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
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

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.
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 bisphosphonate 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
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.
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

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<td>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.</td>
<td>Patients who have taken an oral bisphosphonate &lt;3 years with no clinical risk factors</td>
<td>Recommendations for patients with osteoporosis or other nonmalignant bone diseases who have been taking oral bisphosphonate therapy &lt;3 years are not contraindicated.</td>
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<td>Routine dental treatment generally should not be modified solely because of bisphosphonate.</td>
<td></td>
<td>Not necessary to alter routine dental management.</td>
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<td>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.</td>
<td>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.</td>
<td>Recommendations for patients with osteoporosis or other nonmalignant bone diseases who have been on long-term oral bisphosphonate therapy (empirically defined as &gt;3 years) are not contraindicated.</td>
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<td>Periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis and active abscesses involving bone should be treated immediately, since they are osteonecrosis risks.</td>
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<td>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.</td>
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<td>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.</td>
<td>Implant placement: No contraindication, but appropriate informed consent is recommended and should be documented.</td>
<td>Implant placement: No contraindication.</td>
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<td>Implants: Treatment alternatives, including but not limited to periodontal, endodontic or prosthetic treatments should be discussed.</td>
<td>Extraction or periapical surgery: Routine endodontic therapy, not beyond the apex, is preferable.</td>
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<td>Oral and maxillofacial surgery: Endodontic therapy should be discussed as an alternative to extractions.</td>
<td>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.</td>
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<td>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.</td>
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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?
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<td><strong>Management of infection:</strong> Oral antimicrobial rinse use is recommended. Systemic antibiotic therapy is indicated if erythema, suppuration and/or sinus tracts are present.</td>
<td><strong>Management of infection:</strong> Oral antimicrobial rinse use is recommended. Systemic antibiotic therapy is indicated if there is evidence of an infection.</td>
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<td><strong>Surgical management:</strong> 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. <strong>Soft vinyl appliances or obturators covering, but not resting on exposed necrotic bone, may prevent further trauma to soft tissues.</strong> <strong>Existing prosthetic appliances should be reevaluated for fit. Soft denture relines may be recommended.</strong></td>
<td><strong>Surgical management:</strong> Delay if possible. <strong>Areas of necrotic bone that are a source of soft tissue irritation should be recontoured without exposing additional bone.</strong> <strong>Loose segments of bony sequestrum should be removed without exposing uninvolved bone.</strong> <strong>The extraction of symptomatic teeth within exposed, necrotic bone should be considered.</strong> <strong>Elective dentoalveolar surgical procedures should be avoided.</strong></td>
<td><strong>Surgical management:</strong> Conservative approach or delay. <strong>Sharp bone edges should be removed to prevent trauma to adjacent soft tissues.</strong> <strong>Loose segments of bony sequestra should be removed without exposing uninvolved bone.</strong> <strong>Extraction of symptomatic teeth within exposed, necrotic bone should be considered.</strong> <strong>Segmental jaw resection may be required for symptomatic patients with extensive necrotic bone or pathologic fracture.</strong> <strong>Hyperbaric oxygen: The efficacy of this approach has not been established.</strong></td>
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<td><strong>Discontinuation of bisphosphonate:</strong> 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.</td>
<td><strong>Discontinuation of bisphosphonate:</strong> 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. <strong>Oral bisphosphonate therapy</strong> Discontinuation of oral bisphosphonate is associated with gradual improvement. If systemic conditions permit, consider modification or cessation in consultation with physician.</td>
<td><strong>Discontinuation of bisphosphonate:</strong> No published data that stopping bisphosphonates will resolve ONJ. Indication for which the patient is receiving bisphosphonates should be considered.</td>
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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.

References


