

Medication-Related Osteonecrosis of the Jaw: A Reflection of Current Preventative and Therapeutic Guidelines: A Review

Hassan Dib, Wael Khalil, Houssam Jassar and Mohamad Houmnani

ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) is a serious side effect of bisphosphonates, denosumab, and antiangiogenic drugs. Although the literature is rich with research work discussing MRONJ, the pathogenesis of this devastating condition has not been adequately understood yet. Roles of infection, immunity and genetic predisposition have been extremely unclear. Moreover, many controversies have been governing risk assessment and management guidelines. In 2003, 36 cases of osteonecrosis of the jaw (ONJ) associated with the use of either pamidronate or zoledronate were reported. Furthermore, in 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) suggested the term “medication-related osteonecrosis of the jaw” (MRONJ) to describe jaw osteonecrosis related to the use of medications. This review sheds the light on recent research work discussing the pathogenesis of MRONJ. Moreover, it suggests possible guidelines for risk assessment and management based on information gathered from different research papers found in the literature.

Keywords: Bisphosphonate, MRONJ, pathogenesis, risk factors.

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H. Dib*

Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon.

(e-mail: dibhassan@gmail.com)

W. Khalil

Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon

(e-mail: waelkhalil74@hotmail.com)

H. Jassar

Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon

(e-mail: h.jassar@ul.edu.lb)

M. Houmnani

Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon

(e-mail: mhd_houmani@hotmail.com)

**Corresponding Author*

I. INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a serious medical condition, if left untreated, is associated with poor quality of life [1]. Medications usually associated with the development of this condition include, but are not limited to, bisphosphonates and the monoclonal antibody Denosumab [2]. The latter medications are commonly efficient in preventing bone resorption in osteoporosis and cancer patients. Even though the benefits in preventing bone resorption are very well established [3], [4], the development of MRONJ in some patients taking these medications has become a controversial subject of interest to oncologists and oral surgeons.

Diagnosis and staging of MRONJ have been thoroughly discussed in the literature. Although most physicians and oral surgeons agree on the wide use of imaging techniques in MRONJ diagnosis, whether stage 0 exists or is a necessary diagnosis, it hasn't been yet established [2].

Given how devastating MRONJ can be, identifying reliable guidelines and risk factors is of great importance. Recent research has focused on identifying the risk factors that dentists and physicians need to be aware of in these patients. Recent data have shed the light on some guidelines that can be useful to both dentists and physicians in dealing with MRONJ patients or with patients at risk [2], [5].

In this review, recent research on MRONJ focusing on staging, pathogenesis, risk factors, treatment options, and guidelines will be discussed.

II. RELATION BETWEEN DRUGS AND MRONJ

Although the mechanisms governing the progression to osteonecrosis have not yet been well identified, it is important to elucidate the biological mechanisms through which osteonecrosis develops, and the roles of anti-angiogenic drugs in MRONJ development. Research has suggested different mechanisms through which different drug families can induce MRONJ [2].

In addition to bisphosphonates and denosumab, anti-angiogenic drugs, which are prescribed in some cancer cases to block the development of blood vessels that support tumor growth, have also been associated with MRONJ. Interestingly, some differences were noticed between MRONJ associated with antiangiogenics and that associated with antiresorptive [6]. These differences might be the subject of future research aiming at understanding the pathogenesis and treatment of MRONJ induced by different drug families.

III. ETIOPATHOGENESIS

Recent research has shown interesting immunological/physiological involvements in MRONJ development. Taking into account that MRONJ can be preceded by oral infection, many studies have focused on the roles of infection in MRONJ development [2]. Bacterial infection can contribute directly to MRONJ development through the microbe itself, or indirectly through the immune system [7]. Whether medications manipulate the immune system or increase the rates of microbial infections, or both, is yet to be clearly investigated.

A recent study involving experimental rats has shown that periapical infection combined with mandibular localization increased the risk of MRONJ following tooth extraction [8]. Although the roles of infection in MRONJ development have already been suggested, the significance of this research work is in suggesting an animal model to study the roles of infection in the pathology of MRONJ. Other studies have shown that gamma- delta T cells may be activated by bisphosphonates (BPs), which can disrupt the normal response of the immune system to infection, inducing further damage. We know that BPs may increase the risk of local infection and that they may interact with different subsets of T cells. Moreover, the effect of BPs on monocyte/macrophage survival and function can also be a possible mechanism [7].

In a recent study conducted by Patntirapong *et al.*, biomaterials coated with bisphosphonates were used to study the in vivo effect of bisphosphonates on the viability of macrophages. Bisphosphonates directly impacted the survival of macrophages by decreasing their viability. Macrophage cell death is a mechanism thought to be, at least in part, responsible for the development of MRONJ in patients taking BPs [9].

Physiological mechanisms include, but are not limited to, inhibition of bone remodeling and inhibition of angiogenesis which can be induced by doses of BPs. BPs are known to inhibit the function of keratinocytes, which can lead to further damage [7]. How inhibition of keratinocytes can contribute to MRONJ development is yet to be fully elucidated. Bacterial invasion, however, is a plausible explanation. It was shown that bisphosphonates could induce senescence in normal human keratinocytes, at least in part through geranylgeranylation of the mevalonate pathway [10].

Genetic predisposition was associated by some studies with MRONJ development. Genetic predisposition involving the CYP2C8 gene or farnesyl pyrophosphate

synthase gene has gained interest as possible predisposes. It was shown that polymorphism in farnesyl pyrophosphate synthase and P450 CYP2C8 genes are associated with MRONJ [10].

Although drugs mostly associated with MRONJ are bisphosphonates and denosumab, research on antiangiogenic drugs has shown their possible association with MRONJ [6]. Antiangiogenics are mostly used to treat cancer by blocking the blood vessels nourishing the tumor mainly in cases of ovarian cancer, metastatic renal cell cancer, breast cancer, colorectal cancer, non-small-cell lung cancer (NSCLC), and glioblastoma multiforme. Antiangiogenics are known to block the VEGF pathway, a pathway that stimulates tumor growth [11]. Since VEGF is known to have roles in osteogenesis, it is possible that antiangiogenics induce MRONJ though VEGF blocking.

Reference [12] showed that most patients taking antiangiogenics presented with bone exposure, whereas 25 percent of patients on antiresorptive didn't have frank bone exposure. This difference, in addition to differences in the underlying malignancies, are worth studying so that clear pathogenic mechanisms governing MRONJ can be well established [6].

IV. DIAGNOSIS AND STAGING

Differential diagnosis of osteonecrosis of the jaw (ONJ) includes other conditions such as post-extraction osteomyelitis, sinusitis, gingivitis/periodontitis, periapical pathosis, and some forms of cement-osseous dysplasia showing secondary sequestration [2].

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), patients with MRONJ are those who are currently or have previously been treated with antiresorptive or antiangiogenic agents, as well as those who have an exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks. Furthermore, patients with MRONJ do not have a history of jaw radiation treatment or evident metastatic disease to the jaws [13].

References [14], [15] showed that according to AAOMS stages of MRONJ can be summed up as follows:

Stage 1: Exposed bone associated with no symptoms and no significant inflammation/infection in adjacent or regional soft tissue

Stage 2: Exposed bone associated with pain, infection, and swelling of adjacent or regional soft tissue inflammation and/or secondary infection

Stage 3: Exposed bone associated with pain, inflammatory swelling, and/or secondary infection, in addition to bone fracture, an extraoral fistula, oral-antral fistula, or osteolysis (radiographic evidence) extending to the inferior side of the mandible or the floor of the maxillary sinus.

As for the prodromal stage, namely, stage 0, controversy has always governed defining this stage. Stage 0 was described by AAOMS, as a stage with no apparent necrotic bone, but with one or all of the above symptoms. However, many professionals have considered stage 0 diagnosis as

misleading or exaggerating and can be associated with devastating effects due to overdiagnosis [2].

Plain radiographs are often used to detect early changes, usually associated with ONJ. Imaging can detect thickening in the lamina dura, the increased trabecular density of the alveolar bone, or the widening of the periodontal ligament space. In addition, radiography can be used to follow up the progression of the condition [7]. Computed tomography has many advantages over plain radiography in terms of lesion detectability [16]. Magnetic resonance imaging (MRI) can be useful as well in detecting early changes preceding the incidence of ONJ, including increased signal intensity due to jawbone edema [16], [17]. Positron emission tomography (PET) is also useful to detect the early stages of the disease [7]. In patients with a high risk of ONJ, cone-beam CT (CBCT) imaging can be useful to diagnose periodontal and periapical cases. For stage1-stage 2, CBCT imaging can be advantageous as well. For surgical considerations in advanced cases, PET and MRI are very beneficial [2], [7].

V. RISK OF MRONJ DEVELOPMENT

According to the Scottish Dental Clinical Effectiveness Program (SDCEP), which is an initiative of the Scottish National Dental Advisory Committee (NDAC), patients can be classified into two main groups, according to the risk of MRONJ: Low-risk group and high-risk group.

A. Low-risk Group includes:

- 1) Osteoporosis and non-malignant disease bearing patients treated for their condition with oral bisphosphonates for less than 5 years, and who are not concurrently being treated with systemic glucocorticoids (such as cortisone, hydrocortisone, prednisolone, methylprednisolone, betamethasone, etc.).
- 2) Osteoporosis patients and patients having non-malignant diseases, such as Paget's disease, treated for their condition with intravenous bisphosphonates for less than 5 years, and who are not concurrently being treated with systemic glucocorticoids.
- 3) Osteoporosis and non-malignant diseases patients, such as Paget's disease, treated for their condition with denosumab, and who are not being treated with systemic glucocorticoids.

B. High-risk group includes:

- 1) Osteoporosis patients and patients having non-malignant diseases, such as Paget's disease, treated for their condition with oral bisphosphonates or quarterly or yearly infusions of intravenous bisphosphonates for more than 5 years
- 2) Osteoporosis non-malignant diseases patients, such as Paget's disease, treated for their condition with bisphosphonates or denosumab for any length of time and who are being concurrently treated with systemic glucocorticoids.
- 3) Cancer patients treated with anti-resorptive or anti-angiogenic drugs (or both), as part of the management of their malignant condition.
- 4) Patients with a previous diagnosis of MRONJ.

Dentists must consider all these risk factors in patients who might develop MRONJ. Dentoalveolar surgery or any other surgery linked to tooth extraction being a precipitating event is considered a risk factor because of the high incidence of MRONJ following these procedures [6]. However, this does not mean that these procedures can cause MRONJ. MRONJ is caused, at least in part, by the procedures described in the pathogenesis section. Oral procedures can trigger the occurrence of MRONJ in patients at risk, and this is why risk assessment by the dentist before suggesting any oral procedure is of great importance. Interestingly the incidence of MRONJ following tooth extraction in cancer patients is higher than that in osteoporosis (2.9% vs 0.15%).

Another dental procedure to consider is the placement of dental implants. Although the exact risk of MRONJ associated with this procedure has not been well established, it is recommended to avoid this dental procedure in patients with a high risk of MRONJ (mainly cancer cases treated with AT or antiangiogenic drugs).

In a 2018 study conducted by Loyson *et al.*, the risk of the early development of osteonecrosis of the jaw was studied in the case of sequential treatment with bisphosphonate followed by denosumab. It was shown that the treatment with BPs, sequentially followed by treatment with denosumab, is associated with a higher risk for early development of osteonecrosis of the jaw as compared to patients treated with BPs alone. Patients of the study were cancer patients with secondary tumors in the bones. Interestingly, patients treated with denosumab alone showed a similar risk compared to patients treated sequentially with both drug families. Accordingly, the authors suggested that treating with denosumab alone is as safe as treatment with a bisphosphonate, sequentially followed by denosumab treatment.

Moreover, the authors of this study reported an inverse correlation between the time of denosumab exposure, following bisphosphonate treatment, and the number of patients developing osteonecrosis. An effect involving sensitization of the jaw was discussed [18] but due to the small number of patients, this conclusion should be considered with caution.

The research addressed the levels of biological markers in MRONJ. Scientists have discussed the possibility of associating changes in the levels of some biological markers such as the C- terminus telopeptide (CTX) to the incidence of MRONJ, and perhaps MRONJ diagnosis [19]. Some of these studies have shown lower levels of CTX in MRONJ patients. Whether or not levels of CTX or other biological markers can be used to assess the risk of MRONJ in healthy subjects is yet to be identified.

VI. SUGGESTED TREATMENT OPTIONS

Controversies have always governed the adequacy of different therapeutic options that include conservative therapy and/or surgery. Conservative therapy focuses on oral hygiene, adequate antibiotic treatment, and antimicrobial rinses. Bone marrow stem cell intralesional transplantation and Laser therapy have also been suggested.

Teriparatide (a bioactive portion of parathyroid hormone) has shown encouraging results as a conservative therapy medication. It has been successfully used as an anabolic agent in the treatment of some varieties of osteoporosis, and it is occasionally used to accelerate bony fractures healing.

In cancer, the need for teriparatide may be more important than its need in osteoporosis patients, especially in those with low risk for bone fracture.

Some experiments have shown promising results with topically applied ozone, bone marrow stem cell, and addition of pentoxifylline and tocopherol to the standard antibiotic regimen [2], [20].

VII. RISK ASSESSMENT

Using CTX level as a biomarker to evaluate MRONJ risk is yet not reliable. Therefore, dental practitioners should rely on another method and need to stratify patients according to the following three main factors:

- 1-Factors related to patient health status
- 2-Factors related to treatment
- 3-Factors related to the dental procedure

In each factor, low or high risks can be faced according to Table I.

TABLE I: FACTOR AND RISK

Factor	Low Risk	High Risk
Factors related to the patient	Young age	
	No comorbidities	Age >65
	Healthy periodontium	Comorbidities
	Good oral hygiene	Active periodontitis
	Non-smoker	Bad Oral hygiene Smoker
Factors related to the treatment		For Malignancy treatment
	For Benign treatment	BP IV or denosumab or long duration or PO for more than 2 years
	BP (PO) or denosumab or BP annual one IV injection	Associated medications:
	For less than 2 years	1. Immunosuppressors
		2. Corticosteroids
Factors related to the procedure		Multiple extraction >4 teeth
	Simple extraction	Difficult extraction
		Surgical extraction
		Surgery with periosteal raising

The combination of these three factors has been correlated with the result in patient stratification risk. The highest risk of stratification results from the combination of three high-risk actors and the lowest risk results from the combination of three low-risk factors.

Despite patient risk stratification, some general rules are to be followed. These General guidelines and recommendations include:

1. Recognition of risk factors associated with MRONJ.
2. Risk assessments and stratifications [21].
3. Insist on Oral hygiene.

4. Individualized treatment plan based on the least invasive procedure possible and minimizing procedure manipulating bone or periosteum.

In patients presenting high risk, a collaboration between a physician or an oncologist and an oral and maxillofacial surgeon is essential when planning a treatment plan considering options including medication cessation, of the non-surgical treatment plan as an alternative to surgical procedures, working without local anesthetic infiltration (regional block), working under general anesthesia, extensive antibiotic prophylaxis few days before oral surgical procedure and extend to days or weeks postoperatively (until securing complete clinical healing) [21], [22] using a broader molecule (such as amoxicillin and metronidazole or clindamycin) than conventional antibiotic prophylaxis (ABP) should also be considered.

This liberal approach in antibiotic prescription can be justified by the fact that due to the high morbidity situation of MRONJ the beneficial effect of extensive ABP might outweigh the risk of overmedication especially when the risk is significant [23].

VIII. CONCLUSION AND SUGGESTIONS FOR FUTURE RESEARCH

Reviewing the literature provides vital information about MRONJ diagnosis, staging, and clinical guidelines that need to be considered. However, a devastating condition like MRONJ requires extensive research aiming at understanding its pathogenesis. Whether the immune system starts this condition, the microbial infection or both is yet to be understood. We think that looking at the disease from a biological perspective is very vital. In addition to helping us better understand the condition, it can help in setting the guidelines for risk assessment and treatment options in a more precise manner. Moreover, the roles of genes and anti-angiogenic drugs in the pathogenesis of MRONJ are yet to be elucidated. We think that clinical research combined with adequate animal model research will improve our understanding of MRONJ.

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