

Medication-related osteonecrosis of the jaw: An update

ABSTRACT

Antiresorptive medications, such as bisphosphonates and denosumab, are an important class of medication used to treat a wide range of diseases from osteoporosis to multiple myeloma. Unfortunately, they are also associated with a rare but devastating side effect – medication-related osteonecrosis of the jaw (MRONJ). First reported in 2003, much research has been done into the area; however, the exact pathophysiology continues to elude clinicians and researchers. What has been ascertained is that intravenous treatment, duration of treatment, and tooth extraction are major risk factors. Staging and treatment guidelines have been proposed; however, there has been no universal acceptance, and clinicians rely on various position papers. Over the next 30 years, the aging population is set to double, and with it, the prescription of antiresorptive medication and incidence of MRONJ will undoubtedly increase. In 2013, Gupta *et al.* published a paper on bisphosphonate-related osteonecrosis of the jaw; however, there have been many changes since then. This paper aims to provide a succinct update on those changes.

Keywords: Antiresorptive, bisphosphonate, denosumab, osteonecrosis

INTRODUCTION

Bisphosphonates, first synthesized in Germany in 1865 and used for industrial purposes such as antiscaling agents, are now an important medication prescribed by oncologists, geriatricians, rheumatologists, and hematologists.^[1-3] Bisphosphonates are structurally derived from inorganic pyrophosphates; like their endogenous counterpart, they too have an intrinsic affinity for hydroxyapatite of the bone mineral, inhibiting calcification. In addition to this, bisphosphonates are able to prevent bone resorption by preventing hydroxyapatite breakdown.^[4] More recent research suggests that bisphosphonates likely prevent osteocyte and osteoblast apoptosis.^[5] These perceived functions were the rationale behind introducing bisphosphonates as an antiresorptive agent for the treatment of high bone turnover disease since the 1970s.^[3] They are now licensed in the UK for a wide range of bone disorders such as osteoporosis, hypercalcemia of malignancy, Paget's disease of the bone, and multiple myeloma.^[6]

Although it was noted in 2001 that there was an increase in referrals for jaw pain and nonhealing ulcers, it was

not until 2003 that Marx *et al.* reported the first cases of bisphosphonate-related osteonecrosis.^[7] They identified 36 patients with painful bone exposure in the mandible or maxilla; all patients were receiving a form of bisphosphonate medication. Several further case reports quickly followed, and osteonecrosis of the jaw became a recognized side effect of bisphosphonate treatment – bisphosphonate-related osteonecrosis of the jaw (BRONJ).^[8,9]

Denosumab, an antiresorptive agent, is a monoclonal antibody to the receptor activator of nuclear factor- κ B ligand (RANKL).^[10] By preventing the binding of RANKL to its

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receptor, denosumab inhibits the differentiation and function of osteoclasts.^[11] Due to this common ability to suppress osteoclast activity, denosumab is often seen as a modern-day alternative to bisphosphonates; they are currently licensed in the UK for the treatment of osteoporosis, prevention of skeletal-related events in patients with bone metastases, and giant cell tumor of bone.^[12]

In 2010, Aghaloo *et al.* reported a case of osteonecrosis of the jaw, which they felt was related to the patient's use of denosumab.^[13] Following this, and further similar reports, The American Association of Oral and Maxillofacial Surgery (AAOMS) proposed changing the nomenclature of BRONJ. To accommodate the growing number of jaw osteonecrosis cases associated with denosumab use, they favored medication-related osteonecrosis of the jaw (MRONJ).^[14]

The world population is increasing, and moreover, the elderly population is increasing. Epidemiological studies show that the proportion of the world population over the age of 60 years is set to double by 2050.^[15] As a consequence, current predictions are that the cancer and osteoporotic burden in the elderly is also likely to dramatically increase.^[16,17] This will likely increase the usage of antiresorptive medications and inherently, the risk of side effects from these medications, such as MRONJ. It is imperative that both clinicians prescribing antiresorptive agents and those diagnosing and treating MRONJ are aware of the most recent research.

In 2013, Gupta *et al.* published a paper in the *National Journal of Maxillofacial Surgery*, entitled "BRONJ," outlining the etiology, epidemiology, and treatment.^[18] However since then, as well as the above-mentioned change in nomenclature, there has been much progress. This paper aims to provide an update on these changes.

METHODS

A bibliographic search was carried out using PubMed and Medline ending in December 2020. The search terms used were: BRONJ, MRONJ, bisphosphonate, and denosumab.

Medication related osteonecrosis of the jaw definition

MRONJ is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial area that has persisted for longer than 8 weeks, in a patient who has been treated with antiresorptive or antiangiogenic medication, without a history of radiation therapy to the jaws or obvious metastatic disease.^[14] This definition was created in 2014 when the AAOMS revised

their previous position paper to address growing concerns regarding underreporting of disease. The previous definition had only included exposed bone; however, a large European study showed that up to a quarter of MRONJ diagnoses were missed as they had a nonexposed variant.^[19,20]

Pathophysiology

Since the first cases of MRONJ were reported, significant progress has been made in understanding the pathophysiology of the disease. However, the topic is still of some debate between clinicians and researchers, and multiple hypotheses have been proposed.^[21,22] Unlikely to be attributable to one solitary cause, it is rather a disease of multifactorial cause.

Inhibition of bone remodeling

Osteoclasts, tightly regulated by the RANK/RANKL/osteoprotegerin signaling pathway, play a vital role in bone healing and remodeling.^[23] Antiresorptive drugs such as bisphosphonates and denosumab reduce osteoclast activity, by inhibiting differentiation and function and inducing apoptosis, thereby leading to decreased bone resorption and remodeling.^[24] Although osteoclast activity is present in all skeletal sites, it should be noted that osteonecrosis only occurs in the alveolar bone of the maxilla and mandible.^[25] Animal studies have shown that alveolar bone exhibits an increased rate of remodeling when compared to other bones in the axial or appendicular skeleton, which may explain the predisposition of osteonecrosis occurring in the jaw.^[26,27] Since denosumab and bisphosphonates, although via different mechanisms, both inhibit osteoclast function, altered bone remodeling is thought to be a central factor in the development of osteonecrosis of the jaw.^[23]

Infection and inflammation

Multiple bacteria have been isolated in cases of MRONJ; however, there was an almost universal presence of *Actinomyces*.^[28,29] *Actinomyces* species are the most common microflora in the oral cavity, and through their formation of a biofilm, they are able to facilitate the adherence of other microorganisms, thus resulting in a mixing pot of bacteria primed for the development of infection.^[30] Despite these findings, there is no clear evidence to link infection with the development of osteonecrosis. However, one mechanism may be via infection-induced bone resorption, independent of osteoclasts.^[22]

Tooth extraction is the most common inducing factor for MRONJ; extraction is often indicated due to periapical infection or inflammation.^[31] Animal models have been developed which show that dental disease combined with

the use of antiresorptive treatment, even in the absence of tooth extraction, is sufficient to cause MRONJ.^[25,32]

Inhibition of angiogenesis

Angiogenesis, mediated by vascular signaling molecules such as vascular endothelial growth factor (VEGF), is the formation of new blood vessels.^[33] An interruption in blood supply can cause osteonecrosis; therefore, inhibition of angiogenesis has been proposed as a leading hypothesis in the pathophysiology of MRONJ.^[31,34] Certain bisphosphonates are known to reduce circulating levels of VEGF and consequently reduce angiogenesis *in vitro*.^[35]

This theory is further supported by recent reports of patients developing osteonecrosis of the jaw, occurring after administration of antiangiogenic medication, such as sunitinib or bevacizumab.^[36,37]

Epidemiology

Oral bisphosphonates

The prevalence of MRONJ in patients taking oral bisphosphonates for the treatment of osteoporosis can range up to 0.04%.^[38,39] A study by Lo *et al.* found that the prevalence increased to 0.21% in patients receiving oral bisphosphonates for more than 4 years, demonstrating an apparent relationship to the duration of treatment.^[40] The incidence ranges from 1.04 to 69 per 100,000 patient-years.^[41,42]

Intravenous bisphosphonates

The prevalence of MRONJ in those prescribed intravenous bisphosphonates as compared to oral for the treatment of osteoporosis is significantly higher (0.348%).^[39] The incidence for these patients ranged from 0 to 90 per 100,000 patient-years.^[43]

Patients receiving intravenous bisphosphonates for cancer had a prevalence of up to 0.186%.^[44] The prevalence increased dramatically to 14.8% following a tooth extraction, indicating that tooth extraction is a major risk factor for the development of MRONJ.^[45] The incidence ranges up to 12,222 per 100,000 patient-years.^[39]

Subcutaneous denosumab

In patients with cancer receiving denosumab, the prevalence of osteonecrosis ranges from 0.7% to 1.9%.^[14,46] A large 10-year study of the adverse effects of denosumab treatment in osteoporosis identified 11 cases of MRONJ with a prevalence of 0.04%.^[47] The incidence is 52 and 2316 per 100,000 patient-years for osteoporosis and cancer patients, respectively.^[39,47]

Risk factors

Local factors

A 4-year retrospective study at a tertiary cancer center in Kerala demonstrated a significant association with dental intervention.^[48] Studies have shown that tooth extractions are a precipitating event in over 50% of MRONJ cases and are associated with a 33-fold increase in risk for MRONJ.^[49,50] Denture use has been associated with an increased risk for MRONJ.^[51] Patients who have concomitant oral diseases, such as periodontal disease or periapical pathology, are known to be at an increased risk of MRONJ.^[45,52]

Systemic factors

An increase in duration of bisphosphonate use is associated with an increased risk of MRONJ, particularly when taken for longer than 4 years.^[40] Concurrent use of steroids also increases the risk of MRONJ, likely due to decreased immunity and delayed wound healing.^[52] MRONJ has also been linked with older age, particularly above 65 years, and coexisting diagnosis of diabetes mellitus.^[14,38,53]

Staging

The current clinical staging system in use was developed by Ruggiero *et al.* and has been adopted by AAOMS.^[14,54] AAOMS describes four stages of MRONJ (0–3), which are used to guide clinical management. The American Society of Bone and Mineral Research (ASBMR) has also identified a staging system, however, with only three stages (1–3).^[38]

At risk

Patients are deemed to be at risk if they have been treated with intravenous or oral antiresorptive or antiangiogenic medication, however, have no necrotic bone, and are asymptomatic.

Stage 0

Stage 0 describes patients who have no clinical evidence of necrotic bone but present with nonspecific symptoms such as odontalgia, jaw pain, or sinus pain; clinical findings such as increased tooth mobility or periapical fistula; or radiographic findings such as alveolar bone resorption, change in trabecular pattern, osteosclerosis, or periodontal ligament thickening.

Stage 0 was newly added to the AAOMS Staging Guidelines, as several case studies had reported that almost 50% of patients with stage 0 disease were progressing to a higher stage.^[55,56] However, the ASBMR does not recognize stage 0 as they have concerns that inclusion may lead to an overdiagnosis of MRONJ. This could lead to detrimental effects to patients' skeletal health if antiresorptive treatments were to be incorrectly discontinued.^[39,51]

Stage 1

These patients have exposed and necrotic bone or a fistula that probes to bone, however, are asymptomatic, and have no evidence of infection.

Stage 2

Stage 2 patients present with exposed and necrotic bone or a fistula that probes to bone, associated with pain, and evidence of infection.

Stage 3

Stage 3 patients demonstrate exposed and necrotic bone or fistulas that probe to bone with evidence of infection and at least one of the following – exposed necrotic bone extending beyond the region of the alveolar bone, pathological fracture, extraoral fistula, oro-antral communication, or osteolysis.

Management Prevention

Prevention is an important aspect of any management plan, and there is evidence that prevention can achieve up to a threefold decrease in the incidence of MRONJ.^[57,58] The first step should be to ensure the appropriate prescription of antiresorptive and antiangiogenic medication.^[59] In the instance that these medications are indicated, there is strong evidence to support early inclusion of a dental professional to ensure the patient is dentally fit prior to commencing treatment.^[57,60,61] Assessment should include examination of the dental hard and soft tissues for evidence of disease and also any dental prosthesis.^[59] All retained roots, unrestorable teeth, and teeth with a limited prognosis unlikely to be retained in the long term should be extracted or considered for extraction prior to starting therapy.^[59,62] Partially erupted third molars and impacted third molars with associated odontogenic cysts should also be considered for extraction.^[62] An important aspect of the dental review will be instructions on oral hygiene and information regarding signs and symptoms of MRONJ.^[14,63]

Drug holiday

Many guidelines advocate the use of a “drug holiday” or a cessation in antiresorptive/antiangiogenic medication; however, there is no compelling evidence to support this guidance.^[14,39,61]

Conservative treatment

In the absence of a universal guide for the management of MRONJ, the generally accepted treatment goals are pain relief, control of infection, and limitation of bone necrosis.^[14,39] AAOMS, ASBMR, and the Canadian Association of Oral and Maxillofacial Surgeons all advocate the use of analgesics, topical antibiotic mouth rinses, and

systemic antibiotic therapy.^[14,39,64] This approach, while not resolving the lesion, does appear to provide long-term relief.^[65,66] Recent research has suggested the use of novel treatment ideas such as platelet-rich plasma, hyperbaric oxygen, laser treatment, and parathyroid hormone.^[67,68] However, the efficacy of these treatment methods is yet to be established.

Surgical treatment

Historically, guidance discouraged the use of surgical intervention for the management of MRONJ unless there was a progression of disease. However, more recent reports demonstrate significant success with a surgical approach.^[69,70] The premise behind this being sharp, exposed bone can further increase the risk of further inflammation and should therefore be removed.^[71]

CONCLUSION

MRONJ is a relatively rare complication of antiresorptive and antiangiogenic medication. However, with the elderly population set to double by 2050, the prescription of these medications and thus side effects are bound to increase. Prevention has been shown to be the cornerstone of management of this disease. This review has also noted a deficiency in scientific research on MRONJ, its risk factors, and epidemiology within India, with most studies confined to case reports. This is certainly an area that requires addressing.

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Conflicts of interest

There are no conflicts of interest.

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