blood capillaries growth.[39,40] A careful follow-up for the evolution to a greater stage is necessary.

Stage 1 If exposed and necrotic bone or fistulae are present, they are rinsed with antiseptic fluids and covered with an adhesive paste, 3 times a day. In the absence of healing tendency, after 8 weeks, it is possible for a surgical debridement approach.[41]

Stage 2 After 2 weeks of medical therapy to reduce inflammatory symptoms, a surgical debridement is indicated. It should be more conservative as possible but extended as large as necessary to a complete removal of affected bone.[41] Antibiotic and antiphlogistic treatments are administered. Follow-up examinations are necessary.

Stage 3 Marginal or segmental osteotomies are recommended for severe cases.[42,43,44,45,46] Invasive surgery is indicated only if it could improve patient's quality of life. In other cases or if patient rejects surgery, a conservative approach to control symptoms and to prevent the osteonecrosis progression is administered.[42]

CONCLUSION

The pathophysiology of MRONJ is not completely elucidated, and an effective and appropriate therapy is still to be decided. It is crucial in future to improve the current knowledge about MRONJ and develop better strategies for its prevention and treatment. Governments and institutions should stimulate and support future research in this direction.

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Conflicts of interest

There are no conflicts of interest

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Figures and Tables

Table 1

Molecule	Category	Indication	Trade name
Alendronate	Bisphosphonate	Osteoporosis	Fosamax
Bevacizumab	Humanized monoclonal antibody	Metastatic colorectal carcinoma, nonsquamous nonsmall cell lung carcinoma, glioblastoma, metastatic renal cell carcinoma	Avastin
Denosumab	Receptor activator of nuclear factor kappa-B-ligand inhibitors	Bone metastases osteoporosis	Xgeva Prolia
Ibandronate	Bisphosphonate	Osteoporosis	Boniva
Neridronate	Bisphosphonate	Osteogenesis imperfect Paget's disease of bone	Nerixia
Pamidronate	Bisphosphonate	Bone metastases	Aredia
Risedronate	Bisphosphonate	Osteoporosis	Actonel
Sirolimus	Mammalian target of rapamycin pathway	Organ rejection in renal transplant	Rapamune
Sorafenib	Tyrosine kinase inhibitors	Hepatocellular carcinoma, renal cell carcinoma	Nexavar
Sunitib	Tyrosine kinase inhibitors	Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumor	Sutent
Tiludronate	Bisphosphonate	Paget's disease of bone	Skelid
Zolendronate	Bisphosphonate	Bone metastases osteoporosis	Zometa Reclast

Medication-related osteonecrosis of the jaw-related medications

Table 2

Medication-related risk factors	
Molecule	Way of administration
Total amount	Length of the therapy
Systemic and other risk factors	
Disease	Concurrent pathologies (diabetes, rheumatoid arthritis, dialysis, anemia, hypocalcemia, immunosuppression, osteomalacia)
Genetic factors	Age
Eripoietic factors	Obesity
Tobacco	Sex
Steroid therapy	Alcohol
Local factors-related risk factors	
Microtrauma	Inflammatory disease
Oral surgery	Removable prosthesis
Anatomic conditions	Oral implantology

Medication-related osteonecrosis of the jaw risk factors

Table 3

Therapy	Osteoporotic patients	Therapy	Cancer patients
Placebo[21,22]	0-2×10,000	Placebo[24-26]	0-1,9×10,000
Oral bisphosphonates <4 years[23]	10×10,000	Zolendronate[19,20,24-26]	33-110×10,000
Oral bisphosphonates >4 years[23]	21×10,000	Bevacizumab[27]	20×10,000
Zolendronate for 3 years[21]	1,7×10,000	Zolendronate + Bevacizumab[27]	90×10,000
Denosumab[22]	4×10,000	Denosumab[19,25]	70-190×10,000

Osteonecrosis of the jaw risk (cases per 10,000 patients)

Table 4

Stage	Marx 2007[32]	AAOMS 2009[2]	SICMF–SIPMO 2012[30]
At risk category		No evidence of exposed or necrotic bone in patients who have been treated with bisphosphonates	
Stage 0	Subclinical damage, microscopically represented by beginner hypocellularity osteoclast apoptosis and decrease of endosteal osteoblast	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone	
Stage 1	A: Painless exposed bone <1 cm B: Painless exposed bone >1 cm	Exposed/necrotic bone in patients who are asymptomatic and who have no evidence of infection	Focal BRONJ Clinical signs and symptoms: Bone exposure; sudden dental mobility; nonhealing postextraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity; and/or hypoesthesia/paraesthesia of the lips CT finding: Increased bone density limited to the alveolar bone region (trabecular thickening and/or focal osteosclerosis), with or without the following signs: Markedly thickened and sclerotic lamina dura; persisting alveolar socket; and/or cortical disruption 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge)
Stage 2	A: Painful and infected single exposed bone<2 cm B: Painful and infected single exposed bone>2 cm	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Diffuse BRONJ Clinical signs and symptoms: The same as Stage 1 CT findings: Increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: Prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and/or oroantral fistula 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge)
Stage 3	A: Multiple exposed bone areas without clinical findings of osteolysis, orocutaneous fistula, or pathological fractures B: Exposed bone >3 cm or with clinical findings of osteolysis, or orocutaneous fistula, or pathological fractures	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: Pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor	Complicated BRONJ The same as Stage 2, with one or more of the following Clinical signs and symptoms: Extraoral fistula; displaced mandibular stumps; nasal leakage of fluids CT findings: Osteosclerosis of adjacent bones (zygoma, hard palate); pathologic mandibular fracture; and/or osteolysis extending to the sinus floor

AAOMS=American association of oral and maxillofacial surgeons, SICMF=Italian society for maxillofacial surgery, SIPMO=Italian society of oral pathology and medicine, BRONJ=Bisphosphonate related osteonecrosis of the jaw, CT=Computed tomography

Different bisphosphonate related osteonecrosis of the jaw staging systems