Review Article

Medication-related osteonecrosis of the jaw: a narrative review of risk factors, diagnosis, and management

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Background and Objective: This article provides a detailed and up-to-date narrative review of the risk factors, diagnosis, and management of medication-related osteonecrosis of the jaw (MRONJ). MRONJ is an emerging topic of research, and there is a growing list of new drugs associated with MRONJ, diagnostic strategies, and treatment techniques that may aid in management.

Methods: A comprehensive review of the literature in English was conducted, using databases such as PubMed, OVID, UpToDate, and Lexicomp to find relevant articles and information and prioritizing articles from 2014 to 2021.

Key Content and Findings: MRONJ is an uncommon disease in patients exposed to antiresorptive and/or antiangiogenic agents, such as those with osteoporosis and/or cancer. Dentoalveolar surgery is the most common initiating factor for MRONJ, and there are many patient-related and medication-related factors that increase risk for occurrence. Diagnosis is primarily based on clinical factors, and MRONJ presentation may range from an asymptomatic, localized lesion with no sequelae to infected bone leading to pathologic fracture requiring major oral surgery. Prevention plays a key role in management and should take place before initiation of drug therapy, as well as during and after drug therapy. For treatment, conservative measures typically provide symptomatic relief, while surgical resection has been shown to be more curative.

Conclusions: MRONJ may lead to significant morbidity in affected patients, and providers must use the most up-to-date information to characterize patient risk, detect disease early, and treat appropriately based on severity.

Keywords: Osteonecrosis; bisphosphonate; denosumab; antiangiogenic

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Introduction

According to the American Association of Oral & Maxillofacial Surgeons (AAOMS), medication-related osteonecrosis of the jaw (MRONJ) is defined as (I) current or previous treatment with an antiresorptive, such as bisphosphonate (BP) and denosumab, or antiangiogenic agents; (II) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks; and (III) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws (1). Those at risk for MRONJ

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include osteoporotic and oncologic patients treated with antiresorptive and/or antiangiogenics. Cancer patients treated with high-dose antiresorptives are at the highest risk with an incidence of up to 1.9% (1), but recent population-based studies reveal an incidence of up to 6.6% (2) . Of note, MRONJ is a rare disease and studies with smaller sample sizes tend to overestimate incidence.

Since the release of the AAOMS white paper in 2014, there has been a growing list of contributory drugs and risk factors, strategies for diagnosis, and treatment techniques. This narrative review aims to provide an up-to-date and detailed summary of the risk factors, diagnosis, and management for MRONJ. We present this article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-106/rc).

Methods

A search of the literature was performed, using PubMed, OVID, Lexicomp, and UpToDate databases for articles published from 2002 to 2021, prioritizing articles from 2014 until and including 2021, in English. Medical Subject Heading search terms and free text terms in different combinations were used to research the subjects addressed in this review. The following terms and variants were searched: medication-related osteonecrosis of the jaw, bisphosphonate-associated osteonecrosis of the jaw, antiresorptive, antiangiogenic, extraction, periodontal disease, periapical disease, cancer, pathogenesis, bone remodelling, infection, immunity, diagnosis, computed tomography (CT), *Actinomyces*, C-terminal cross-linking telopeptide (CTX), drug holiday, conservative therapy, surgical therapy, teriparatide, and statin. Articles were sorted by cited references, and systematic reviews of randomized controlled trials and prospective cohorts were prioritized. This search was supplemented by reviewing the references of pertinent articles and including them in the search. Articles with full-text available online were selected and analyzed. Data were presented in text in the form of a narrative review. Citations were tracked using Mendeley version 1.19.8. The search strategy has been summarized in *Table 1* and an example using OVID-Embase has been employed in *Table 2*.

Discussion

Etiology and risk factors

MRONJ has a multifactorial etiology and occurs from a combination of initiation factors, patient related factors, and medication related factors.

Initiation factors

Invasive procedures

Dentoalveolar surgery is a major risk factor precipitating osteonecrosis of the jaw (ONJ) in antiresorptive and/or antiangiogenic treated patients. In particular, tooth extraction has been cited in prospective trials as the common precipitating factor in 61.8% of MRONJ cases (3). Following tooth extraction, AAOMS estimates the risk of developing MRONJ at 0.5% and up to 14.8% in patients exposed to oral and intravenous (IV) BPs, respectively (1). There is a lack of data defining MRONJ risk following dental implant placement, endodontic, or periodontal procedures that involve manipulation of bone, but the AAOMS estimates a comparable risk with tooth extraction (1).

Other initiation factors

MRONJ may also occur spontaneously from mucosal trauma, thin overlying mucosa, or excess biting force. A randomized controlled trial in rats demonstrated that oral mucosa injury was an initiating factor for MRONJ, but was less likely to induce ONJ than tooth extraction (4). Chronic irritation from an ill-fitting denture causing mucosal trauma may act as an initiating factor for MRONJ (5). Studies have demonstrated an increased prevalence of MRONJ among denture wearers in cancer patients treated with IV BPs (6).

MRONJ is more prevalent in areas of bony prominences, such as exostoses, tori, and mylohyoid ridge, because the overlying mucosa is thin and poorly vascularized (7). Thin overlying mucosa and large tori that are often traumatized may lead to ulceration and possible initiation of MRONJ pathogenesis (5).

Excess biting force leading to microdamage may be another cause of spontaneous MRONJ. In rats exposed to IV BP, a decrease in bone remodelling led to a significantly greater amount of microcrack accumulation compared with placebo (8). These microcracks have been suggested to compromise the biomechanical integrity of the jawbone and to act as a nidus for infection and subsequent osteonecrosis (8). Excess biting forces may also explain the 2-fold increase in incidence of MRONJ in the mandible compared with the maxilla (9). In particular, the posterior mandible is subject to the highest loading forces and reflects the greatest prevalence of MRONJ (9). Traumatic occlusion may also be a contributing factor.

Patient-related factors

Oral risk factors

Patients may present with oral or systemic factors that

Table 1 The search strategy summary

Items	Specifications
Date of search	December 21st, 2020–December 19th, 2021
Databases and other sources searched	PubMed, OVID, Lexicomp, UpToDate
Search terms used	MeSH terms: bisphosphonate-associated osteonecrosis of the jaw, periodontal diseases, periapical diseases, tooth extraction, diphosphonates, denosumab, angiogenesis inhibitors, etiology, infection, bone remodeling, diagnosis, immunity, tomography, X-ray computed, *Actinomyces*, teriparatide
	Free text terms: medication-related osteonecrosis of the jaw, bisphosphonates, antiresorptives, antiangiogenics, cancer, pathogenesis, c-terminal cross-linking telopeptide, drug holiday, conservative therapy, surgical therapy, statin
	Please see *Table 2* for detailed search strategy using OVID-Embase
Timeframe	2002–2021
	Priority has been placed on articles published after the AAOMS 2014 white paper on MRONJ. Older articles were included to explain bisphosphonates and MRONJ in the context of what is known
Inclusion and exclusion criteria	All study types were included, in English, with available full text online
Selection process	JG Thomas independently conducted the collection and assembly of data, then data analysis, interpretation, and final approval was conducted by all authors

AAOMS, American Association of Oral & Maxillofacial Surgeons; MeSH, Medical Subject Headings; MRONJ, medication-related osteonecrosis of the jaw; N/A, not available.

Table 2 Detailed search strategy using OVID-Embase

Search strategy	Database
Keywords: ((bisphosphonate-associated osteonecrosis of the jaw) OR (medication-related osteonecrosis of the jaw)) AND ((periodontal diseases) OR (periapical diseases) OR (tooth extraction) OR (diphosphonates OR bisphosphonates OR antiresorptives) OR (denosumab) OR (angiogenesis inhibitors AND antiangiogenics) OR (etiology) OR (infection) OR (immunity) (bone remodeling) OR (cancer) OR (diagnosis) OR (C-terminal cross-linking telopeptide) OR (tomography, X-ray computed) OR (*Actinomyces*) OR (drug holiday) OR (conservative therapy) OR (surgical therapy) OR (teriparatide) OR (statin))	OVID-Embase

increase their risk for MRONJ. Oral risk factors include periapical and periodontal disease, ill-fitting dentures, and traumatic occlusion. Periapical and/or periodontal disease are found more commonly among patients who develop MRONJ compared with those at high risk but don't develop MRONJ (10,11). In mice models, the combination of periapical or periodontal disease and IV BP therapy was sufficient to induce MRONJ (12,13). Clinically, most reported MRONJ cases occur after extraction of teeth with periapical disease or periodontal disease (12). Additionally, improvements in dental hygiene has shown to prevent MRONJ in cancer patients (14). However, inflammatory dental disease as a risk factor for MRONJ may be confounded by tooth extraction, a strong initiating factor.

As described in the initiating factors section, ill-fitting dentures and traumatic occlusion may lead to spontaneous MRONJ from mucosal trauma and microcrack accumulation.

Systemic risk factors

Systemic risk factors include cancer type and comorbidities that impair immunity. Cancer types at risk for MRONJ from antiresorptive therapy include primary bone malignancy, such as multiple myeloma, and solid tumours with bone metastases, such as breast, prostate, and lung cancers (15). MRONJ occurrence is the greatest in multiple myeloma, followed by lung, prostate, and breast cancer (15).

Cancer types at risk for MRONJ from antiangiogenics include metastatic renal cell carcinoma, ovarian cancer, breast cancer, colorectal cancer, non-small-cell lung cancer, and glioblastoma multiforme (16). Antiangiogenic-related MRONJ occurrence among antiresorptive-naïve cancer patients is the greatest in metastatic renal cell carcinoma, followed by metastatic colorectal cancer and metastatic breast cancer (16). Metastatic renal cell carcinoma demonstrates a further increase in MRONJ incidence when treated with antiangiogenics in combination with antiresorptives, especially with sunitinib or bevacizumab and IV zoledronate (17,18).

Comorbidities that impair immunity include rheumatoid arthritis, uncontrolled diabetes, chronic corticosteroid use, and smoking. All of these factors are inconsistently associated with an increased risk of MRONJ. Rheumatoid arthritis patients who develop osteoporosis as a complication may be prescribed an oral BP, which poses a theoretically low risk for MRONJ (19). Randomized controlled trials in mice demonstrate that rheumatoid arthritis is significantly associated with MRONJ if IV zoledronate is given at an oncological dose (20). However, most rheumatoid arthritis patients receive a much lower dose, thus this association is weak.

Uncontrolled diabetes is thought to increase MRONJ risk through multiple pathways of injury. High blood sugar alters macrophage function, inhibits bone remodelling, and leads to microvascular ischemia—all of which contribute to MRONJ pathogenesis (21). Diabetic mice have shown a higher prevalence of MRONJ, but human studies show variable association with MRONJ (21). Thus, uncontrolled diabetes is not an established risk factor for MRONJ.

Chronic use of glucocorticoids has been shown to cause osteonecrosis at sites other than the jaw, such as the hip, from a decrease in bone perfusion and osteocyte apoptosis (22). However, controlled trials in cancer patients treated with antiresorptives and concomitant glucocorticoids only showed a marginal increase in MRONJ incidence compared to those treated with antiresorptives alone (3).

Smoking is thought to be a risk factor for MRONJ, but evidence is equivocal (15,23). Smoking is associated with poor oral health, which in turn, increases risk for MRONJ (23).

Medication-related risk factors

Medication-related risk factors pertain to treatment with BPs, denosumab, and antiangiogenics. There is also a growing list of drugs associated with MRONJ.

Antiresorptives

Antiresorptive therapy include BPs and receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors, both of which inhibit bone remodeling for the management of osteoporosis, primary bone malignancy, and solid tumours with bony metastases. BPs are classified via their side chain groups into either nitrogen containing BPs (N-BPs) or simple BPs (S-BPs), which have differing mechanisms of action (24). N-BPs inhibit farnesyl pyrophosphate synthase to block cholesterol biosynthesis leading to osteoclast apoptosis (24). S-BPs do not contain nitrogen and are instead metabolized into non-hydrolysable adenosine triphosphate (ATP), which is cytotoxic and accumulates in osteoclasts to trigger apoptosis (24). The ability for BPs to inhibit farnesyl pyrophosphate synthase determines potency, where the presence of a nitrogen containing side chain may increase a BPs antiresorptive potency by 10–10,000 folds with respect to S-BPs (24). For its strong affinity for hydroxyapatite and high molecular stability, BPs typically have a very long half-life and may persist in bone for the patient's lifetime (24).

Denosumab is a human monoclonal antibody with affinity for the cytokine RANK-L (25). Normal bone remodelling depends on a balance of RANK-L and osteoprotegerin, both released by osteoblasts (25). RANK-L binds to its receptor (RANK) on osteoclast and osteoclast precursors to trigger bone resorption, whereas osteoprotegerin binds RANK-L to prevent its interaction with RANK (25). Like osteoprotegerin, denosumab binds RANK-L to inhibit the activation, migration, differentiation, and fusion of hematopoietic cells of osteoclast lineage to decrease bone resorption (25). Different from BPs, denosumab does not accumulate in bone tissue, thus is fully reversible with a half-life of approximatively 25–28 days (25).

It has been well established that the risk of MRONJ in antiresorptive exposed patients depends on dose, schedule, and duration (1). For BPs, there is a greater risk of MRONJ with IV compared with oral administration because of increased bioavailability (140-fold); zoledronate compared with pamidronate because of increased potency (100-fold); treatment duration over four years; and IV zoledronate on a monthly compared with 12-week dosing schedule because of greater cumulative dose (24,26,27). Similarly, there is a greater risk of MRONJ when denosumab is prescribed at the higher dose and frequency of 120 mg every month to treat cancer versus 60 mg every 6 months to treat osteoporosis (28). Recently, studies have demonstrated that by extending the dosing interval of IV zoledronate from 4 to 12 weeks in breast cancer patients, MRONJ incidence decreased without an increase in skeletal related event (29). There has been limited safety data addressing the effect

of extending the dosing interval for denosumab from 4 to 12 weeks in preventing skeletal related events (30).

Antiangiogenic agents

Antiangiogenic agents are increasingly being used in targeted cancer therapy to inhibit tumour angiogenesis (31). By modulating growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), these drugs prevent the formation of new blood vessels from pre-existing ones to inhibit tumour growth (31). There are three categories of antiangiogenic agents targeting VEGF, including anti-VEGF monoclonal antibodies (bevacizumab), VEGF decoy receptor (aflibercept), and small molecular tyrosine kinase inhibitors (TKIs) that block VEGF receptors downstream (sunitinib, cabozantinib, sorafenib, dasatinib) (31). Moreover, other agents that target mammalian target of rapamycin (mTOR) inhibit angiogenesis by affecting the production of VEFG and PDGF (temsirolimus, everolimus) (31).

The antiangiogenics mentioned above have been shown to be associated with MRONJ in antiresorptive naïve patients (16). In addition, antiangiogenics in combination with antiresorptives demonstrate a greater risk of MRONJ than in those treated with antiresorptives alone, especially bevacizumab or sunitinib in combination with IV zoledronate (17,18).

Drug of emerging importance related to MRONJ

There has been an increasing number of case reports demonstrating that MRONJ is not limited to antiresorptives and antiangiogenic agents, but may also be associated with other drugs. Raloxifene, methotrexate, and tocilizumab have demonstrated a link with MRONJ, although the relationship is insufficiently characterized.

Raloxifene is a selective estrogen receptor modulator used to prevent osteoporosis in post-menopausal women (32). Raloxifene is preferred over BPs in younger patients with fewer risk factors for new osteoporotic fractures (32). Although the relationship between MRONJ and raloxifene is not as strong compared to its association with other antiresorptives, case reports have described MRONJ in raloxifene treated patients without a history of BP use (33,34). Further studies with sufficient power are required to explore this rare clinical event.

Methotrexate is an antimetabolite that inhibits DNA synthesis and replication (35). Methotrexate and BPs may be used to treat rheumatoid arthritis, and complications leading to oral bone exposure may arise from both these medications. Methotrexate may cause lymphoproliferative disorder, which rarely manifests in the oral cavity to cause bone exposure (35). Recently, Henien *et al.* described 2 cases of MRONJ in long-standing arthritis patients treated with low-dose methotrexate in the absence of lymphoproliferative disorder, antiresorptives, or antiangiogenics (36).

Tocilizumab is an anti-interleukin-6-receptor monoclonal antibody used to treat rheumatoid arthritis. In 2018, Bindakhil and Mupparapu reported a case of osteomyelitis with features of MRONJ in a osteoporosis and rheumatoid arthritis patient treated with tocilizumab, with no history of BP use (37). Furthermore, tocilizumab and sarilumab, another inhibitor of interleukin-6 signalling, are currently being investigated in clinical trials for off-label use to reduce mortality in critically ill COVID-19 patients (38). As a result of increased use, there is a potential risk that dentists may encounter a higher number of patients at risk for MRONJ in the future.

Pathogenesis

Oversuppression of bone remodeling

The oversuppression of osteoclastic bone resorption by antiresorptives may play a role in the development of ONJ. Since both BP and denosumab are associated with ONJ but inhibit bone turnover through different mechanisms of action, this strongly suggests that oversuppression of bone is a contributory factor. Suppressing bone turnover leads to the accumulation of non-renewed, hypermineralized bone and a decrease in microvasculature, which predisposes the bone to osteonecrosis upon injury. The differential predisposition of MRONJ for the jaws occurs because alveolar bone shows increased remodeling rates compared to bones in the axial and appendicular skeleton, as per animal data (39). As a result, antiresorptives preferentially target osteoclasts at sites of increased turnover in the jaws. This preference is also seen at local sites of increased turnover, such as extraction sites or areas of periodontal/periapical inflammation, which demonstrate higher accumulation of BPs as per mouse data (40). Preliminary clinical findings show that the administration of teriparatide, a synthetic recombinant human parathyroid hormone, has shown to improve MRONJ symptoms (41). Teriparatide indirectly stimulates osteoclasts to counter suppression during antiresorptive therapy, which supports the oversuppression of bone remodeling hypothesis.

However, a clinical study showed that bone turnover in the mandible and maxilla is not overly suppressed by BPs, thus oversuppression is likely not the sole causative factor for MRONJ (42). Additionally, ONJ has yet to be reported

among patients with metabolic conditions of reduced bone turnover, such as hypoparathyroidism.

Infection and impaired immunity

Infection and impaired immunity may be possible contributing factors to MRONJ development. Poor oral hygiene and inflammatory dental disease have shown to be highly associated with MRONJ. Bacteria are also commonly cultured from biopsy of necrotic bone, which implicates infection as a pathological mechanism. However, there is uncertainty about whether necrosis precedes or follows infection and the role of infection as a pathological trigger has been questioned.

The oral cavity is particularly susceptible to infection and osteonecrosis because of the presence of potentially pathogenic bacteria, frequent opportunities for injury, and close proximity to bone (43). During injury, wound healing is impaired by antiresorptive-mediated local immune depression, which facilitates infection leading to necrosis (43).

BPs have been shown to cause direct soft tissue and immune cell toxicity. *In vitro* studies demonstrate that BPs localize to oral epithelium to induce apoptosis and decrease proliferation, which predisposes the oral mucosa to breakdown or disrupted healing after trauma (44,45). Upon disruption of the oral mucosal barrier, bacteria invade the wound site and trigger an inflammatory response which increases bone resorption. Bone resorption is exacerbated in the presence of BPs, which inhibit bone remodelling. BPs have also been shown to alter macrophage migration and morphology, leading to local immune depression to facilitate infection (43). A clinical study has shown greater macrophage immunosuppression in MRONJ compared with osteonecrosis from other causes, which supports a link between the two (46).

Denosumab does not cause soft tissue toxicity, but RANK receptors are present on immune cells, such as macrophages (47). Through inhibition of RANK-L, denosumab decreases macrophage function and survival (47), which may contribute to infection in MRONJ.

Angiogenesis inhibition

Inhibition of angiogenesis may contribute to MRONJ pathogenesis through bone ischemia leading to necrosis upon injury. Both IV zoledronate and antiangiogenic agents inhibit angiogenesis. *In vitro* studies demonstrate that zoledronate inhibits endothelial cell proliferation, migration, and adhesion (48), and cancer patients treated with IV zoledronate demonstrate lower circulating VEGF levels (49). In cancer patients treated with IV zoledronate, inhibition of angiogenesis, measured through serum VEGF levels, has been shown to be a potential predictive marker for MRONJ (50).

Antiangiogenics, such as sunitinib, have shown causative effects in MRONJ development. A metastatic renal cell carcinoma patient with established MRONJ from IV zoledronate and concomitant sunitinib exhibited improved symptoms upon discontinuation of sunitinib (51). This same patient experienced worsening of MRONJ symptoms upon resumption of sunitinib (51), supporting the role of the involvement of antiangiogenics in MRONJ pathogenesis.

The inhibition of angiogenesis is not likely to be the central factor in MRONJ development because MRONJ has been shown to occur in the absence of angiogenesis inhibition. For instance, *in vitro* studies have shown that denosumab does not inhibit angiogenesis (52).

Diagnosis

Currently, the diagnosis of MRONJ based on clinical parameters alone. Findings during imaging are non-specific but may contribute to early detection and provide aid in surgical treatment planning. Histologic features are not specific for MRONJ among other osteonecrotic lesions. The relationship between blood tests and MRONJ has yet to be established.

Clinical presentation

The hallmark sign of MRONJ is exposed areas of bone that persists for greater than 8 weeks, despite appropriate management (53). These areas of exposed bone may remain asymptomatic for weeks, months, or years, and symptoms may not arise until the surrounding soft tissue becomes inflamed (53). Before osteonecrosis becomes clinically detectable, a patient may present with non-specific oral, dental, or soft tissue symptoms. Common intraoral findings include tooth mobility, non-healing ulcerations, and local bone or soft tissue infections (53). Some patients may experience paresthesia in the affected areas because of neurovascular compression from surrounding inflammation (53). Patients with orofacial pain may experience non-odontogenic tooth pain, dull aching mandibular bone pain that may radiate to the temporomandibular joint, and maxillary sinus pain (53). Chronic maxillary sinusitis secondary to osteonecrosis with or without oral antral fistula may be a presenting symptom in patients with maxillary bone involvement (53). Intraoral or extraoral fistulae may develop when necrotic bone becomes secondarily infected (53).

After reviewing patient symptoms, follow-up with a thorough medical history is required to distinguish a clinical picture of MRONJ. Investigations into initiating factors, patient-related factors, and medications-related factors can be used to determine which patients are at high risk. Excluding a history of radiation therapy and metastases to the jaws is crucial for diagnosis, especially because many candidates for MRONJ present with cancer.

The size and severity of lesions are classified by the AAOMS on a grading system from stage 0 to stage 3.

Imaging

The American Society of Clinical Oncology (ASCO) and Cancer Care Ontario recommends that a routine dental exam with radiographs and any pending dental problems be tended to before commencement of BPs (54). As a baseline, intraoral radiographs and a panoramic image should be taken (54). Intraoral and panoramic imaging are important tools for detecting dental disease and monitoring for osteonecrotic changes in the jaws. The presence of dental disease, such as periodontal and periapical disease, increases risk of MRONJ and should be detected early. Early stage MRONJ often show little abnormalities on plain radiographs because of a lack of decalcification, but non-specific findings may be present. CT is more sensitive to changes in bone density than plain radiographs and have an enhanced ability to detect early osteonecrotic changes. In descending order of prevalence, radiographic features of MRONJ include mixed lytic-sclerotic areas, osteolytic changes, osteosclerosis, cortical bone erosion, poorly healing or non-healing extraction socket, periodontal ligament widening, mandibular canal involvement, and thickening of the lamina dura (55). More progressed disease may also reveal periosteal reaction, sequestrum, pathological fracture, and density confluence of cortical and cancellous bone (55).

CT may be used to delineate ONJ lesions for surgical treatment planning, but imaging may underestimate the extent and severity of affected bone (53). CT is accurate for detecting changes in progressed MRONJ after bony destruction but has limited ability to detect early changes in bony architecture with early disease. As an adjunct for surgical treatment planning, fluorodeoxyglucose (FDG) positron emission tomography (PET) with CT may be used, which has shown to detect metabolic changes in ONJ before bone destruction that may not be detected with conventional plain film and CT imaging (56). FDG PET-CT may facilitate the decision between marginal versus segmental resection, depending on FDG uptake superior versus inferior to the mandibular canal (57).

Biopsy and pathology

The histopathological features of MRONJ does not provide a conclusive diagnosis distinguishing osteonecrosis from other causes, such as osteoradionecrosis and chronic osteomyelitis. Factors such as bone status (vital, necrotic, reactive), presence of osteoclasts, inflammation, vascularization, and presence of bacteria were not specific for MRONJ (58,59). Instead, histologic staining for *Actinomyces* species is a common finding among MRONJ lesions (58). In advanced stages, exposed bone may become secondarily infected and can involve surrounding soft tissue. Signs of secondary infection include purulent discharge from exposed bone and soft tissue erythema. In these cases, microbial culture may be used to guide antibiotic therapy in an attempt to resolve infection. Typically, microbial culture of exposed bone reveals normal oral microbes, but patients with extensive soft tissue involvement may show biofilms with bacteria in combination with fungi and viruses, which are difficult to treat without targeted therapy. If surgical intervention is chosen, biopsy of resected bone may be useful in ruling out other pathology, such as jaw metastases in cancer patients (60). Histologic analysis of resected bone margins may not correlate with clinical outcome because relevant prognostic factors have yet to be identified (60). Resected bone does not exhibit any unique physical properties that would lead to reliable MRONJ diagnosis.

Serum testing

CTX is released during type 1 collagen degradation, and serum levels are used as a biomarker for bone turnover (61). Antiresorptives lead to lower CTX levels, and Marx *et al.* previously proposed that fasting CTX levels below 150 pg/mL suggests oversuppression of bone turnover, which may serve as a prognostic factor for MRONJ risk (62). However, this strategy has not been supported by the literature, and CTX <150 pg/mL is not associated with an increased prevalence of MRONJ (61).

Management

Prevention before therapy

Prior to commencement of antiresorptive and/or antiangiogenic therapy, the patient should be informed that these medications are associated with a low incidence of MRONJ. Risk can increase if the appropriate measures are

not taken by patients and health care providers. MRONJ may be prevented by limiting patient related factors, initiation factors, and medication related factors.

Patients should be counselled to minimize modifiable risk factors for MRONJ, such as poor oral hygiene, smoking, and uncontrolled diabetes mellitus (11). Preventive measures before the onset of treatment and regular follow-up every 3 months have shown to significantly reduce the incidence of MRONJ (63).

If the underlying condition permits, commencement of medications should be delayed until appropriate dental treatment is rendered, such as scaling, restoring caries, controlling periodontal and periapical disease, extracting non-restorable and/or hopeless teeth, relining ill-fitting dentures, and possible removal of bony tori. Controlling dental disease before therapy will reduce the risk for MRONJ and minimize the need for extractions during therapy. Ideally, all extractions should take place before therapy, and medications should be suspended until adequate mucosal healing at 45–60 days (11). Removable dentures should be inspected for sore spots or areas of mucosal trauma, especially along the lingual flange, and relined if necessary (5). Prophylactic excision of bony prominences, such as exostoses or tori, may play a role in decreasing the risk of MRONJ (7). The choice to excise should be determined case-by-case and is based on the extent of surgery required, the frequency of traumatizing bony prominences, and the thinness of overlying mucosa.

In regard to medication-related triggers of ONJ, health care providers should be aware of the following updates to clinical guidelines. ASCO demonstrated that there was no difference in skeletal related events when patients with metastatic breast cancer were treated with 4 mg of IV zoledronate every 3–4 weeks or every 12 weeks (64). Thus, a longer dosing should be considered, when possible, to avoid an increased risk of MRONJ from more frequent exposure. Also, the Food and Drug Administration (FDA) demonstrated little benefit to IV zoledronate or oral alendronate use beyond 3 or 5 years, respectively, in the post-menopausal osteoporosis population who do not have a high risk of fracture (65,66). Specifically, there was no difference in bone mineral density or fracture incidence in osteoporosis patients who continued BP therapy past 3–5 years when compared to placebo (65,66). Therefore, discontinuation of BP therapy after 3–5 years should be considered, when possible, to decrease the risk for MRONJ from long-term use.

Prevention during/after therapy

During antiresorptive and/or antiangiogenic therapy, conservative dental treatments are recommended, such as scaling, restorative, and endodontic treatment, in order to maintain good oral health (11). Orthodontic treatment is possible, but longer treatment times and poor tooth movement should be expected because of decreased bone remodeling from antiresorptive therapy (67). Adjustments to removable prostheses should be made if compression to soft tissue is present, and fixed prostheses should be planned with supragingival margins to facilitate oral hygiene (11).

Additional considerations should be taken for invasive procedures that involve manipulation of alveolar bone. Elective dentoalveolar surgery, such as implant and mucogingival surgery, should be avoided, but surgery is indicated if aimed at eliminating infection that cannot otherwise be resolved (11). Withholding antiresorptives and/or antiangiogenics prior and after dentoalveolar surgery (drug holiday) may be considered. Drug holidays are typically initiated 1 week prior to an invasive procedure (except bevacizumab), and drug resumption occurs 4–6 weeks after or until adequate mucosal healing (11). The use of drug holidays for BPs is controversial, and the current ASCO guidelines state that there is insufficient evidence to support or refute its use, considering its long half-life (68). It is thought that withdrawal of BPs decrease localization to the extraction site to prevent BP antiangiogenic effects to promote wound healing (11). However, since BPs remain in the bone for years after termination of therapy, a drug holiday may be ineffective (69).

For denosumab prescribed for osteoporosis, the dosing schedule includes a 6-month latency, wherein invasive procedures may be performed, thereby avoiding the need for a drug holiday. Invasive procedures should be performed 4 weeks after the last injection of denosumab, beyond its half-life, and no later than 6 weeks before the next injection (11). For denosumab prescribed in cancer patients with a 1-month dosing schedule, the provider must decide if the benefits outweigh the risks for a drug holiday. A drug holiday may be beneficial in preventing MRONJ because of the short half-life, but denosumab has shown an increased rate in progression-free survival compared with BP in cancer patients (69). Currently, there are no studies that show drug holiday for denosumab has any effect in preventing MRONJ (69).

Bevacizumab should be suspended for 6–7 weeks before an invasive procedure because of its increased risk for

wound healing complications (70). Bevacizumab may be resumed 4–6 weeks after surgery, and other antiangiogenics, like sunitinib and everolimus, may follow the typical course for drug holidays (11).

There are limitations in studying the effectiveness of drug holidays because MRONJ has a low incidence and there is a great variation within patients, impairing the ability to conduct high quality studies. If a drug holiday is chosen, this decision must be agreed upon with the prescribing physician and must be in the best interest and safety of the patient.

Other preventive measures for dentoalveolar surgery in high-risk patients include antibiotic prophylaxis and applying autologous platelet concentrates. In invasive procedures, peri-operative antibiotics have shown to have a protective effect against MRONJ by mitigating infection (71). Penicillin, tetracyclines, and metronidazole have shown a moderate effect for MRONJ prevention (71). Platelet concentrates are commonly used in regenerative procedures in dentistry to promote soft tissue wound healing, but its use in preventing MRONJ at extraction sites is not established. There is no significant difference between using or forgoing platelet concentrates to prevent MRONJ after extraction, but its use has not shown to be detrimental (72).

Treatment of MRONJ

The treatment goals for MRONJ include (I) preventing the spread of MRONJ or new sites of necrosis; (II) preserving quality of life by relieving symptoms of pain and controlling infection; (III) educating the patient about the importance of oral hygiene and follow-ups with the dentist (53). Treatment depends on the severity of MRONJ lesion, and AAOMS recommends a graded approach. Generally, treatment is divided into conservative and aggressive therapy. Conservative therapy comprises of good oral hygiene, antimicrobial mouth rinses, systemic antibiotics, and limited debridement (68). Aggressive therapy includes surgical intervention, such as mucosal flap elevation, resection of necrotic bone, and soft tissue closure (68).

Regardless of stage of disease, removal of necrotic bone and loose sequestrae should be considered to relieve source of soft tissue irritation (1). Moreover, extraction of symptomatic teeth within exposed, necrotic bone does not appear to exacerbate the established necrotic process and should be considered to preserve quality of life (1). Stage 0 patients should be informed that there is approximatively 50% chance of progression to stage 1, 2, or 3 and appropriate conservative measures should be taken (73). Conservative measures are the first choice in MRONJ therapy and are effective for stages 0 and 1 (74). However, this approach in stage 2 and 3 most often provides symptomatic relief and may not lead to complete resolution (75). Approximatively less than 20% to above 50% of MRONJ lesions resolve via conservative management (75). Aggressive therapy is a more curative option but is only indicated in severe MRONJ with pathological fracture, extensive osteolysis, and extraoral and/or intraoral fistula (76). Aggressive therapy is also indicated in symptomatic MRONJ refractory to conservative measures (76). A 90% success rate has been reported in MRONJ managed via surgical resection (77).

Aggressive therapy is more predictable in early stage MRONJ because complete resection of necrotic bone is possible without injury to adjacent anatomical structures (76). It is thought that necrotic bone has no ability to revitalize and acts as a nidus for infection and further progression (78). Therefore, the rationale of removal of necrotic bone in stage 1 or 2 MRONJ is to promote complete healing without local infection and improve quality of life (78). Giudice *et al.* prospective cohort has shown high success in lesion downstaging and mucosal healing with stage 1 and 2 surgical intervention (78). Also, El-Rabbany *et al.* systematic review and meta-analysis compares surgical versus medical therapy for MRONJ, which demonstrates better resolution with lower rates of relapse in the surgery group (79). Nevertheless, the decision for early surgery should be balanced by patient health status and compliance. A patient may be a greater candidate for conservative therapy with increased compliance for keeping the affected area clean and attending follow-up appointments.

Later stage MRONJ patients suffer higher morbidity because of the size of resection required, which may lead to anesthesia or paresthesia of the mandibular nerve, discontinuity of the mandible, and/or hemimaxillectomy (76). In larger defects, reconstruction techniques include local and free flaps. Pedicled buccal fat pad flaps have a very rich vascular supply and have shown reasonable success in oral mucosa reconstruction in defects up to 62 mm × 18 mm (80). These local flaps demonstrate no severe donor site morbidity and high aesthetics because of good color match to adjacent oral mucosa (80). Free flaps with microvascular reconstruction may be used to address larger defects. Caution should be taken when using autogenous grafts in cancer patients with bone malignancy because the

possibility of transferring cancer cells to the oral cavity (81). Studies have yet to assess this risk, but reports from case studies have demonstrated that free flaps have over 96% success rate in MRONJ reconstruction (82). Fibular grafts are favoured in cancer patients because the fibula has a low incidence of primary bone malignancy or metastatic bone disease (60). Typically, grafts from the iliac crest and scapula are preferred for oral reconstruction because of rich bone marrow, but they are more commonly affected by malignancy (60). A PET scan or bone scintigraphy may be used to assess donor site viability and to rule out cancer (60).

An additional consideration for cancer patients is that bone morphogenic proteins are contraindicated because they promote cancer development, which limits their use in reconstruction (83). For patients without a history of bone malignancy, case reports have shown preliminary results supporting the use of bone morphogenic proteins for reconstruction in severe MRONJ (84).

Emerging therapies for MRONJ

Other emerging therapies have limited data demonstrating a potential benefit and none are considered a standard approach as of today.

Teriparatide has been FDA approved for treatment of osteoporotic patients without cancer or prior radiation to bone (41). For its ability to stimulate bone remodelling, teriparatide has been suggested as treatment for MRONJ refractory to conventional conservative measures prior to pursuing surgical intervention. A small randomized trial studying patients with MRONJ secondary to osteoporosis or bone malignancy showed a significantly greater rate of resolution in patients supplemented with teriparatide compared to conservative measures alone (85). This study found no incidence of new malignancy or worsening of pre-existing malignancy after 8 weeks of intermittent, low dose teriparatide treatment (85). However, this study was underpowered and follow-up was insufficient to properly characterize these safety endpoints. Teriparatide has shown an increased rate of osteosarcoma in preclinical trials, but post-marketing surveillance has yet to demonstrate a relationship between osteosarcoma and teriparatide in humans (85). Its use remains controversial and further studies are required.

Statins are 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors typically used for hyperlipidemia but have also shown angiogenic, immunomodulatory, and antibacterial properties (86). Adachi *et al.* propose that Statins may play a role in the prevention of MRONJ. In rats at high risk for MRONJ, a single local injection of Fluvastatin into the socket following extraction significantly prevented MRONJ development (86). Further studies are required to assess its effects in humans.

Summary

The patients at highest risk for MRONJ are those treated with antiresorptives at an oncologic dose after dentoalveolar surgery. Diagnosis is primarily based on clinical factors, but imaging may help determine sites of oral disease at high risk of MRONJ and the extent of an MRONJ lesion for surgical treatment planning. MRONJ may be prevented by treating oral disease before initiation of antiresorptive therapy and avoiding dentoalveolar surgery during/after antiresorptive therapy. MRONJ lesions should be managed conservatively in stage 0 and 1 but treated surgically in stage 2 and 3.

Among these findings, there are many emerging risk factors, strategies for diagnosis, and treatment methods. A major limitation of MRONJ research is that it is a rare clinical entity and studies are typically underpowered to observe a significant result. Therefore, large scale studies are required in the future to observe new ways to characterize patient risk, detect disease early, and treat appropriately based on severity. Through this research, providers are able to use the most up-to-date information to advance clinical care for MRONJ patients.

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Footnote

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