Received: 24 October 2022 | Revised: 12 March 2023 | Accepted: 24 March 2023

DOI: 10.1111/jgs.18414

REVIEW ARTICLE

Journal of the
American Geriatrics Society

Medication-related osteonecrosis of the jaw: A disease of significant importance for older patients

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[Correction added after first online publication on 13 June 2023 Deepak Ipe's Degree has been corrected.]

Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is clinically defined as a non-healing jawbone ulcerative-necrotic lesion appearing after dental therapy or minor trauma in patients treated previously with antiresorptive, anti-angiogenic or immunomodulators. Older patients with osteoporosis and cancer receive these pharmacological agents regularly. As these patients are long-term survivors, efficient treatment is of paramount importance for their quality of life.

Methods: Literature searches via PubMed were conducted to identify relevant MRONJ studies. Basic information on MRONJ classification, clinical features, and pathophysiology is presented herein as well as various clinical studies dealing with MRONJ in patients with osteoporosis and cancer. Lastly, we discuss current managment of patients and new trends in treatment of MRONJ.

Results: Although close follow-up and local hygiene have been advocated by some authors, severe forms of MRONJ are not responsive to conservative

therapy. At present, there is no "gold standard" therapy for this condition. However, as the physiopathological basis of MRONJ is represented by the anti-angiogenic action of various pharmacological agents, new methods to increase and promote local angiogenesis and vascularization have recently been successfully tested in vitro, limited preclinical studies, and in a pilot clinical study. **Conclusions:** It appears that the best method implies application on the lesion of endothelial progenitor cells as well as pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) and other related molecules. More recently, scaffolds in which these factors have been incorporated have shown positive results in limited trials. However, these studies must be replicated to include a large number of cases before any official therapeutic protocol is adopted.

KEYWORDS

bisphosphonates, bone resorption, denosumab, MRONJ, osteoporosis

INTRODUCTION

Medication-related osteonecrosis of jaw (MRONJ) is defined as an area of exposed bone or fistula which develops after administration of anti-resorptive medication alone or in combination with anti-angiogenic drugs or immunomodulators for osteoporosis and cancer, two major conditions frequently described in older patients.[1–9]

In the context of anti-resorptive and anti-angiogenic therapy, age older than 65 years represents a significant risk factor associated with the development of MRONJ.[3–6] Moreover, a recent retrospective statistical study evaluating 70 MEDLINE published studies indicates that the mean age of the MRONJ patient is 62 years.[9] Therefore, we should consider MRONJ as a condition affecting with predilection the old-age patient.

As an osteoporosis-related fracture occurs every 3 s, bisphosphonates are widely administered as an anti-resorptive medication around the world. In the US, 150 million bisphosphonate prescriptions were administered between 2005 and 2009 as they have been shown to significantly decrease the risk of fractures. Bisphosphonate therapy is associated with an overall drop of 40%–70% in vertebral fractures and a decrease of up to 50% in hip fractures justifying the high rates of administration of these agents in the old age population.[10] Therefore, we can also assume that this selected older population is exposed to the risk of developing MRONJ.

Anti-angiogenic medication is widely indicated for a variety of cancers. Mauceri et al.[11] have indicated that MRONJ develops after oncological therapy with anti-vascular endothelial growth factor (anti-VEGF)

Key points

- MRONJ is an underdiagnosed condition which develops after dental therapy or minor oral trauma, especially in older patients treated previously with bisphosphonates, denosumab or anti-cancer agents.
- Bisphosphonates and denosumab are administered to counteract hypercalcemia induced by osteoporosis or cancer metastasis while anti-cancer agents have an anti-angiogenic action.
- The number of MRONJ cases will likely increase as the population ages and more patients will require anti-resorptive therapy for their osteoporosis and cancer including bone metastasis.

Why does this paper matter?

As the global population is aging, the number of patients with cancer and osteoporosis requiring administration of bisphosphonates, denosumab and anti-angiogenic agents, will significantly increase. Most likely, the number of MRONJ cases will increase in senior patients. There is no "gold standard" therapy for this underdiagnosed condition and long-term outcomes using bone reconstruction methods are limited by high rates of failure. Since the pathophysiological basis of MRONJ is represented by the anti-angiogenic action of anti-resorptive agents, new alternatives to increase local angiogenesis must be identified. Meantime, it is very important to diagnose

monoclonal antibody, mammalian target of rapamycin (mTOR) inhibitors, receptor activator of nuclear factor κB ligand (RANKL) inhibitor and tyrosine kinase inhibitors (TKIs), all anti-angiogenic factors. Non-healing osteonecrosis of the mandible and maxillary is also seen in patients treated with denosumab, a monoclonal antibody and an RNKL inhibitor used to counteract bone destruction associated with osteolytic cancer lesions.[12] MRONJ has also been associated with herceptin and pertuzumab, monoclonal antibodies administered in Her2-positive breast cancer patients.[13] Interestingly, MRONJ has been observed in patients with acute myelodysplastic leukemia treated with bemcentinib via an anti-angiogenic mechanism and interference with the host immunological profile.[14] Owosho et al.[15] have also reported cases of MRONJ, after ipilimumab, a monoclonal antibody administered in patients with malignant melanoma, and acts by inhibiting the immune system via CTLA-4 activation. Lastly, MRONJ has also been described after therapy surface of T-cells in a variety of cancers such as lung cancer.[16]

In 2018, excluding non-melanocytic skin cancers, 13% of global cancer cases representing 2.3 million new cancer cases were identified in patients 80 years or older. Unfortunately, by 2050, it is predicted that 6.9 million new cases will be diagnosed annually worldwide in patients over 80 years of age representing more than 20% of all diagnosed cancers.[7] The burden of cancer might be higher in some parts of the world, especially in Europe which currently shares 25% of the global cancer cases although it represents only 9% of the world population.[8]

Some authors have described MRONJ in rare cases after tumor necrosis factor-alpha (TNF-α) inhibitors, administered in immune-mediated inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease which may be seen in older patients as well.[17–20] However, from a histological perspective, regardless of the patient's age or the clinical context, MRONJ is characterized by the presence of osteoclasts, inflammatory cells and reactive bone formation, all in close proximity to necrosis.[21] All of these could explain the oral pain and dysphagia as described in patients with MRONJ.[22] Unfortunately, until now, therapy in MRONJ patients is not satisfactory and molecular factors and pathways promoting the development of cellular and molecular abnormalities leading to bone destruction, characteristic of MRONJ, are not completely understood.

MRONJ CLINICAL FEATURES AND CLASSIFICATION

MRONJ develops in patients with no history of metastases or radiation therapy to the head and neck region, after therapy with anti-resorptive and/or anti-angiogenic molecules and immunomodulatory factors. These patients would develop, most commonly in the oral cavity, a non-healing ulcerated exposed area or a fistula leading to a necrotic area of the jaw after dental therapy or minor oral-facial trauma.[23]

A significant number of MRONJ patients (94%) present with asymptomatic exposure of bone while up to 4.5% of cases develop mandibular fractures after dental therapy.[12] Therefore, early detection of MRONJ before the development of bone exposure is of paramount importance in these patients. The earliest signs of MRONJ are suggested by radiological evaluation showing osteolysis and associated osteosclerosis, increased thickness of lamina dura, enlargement of the periodontal ligament space, increased thickness of the mandibular cortex, enhancement of the mandibular canal and periodontal bone destruction.[24,25]

Initially, Weitzman[26] suggested that MRONJ lesions should be classified according to the size of necrosis and severity. The size is measured as the largest diameter of single and multiple lesions and includes stage 1, less than 0.5 cm, stage 2, larger than 0.5 cm but less than 0.99 cm, stage 3, less than 2 cm and stage 4, larger than 2 cm.[26]

Based on the extent of clinical features, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has proposed a classification of MRONJ in four stages. A group "at risk" is described as including all those that have received anti-resorptive medication.[2] Stage 0 is characterized by non-exposed bone, but patients will present with abnormal radiological tests such as, alveolar bone loss or resorption not related to chronic periodontal disease and osteosclerosis and variable pain while in stage 1 (clinical evaluation identifies fistulas that lead to an area of bone necrosis but remarkably without evidence of inflammation or infection). Compared with stage 1, at stage 2, the patients are symptomatic with obvious signs of infection such as erythema and purulent discharge (Figure 1A,B; Table 1). The most severe stage is stage 3, characterized by exposed and necrotic bone, extensive infection and one or several associated features such as pathologic fracture, extraoral fistulas, oral antral/oral

MRONJ at an incipient stage allowing early therapy and finding new efficient therapeutic methods to improve the patients' quality of life. Although scaffolds embedded with pro-angiogenic molecules as well as progenitor endothelial cells have been tested in experimental settings, more research is needed before any factor becomes the "gold standard" for MRONJ therapy.

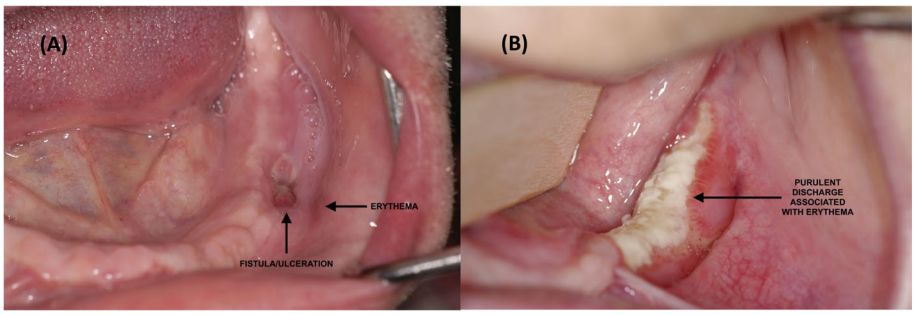

FIGURE 1 (A) This photo represents an older edentulous patient with stage 2 MRONJ according to AAOMS criteria, but stage 1 according to Weitzman criteria, as the lesion measures less than 0.5 cm. (B) This photo was taken from an 88-year-old female patient with stage 2 MRONJ according to AAOMS criteria (or stage 4 according to Weitzman criteria, as the lesion expanded over more than 2 cm).

TABLE 1 MRONJ: Classification, clinical features, and management.

Patient type	Features	Current management
"At risk"	• None	• Multidisciplinary observation • Oral hygiene (2; 27)
Stage 0 MRONJ	• Radiological investigation will show alveolar bone resorption • Local pain	• Multidisciplinary observation • Oral hygiene • Analgesics (2; 27)
Stage 1 MRONJ	• Bone necrosis • Oral Fistulas • No inflammation seen	• Oral hygiene • Removal of mobile bone sequestrum • Analgesics • Marginal resection/alveolectomy • Periodic evaluation (2; 27)
Stage 2 MRONJ	• Bone necrosis • Oral Fistulas • Local erythema • Purulent discharge	• Oral hygiene • Removal of mobile bone sequestrum • Analgesics • Systemic antibiotics • Segmental resection/partial infrastructure -maxillectomy • Periodic evaluation (2; 27)
Stage 3 MRONJ	• Exposed necrotic bone • Mandibular/maxillary/zygomatic bone necrosis • Osteolysis of the sinus floor • Pathologic fracture • Extra-oral fistulas • Oral antral communication • Oral nasal communication	• As in stage 2 (2; 27)

nasal communications, osteolysis involving the inferior border of the sinus or necrosis involving the zygomatic bone, mandible, and maxillary sinus[24] (Figures 2 and 3, Table 1).

MRONJ must be differentiated from squamous cell carcinoma (SCC). This is extremely difficult in those patients at risk for this type of cancer who have been treated with anti-resorptive agents.[28] Also, MRONJ must be distinguished from osteoradionecrosis of the jaw (ORNJ), osteomyelitis of the jaw (OMJ) and very rarely from oral Langerhans cell histiocytosis and idiopathic lingual mandibular sequestration, an extremely rare condition of unknown etiology.

All of these conditions are characterized by the presence of bone necrosis and inflammation.[29–32] Therefore, the anatomopathological examination corroborated with clinical information is of paramount importance in making the correct diagnosis. However, the presence of osteoclasts, lymphocytes and plasma cells are definitory for MRONJ.[33]

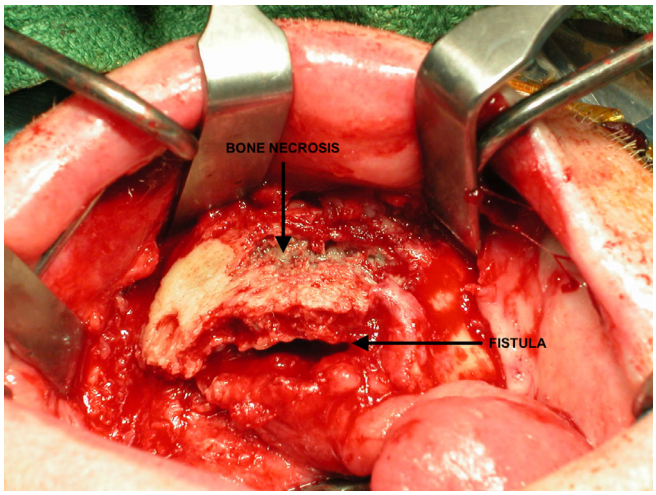

FIGURE 2 This photo was taken from a 72-year-old female with stage 3 MRONJ according to AAOMS criteria treated by surgical resection. There is obvious extensive necrosis and hemorrhage.

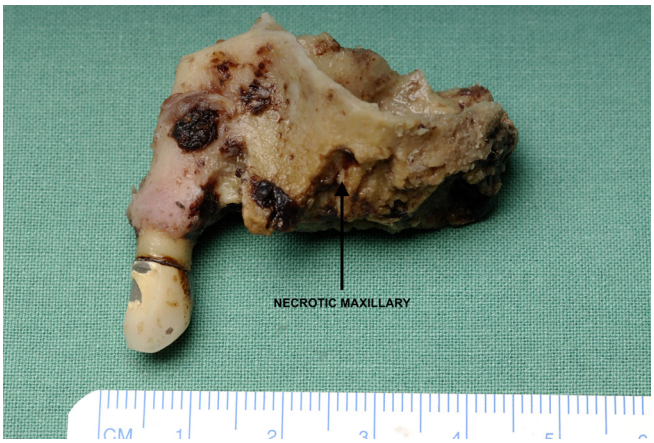

FIGURE 3 This photo represents a stage 3 MRONJ resection specimen in which the necrosis was extending into the maxillary bone in a 72-year-old female patient.

Physiopathology

Recent theories suggest that MRONJ is the result of the inhibition of local angiogenesis and increased osteoclast activity in concert with local inflammation and/or infection[34] (Figure 4). Yapijakis et al.[35] suggest that MRONJ might have a genetic basis as described in a sub-group of hypertensive patients. More specifically, it seems that MRONJ develops in patients with hypertension that have the D variant of the ACE gene.[35] This was described in both homozygous and heterozygous individuals for the D-ACE gene.[35] Further, patients with inflammatory rheumatic conditions are more prone if they have osteoporosis treated with bisphosphonates.[36] Therefore, it is best to assume that MRONJ has multi-factorial pathogenesis, the toxic effect on bone cells and the anti-angiogenic mechanism of bisphosphonates have been of paramount importance[3,37–39] Histological and molecular evaluation of tissue taken from MRONJ patients has revealed that the condition is characterized by numerous multinucleated, giant osteoclasts. Also, a dendritic cell-specific transmembrane protein (DC-STAMP) is noted in the presence of cell–cell fusion of osteoclasts, an element indicating active osteoclast formation. This would suggest that cell–cell fusion is a key element in the physiopathology of this condition, but the significance of these findings is poorly understood.[40]

The anti-angiogenic effect induced by both bisphosphonates and some anti-cancer pharmacological agents inhibits endothelial cell growth and development promoting necrosis.[41] Moreover, Ferretti et al.[42] have shown that in patients with metastatic breast cancer, zoledronic acid promotes a reduction in VEGF and angiogenesis as well as fibroblast growth factor-2 (FGF-2) and matrix metalloproteinase-2 (MMP-2) altering the local tissue environment status quo. Also, anti-angiogenesis related MRONJ has been recently described after bevacizumab, which is indicated in various types of cancer.[43] Remarkably, zoledronate and risedronate inhibit angiogenesis but this effect is independent of biochemical pathways leading to osteoclast dysfunction suggesting that these two effects induced by bisphosphonates are independent of each other.[44] Interestingly, in animal models with experimental periodontitis, low-dose risedronate inhibits osteoclast function and bone resorption but at a higher dosage it impairs angiogenesis.[45] Kaneko et al.[46] have reported that zolendronic acid increases local inflammation, promoting overexpression of IL-1β via an NLRP3 inflammasome. Overall, local inflammation could worsen bone destruction induced independently of this mechanism.

Decaux and Magremanne[16] indicate that MRONJ could also be the result of decreased bone turnover after alteration of osteoclast functionality induced by chemotherapeutic agents such as epacadostat and pembrolizumab. Also, as in the case of bisphosphonate therapy, the associated infection and inflammation would accelerate the course of osteonecrosis.[15]

More recently, Isawa et al.[47] have indicated that denosumab acts as an anti-RANKL antibody. However, it is known that RANKL, a member of the RANK-RANKL-OPG pathway, is a very important factor activating osteoclastogenesis. More specifically, RANKL is expressed not only by osteoclasts but also by T lymphocytes, in turn promoting osteoclastic cell growth and development via an immunological mechanism.[16] Since denosumab has an anti-RANKL action it will also impair osteoclast formation. Experimental studies conducted in a murine

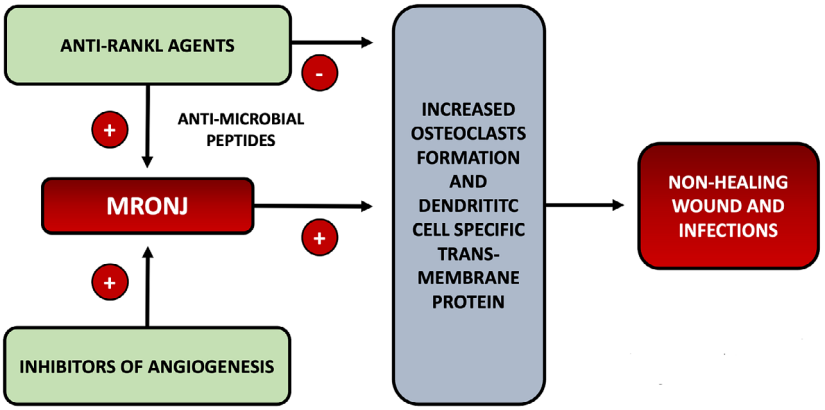

FIGURE 4 MRONJ physiopathology. Both anti-RANKL agents and inhibitors of angiogenesis appear to contribute to MRONJ with activation of increased osteclast fomation which can lead to a non-healing wound.

model have shown that subjects treated with denosumab have impaired osteoclastogenesis while displaying normal tooth growth.[44] Therefore, in some cases of MRONJ described after therapy with RANK-ligand inhibitor, denosumab, other molecular mechanisms including an anti-angiogenic pathway must be activated.

The associated infection, induced and promoted by a non-healing MRONJ lesion is also a very important factor which needs further investigation. Recent studies have indicated that both bisphosphonates and anti-RANKL agents induce local synthesis of antimicrobial peptides (AMPs) such as human alpha and beta-defensins which could have an etiopathogenic role in MRONJ. According to Thiel et al (2020), the defensins might represent a therapeutic target in patients with MRONJ induced by dental trauma after anti-resorptive therapy.[48]

However, despite all these data, at the transcriptional level, the mechanisms of MRONJ have not been thoroughly investigated. Recent research suggests that several factors modulating osteoclast function could have a major role in the physiopathology of this condition. In this context, NFATc1, a major upstream activator of osteoclasts and BCL6, a factor with robust anti-osteoclastic action might have a role of paramount importance in MRONJ pathogenesis.[49] However, their role is yet to be fully understood and more experimental data is needed, as important clues may elucidate the precise mechanism and the specific factors involved in MRONJ physiopathology and pathogenesis.

MRONJ in patients with osteoporosis

Numerous studies have revealed that anti-resorptive therapy for osteoporosis induces MRONJ. In a study conducted on 2,819,310 patients which identified 1603 cases of osteoporosis treated with bisphosphonates, MRONJ developed in 0.06% of patients suggesting an incidence rate of 22.9 per 100,000 person-years.[6] Interestingly, in a study conducted on 283 patients presenting with necrosis in the mandible area, only 25.6% met the diagnostic criteria for MRONJ. However, 52.5% of these MRONJ patients were on anti-resorptive therapy including bisphosphonates for osteoporosis.[50] Bagan et al.[51] have described MRONJ in patients treated with the anti-RANKL denosumab but who had a history of bisphosphonate intake as well. In this study, the most important triggering factor was also represented by dental extraction which was followed in 90% of patients by bone exposure pathognomonic for MRONJ.[51] These data have been confirmed more recently by a pilot study conducted in 86 female patients with a mean age of 73.9 years (range 45–97), which indicated that 80% of these patients were taking bisphosphonates for osteoporosis and nearly 60% of them developed MRONJ after tooth extraction, implant surgery and non-fitting denture use.[52] A two-center retrospective study conducted in patients with bisphosphonate-induced MRONJ indicated that in almost all patients with osteoporosis, the condition was triggered by dental extraction. About 65% of these cases were cured by conservative and surgical therapies while the remaining cases did not heal. The authors have determined that the context of osteoporosis, orally administered bisphosphonates over a shorter duration of time as well as the localization of necrosis around the frontal and premolar maxilla, represent factors associated with a better outcome.[53]

MRONJ in patients with cancer

Migliorati suggests that in cancer patients, MRONJ development may be seen after treatment with both denosumab and bisphosphonates, and after anti-angiogenic treatment.[3] Most commonly, these patients would receive only anti-resorptive therapy or combined anti-resorptive medication and only a small number would be treated with anti-angiogenic molecules.[54] Poxleitner et al.[55] have

conducted an extensive retrospective analysis evaluating all the PubMed and Cochrane Library data relevant to MRONJ and found that the scientific evidence describing the association between MRONJ, and various pharmacological anti-cancer and anti-resorptive agents are moderate to low. A retrospective review of the literature published between 2003 and 2019, reports more than 15,000 cases of MRONJ described in 1300 publications. The overall incidence of MRONJ in cancer patients treated with bisphosphonates is up to 6.7%. In the same population group, denosumab-induced MRONJ was present in 1.7% of cases.[56]

More specifically, in patients with hematologic neoplasia and those with bone metastases caused by a variety of cancers, the incidence varies from 1% to 20%. Also, MRONJ is seen in 0.8%–4.6% of myeloma patients, especially in those that had a tooth extraction.[47] A retrospective cohort study was conducted on 93 patients undergoing a dental extraction, previously diagnosed with a variety of cancers such as breast, lung and prostate cancer, multiple myeloma, gastrointestinal tumors, sarcomas and monoclonal gammopathies, revealed some interesting findings in patients treated with either bisphosphonates or denosumab. In both instances, the risk of developing MRONJ is significantly increased, regardless of medication type, or if the dental extraction was performed for periodontal disease, vertical root fracture or periapical pathology. In addition, the authors also found that local inflammation/infection increased the risk of developing MRONJ.[57] However, some authors have indicated that compared with the number of older patients with osteoporosis developing MRONJ after bisphosphonates or anti-RANKL denosumab, the incidence of MRONJ is significantly higher in cancer patients receiving the same type of anti-resorptive therapy.[58] Svejda et al.[59] suggest that MRONJ develops in 15% of cancer patients since in these cases the administration of high doses of bisphosphonates, anti-RANKL and anti-angiogenic agents is required at shorter intervals of time. In these cases, the development of MRONJ seems to be accelerated by concomitant administration of glucocorticoid medication, diabetes mellitus and any other cause that promotes a local inflammatory reaction such as poorly fitting dentures and inappropriate oral hygiene.[60]

Therefore, one may conclude that at least for the aforementioned agents, MRONJ appears at a higher rate in cancer patients, as the dosage and frequency of administration of MRONJ-inducing agents are different than in osteoporosis. Overall, the general "anti-angiogenic" effect induced in these patients could be significantly higher than in osteoporosis patients. However, all these mechanisms remain to be verified in experimental and clinical studies. Remarkably, in cancer patients, MRONJ occurs earlier, after only 4 months of combined therapy with bone resorption inhibitors and vascular endothelial growth factor receptor tyrosine kinase inhibitors, compared with only bone resorption therapy inhibitors in which case the lesion develops after 25 months of treatment. Also, during the first year, only 1.1% of those treated with only anti-resorptive therapy developed MRONJ compared with 6.7% in the experimental group treated with combined therapy.[60]

Current management of MRONJ patients

Prevention of MRONJ is of paramount importance and consists of surgical or dental evaluation with potential treatment to the oral-facial region before therapy with anti-resorptive and anti-angiogenic agents is initiated. Some studies have indicated that administration of antibiotics and oral hygiene before the dental or surgical intervention would prevent the development of MRONJ.[23] Currently, there are no formal prevention protocols accredited by any medical specialty regarding the management of patients at risk of MRONJ and frequently prevention and therapy are left to the patient.[61] A recent study conducted on 129 dental practitioners in the UK has indicated that more than 90% of these have poor knowledge of the medications that promote MRONJ while only 40% are comfortable treating patients with antiresorptive-related MRONJ.[62] Therefore, education of both medical professionals as well as patients regarding the risk of developing MRONJ after administration of anti-resorptive and anti-angiogenic medication is likely to improve the prevention of this debilitating condition.[23,63] In addition, recent studies indicate that the best management of patients at risk of developing MRONJ requires a multidisciplinary team including dental, medical, oncological, and nursing specialists.[23,27]

In patients that develop MRONJ, discontinuation of the medication that has promoted the condition is associated with worsening the primary condition.[64] Hence the difficulty in treating MRONJ. Therefore, several non-operative and operative surgical management methods have been advocated by various groups. However, there is no "gold standard therapy" for MRONJ.

Regarding the non-operative interventions, at present, most of the suggested therapeutic guidelines indicate personal opinions, mostly applicable only to bisphosphonate-related MRONJ and therefore have a low level of evidence requiring verification in well-designed clinical studies.[65] However, the non-operative management of MRONJ focuses on counteracting the associated infection and pain, improving the stage of disease and healing, and includes the administration of topical

antimicrobial mouth rinses and antibiotics. The aim of non-operative management of MRONJ is the formation of a sequestrum around the lesion which subsequently can be removed to allow bone healing.[23,65,66] In this setting, chlorhexidine gluconate 0.12% or 0.2% represents an efficient topical bacteriostatic-bactericidal agent which acts by decreasing oral bacterial population including the biofilms that promote the infection,[65–67] However, oral antibiotics are the most important agents to treat infection in MRONJ. As the infections associated with this disease are polymicrobial including organisms such as Actinobacteria, Bacteroides, Firmicutes and Fusobacteria, broad-spectrum antibiotics such as amoxicillin/clavulanic acid, ampicillin, metronidazole or clindamycin are recommended.[65,66] In MRONJ cases characterized by the presence of organisms that are resistant to oral antimicrobials, intravenous antibiotics may be administered for up to 6 weeks.[66]

The use of ozone therapy or hyperbaric oxygen is discouraged in MRONJ as there is no proof that these approaches are beneficial.[23] Some authors have reported that vitamin D may prevent the development of MRONJ in some older patients, but its mechanism of action is not known.[23] Interestingly, some authors have also reported encouraging results after vitamin E and pentoxifylline administration but only in limited cases. In addition, the mechanism of action of these agents in this clinical context is not completely understood.[23] However, teriparatide, a low-dose recombinant human parathyroid hormone has shown promising results in improving clinical symptomatology in patients improving the MRONJ stage after 6 months of therapy.[23,65] Given these data, more clinical studies are needed before the role of teriparatide could be established.

Surgical therapy in MRONJ is advocated by numerous groups that have obtained positive results. More specifically, positive results have been reported after marginal resection of the mandible or maxilla in 90% of MRONJ cases with oral and parenteral bisphosphonate administration. In MRONJ that is refractory to limited resection, segmental resection should be attempted after marginal intervention.[68] Some authors have indicated that the best results have been obtained if surgical resection was followed by smoothening bone edges and a bilayer wound closure of the viable remaining bone.[69] Free flap microvascular reconstruction is also another surgical approach for MRONJ stage 2 and 3 with a rare non-union rate and recurrence of 5% which is statistically acceptable.[70] However, some studies have revealed that at 55 weeks after surgery, an efficient mucosal wound closure was noted in less than 30% of MRONJ patients.[71] Other groups have reported complete healing in up to 80% of cases for 8 years.[72] Patients with MRONJ stage 2 improved to MRONJ stage 1 in more than 80% of cases but only 38% of patients with stage 1 disease improved after surgery.[71] However, more recent data evaluating 70 MEDLINE studies while confirming previously reported information on the surgical outcomes in patients with stage 2 and 3 disease, suggests that mucosal closure is seen in all the patients diagnosed with MRONJ stage 1 regardless of the inducing pharmacological agent.[9]

Interestingly, recent research suggests that for the best therapeutic outcome, therapy of MRONJ patients should be personalized, based on the pattern of periosteal reaction which is described in more than 20% of patients. Soutome et al.[67] indicate that surgical therapy in these patients is better than a conservative approach and the outcome depends on the presence of a periosteal reaction; MRONJ patients without such periosteal inflammation have the best clinical outcome.[67] The type 1 periosteal reaction is characterized by new bone formation parallel with the mandible without any interposing gap, while type 2 lesion is diagnosed by the presence of a gap between the newly formed bone and the mandible. However, the most severe lesion is represented by the periosteal reaction type 3 which is diagnosed by a large irregular space between the mandible and the newly formed bone.[67] Overall, it was suggested that for efficient therapy of the MRONJ patients, any osteolytic areas, as well as type 3 periosteal lesions should be surgically removed.

Current guidelines recommended for MRONJ stage 1 include antimicrobial rises, oral antibiotics and removal of bone sequestrum to facilitate bone healing, and in some cases, depending on the general status of the patient and the associated conditions, bone resection. In stage 2 and 3 diseases, apart from pain control, and systemic antibiotics, surgical resection of the mandible or partial maxillectomy is required.[23,65]

New trends in MRONJ patients' treatment

Recently, regenerative therapies have been tried in MRONJ. However, despite the successful development of biomimetic materials that can replace damaged bone (structurally speaking), most of the available biomaterials do not induce a sufficient formation of blood vessels. This lack of a functional vasculature to support the graft is the biggest bottleneck for cell-based regenerative therapies. In bone tissue engineering, adequate vascularization is crucial for the timely and adequate transport of nutrients and waste removal, and the provision of progenitor cells for tissue remodeling and repair. Indeed, vascularization and bone formation are highly linked as angiogenesis

precedes osteogenesis during both embryonic development and adult bone healing which is characterized by several phases including a proliferative phase in which angiogenesis is a major component.[73]

Angiogenesis, the formation of new blood vessels via sprouting, is a complex process whereby endothelial cells migrate out from pre-existing vessels and form new connections to increase the vascular network. Moreover, the vasculature in bone appears to be formed mainly or perhaps even exclusively by angiogenesis. This vascularization event in the intramembranous jaw bones occurs similarly to that observed during endochondral angiogenesis, which suggests that similar molecular mechanisms are involved.[74] Mesenchymal cells condense to form sponge-like structures and differentiate into osteoprogenitors and osteoblasts which secrete extracellular matrix and form ossification centers and, ultimately, fully differentiated osteocytes. Matrix proteins and pro-angiogenic factors generated by the ossification centers then attract new blood vessels. The subsequent vascularization of the developing flat bone then promotes osteogenesis.[74]

In this context, it is well known that poor angiogenesis is a common and vital barrier to tissue regeneration. Regenerating tissue over 200 nm exceeds the capacity of nutrient supply and waste removal from the tissue and, therefore, requires a well-developed network of blood vessels.[75] A local well-developed vascular network with fully functional endothelial cells is of paramount importance in this setting. However, bisphosphonates and other anti-resorptive agents have a major inhibitory action on endothelial cells and progenitor elements as well as on the microvessel sprouting, Therefore, the greatest issue in MRONJ therapy remains the counteracting of the direct anti-angiogenic action induced by a variety of pharmacological agents.[76] Experimental research conducted in a murine model has revealed that MRONJ therapy with endothelial progenitor cells (EPCs) is very efficient and significantly decreases necrosis while increasing VEGF levels in serum and tissue, significantly improving fibroblast and epithelial cell function.[77]

Moreover, recent in vitro studies have provided encouraging data indicating that the addition of endothelial progenitors would prevent the anti-fibroblastic effect of zolendronic acid and dexamethasone, increasing vascularization and ultimately preventing MRONJ.[78] This has led to several types of tissue engineering approaches combining the use of angiogenic growth factors and/or transplantation of proangiogenic cells, such as endothelial progenitor cells within scaffolds. While feasible, in vivo recapitulation of the events involved in appropriate cellular differentiation, proliferation and formation into functional structures is very difficult. However, the use of only proangiogenic cells also has significant disadvantages, since perivascular cells, including mural cells, are obligatory for the formation of native, multilayered mature microvessels.[79] Therefore, these proangiogenic cells should be used in parallel with vascular growth factors such as VEGF as well as other pro-angiogenic molecules embedded in tissue engineering scaffolds.

A pilot clinical study conducted in patients with stage 2 and 3 MRONJ, has recently revealed that these patients could be successfully treated by a scaffold containing l-platelet-rich fibrin (L-PRF) and an adipose-tissue stromal vascular fraction (SVF) which includes endothelial progenitor cells and mesenchymal stromal cells (MSC). This pilot study showed that complete healing of the buccal mucosa takes place within a month while robust bone formation is noted.[80] However, this study should be further replicated to include large cohorts of patients and more clinical and laboratory data are needed to verify the safety and dynamics of this therapeutic approach.

Although in some cases close regular follow-up and local hygiene can be effective, surgery with removal of the necrotic area is still indicated. Theoretically, optimal healing in MRONJ patients would require the application of pro-angiogenic and endothelial progenitor cells as well as pro-angiogenic growth factors including VEGF and other molecules with similar action. As the world population ages, the number of patients with osteoporosis and bone metastases will likely increase significantly.[7,10] However, as large numbers of these patients are treated with bisphosphonates and other anti-resorptive agents the number of MRONJ cases will also increase. Therefore, finding a new improved method to treat this condition is of paramount importance for improving the patients' quality of life.

AUTHOR CONTRIBUTIONS

Bridget Boston: initial data collection, manuscript drafting, data evaluation and analysis, conclusions, digital imaging, manuscript updating. Deepak Ipe: initial data collection, manuscript drafting, data evaluation and analysis, manuscript updating. Bogdan Capitanescu: manuscript drafting, data evaluation and analysis. Andrei Gresita: manuscript drafting, data evaluation and analysis. Stephen Hamlet: manuscript drafting, data evaluation and analysis. Robert Love: manuscript drafting, data evaluation and analysis. Michael Hadjiargyrou: manuscript drafting, data evaluation and analysis, manuscript updating. Chien-Ling Huang: manuscript drafting, data evaluation and analysis. Iulian Nusem: manuscript drafting, data evaluation and analysis. Rodica Ileana Miroiu: manuscript drafting, data evaluation and analysis, manuscript formatting and updating. Aurel Popa-Wagner: manuscript drafting, data evaluation and analysis. Patrick Hans-Heinrich Warnke: manuscript drafting, data evaluation and analysis. Eugen

Bogdan Petcu: initial data collection, manuscript drafting, data evaluation and analysis, conclusions, digital imaging, manuscript updating and overall supervision of the project.

ACKNOWLEDGMENT

Open access publishing facilitated by Griffith University, as part of the Wiley - Griffith University agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

No specific funding was received for this work.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

SPONSOR'S ROLE

Not applicable.

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How to cite this article: Boston B, Ipe D, Capitanescu B, et al. Medication-related osteonecrosis of the jaw: A disease of significant importance for older patients. *J Am Geriatr Soc*. 2023;71(8):2640-2652. doi:10.1111/jgs.18414