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Osteonecrosis of the Jaw: An Update and Review of Recommendations

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Key Words
Osteonecrosis · Maxilla · Mandible · Bisphosphonates · Oral health

Abstract
Bisphosphonates have had a very positive impact as therapeutic agents for cancer and osteoporosis, but have also been associated with osteonecrosis of the jaw (ONJ) which has emerged as an idiosyncratic oral complication. Bisphosphonate-associated ONJ has generated wide attention despite its considerably rare occurrence. Many speculations exist as to why bisphosphonates may increase the incidence of ONJ. The American Society for Bone and Mineral Research established a task force on bisphosphonate-associated ONJ and recently released a summary report of their findings. A case definition delineated a confirmed case of ONJ as 'an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region'. Treatment recommendations have been developed by the American Dental Association, the American Association of Oral and Maxillofacial Surgeons and the American Society for Bone and Mineral Research. Considering the scientific evidence, little is known about the true incidence and pathophysiology, and many questions persist. New epidemiologic studies are surfacing and attempts to ameliorate the condition may shed light on the likely complex etiology. The bones of the oral cavity provide a unique environment relative to blood flow, oral microbiota, bone structure and function. Although little is known of the mechanisms and course of ONJ, even less is known about the spectrum of issues of altered healing that could fall short of defined ONJ.

Introduction

Osteonecrosis of the jaw (ONJ) is a recently described condition that has been attributed to the use of bisphosphonates. In 2006–2007, the American Society for Bone and Mineral Research (ASBMR) organized a task force of experts including dental specialists, oncologists, endocrinologists, radiologists, epidemiologists and NIH representatives. A case definition for bisphosphonate-associated ONJ was established, as 'an area of exposed bone

Abbreviations used in this paper

AAOMS	American Association of Oral and Maxillofacial Surgeons
ADA	American Dental Association
ASBMR	American Society for Bone and Mineral Research
ONJ	osteonecrosis of the jaw

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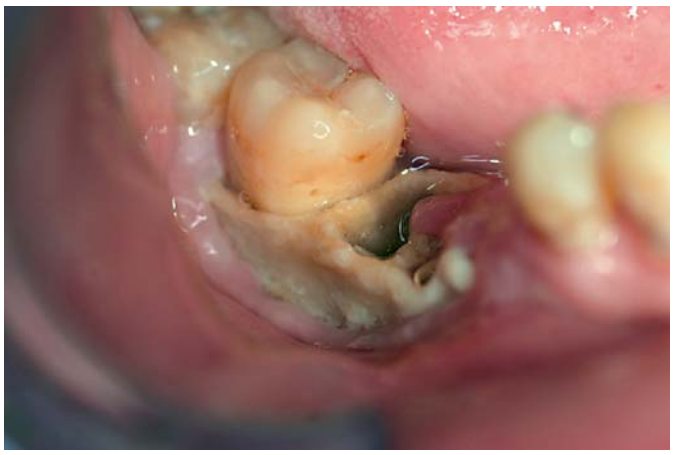

Fig. 1. ONJ in the posterior mandibular region of a 45-year-old male with metastatic renal cancer treated with Zometa over a period of 3 years. Eighteen months earlier, the patient had undergone extraction of the first molar tooth.

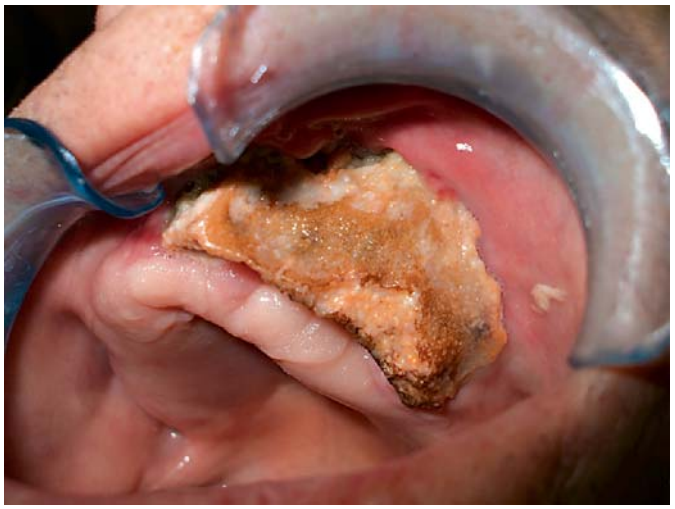

Fig. 2. Spontaneously occurring ONJ lesion in a 78-year-old male with metastatic prostate cancer treated with Zometa over a period of 5 years.

in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region' [Khosla et al., 2007]. A suspected case has the same qualifications but is present for less than 8 weeks. Having an established definition of ONJ is very important, as there was no consensus on the definition before, which hindered the reporting and determination of the incidence of ONJ.

The incidence of ONJ has been estimated from a variety of sources and has been complexed by the lack of a case definition and established research studies. Nearly all publications through the end of 2007 on this topic were case reports, editorials and reviews. A simple Medline search using the terms 'osteonecrosis' and 'jaw' reveals more than 500 articles with nearly two thirds of these articles published in the past 4 years. The ASBMR task force estimated incidence, based on publications and pharmaceutical company reports, to be between 1 and 10% of patients taking intravenous bisphosphonates for the treatment of cancer and less than 1% in patients with osteoporosis or Paget's disease [Khosla et al., 2007].

Most studies indicate that oral trauma is a precipitating factor for ONJ with many cases involving a history of tooth extraction or oral surgical procedures preceding the development of ONJ (fig. 1). Fewer cases are reported as 'spontaneous' (fig. 2), but it is often difficult to discern if trauma has preceded the lesions since the oral cavity is lined with thin mucosa that is easily traumatized during function.

Why the Jaw?

The condition of bisphosphonate-associated ONJ appears to be isolated to the bones of the oral cavity with one exception [Polizzotto et al., 2006]. Osteonecrosis can occur in skeletal sites such as the hip and knee where it is described as avascular osteonecrosis, but to date, patients taking bisphosphonates have not been prone to osteonecrosis in these regions, suggesting a different etiology exists at different skeletal sites. The incidence of inflammatory conditions, osteomyelitis, and surgical procedures to the jaw and facial bones is increased in patients on intravenous bisphosphonates [Wilkinson et al., 2007]. This has been used as evidence that these patients are more prone to unique oral complications of bisphosphonates. Many speculations exist regarding why the jaw is the target site of bisphosphonate-associated osteonecrosis.

Embryologic Origins

The mandible and maxilla, the 2 bones that make up the jaw, both develop via intramembranous bone formation. The maxilla and mandible are embryologically derived from pharyngeal arch 1. During development, neural crest cells migrate into and fill the arch with mesenchyme [Ravanelli and Klingensmith, 2006]. The only reported case of bisphosphonate-associated osteonecrosis that did not occur in the oral cavity was identified in

a 64-year-old male with multiple myeloma. In addition to ONJ after tooth extraction, the patient presented with osteonecrosis of the external auditory canal, which resulted in nonhealing ulceration following surgical correction [Polizzotto et al., 2006]. The linings of the external auditory canal derive from pharyngeal pouch 1/cleft 1 and the bones of the ear, with the exception of the malleus, derive from pharyngeal arch 2. In addition to the maxilla and mandible, the temporal and zygomatic bones derive from the pharyngeal arch 1 and compose the membranous viscerocranium. There are no known reports of osteonecrosis affecting the temporal or zygomatic bones, nor other bones that form from intramembranous bone formation and make up the cranium such as the parietal or occipital bones.

Bone Turnover

Bisphosphonates are potent antiresorptive agents that impact bone turnover via their inhibition of osteoclasts, and hence have the potential to affect osseous healing. Outside the oral cavity, many studies have addressed this question relative to fracture healing. Most clinical studies indicate that patients on bisphosphonates heal normally following traumatic fracture [McDonald et al., 2007]. In experimental models, the callus apparently forms normally, but is not remodeled to the same extent as in the absence of a bisphosphonate [McDonald et al., 2007]. Studies show that the callus is larger and that the biomechanical strength is improved. Continuous dosing with bisphosphonates can delay callus remodeling and leave an irregular woven bone callus versus a lamellar bone callus.

The question arises whether bisphosphonate inhibition of bone turnover could predispose bisphosphonate patients to ONJ at sites of oral trauma. In the oral cavity, a scenario similar to fracture healing might be an extraction site filled with woven bone that does not remodel into mature trabecular bone with a cortical shell at the interface of the mucosa. There is a clear need for studies of healing of extraction sites after tooth extraction in the presence of bisphosphonate therapy. Reports of biopsy material from ONJ lesions have indicated that osteoclasts are present in these lesions, but the extent of their function is unclear [Hansen et al., 2007].

If an inhibition of bone turnover is critical for ONJ and bisphosphonate use is associated with osteonecrosis (found only in the jaw), then a distinctive effect of bisphosphonates should be present regarding bone turnover in the oral cavity. For example, do bisphosphonates preferentially sequester in the bones of the jaw? This is not clear, but reports in the literature often suggest that bone turnover in the jaw is greater than in other skeletal sites. Since bisphosphonates are incorporated at active turnover sites, this would set up a scenario of increased bisphosphonate levels in the bones of the jaw. Studies to support this phenomenon are needed. Further, caution should be exerted in the interpretation of reports that indicate the jaw is a site of increased bone turnover. The mandible (a site of ONJ predilection) consists of dense cortical and trabecular bone that has a higher ratio of cortical/trabecular bone than that of the vertebrae. Bone turnover rates at the angle of the mandible (a cortical site) are very different than the alveolar cortical bone. Most studies indicate higher turnover rates at the alveolar bone, likely due to the mechanical influence of the teeth in the alveolus [Huja et al., 2006]. However, ONJ is not necessarily a tooth-associated disorder and often affects the mandibular lingual cortical plate. It would be valuable to have well-designed studies of bone turnover in various sites of the mandible along with levels of bisphosphonates in those sites and to correlate these findings with the incidence of ONJ.

That the inhibition of bone turnover is critical for ONJ is the basis of recent recommendations to screen patients' serum bone resorptive markers as an index of ONJ risk [Marx et al., 2007]. There is not yet scientific evidence to support this recommendation. It is not clear how accurate such serum bone resorptive markers are and whether their systemic measurement reflects what is occurring at the local environment.

In support of a role for inhibition of osteoclastic remodeling in the pathogenesis of ONJ are patients with genetic osteoclast defects where reports of increased incidence of oral infection and osteomyelitis are common [Junquera et al., 2005]. In the case of chloride channel mutations, a recent report indicated nearly 16% of patients experienced osteomyelitis in the oral cavity [Waguespack et al., 2007]. Although this is not ONJ, it illustrates that compromised remodeling is associated with oral complications. Such compromises may be associated with an increased risk for ONJ.

Angiogenesis

Bisphosphonates are reported to be antiangiogenic agents [Conte and Coleman, 2004] and as such could compromise vascular support at an extraction site, predisposing it to necrosis. Again, for this to be a key factor in the predilection of ONJ would dictate that angiogenesis is different in the bones of the jaw and/or more selectively targeted than other bones. Studies of angiogenesis are lacking, but reduced blood flow to the jaw compared

Table 1. Risk factors for ONJ

ADA	AAOMS	ASBMR
Drug related: – Intravenous bisphosphonate therapy – Prolonged use of oral bisphosphonates – Concomitant use of estrogen or glucocorticoids – Chemotherapeutic drugs	Drug related: – Potency of the particular bisphosphonate [zoledronate (Zometa) > pamidronate (Aredia) > oral bisphosphonates] – Longer duration of oral bisphosphonate therapy (>3 years) – Corticosteroid therapy – Chemotherapeutic agents	Drug related: – Intravenous bisphosphonate therapy – Duration of exposure to bisphosphonate treatment (oral bisphosphonates >3 years) – Glucocorticoids – Anticancer therapy
Local: – Dental procedures that traumatize bone, such as dental extractions – Tori and other bony exostoses – Trauma from dentures – Periodontitis – Presence of oral infection – Poor oral health – History of radiation therapy – Presence of myeloma or metastatic cancer at the osteonecrosis site	Local: – Dentoalveolar surgery (extractions, dental implant placement, periapical surgery, periodontal surgery involving osseous injury) – 2:1 incidence in mandible vs. maxilla – Areas with thin mucosa overlying bony prominences (tori, bony exostoses, and the mylohyoid ridge) – Concomitant oral disease – Poor oral hygiene – Alcohol and/or tobacco abuse	Local: – Dental extraction – Oral bone manipulating surgery – Intraoral trauma – Poor fitting dental appliances – Preexisting dental or periodontal disease – Alcohol and/or tobacco abuse
Demographic and systemic: – Older than 65 years old – Cancer • Multiple myeloma and cancer metastatic to bone (breast, lung and prostate > other cancers) • Tumor burden and stage • Extent of skeletal involvement • History of stem cell transplantation – Diabetes – Degree of immunosuppression	Demographic and systemic: – Increased age – Race: Caucasian – Cancer diagnosis: multiple myeloma > breast cancer > other cancers – Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis – Diabetes	Demographic and systemic: – Comorbid conditions (i.e. malignancy) – Cancer

to other skeletal sites does not appear to be a prevailing issue. One of the recent oral pathology studies indicated that vessel obliteration was not a common finding in ONJ biopsies [Hansen et al., 2007]. Furthermore, one putative bisphosphonate target for inhibiting angiogenesis, soluble vascular endothelial growth factor receptor 1, was unchanged in the serum of patients with ONJ [Alonci et al., 2007]. Further studies evaluating the vascular response in the jaw and/or investigating the impact of other antiangiogenic agents on the bones of the oral cavity would be beneficial to garner more information.

Microbiology

The unique microbiota of the oral cavity is an important factor for consideration in ONJ. All ONJ cases in the literature have an oral portal of the lesion. Often, extraoral fistulas are present, but this is not the initial presentation nor the actual ONJ lesion. Biopsies of ONJ lesions routinely report the presence of oral microflora [Hansen et al., 2007]. However, as the oral cavity is not an aseptic environment, biopsies of any lesions would likely yield oral bacteria and hence their role as an etiologic agent versus a bystander needs to be determined. There is a trend in the literature for a high incidence of oral disease (for example, periodontal and/or endodontic) in patients who develop ONJ [Marx et al., 2005] and some lesions respond to antibiotic therapy.

Metastasis

A disturbing case report was recently presented in the literature where jaw resections were performed in 2 patients with nonresponsive ONJ lesions. Tumor cells were found in noncontiguous areas of the tissue [Bedogni et al., 2007]. Solid tumor metastasis to the jaws is not frequent but does occur at an incidence of 1% [Keller and Gunderson, 1987]. Interestingly, it is more likely to present in the mandible and often in patients with multiple myeloma [Lambertenghi-Deliliers et al., 1988; D'Silva et al., 2006]. Whether this is associated as a contributing factor to ONJ is unknown.

Table 2. Recommendations for patient care prior to initiating bisphosphonate therapy

ADA	AAOMS	ASBMR
Comprehensive oral evaluation recommended	Thorough oral examination recommended	Dental examination recommended for patients starting intravenous bisphosphonates for bone metastases, not necessary for patients initiating oral bisphosphonates for osteoporosis, nonmalignant bone diseases
Patient education: – Very low risk (estimated 0.7 cases per 100,000 person-years' exposure) of developing ONJ associated with oral bisphosphonate therapy – Good oral hygiene, regular dental care best way to lower the risk – Risk may be minimized but not eliminated – No diagnostic techniques to identify individuals at increased risk – Provide information about the early signs of development of ONJ – Contact dentist concerning any oral problems – Encourage to consult with treating physician about any health risks	Patient education: – Importance of dental hygiene and regular dental evaluations – Instruction to report any pain, swelling or exposed bone	Patient education: – Very low risk of developing ONJ with routine oral therapy for osteoporosis or Paget's disease (estimated between 1/10,000 and 1/100,000) – Risk of developing ONJ with intravenous therapy for malignancy estimated between 1 and 10% – Risks and benefits of bisphosphonates – Encouragement to maintain good oral hygiene and to have regular dental care – Risk factors for developing ONJ – Signs and symptoms of ONJ – Instruction to report any oral problems to dentist and physician
Dental care: – Dentists should follow existing guidelines for the prevention of oral complications of cancer therapy – Elimination of all potential sites of infection – Attain a state of good oral health to keep dental needs to maintenance appointments during active phase of bisphosphonate therapy – *Extraction of teeth* as soon as possible – *Periodontal health* status determined and appropriate therapy provided – *Restorative dentistry* performed to eliminate caries and defective restorations – *Prosthodontic appliances* evaluated and adjusted for fit, stability and occlusion – *Prophylaxis* performed and oral hygiene instructions given	Dental care: *Recommendations for (oncology) patients initiating intravenous bisphosphonate therapy* – If systemic conditions permit, initiation of bisphosphonate therapy should be delayed until dental health is optimized; this decision should be made in conjunction with the treating physician – *Nonrestorable teeth and teeth with a poor prognosis* should be extracted Bisphosphonate therapy should be delayed until the extraction site has mucosalized (14–21 days) or until there is adequate osseous healing – *Necessary elective dentoalveolar surgery and other invasive dental procedures* should be completed – Optimal *periodontal health* should be achieved – *Denture patients* should be examined for areas of mucosal trauma – *Dental prophylaxis, caries control and conservative restorative dentistry* are critical to maintaining functionally sound teeth; this level of care must be continued indefinitely	Dental care: *Recommendations for patients with malignancy initiating bisphosphonate therapy* – *Invasive dental procedures:* If the patient's clinical condition permits a delay in initiating bisphosphonate therapy, invasive dental procedures should be performed and healing completed before starting treatment with a bisphosphonate; otherwise, bisphosphonate therapy should be instituted concomitantly with dental therapy with careful follow-up to ensure complete healing of the surgical site

Soft Tissue Toxicity

An emerging hypothesis of ONJ pathogenesis is that of soft tissue toxicity. The oral cavity has relatively thin mucosa in many areas and the underlying osseous structure approximates the mucosa. A hypothesis was recently proposed that bisphosphonates are toxic to epithelium and hence the ONJ lesion represents a nonhealing mucosal lesion [Reid et al., 2007]. This is supported by findings of bisphosphonates shown to irritate local tissue injection sites and cause mucosal ulceration [Rubegni and Fimiani, 2006]. More research is needed to support or refute this hypothesis.

Table 3. Recommendations for patient care during bisphosphonate therapy – oral

ADA	AAOMS	ASBMR
Patient informed of dental treatment needed, alternative treatments and associated risks of ONJ. Documentation of discussion of risks, benefits and treatment options and patient's written acknowledgment of discussion and consent for treatment should be obtained. Routine dental treatment generally should not be modified solely because of bisphosphonate. **Trial sextant approach:** When medullary bone and/or periosteum will be involved in multiple areas, 1 area should be treated followed by a 2-month observation period, treating with antimicrobials. With successful healing at 2 months, treatment may advance to other areas. Periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis and active abscesses involving bone should be treated immediately, since they are osteonecrosis risks. **Periodontal disease:** Nonsurgical therapy recommended with prolonged course. If necessary, surgical treatment aimed at accessing root surfaces, with limited, modest bone recontouring. Guided bone or tissue regeneration should be judiciously considered. **Implants:** Treatment alternatives, including but not limited to periodontal, endodontic or prosthetic treatments should be discussed. **Oral and maxillofacial surgery:** Endodontic therapy should be discussed as an alternative to extractions. If extractions or bone surgery are necessary, conservative surgery with primary closure should be considered. Immediately before and after, a chlorhexidine-containing rinse should be used. Prophylactic antibiotics may be utilized during the healing for procedures that involve extensive manipulation of the bone, but are not mandatory or even recommended. **Endodontic therapy:** Endodontic treatment preferable to surgical manipulation. Routine endodontic technique should be used, periapical manipulation is not recommended. If endodontic surgery is required, recommendations for oral and maxillofacial surgery procedures should be followed. **Restorative procedures and prosthodontics:** Routine restorative procedures are recommended. Prosthodontic appliances should be adjusted for fit.	*Patients who have taken an oral bisphosphonate <3 years with no clinical risk factors* **Elective dentoalveolar surgery:** Elective dentoalveolar surgery is not contraindicated in this group. No alteration or delay in the planned surgery is necessary. **Implant placement:** Informed consent should be provided related to possible future implant failure and osteonecrosis if the patient continues to take an oral bisphosphonate. Such patients should be placed on a regular recall schedule. Prescribing provider should be contacted to monitor the patient. Alternate dosing of the bisphosphonate, drug holidays or an alternative to the bisphosphonate therapy are suggested. *Patients who have taken an oral bisphosphonate for <3 years and have also taken corticosteroids concomitantly* AND *patients who have taken an oral bisphosphonate for >3 years with or without any concomitant prednisone or other steroid medication* **Elective dentoalveolar surgery:** Prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least 3 months prior to oral surgery, if systemic conditions permit. Bisphosphonate should not be restarted until osseous healing has occurred.	*Recommendations for patients with osteoporosis or other nonmalignant bone diseases who have been taking oral bisphosphonate therapy <3 years* Not necessary to alter routine dental management. *Recommendations for patients with osteoporosis or other nonmalignant bone diseases who have been on long-term oral bisphosphonate therapy (empirically defined as >3 years)* **Periodontal disease:** Nonsurgical therapy should be used as an initial therapy. If surgical treatment is necessary, it should be aimed primarily at reducing or eliminating periodontal disease. Modest bone recontouring may be considered when necessary. **Implant placement:** No contraindication, but appropriate informed consent is recommended and should be documented. **Extraction or periapical surgery:** Routine endondontic therapy, not beyond the apex, is preferable. **Anticipation of invasive dental procedures:** There are no data to suggest stopping the bisphosphonate for a period before and after the procedure will improve dental outcomes.

Table 4. Recommendations for patient care during bisphosphonate therapy – intravenous

ADA	AAOMS	ASBMR
No recommendations available	*Recommendations for asymptomatic (oncology) patients receiving intravenous bisphosphonates*	*Recommendations for patients with malignancy initiating or already receiving bisphosphonate therapy*
	Procedures involving direct osseous injury: Should be avoided.	**Elective dentoalveolar surgical procedures:** Are not recommended.
	Extraction of symptomatic teeth: Nonrestorable teeth should be treated by removal of the crown and endodontic treatment of the remaining roots.	**Extraction of symptomatic teeth:** If possible, nonsurgical endodontic or periodontal therapy should be utilized. Only if the tooth is excessively mobile and presents an aspiration risk should it be extracted.
	Placement of dental implants: The placement of dental implants should be avoided in the oncology patient exposed to the more potent intravenous bisphosphonate medications (zoledronic acid and pamidronate) on a frequent dosing schedule (4–12 times per year).	**Periapical or periodontal surgery:** Are not recommended.
	Intravenous bisphosphonate use for the treatment of osteoporosis	*Intravenous bisphosphonate use for the treatment of osteoporosis*
	Since the dosing schedule for osteoporosis is far less frequent than for adjunct treatment of oncology patients, the risk of developing ONJ may be equivalent to or possibly less than that of oral therapy for osteoporosis.	To date, there have been no findings to suggest a difference in the risk of ONJ associated with intravenous administration at the doses approved for osteoporosis compared with oral bisphosphonate therapy for management of osteoporosis.

Professional Position and Recommendations

Several different professional organizations have described the signs, symptoms, risk factors and approaches to treating patients at risk for and afflicted by ONJ. A summary and comparison of 3 prominent groups, the American Dental Association (ADA), the American Association of Oral and Maxillofacial Surgeons (AAOMS) [2007] and the ASBMR [Khosla et al., 2007], is provided in tables 1–5. The ADA recommendations were compiled from 2 different publications, the ADA Council on Scientific Affairs expert panel recommendations on dental management of patients receiving oral bisphosphonate therapy [American Dental Association, 2006] and the American Academy of Oral Medicine position paper on managing the care of patients with bisphosphonate-associated osteonecrosis [Migliorati et al., 2007].

Many of the salient features are in agreement across the professional recommendations, but there are some differences. The ADA is the most cautious in approaching dental care needs in patients on oral bisphosphonates. The AAOMS is the most supportive of taking drug holidays for patients on bisphosphonates undergoing oral surgical procedures and with established ONJ. All 3 groups agree that patient communication regarding the risks of ONJ is very important. As to treatment, they all agree that the use of hyperbaric oxygen has not been established to be of a benefit in ONJ patients and that management of infection is important in these patients.

Unanswered Questions

Many unanswered questions persist regarding ONJ, including:

- How do bones of the oral cavity differ in anatomy, physiology and response to bisphosphonates versus other skeletal sites?
- What are the most accurate diagnostic approaches to detect early stages of ONJ and what signs or factors can be used to predict who will develop ONJ?
- Is there an effective animal model of ONJ to facilitate research?
- What is the role of microflora in ONJ?
- What is the role of soft tissue toxicity?
- Is there an association between metastasis to the jaw and ONJ lesions?
- How can we minimize the risk of ONJ and still reap the strong therapeutic benefits of bisphosphonates?

Table 5. During bisphosphonate therapy – treating established ONJ

ADA	AAOMS	ASBMR
	Treatment objectives: Eliminate pain, control infection, minimize progression or occurrence of bone necrosis.	Treatment objectives: Pain, infection and necrosis should be managed by a qualified dental specialist.
Management of infection: *Oral antimicrobial rinse* use is recommended. *Systemic antibiotic therapy* is indicated if erythema, suppuration and/or sinus tracts are present.	Management of infection: *Oral antimicrobial rinse* use is recommended. *Systemic antibiotic therapy* is indicated if there is evidence of an infection.	Management of infection: *Oral antimicrobial rinse* use is recommended. *Systemic antibiotic therapy* is indicated if there is evidence of an infection. Establishing and maintaining an 'infection-free' oral environment is especially important for patients with multiple myeloma who are being considered for stem cell transplantation.
Surgical management: Area of ONJ should only be treated to eliminate sharp edges of bone that may traumatize soft tissues. Follow-up every 2–3 weeks. *A surgical approach* to remove necrotic bone and close the site with healthy mucosa may be considered for patients with multiple myeloma who require hematopoietic stem cell transplantation. If surgical procedure is needed, patients should be informed of the possible risks and benefits. *Soft vinyl appliances or obturators* covering, but not resting on exposed necrotic bone, may prevent further trauma to soft tissues. *Existing prosthetic appliances* should be reevaluated for fit. Soft denture relines may be recommended. The role of *hyperbaric oxygen therapy* for the treatment of ONJ is not known.	Surgical management: Delay if possible. *Areas of necrotic bone* that are a source of soft tissue irritation should be recontoured without exposing additional bone. *Loose segments of bony sequestrum* should be removed without exposing uninvolved bone. *The extraction of symptomatic teeth within exposed, necrotic bone* should be considered. *Elective dentoalveolar surgical procedures* should be avoided. *Surgical debridement/resection* in combination with antibiotic therapy may offer long-term palliation with resolution of acute infection and pain. The potential for failure because of effects of the bisphosphonates needs to be recognized. Consideration for vascularized tissue transfer should be given. *Hyperbaric oxygen:* The efficacy of this approach has not been established.	Surgical management: Conservative approach or delay. *Sharp bone edges* should be removed to prevent trauma to adjacent soft tissues. *Loose segments of bony sequestra* should be removed without exposing uninvolved bone. *Extraction of symptomatic teeth within exposed, necrotic bone* should be considered. *Segmental jaw resection* may be required for symptomatic patients with extensive necrotic bone or pathologic fracture. *Hyperbaric oxygen:* The efficacy of this approach has not been established.
Discontinuation of bisphosphonate: There is no scientific evidence to support discontinuation of bisphosphonate therapy to promote healing of necrotic osseous tissues in the oral cavity. The discontinuation of therapy, along with the associated risks and benefits, must be discussed with the oncologist who prescribed the bisphosphonate.	Discontinuation of bisphosphonate: *Intravenous bisphosphonate therapy (oncologic)* Discontinuation shows no short-term benefit. If conditions permit, long-term discontinuation may be beneficial in stabilizing established sites, reducing risk of new sites and symptoms. Risk and benefits of continuing therapy should be considered by the oncologist in consultation with the oral and maxillofacial surgeon and the patient. *Oral bisphosphonate therapy* Discontinuation of oral bisphosphonate is associated with gradual improvement. If systemic conditions permit, consider modification or cessation in consultation with physician.	Discontinuation of bisphosphonate: No published data that stopping bisphosphonates will resolve ONJ. Indication for which the patient is receiving bisphosphonates should be considered.
Additional considerations: If ONJ is suspected, contact the FDA's Medwatch program at www.fda.gov/MedWatch/report.htm or 1-800-FDA-1088.		Additional considerations: Report to appropriate agencies, including the manufacturer of the agent implicated.

Conclusions

ONJ presents as a clinical complication and a scientific enigma. The pathobiology is intriguing, the risk indeterminate and the clinical care challenging. That bisphosphonates are effective drugs for the treatment of skeletal malignancy and metabolic bone diseases is established and hence there is a need to better understand the risks, causes and treatment of their associated effects. Clearly, more clinical and basic science research is needed to progress this rapidly moving area to a level that can benefit the hundreds of thousands of patients using these medications.

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