The effects of osteoclast modifiers on the oral cavity: a review for prescribers

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Purpose of review
Osteonecrosis of the jaw associated with therapeutic osteoclast modifiers is a rare but serious event. The consequences of osteonecrosis can be devastating despite current treatment. With the increase in diversity of agents and significant increase in the prevalence of osteoclast modifiers prescribed by oncologists understanding diagnosis and management of osteoclast modifiers-related osteonecrosis of the jaws (OMRONJ) is necessary. The risk of osteonecrosis when osteoclast modifiers are used for management of osteoporosis is much less than osteoclast modifiers used in the oncology setting. A basic understanding of the oral exam and current management will lead to more effective communication and more effective prevention of devastating OMRONJ.

Recent findings
An indistinguishable rate of ONJ seen with new therapeutic agents is becoming apparent and relevant preventive therapy and counseling of the patient is indicated. Currently there is no comprehensive clinical guideline that unifies oncologists and oral health providers in the prevention and management of OMRONJ.

Summary
Communication and proper planning with each patient's provider is the most effective strategy to prevent OMRONJ. A team composed of an oncologist, oral and maxillofacial surgeon and dentist competent in managing this condition is necessary. An understanding of the cause and development of OMRONJ can give the prescriber an improved perspective to communicate with oral health professional colleagues. Current guidelines emphasize the need for dental management prior to the use of osteoclast modifiers for the prevention and management of osteonecrosis of the jaw.

Keywords
bisphosphonates, denosumab, osteoclast modifiers-related osteonecrosis of the jaws, osteonecrosis of the jaws, RANKL inhibitor

INTRODUCTION

Osteoclast modifier-related osteonecrosis of the jaws (OMRONJ) and secondary bacterial bone infection have been reported as adverse effects of osteoclast modifier treatment, most commonly associated with the intravenously administered bisphosphonates [1] and more recently with denosumab and is correlated with the total dose, duration and potency of osteoclast modifier [2]. Approximately two-thirds of cases are identified following dental extractions [3], although OMRONJ can develop after progressive periodontal disease, denture trauma and idiopathically in some cases. Severe cases can progress to pathologic fracture of the jaw and orocutaneous fistula. Comorbid risk factors have been suggested to include tobacco use, diabetes, concurrent immunosuppressive therapy, medications with antiangiogenic effects, and ongoing cancer chemotherapy therapy [4]. The proposed mechanisms of action include hypercoagulability, fat emboli of small blood vessels and increased intrabony pressure due to hypertrophic lipid cells leading to mechanical obstruction of the blood flow [5]. OMRONJ may be asymptomatic and therefore

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may be under-reported in the literature and even when symptomatic, complaints may mimic more common dental or periodontal problems, presenting with discomfort, rough exposed bone, mobile teeth, pain and purulent discharge. As these are primarily oral complaints patients may not report these to medical providers, and the lesions commonly arise in difficult to visualize areas without dental equipment and excellent lighting.

BACKGROUND

The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines bisphosphonate-osteonecrosis of the jaw (BONJ) as current or previous treatment with bisphosphonates, exposed bone for more than 8 weeks and no history of radiation to the jaws. Although this is a nonspecific definition it does differentiate between commonly misdiagnosed conditions and BONJ including osteoradionecrosis (ORN) and trauma. AAOMS suggests a general staging of BONJ. The risk of developing BONJ is increased if bisphosphonates were taken for more than 3 years and in the presence of comorbidities such as corticosteroid use [6].

General guidelines have been developed for the prevention and care of patients prescribed osteoclast modifier [7–9]. It is strongly recommend that all patients, who are being considered for osteoclast modifier treatment, and those already undergoing treatment, should receive a thorough dental assessment and appropriate preventive management prior to initiation of these agents [6]. Few studies have assessed outcomes of intervention, and new approaches to therapy are needed [10–12].

Denosumab, a RANK-ligand (RANKL) inhibitor, is a viable alternative to bisphosphonates in the prevention of skeletal-related events (SRE) in solid tumor malignant diseases and possibly osteoporosis patients. There is no evidence of drug recycling with RANKL inhibitors, which could reverse adverse effects with cessation of the medication. Denosumab may be a preferred therapy to bisphosphonates in some cancer patients, although it is not without significant adverse effects. Despite large phase III studies there are limited data to elucidate the risk of osteonecrosis or impaired bone healing associated with bone manipulation [13]. Therefore it is imperative for providers to understand the effects of osteoclast modifier on bone metabolism, prevention, diagnosis and management and how it should affect treatment decisions.

Bisphosphonates and denosumab share the same physiological end target, the inhibition of the function of osteoclasts with decreased bone turnover in order to maintain bone mineral density. A major difference between denosumab and bisphosphonates relative to the osteoclast is that bisphosphonates are internalized to act upon cells, whereas denosumab acts extracellularly [14▪]. As such, bisphosphonates must be present in the circulation and available for re-uptake into bone for prolonged periods in order to function [14▪]. This recycling of bisphosphonates back onto bone mineral surfaces has been proposed as a reason for the long duration of action of bisphosphonates [15]. This helps to explain why the effects of bisphosphonates are less rapidly reversible after stopping treatment than those of denosumab [14▪]. Another way in which denosumab differs from bisphosphonates is its distribution in bone [14▪]. As denosumab is an antibody, this agent is capable of distributing throughout the extravascular space [14▪]. In particular, there is no evidence of sustained binding of denosumab to bone surfaces [14▪]. Denosumab is primarily a circulating soluble protein [14▪], which may lead to more profound inhibition of bone remodeling than that seen with bisphosphonates [14▪]. The strong affinity of bisphosphonates for hydroxyapatite and bone mineral may limit their even distribution throughout the skeleton, particularly to sites deep within the bone and into alveolar bone [14▪]. However, bisphosphonates with lower affinity for bone mineral appear to penetrate deeper into the network in other research studies [16▪]. A phase I study conducted in postmenopausal women has shown that a single subcutaneous administration of denosumab was able to reduce bone resorption within 12 h in a dose dependent manner [9]. Compared with alendronate therapy, denosumab treatment results in greater gains in bone mineral density after 1 year at all sites, including cortical bone sites [14▪]. As denosumab is a circulating antibody, it is expected to reach all sites within bone, including intracortical sites, which may not occur with bisphosphonates [14▪]. The effects of denosumab on bone turnover are quickly reversible with discontinuation, which can lead to a transient rebound phenomenon, and can be restored with subsequent retreatment [14▪]. However, the speed of offset of action of bisphosphonates varies depending on their chemical structure, dose, and frequency of administration [14▪].

The absolute incidence of OMRONJ remains unclear, but the incidence of BONJ associated with intravenous bisphosphonates is almost 100-fold greater than that associated with oral bisphosphonates [17▪]. The severity of OMRONJ does seem to be related to potency of medication. The incidence of OMRONJ refractory to conservative measures is significantly higher in patients taking IV forms of osteoclast modifiers [18].

The overall risk of developing OMRONJ for patients being treated for low bone mass with oral bisphosphonates is estimated to be 0.1% [19,20▪], whereas the incidence associated with IV bisphosphonates is 7% [19].

A comprehensive review of BONJ data from 2003 to 2010 by Kuhl revealed that surgery was indicated in 59.7% of patients with BONJ. Resolution or improvement of BONJ was found to be at a rate of 78.4% [20▪]. Of the remaining patients, who were treated with conservative therapy 69% showed improvement or resolution of lesions [20▪].

PREVENTION

Prevention of an osteonecrotic event is possible with appropriate treatment planning, communication, and prophylactic therapy. Prescribers must understand the risks and benefits of all medications prescribed and adequately educate their patients. The patient must understand the potential risk of taking a medication that affects bone metabolism.

As a prescriber, a brief oral exam can grossly elucidate high-risk patients for an osteonecrotic event when taking bisphosphonate or RANKL inhibitors. Extraction of teeth for patients taking medications that effect bone metabolism is the highest risk event that leads to osteonecrosis. The exam can be quickly performed in three brief steps to assess risk of future extraction of teeth. A quick oral health history can be determined by asking if the patient has had any teeth extracted in the last year as well as a history or presence of any dental pain. A brief extraoral exam consists of looking for any asymmetries, swelling, or pain upon palpation. Intraorally broken teeth, multiple missing teeth, large dark holes in teeth would be present in high-risk patients. Loose dentures can cause trauma and remodeling of the alveolar bone. Although a brief exam will allow a determination of risk this is not sufficient to identify risk sites, which requires a complete dental, periodontal and radiographic examination and must be done by a dentist, who is familiar with this process as pain and gross deterioration are not the only risk factors for future tooth extraction.

Counseling and a brief oral exam is important, a referral to a competent dentist in the prevention and management of OMRONJ is necessary. It is important that the referred dentist have adequate time to evaluate the patient prior to the initiation of therapy, if possible. Communication with prescriber and dentist must include the initiation of therapy, dosage, anticipated length of treatment and condition being managed by osteoclastic modifiers. Upon referral the dentist will perform a thorough evaluation including necessary radiographic evaluation and develop a risk stratification for the patient. In high-risk patients prophylactic extraction of teeth may be recommended.

It is necessary that sites of oral infection and sites that may require surgical care be definitively managed prior to or early in the use of osteoclast modifier. This includes dental infection, periodontal diseases, at risk partially erupted third molars, and teeth with advanced dental caries should be extracted in many cases. These decisions may not be made by dental providers who not familiar with oncology care and specifically with osteoclast modifier. If surgery is planned following a few treatment doses of osteoclast modifier this should be expertly delivered, minimally traumatic surgery. Dental prevention including caries prevention protocols, regularly scheduled periodontal cleaning and atraumatic prostheses should be provided. Establishing an ongoing reinforcement of preventive care to prevent advancement of dental disease is paramount.

MANAGEMENT

Management OMRONJ has adapted significantly since the first case was described in 2003. Understanding the pathogenesis of the condition had led to development of treatment protocols. If any team member discovers exposed bone in the oral cavity or new onset pain as described by the patient, a high suspicion of osteonecrosis of the jaws (ONJ) is necessary. OMRONJ will typically present as an area of alveolus with exposed bone with or without pain. The inner aspect of the posterior mandible is the most common location for exposed bone. The exposed bone is typically necrotic and therefore will have no soft tissue coverage. Secondary infections are common as well leading to pain, erythema, suppuration, and halitosis. Supportive measures include surgical and nonsurgical modalities. Supportive measures of patients with exposed bone include 0.12% chlorhexidine rinse every 8 h. Along with PO amoxicillin, 500 mg q 8 h to treat the secondary infection. In some cases, direct trauma from prosthesis may be the stimulus and can be adjusted to relieve the area of necrosis. The potential role of hyperbaric oxygen (HBO) in the management of OMRONJ is currently not known, although studies are ongoing [21]. In ORN, HBO has been shown to have utility in management in multiple studies, although a recent meta-analysis did not show clinical utility [22]. A large study suggests a management of 20 dives prior to surgical intervention followed by 10 postoperative dives [23▪]. The significant cost and patient hardship must be evaluated.

OMRONJ is essentially a medically managed condition, surgical treatment may be necessary in progressive and symptomatic lesions that have not responded to nonsurgical therapy. Conservative debridement can lead to resolution of exposed bone by dental professionals familiar with OMRONJ management. Surgery may be directed to removal of sequestrated bone and soft tissue coverage will be necessary [24▪]. It is recommended that all patients undergoing oral and maxillofacial surgery the patient should rinse with chlorohexidine every 12 h until wound healing is complete [24▪]. As with any osteonecrotic condition resection is sometimes necessary to excise significant portions of necrotic bone, but only after conservative measures have been attempted.

The reality is that many patients are placed on osteoclast modifiers for a many years and will at some time need teeth extractions. In these cases the treatment planning must begin with a thorough exam and consent of the risks of treatment. There is little evidence that suggests that the risk of OMRONJ changes after a patient has been on osteoclast modifier for greater than 2 years. The use of laboratory measures to indicate risk of necrosis has not been proven to be diagnositic but may be used as possible adjuvant tests, including C-telopeptide [24▪,25,26], NTx, parathyroid hormone, and 1,25-dihydroxy vitamin D [27▪]. There is no definitive evidence that a 'drug holiday' is beneficial in bisphosphonate-associated osteonecorsis, it is possible that this may be valuable with the use of denosumab wherein reversible effects have been described [24▪,27▪]. Guidelines currently do not recommend discontinuing bisphosphonates, based upon the long half-life in bone [24▪]. A drug holiday of bisphosphonates when used to treat osteoporosis may see a benefit, although it is not recommended to stop bisphosphonates in cancer patients [24▪,28]. Initial studies that show no change in outcome, if bisphosphonates are stopped [28]. Although there are no studies of the potential impact of discontinuing denosumab, the short half-life suggests this strategy may contribute to bone remodelling and healing. Even in the case of denosumab, the risk of drug holiday and medical morbidities associated are not always more significant than the risk of OMRONJ and current data is severely limited.

DISCUSSION

As more high-level evidence emerges, the relative risk of OMRONJ will allow the development of an appropriate risk management protocol. Current evidence discloses a possible increase in relative risk of DONJ as compared with BONJ. However, the potential for reversal of risk with discontinuing therapy suggests that in the case of denosumab, discontinuing therapy while managing bony lesions may become a part of patient management. Contemporary literature supports the practice of prophylactic dental treatment for patients taking RANKL inhibitors as is currently the standard of care for patients receiving bisphosphonates [29]. Therefore any patient taking medications that modulate bone healing should be assessed for potential risk of the development of ONJ until alternative guidelines are developed.

If any procedure involving bone in the oral cavity is planned, consideration for discontinuing denosumab may be reasonable, based upon current understanding of mechanisms of densoumab action, although the evidence for cessation of bisphosphonates is weak. If a necrotic area is seen this can be measured and staged using criteria for BON and initiation of chlorhexidine rinse with or without antibiotic depending upon presence of clinical infection, and mobilization of bony sequestrate. Consideration for discontinuing denosumab after evaluating medical risk may be appropriate.

CONCLUSION

Although the risk of an osteonecrotic events related to bone modifying agents is rare the morbidity is significant. Appropriate management therefore includes a team approach between the prescriber, dentist, and oral and maxillofacial surgeon. Prescribers should be aware of the strong guidance of the American Society of Clinical Oncology, who has stated that all patients with cancer prescribed zoledronic acid, pamidronate or denosumab receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude assessment.

Communication and prevention are the most important management strategies:

(1) Any drug that has effects on osteoclasts has the potential to cause osteonecrosis of the jaws.
(2) Patients taking RANKL inihibitors may benefit from a drug holiday more than patients taking bisphosphonates in the presence of osteonecrosis fo the jaw.
(3) A team approach is the key to preventing osteonecrosis of the jaw caused by chemotherapeutics.

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Conflicts of interest

None declared.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 408–410).

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