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Review Article

Case-Based Review of Osteonecrosis of the Jaw (ONJ) and Application of the International Recommendations for Management From the International Task Force on ONJ

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Abstract

Osteonecrosis of the jaw (ONJ) has been associated with antiresorptive therapy in both oncology and osteoporosis patients. This debilitating condition is very rare and advances in diagnosis and management may now effectively reduce the risk of its development and offer valuable treatment options for affected patients. This paper provides a case-based review of ONJ and application of the International Task Force on ONJ (referred to as the "Task Force") recommendations for the diagnosis and management of ONJ. The Task Force was supported by 14 international societies and achieved consensus from representatives of these multidisciplinary societies on key issues pertaining to the diagnosis and management of ONJ. The frequency of ONJ in oncology patients receiving oncology doses of bisphosphonate (BP) or denosumab is estimated at 1%–15%, and the frequency in the osteoporosis patient population receiving much lower doses of BP or denosumab is estimated at 0.001%–0.01%. Although the diagnosis of ONJ is primarily clinical, imaging may be helpful in confirming the diagnosis and staging. In those with multiple risk factors for ONJ for whom major invasive oral surgery is being planned, interruption of BP or denosumab therapy (in cancer patients) is advised, if possible, before surgery, until the surgical site heals. Major oral surgery in this context could include multiple extractions if surgical extractions are required, not simple forceps extractions. ONJ development may be reduced by optimizing oral hygiene and postoperatively using topical and systemic antibiotics as appropriate. Periodontal disease should be managed before starting oncology doses of BP or denosumab. Local debridement may be successful in disease unresponsive to conservative therapy. Successful surgical intervention has been reported in those with stage 3 disease; less severe disease is best managed conservatively. Teriparatide may be helpful in healing ONJ lesions and may be considered in osteoporosis patients at a high fracture risk in the absence of contraindications. Resumption of BP or denosumab therapy following healing of ONJ lesions is recommended, and there have not been reports of subsequent local recurrence.

Key Words: Bisphosphonates; denosumab; diagnosis; management; osteonecrosis of the jaw.

This paper provides an overview of osteonecrosis of the jaw (ONJ) diagnosis and management by The International Task Force on ONJ, composed of leading basic scientists and dental and medical experts. This review additionally provides physician and patient tools to assist in the management and understanding of ONJ and can be used in concert with the findings of other recently published international guidelines by the International Task Force on ONJ *(1)*.

Nine key questions were identified that addressed areas germane to the diagnosis and management of ONJ. A search strategy was developed that considered interventions, populations, areas of interest, and outcomes. Electronic searches were conducted for each of the questions for articles published between January 1, 2003, and March 1, 2016, indexed in PubMed or EMBASE databases. Pertinent literature identified in the searches was graded as to their quality of evidence, and topic experts provided relevant literature not captured in the searches.

A case-based discussion is provided to illustrate the findings of the International Task Force on ONJ.

Case

A 65-yr-old female presents with "jaw pain" in the osteoporosis clinic and has experienced a prior vertebral fracture with fall on ice at the age of 60 yr. The patient has been on alendronate 70 mg weekly for the past 7 yr and is now concerned that she may have ONJ as advised by her neighbor. She has a 15-yr history of type 2 diabetes mellitus and is on multidose insulin. Her HbA1C is 8.5%. She has polymyalgia rheumatic and has been on prednisone 5 mg daily for the past 3 yr. She smokes 1 pack of cigarettes per day and sees her dentist infrequently at most every few years.

The patient's bone mineral density (BMD) was recently determined at the femoral neck to be 0.562 g/cm^2, corresponding to a *T*-score of –2.6.

Does She Have ONJ?

ONJ was first described more than a decade ago *(2,3)* and is defined as an area of exposed bone in the oral cavity that does not heal within 8 wk following identification by a healthcare provider in a patient who has been receiving or has been exposed to a bisphosphonate (BP) or denosumab therapy and has not had radiation therapy in the craniofacial region or evidence of local malignancy *(4)*. The new American Association of Maxillofacial Surgeons (AAOMS) definition of ONJ also includes exposure to antiangiogenic agents *(5)*. The diagnosis is confirmed clinically by a dentist or oral surgeon following exclusion of other conditions which can present with pain or local oral symptoms. Additional imaging may be required to clarify the diagnosis and to determine the stage of the condition if present.

Spontaneous oral ulceration with bone sequestration (OUBS) has also been described and shows some shared features with ONJ, although it occurs in the absence of antiresorptive medication. OUBS typically presents on the posterior lingual aspect of the mandible or in association with exostoses. The patient presents with a small ulceration and exposure of underlying nonvital cortical bone. Usually, the nonvital bone base will spontaneously sequester and then efficient healing ensues. Some of these cases can persist beyond 8 wk and the etiopathogenesis is not well understood *(6–16)*. The incidence of OUBS in the general population is still not defined *(17,18)*. This issue begs the question whether this represents a "nonmedication related" form of ONJ. This is still being debated.

Our patient will need to consult with her dentist and any referred dental specialist to confirm if she has ONJ.

If Present, What Is the Stage of Her ONJ?

Determining the stage of the ONJ lesion is helpful in establishing prognosis and the best management strategy *(19–21)*. Patients with stage 1 disease have exposed bone and are asymptomatic without evidence of significant adjacent or regional soft tissue inflammation or infection. Stage 2 disease is characterized by exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection. Stage 3 disease is characterized by exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection in addition to a pathological fracture, an extraoral fistula or oral antral fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus (*see* Fig. 1—stages 1–3).

Bone pain and radiographic features of osteosclerosis may present as an early prodromal phase (sometimes referred to as "stage 0") of ONJ. In such individuals, it is essential to exclude other conditions that can cause odontalgia as listed in Table 1. Such individuals require close follow-up to ensure early detection of ONJ should it develop.

As approximately 50% of such lesions do not progress to clinically evident ONJ, the International Task Force on ONJ did not include preclinical ONJ as a defined stage of this condition.

Why Does ONJ Develop?

The pathophysiology of ONJ is still unclear. It is not known whether necrosis precedes or follows infection. Infection and inflammation clearly play a significant role in the development of ONJ *(22–26)*. BPs may increase the risk of local infection and may possibly contribute to impaired healing of the oral mucosa *(27–32)*. BPs may also activate gamma delta T cells with altered production of proinflammatory cytokines and impairment of the immune response to infection *(33–35)*. Suppression of bone remodeling by BPs or denosumab may also contribute to the development of ONJ *(36–41)*. Antiangiogenic properties of high doses of BPs have been reported as a possible mechanism for the development of ONJ *(42–44)*. It is possible that BPs may affect monocyte and macrophage function and survival contributing to an increased risk of ONJ. There may be genetic susceptibility to the development of ONJ with polymorphisms in the cytochrome P450 gene, CYP2C8 gene, or farnesyl pyrophosphate synthase gene, which may increase the risk of developing ONJ *(45–47)*.

Are Biomarkers Useful in Predicting the Risk of ONJ?

Investigators have suggested that serum C-terminal telopeptide (sCTX), a marker of bone resorption, would be useful in predicting the risk of ONJ *(48)*. Based on data from only 17 patients who developed ONJ following therapy with alendronate or risedronate, it was proposed that a serum sCTX value of >0.15 ng/ml constituted a low risk of ONJ; sCTX values between 0.10 and 0.15 ng/ml indicated a moderate risk; and sCTX values <0.10 ng/ml implied a high risk of ONJ. It was further suggested that surgery should be avoided in high-risk individuals identified with bone turnover markers. Studies in individuals with ONJ,

Osteoporosis Medications, Dental Health, and Osteonecrosis of the Jaw (ONJ):

What You Need to Know

Brought to you by the International Task Force on ONJ

Osteoporosis causes bones to become weak and break (fracture) easily. These fractures can happen from simple falls or even from usual day-to-day activities (eg lifting, bending). Any bone can fracture with osteoporosis; however, the most common fractures are of the spine, hip, and wrist. Osteoporosis can affect men and women of all ages but is most common amongst women after menopause.

Fractures from osteoporosis are preventable with appropriate medications. Bisphosphonates are a class of drugs which can safely and effectively decrease the risk of fracture in osteoporotic patients. They represent a major advance in the treatment of osteoporosis and other bone diseases. Some of the oral bisphosphonates which are commonly prescribed include alendronate (Fosamax, Binosto), ibandronate (Boniva) and risedronate (Actonel, Atelvia)). Zoledronic acid (Aclasta, Reclast) given intravenously once yearly is also used for osteoporosis. Bisphosphonates remain in the skeleton for several years even after they are stopped. Bisphosphonates help reduce the risk of fracture and help maintain healthy bones. Denosumab (Prolia) is also an effective treatment for osteoporosis and can effectively lower the risk of fracture. Denosumab is given twice yearly by subcutaneous injection and does not remain in the skeleton for prolonged periods of time.

What is Osteonecrosis of the Jaw?

Osteonecrosis of the jaw (ONJ) is a rare oral condition in which the jaw *bone's* ability to heal is impaired and may cause a wound which does not heal. The bone is bare and is not covered by the oral tissues. This bare bone can become infected and lead to pain and swelling. The bone can then break and the infection may be difficult to heal. ONJ does not affect the jaw *joint (temporomandibular joint or TMJ)*, and pain or discomfort in the jaw *joint* is not related to ONJ or to bisphosphonate or denosumab treatment. Though sometimes painful and progressive, ONJ can be present without symptoms; it usually heals with appropriate treatment.

How is ONJ Diagnosed?

Dentists or oral surgeons can diagnose ONJ by examining the soft tissue covering the jaw bones. If the jaw bone is not covered by a healthy soft tissue lining and remains uncovered or exposed for more than 8 weeks of appropriate treatment, this confirms the diagnosis of ONJ.

ONJ can occur in the general population in the absence of any bisphosphonate or denosumab therapy or other drugs, and usually heals within 12 weeks. ONJ can also develop in people who have risk factors for ONJ including poor blood supply to the bone cells in the jaw. It can also develop after major dental surgery which involves cutting the bone, chemotherapy, steroid therapy (such as prednisone) and from poor dental health and diabetes.

Is ONJ Caused by the Osteoporosis Therapy -- Bisphosphonates or Denosumab?

ONJ has been noted in patients with cancer receiving high doses of intravenous zoledronic acid or denosumab to reduce the complications associated with cancer that has spread to the bones. In these patients, the risk increases with higher doses and with longer duration of treatment. In patients with cancer, ONJ has been estimated to occur in 1 to 15% of individuals receiving high dose bisphosphonate or denosumab therapy.

In patients with osteoporosis, denosumab or bisphosphonate medications are used in lower doses (much lower than in patients with cancer) and the risk appears to be only minimally higher then seen in the general population not taking any bisphosphonate or denosumab therapy. The risk of ONJ with low dose bisphosphonate or denosumab treatment in osteoporosis patients is estimated to be between 1 in 10,000 and 1 in 100,000 per year of use and appears to be increased only slightly, if at all, compared with the risk for ONJ in the general population who have not taken any osteoporosis therapy.

Fig. 1. ONJ patient brochure. ONJ, osteonecrosis of the jaw.

How can ONJ be Prevented?

The International ONJ Task Force recommends that everyone should maintain good oral hygiene and see their dentist every 6 months (or as recommended based on oral disease risk). Routine dental work, such as dental cleaning, fillings or root canals should be performed as usual and do not require stopping your osteoporosis treatment.

It is important to stop smoking. If possible, before starting high dose intravenous bisphosphonate or denosumab therapy in patients with cancer, a detailed dental examination should be completed with X-rays of the jaw bones. Any necessary dental surgery should be completed before starting high dose intravenous bisphosphonate or denosumab therapy in patients with cancer.

The recommendations for patients with osteoporosis receiving low dose bisphosphonate or denosumab therapy are similar to those which apply to all individuals. They include maintenance of good oral hygiene and visiting your dentist regularly. If oral surgery is needed, it is ideal to have the surgery completed before starting low dose oral or intravenous yearly bisphosphonate therapy or denosumab therapy if possible. Individuals with risk factors for ONJ who are taking bisphosphonate or denosumab therapy may be advised to stop treatment after dental surgery and to restart therapy after the surgical site has completely healed. This usually takes place 1-2 months after the surgery. As bisphosphonates and denosumab are extremely important in preventing fractures, this should be discussed with the health care provider who prescribed the osteoporosis treatment.

How is ONJ Treated?

If ONJ does occur, treatment is usually managed by the dentist and/or oral surgeon and includes maintaining good oral hygiene, controlling pain and treating areas of infection with antibiotics and oral antibiotic mouth rinses. Making sure patients take lots of fluids and appropriate nutrition is also necessary. In certain circumstances, surgical treatment is required to remove dead bone tissue. This will be determined by the dentist and oral surgeon.

Summary:

The International Task Force on Osteonecrosis of the Jaw has been established to look at research priorities in order to help us understand the causes of ONJ as well as the most effective forms of treatment.

Osteoporosis is a serious disease. Treatment with bisphosphonates or denosumab is a safe and effective way to reduce your chances of breaking a bone. Talk to your doctor about your concerns and make sure your dentist is aware if you are taking a bisphosphonate or denosumab.

If you are experiencing any of the following symptoms please contact your dentist:

Infection of the gum, drainage of the gums, poor gum healing, numbness of the jaw, jaw pain or swelling or bare bone in the mouth.

A JOINT MESSAGE FROM

The International Task Force on ONJ : ASBMR, AAOMS, CAOMS, CAOMP, ECTS, IBMS, IOF, ISCD, IAOMS, JSBMR, NOF, Osteoporosis Canada , PAOS, TES

Fig. 1. (*Continued*)

however, have not shown a relationship between sCTX and the development of ONJ lesions *(48–53)*. Multiple randomized, placebo-controlled trials have confirmed that BP therapy reduces sCTX and other markers of bone turnover often in excess of 50%. In a randomized trial comparing zoledronic acid annual infusion to placebo (HORIZON study) in 7756 postmenopausal women, the mean sCTX values at 6 mo were at the low end of the premenopausal reference range (0.04–0.18 ng/ml) *(54)*. If the criteria proposed by Marx et al *(48)* were justified, these patients would be moderate- or high-risk; there were just 2 cases of ONJ, one in the zoledronic acid group and the other in the placebo group. The individual with ONJ on zoledronic acid was not in the subset being evaluated with biomarkers and sCTX was not available. The individual with ONJ on placebo did not have a suppressed sCTX and would

Table 1
Causes of Odontalgia to Be Excluded Before Considering the Presence of Early Prodromal Phase of Osteonecrosis of the Jaw

Necrotic dental pulp with apical abscess
Periodontal abscess
Reversible or irreversible pulpitis (could be secondary to bruxism)
Maxillary sinus pain (acute or chronic sinusitis)
Myofascial pain
Dental caries
Neoplastic process in the jaw
Any soft tissue lesion of the alveolar mucosa such as an ulceration causing regional pain

have been considered at low risk of ONJ based on the criteria proposed.

BP therapy commonly lowers sCTX to <0.15 ng/ml; however, ONJ is rare. Low sCTX is simply a reflection of the pharmacological effects of antiresorptive therapy and is not useful in identifying individuals at risk for ONJ.

How Common Is ONJ?

The incidence of ONJ in the osteoporosis patient population has been estimated from controlled clinical trials, case series, retrospective observational studies, or retrospective cohort studies. Currently, prospective data evaluating the frequency of ONJ in the osteoporosis patients are limited. The incidence of ONJ from retrospective administrative database data, especially pooled data from insurance or healthcare databases, is difficult to accurately evaluate. The search terms used may not be reflective of the underlying condition. In osteoporosis patients, the prevalence of ONJ has been estimated to be very low in the magnitude of 0.001%–0.01% as estimated from national surveys completed in Australia, Canada, Germany, United States, and Sweden *(39,55–57)*.

In the US Kaiser Permanente database, the prevalence of ONJ with BP use ranged from 0.05% to 0.21% and appeared to be related to duration of exposure *(58)*. In the HORIZON study, 2 cases of ONJ were observed, one in the placebo group and one in the active therapy group. Four additional randomized controlled trials evaluating 5 mg zoledronic acid in comparison to placebo were reviewed. The adverse event database for 60 MedDRA search terms revealed no additional cases of ONJ. The incidence of adjudicated ONJ in 5903 individuals treated with zoledronic acid in 5 clinical trials was less than 1 in 14,200 patient-treatment years *(54)*. The incidence of ONJ in the osteoporosis patient population is very low and may be only slightly higher than the frequency seen in the general population. Regardless of the very low risk, it is necessary to identify those individuals at higher risk and to take steps to minimize the occurrence of ONJ and its progression.

In the FREEDOM clinical trial of denosumab vs placebo involving almost 8000 postmenopausal osteoporotic women over 3 yr, there were no cases of ONJ. This clinical trial was extended with all patients on open label denosumab, and by the end of 7–10 yr of exposure, 13 cases of ONJ were identified *(38,59)*.

In all cases where the outcome of ONJ was known, healing occurred with conservative therapy and frequent medication was continued without interruption. Estimated total postmarketing exposure to denosumab is 1,960,405 patient-years in 2,427,475 patients as of May 2014 *(60)*. In this large patient exposure, 47 adjudicated cases of ONJ based on the AAOMS criteria have been confirmed. All of these individuals had at least one other risk factor for ONJ including concurrent glucocorticoid use, concurrent chemotherapy, prior BP use, or invasive dental procedures. The ONJ lesions resolved in a third of the cases and are ongoing in another third. The status of the remaining one third is not known *(61)*.

The postmarketing data suggest that the risk of ONJ in the osteoporosis patient population with either BPs or denosumab appears to be only slightly higher than the risk seen in the general population.

OUBS unrelated to antiresorptive therapy may confound these postmarketing data because clinical features may be similar to early-stage ONJ. OUBS lesions can persist for variable time periods ranging from a few days to several months and usually heal with conservative therapy *(62,63)*.

The incidence of ONJ in oncology patient populations is much higher than that seen in osteoporosis patient populations *(64–76)*. There are reasonable data evaluating this finding, including limited prospective studies, retrospective studies, and case series. A recent meta-analysis of 7 randomized controlled trials concluded that the incidence of ONJ in cancer patients receiving denosumab was 1.7% (95% confidence interval: 0.9%–3.1%) *(77)*. In individuals receiving high-dose BP therapy, the incidence of ONJ is between 1% and 15% and appears to be related to dose and duration of exposure *(64–76)*. There is considerable variability in the reported incidence and prevalence of ONJ in association with monthly administration of intravenous (IV) zoledronic acid or pamidronate in oncology patients. There may be confounding variables in this oncology population, including the use of other drugs that impact bone health (glucocorticoid and antiangiogenic drugs including thalidomide, bevacizumab, or sunitinib). There may also be other risk factors for ONJ such as chemotherapy, poor dental hygiene, neutropenia, and pre-existing local infection. The rate of resolution of ONJ may be more rapid in those treated with denosumab in comparison to BPs; however, this finding also requires further prospective data.

The use of IV BP and denosumab in oncology patients involves doses 12–15 times higher than what is used for postmenopausal osteoporosis. As an example, osteoporosis doses of denosumab are 60 mg biannually, and oncology doses to prevent progression of metastatic bone disease is 120 mg

monthly. Therefore, it is not surprising that ONJ is documented more frequently in the oncology population than in the osteoporosis population. The incidence of ONJ was obtained prospectively in 5723 patients with metastatic bone disease enrolled in 3 identical registration trials allowing pooling of data in the comparison of denosumab 120 mg monthly with zoledronic acid 4 mg monthly, where oral exams were completed every 6 mo. There were 89 adjudicated cases of ONJ: 37 (1.3%) were in the zoledronic acid group and 52 (1.8%) were in the denosumab group ($p = 0.13$) *(78)*. The median exposure to the agent was 14 mo in both groups *(69,79,80)*.

Both denosumab and BP therapies in oncology patients result in a clinically significant reduction in the risk of skeletal-related events (which occurred in 35.2% of the studied population) in comparison to the relatively low risk of ONJ of 1.6% *(69)*. Thus, the benefit of high-dose antiresorptive therapy outweighed the risk of ONJ by a factor of 17.

What Is the Role of Imaging in the Diagnosis and Management of ONJ?

Plain radiographs are useful in evaluating the presence of early changes seen with ONJ such as thickening of the lamina dura, increased trabecular density of the alveolar bone, or widening of the periodontal ligament space *(81,82)*. The presence of sequestrum may also be identified on plain films. Limitations of intraoral X-rays include assessment of only a small portion of the mandible and maxilla as well as distortion of the anatomy. Imaging techniques, however, are useful screening tools for the presence of dental disease and the assessment of the severity and extent of ONJ. Imaging is also helpful in the follow-up of patients with ONJ.

Computed tomography (CT) has many advantages over plain films and allows assessment of cortical and trabecular architectures of the maxilla and the mandible. Cortical integrity, periosteal bone reaction, and sequestrum formation can be clearly identified. In ONJ patients, diffuse osteosclerosis is seen *(83,84)*. Thickening of the cortical outline and periosteal bone formation are often present. Sequestration and early fistula track formation as well as incomplete extraction socket healing may be noted *(83,85–88)*. Increased trabecular bone density, which may not be seen on plain films, may be identified on CT images *(89)*. Cone-beam CT provides the same advantages as CT while incurring a significantly lower radiation exposure.

Magnetic resonance imaging (MRI) is useful in identifying the early features of ONJ before the development of exposed bone. A decrease in bone marrow signal intensity on T1-weighted images may be present before the development of the clinical features of ONJ *(84,85,90,91)*. T2-weighted and short T1 inversion–recovery may show increased signal intensity due to bone edema *(85,92)*. With advanced disease, the exposed bone shows decreased signal intensity and the unexposed diseased bone shows increased signal intensity. Sequestra as well as the presence of soft tissue thickening, edema, and lymphadenopathy can also be identified on MRI *(90,93)*. Therefore, MRI does have advantages over CT in evaluating the presence of ONJ, especially in the early stages of the disease.

Isotope bone scanning and positron emission tomography (PET) are sensitive techniques for the detection of early disease. Isotope bone scans have high sensitivity in assessing early disease. PET alone or in combination with CT is also of value in assessing the severity of ONJ. Individuals on antiresorptive therapy experiencing symptoms of bone pain without evidence of exposed bone on oral examination may benefit from radiographic assessment. If the initial panoramic radiographs are unremarkable, they should be repeated at intervals.

In those individuals receiving high-dose IV BPs or denosumab therapy in whom the risk of developing ONJ is significant, early and accurate detection of dental disease is necessary. In such individuals, cone-beam CT imaging should be performed as it is superior to conventional radiographs in diagnosing periapical and periodontal diseases. For those individuals with stage 1 and stage 2 ONJ who are being managed conservatively, cone-beam CT is also helpful in identifying the extent of osteonecrotic change. Additional imaging with MRI, isotope bone scanning, or PET may be of value in patients in whom there might be consideration of surgical intervention.

What Are the Risk Factors for the Development of ONJ?

In the oncology patient population, there are a number of risk factors associated with increased risk of ONJ. In a prospective analysis of ONJ in oncology patients, the majority of patients with ONJ had a precipitating oral event. This included a tooth extraction in approximately two thirds of the patients, coincident oral infection in approximately half of the patients, or other risk factors *(69)*. Corticosteroid use was more common in patients who developed ONJ (73% with ONJ vs 62.3% without ONJ). Also, the use of antiangiogenic agents was associated with an increased risk of ONJ (15.7% with ONJ vs 8% without ONJ). Anemia and diabetes were associated with only a slight increase in the risk of ONJ. Forty-five percent of those with anemia (defined as hemoglobin <10 g/dL) developed ONJ in comparison to 40.9% without anemia. Approximately 22.5% of those with diabetes developed ONJ in comparison to 15.5% without diabetes.

In the oncology population, the risk of ONJ appears to increase in the presence of the following risk factors: IV BP (dose and duration dependent), denosumab, dental extraction, chemotherapy, periodontal disease, oral BP, glucocorticoid, diabetes mellitus, denture use, smoking, hyperthyroidism, dialysis, antiangiogenics, and older age (Table 2).

Table 2
Significant Risk Factors for the Development of Osteonecrosis of the Jaw

Risk factor	Population	Univariate estimates[a]	Multivariate estimates[a]
Age (per decade)	Oncology		OR = 1.09 *(94)*
Age (per year)	Oncology	OR = 1.1 *(65)*	
Anemia	Osteoporosis		OR = 5.2 *(95)*
Bisphosphonate use	Osteoporosis	OR = 14.9 *(96)*	HR = 2.23–3.15 *(97)*
			OR = 2.8 *(98)*
Bisphosphonate use	Oncology	OR = 14.9 *(96)*	OR = 1.06–299.5 *(71,76,95,99–101)*
			RR = 9.5 *(99)*
			HR = 2.23–3.15 *(97)*
Bisphosphonate use—per dose	Oncology		OR = 1.78–2.02 *(76)*
Chemotherapy	Oncology	OR = 3.4 *(65)*	
Chemotherapy and concomitant BP	Oncology	OR = 29.11 *(102)*	
Denosumab	Osteoporosis or oncology		Increased risk inferred from incidence and prevalence data
Dental extraction	Osteoporosis		OR = 6.6 *(95)*
Dental extraction	Oncology	OR = 5.3 *(65)*	OR = 9.09–53.2 *(76,94,95,100,103)*
Denture use	Oncology		OR = 1.43–4.9 *(76,103,104)*
Diabetes	Oncology		HR = 3.40 *(105)*
Erythropoietin therapy	Oncology	OR = 3.9 *(65)*	
Glucocorticoid therapy	Oncology	OR = 6.5 *(65)*	
Glucocorticoid therapy	Oncology or osteoporosis	OR = 2.8 *(96)*	
Hyperthyroidism	Oncology		HR = 3.59 *(105)*
Hemoglobin low	Oncology	OR = 6.8 *(65)*	
Male gender (vs female)	Oncology		HR = 1.68 *(63)*
Osteoporosis	Oncology		OR = 6.11 *(100)*
Osteoporosis	Oncology or osteoporosis	OR = 10.3 *(96)*	
Periodontitis	Oncology		OR = 2.95–13.0 *(104)*
Radiation therapy	Oncology		OR = 24.1 *(95)*
Renal dialysis	Oncology	OR = 3.2 *(65)*	
Smoking tobacco	Oncology	OR = 6.0 *(106)*	HR = 3.44 *(105)*
Suppuration	Osteoporosis		OR = 11.9 *(95)*
Suppuration	Oncology		OR = 7.8 *(95)*

Note: Comparators of disease states are with the population group without disease state.
Abbr: BP, bisphosphonate; HR, hazard ratio; ON, oncology; OR, odds ratio; RR, relative risk.
[a]Only statistically significant ($p < 0.05$) associations are reported on this table.

In osteoporosis patients, the following are important risk factors for ONJ: suppuration, dental extraction, oral BP, and denosumab (Table 2).

Our patient has a number of risk factors including long-term use of BP, diabetes, prednisone, smoking, and poor dental hygiene.

Can ONJ Be Prevented and Should Her BP Be Stopped?

To minimize the development of ONJ in patients at risk, regular dental examinations are encouraged. Oral hygiene should be improved and local infection managed as early as possible *(107–110)*. The use of antibiotics before and after oral surgical procedures has been demonstrated to lower the risk of ONJ *(107,108,111–113)*.

Antimicrobial mouth rinses may also be of value in lowering the risk of ONJ *(108,111)*.

All necessary oral surgeries in oncology patients should ideally be completed before the initiation of high-dose antiresorptive therapy *(112,114–116)*. For oncology patients requiring high-dose IV BPs or high-dose denosumab, dental radiographs should be completed before the initiation of therapy to identify the disease before medication begins. Any invasive dental procedure including dental extractions or implants should ideally be completed before the initiation of antiresorptive therapy. Nonurgent procedures should be delayed if necessary. If ONJ develops,

it is recommended that the antiresorptive drug therapy be withheld until soft tissue closure with a well-epithelialized mucosa is achieved.

There is currently no evidence that interruption of drug therapy in patients requiring dental procedures reduces the risk of ONJ or the progression of the disease. There are a number of factors that need to be considered when evaluating the suitability of the interruption of antiresorptive therapy. BPs that have long-term skeletal retention and cessation for weeks or months may not impact remodeling significantly. However, BPs do have increased skeletal uptake at the sites of local bone injury (isotope bone scan uses labeled BP), and withholding BP therapy following oral surgery may be of value in reducing the local deposition in the mandible and maxilla after oral surgery. In individuals with significant risk factors for ONJ, including oncology patients on high-dose antiresorptive therapy as well as those individuals with multiple risk factors for ONJ, it may be of benefit to withhold BP or denosumab therapy following oral surgery until soft tissue healing occurs.

In determining the suitability of drug interruption, it is necessary to weigh the risks of ONJ with the risk of skeletal-related events in oncology patients and the risk of fracture in those with osteoporosis. The decision to hold therapy should be jointly made between the oral surgeon and the physician treating the underlying osteoporosis. The treatment plan must be individualized for each patient based on comorbidity, risks for ONJ, extent of the planned surgery, as well as the risks for fracture and skeletal-related events.

Patients with osteoporosis receiving BP or denosumab may continue with therapy if a dental procedure (including extractions and implant surgery) is required *(117)*. The decision to continue or hold antiresorptive therapy should be made by the dental health provider in consultation with the patient's physician. This approach is the collective opinion of our task force based on our current understanding of this disease. There are a few published case reports suggesting improved healing of ONJ with the use of teriparatide *(118,119)*.

Our patient has a high 10-yr fracture risk based on FRAX. FRAX recognizes risk factors of prevalent fragility fracture (vertebral fracture in our patient), family history of hip fracture, current cigarette smoking, high alcohol intake, rheumatoid arthritis, prednisone therapy, and other secondary causes of bone loss. Type 2 diabetes (our patient has a 15-yr history of type 2 diabetes mellitus) is a risk factor elevating patients' fracture risk but is not recognized as a FRAX risk factor, and may be a risk not be captured by BMD *(120)*. Our patient also has been on prednisone therapy 5 mg daily for more than 3 mo and is a current smoker. Based on the patient's femoral neck BMD of 0.562 gm/cm^2 (*T*-score of –2.6), her fracture risk would be calculated by FRAX over the next 10 yr to be 34% for major osteoporotic fracture (clinical vertebral, wrist, hip, and humerus fractures). The patient's risk of hip fracture would be 14% over the next 10 yr, and she is at high risk of fracture.

The patient's risk of ONJ with long-term BP is low; however, she also has other important risk factors for the development of ONJ, including history of diabetes, glucocorticoid use, and poor dental hygiene. The patient's BP may be stopped until her dental procedure is complete and the wound healed. Should the patient develop ONJ, teriparatide would be an effective treatment for osteoporosis and may also be of value in healing ONJ.

How Should ONJ Be Managed?

Management is based on the stage of ONJ, the size of the lesions, the presence of the contributing drug therapy, and medical and pharmacological comorbidities. Figures 1 and 2 provide ONJ management guides for the patient and physician, respectively, and Table 3 summarizes the treatment options for ONJ.

Conservative therapy of ONJ focuses on improving oral hygiene, treating active dental and periodontal diseases, topical antibiotic mouth rinses, and systemic antibiotic therapy *(21,67,117,170)*. There are several case reports of the successful treatment of ONJ with teriparatide, which are encouraging; these reports may be considered to facilitate wound healing *(119,171)*. Teriparatide is contraindicated in individuals who have had skeletal radiation and may not be a useful intervention approach for those with malignancy and a prior history of skeletal irradiation.

Experimental treatment approaches require further validation. These treatment approaches include topical ozone *(164)*, bone marrow stem cell intralesional transplantation *(172)*, and addition of pentoxifylline and tocopherol to standard antibiotic regimens *(147)*. Laser therapy has also been proposed to be of benefit *(151,173)*. Localized surgical debridement may be indicated; some authors have reported success with larger resections compared to limited debridement or conservative therapy *(121,174)*. Enhanced healing has been observed in a retrospective survey of patients undergoing antibiotic therapy in addition to surgery followed by low-level laser therapy *(157)*. Surgery, together with platelet-derived growth factor applied to the local site, has achieved good results in stage 2 ONJ cases *(175)*. Hyperbaric oxygen in combination with surgery has been investigated with encouraging results *(122,161)*. Further research is required with these new strategies.

In the absence of debilitating ONJ lesions, it is recommended that conservative therapy consisting of optimal oral hygiene, topical antibiotic rinses, and systemic antibiotics be initiated *(112)*. Nonresponsive cases should be considered for surgery including osteotomy of the affected area with resection margins extending into adjacent normal appearing bone. Soft tissue closure should be completely tension free with no underlying sharp edges of bone that could lead to mucosal breakdown. Microvascular composite tissue grafting at the time of surgical resection may be considered in the presence of a pathological fracture or ONJ if the extension is to the sinus or the inferior border of the mandible. It may also be of value if the osteotomy to healthy

ONJ Key Recommendations for Clinicians

PREVENTION OF ONJ IN PRESENCE OF BISPHOSPHONATE OR DENOSUMAB THERAPY

A. Evaluate Key Risk Factors for ONJ:

- Invasive dental procedure
- Diabetes
- Glucocorticoid therapy
- Periodontal disease
- Denture use
- Smoking
- Anti-angiogenic agents

B. Evaluate Fracture risk:

1. **If risk of ONJ is increased** and

a. risk of fracture is low (< 10% over next 10 years) or moderate (10%-20% over the next 10 years) then stop antiresorptive therapy

b. risk of fracture is high (>= 20% over next 10 years) and major invasive oral surgery is planned, consider stopping antiresorptive therapy. Consider the use of teriparatide during the time off antiresorptive therapy if no contraindications. If contraindication to teriparatide (hypercalcemia, high PTH levels, prior skeletal radiation, malignancy, elevated alkaline phosphatase) are present stop antiresorptive therapy after dental procedure until surgical site heals

c. In all patients with increased risk of ONJ consider antimicrobial mouth rinses, antibiotics and always emphasize good oral hygiene

2. If risk of ONJ is low and

a. risk of fracture is moderate or high, then continue antiresorptive therapy

C. Staging:

- **Stage 1:** Exposed bone, asymptomatic
- **Stage 2:** Exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling or secondary infection
- **Stage 3:** As above + one or more of the following: pathological fracture, extra-oral fistula, oral antral fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus

D. Treatment:

Management is determined by stage, severity of symptoms, functional impairment and overall prognosis

- **Stage 1**: conservative therapy – improve oral hygiene. Treat active dental and periodontal disease, topical antibiotic mouth rinses
- **Stage 2:** as in stage 1 also Rx symptoms, systemic antibiotics if infection is suspected, consider surgical debridement
- **Stage 3**: as in stage 1 also surgical debridement, resection including jaw reconstruction if necessary

Guidelines developed by: ASBMR, AAOMS, CAOMS, CAOMP, ECTS, IBMS, IOF, ISCD, IAOMS, JSBMR, NOF, OSTEOPOROSIS CANADA, PAOS, TES.

Fig. 2. Physicians' quick reference card for ONJ diagnosis and treatment. ONJ, osteonecrosis of the jaw.

Table 3
Summary of ONJ Treatments

Treatment type and supportive trial or study (≥5 patients)	Notes
Bone resection *(121–130)*	Many supporting trials used concomitant antibiotics and demonstrated excellent efficacy in healing ONJ; not all trials demonstrated high cure rates following surgery *(69,131–133)*.
Surgical debridement *(130,134–136)*	Often with antimicrobial rinsing, very successful technique with minority requiring subsequent sequestrectomy
Sequestrectomy *(126,128,137–140)*	Often successful with antibiotics
Prophylactic antibiotics before or immediately after surgery *(111,125,136,137,141,142)*	Antibiotics substantially decrease the rate of recurrence.
Nonsurgical long-term antibiotics *(143,144)*	Some trials showed success with antiseptic rinse, smoothing, and removal of necrotic bone with tweezers; no difference between it and surgical care with respect to remission; some trials with antibiotic-only approach without surgery had limited success *(126,145,146)*.
Nonsurgical antiseptic rinse *(144)*	Some trials demonstrated success with long-term antibiotics, smoothing, and removal of necrotic bone with tweezers.
Antimicrobial rinse (intravenous) *(121,130,139,140,147,148)*	Usually successful in combination with surgery; longer-term antimicrobial therapy before surgery more effective; in some trials, not as effective as primary treatment *(145,149,150)* or with surgery *(133)*
Er:YAG laser therapy *(151–153)*	Er:YAG laser therapy found to be effective in most trials, but not all *(154)*
Nd:YAG laser *(155,156)*	Majority have complete healing; others have shown significant improvement in symptoms.
Low-level laser therapy *(157–160)*	Often in combination with medical or surgical therapy; used primarily for reduction in pain, but also improvements in defect size, edema, and presence of pus and fistulas
Hyperbaric oxygen therapy *(161–163)*	As an adjunct to other therapies such as antibiotics, antiseptics, and surgery; often for symptomatic relief *(142)*; not always found to have clinical impact *(133,149)*
Ozone therapy *(164–167)*	Some supporting trials used concomitant antibiotics; germicidal and analgesic effects
Plasma rich in growth factor therapy *(109)*	Shown to be very successful in combination with surgery
Autologous platelet-rich plasma *(157,168)*	During partial bone resection of patients that failed conservative therapy—80% success in 1 trial; used with laser therapy as well
Platelet-derived growth factor *(123)*	With bone resection
Recombinant human bone morphogenetic protein type 2 therapy *(169)*	All patients healed after 1 yr
Pentoxifylline and alpha-tocopherol therapy *(147)*	With adjunct antimicrobial therapy

Abbr: ONJ, osteonecrosis of the jaw.

tissue leads to a discontinuity defect. This is a rapidly evolving area of investigation and further recommendations will be forthcoming.

In conclusion, the pathophysiology of ONJ is still poorly understood and appears to be multifactorial, with infection playing a key role in the development of ONJ. Drugs have also been associated with ONJ and include antiresorptive agents, amino-BPs, and denosumab, particularly when administered in high doses in the oncology patient population. The benefits of antiresorptive therapy far outweigh the potential risks with major reductions in skeletal-related events in the oncology patient and fracture risk

reduction in the osteoporosis patient. Risk stratification with implementation of ONJ preventive strategies is helpful in reducing the risk of ONJ. Emphasizing good oral hygiene as well as the use of antimicrobial mouth rinses and effective treatment of oral infection is of benefit in improving clinical outcomes. Lower doses of antiresorptive therapy coupled with appropriate use of anabolic therapy may also be of value and require further study. The diagnostic and prognostic factors for ONJ need to be further refined to more effectively identify patients at high risk. Current ongoing prospective studies of patients at risk are expected to provide future insights into clinically useful predictors of ONJ and more effective intervention options for both the osteoporosis patient and the oncology patient populations.

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