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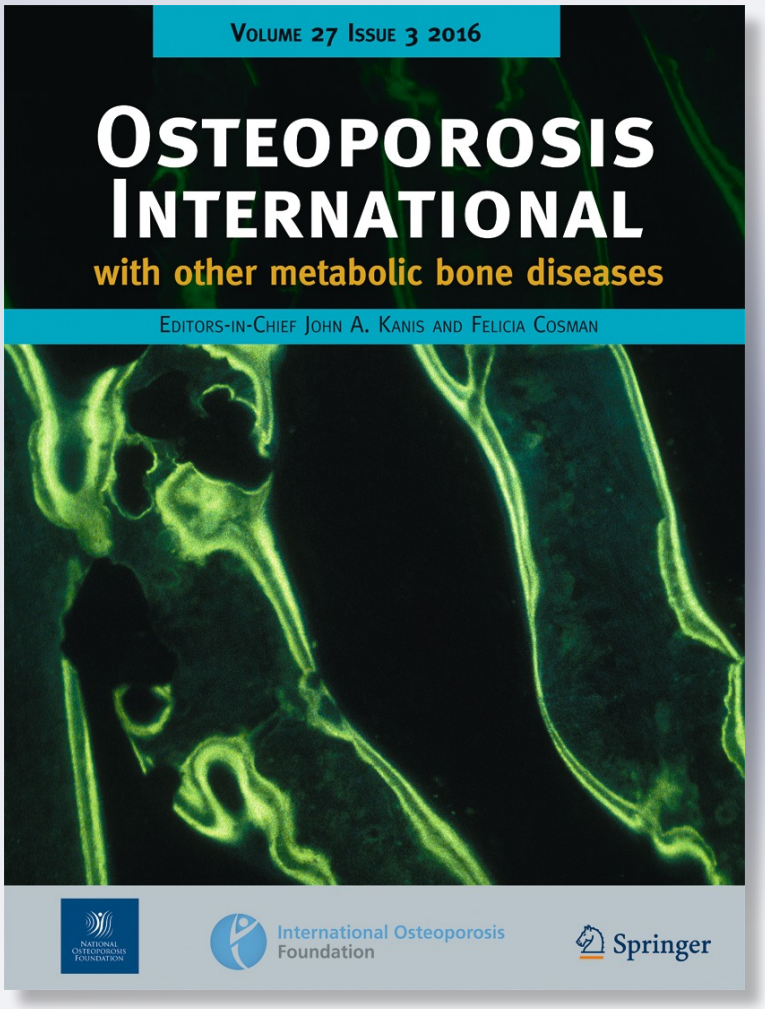

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REVIEW

Osteonecrosis of the jaw (ONJ): diagnosis and management in 2015

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Abstract Osteonecrosis of the jaw (ONJ) has been associated with the use of aminobisphosphonates and denosumab. The vast majority (>90 %) of cases occur in the oncology patient population receiving high doses of intravenous bisphosphonates or subcutaneous denosumab. The incidence of ONJ in the osteoporosis patient population is very low and is estimated at 1–90 per 100,000 patient-years of exposure. In the oncology patient population the incidence appears to be related to dose and duration of exposure, and prevalence has been estimated to be as high as 18.6 %. A number of risk factors in addition to antiresorptive therapy have been identified. These include the presence of periodontal disease, oral surgical procedures with extractions or implants, radiation therapy, chemotherapy, diabetes, glucocorticoid use, and smoking. Antiangiogenic agents appear to contribute to the risk of ONJ, however, data at this time are limited and further evidence is required prior to confirming a causal relationship. ONJ may be prevented with optimization of oral hygiene, the use of oral antimicrobial mouth rinses, as well as systemic antibiotic therapy. Individuals not responding to conservative management or in the advanced stages of ONJ may be considered for surgery, as data over the past several years have demonstrated surgical success in this patient population. Case reports have indicated that teriparatide may enhance healing. A number of experimental therapies are being evaluated and include the use of bone marrow stem cell intralesional transplantation, local application of platelet-derived growth factor, hyperbaric oxygen, tissue grafting, and low-level laser therapy. This paper summarizes the current research as well as the international consensus on the diagnosis and management of ONJ.

Keyword Denosumab · Osteonecrosis · Diagnosis · Treatment · Bisphosphonates

Introduction

Osteonecrosis of the jaw (ONJ) was first reported in 2003 [1]. Since then, a large number of case reports have been published as well as retrospective and limited prospective data. More than 90 % of the cases of osteonecrosis of the jaw are seen in oncology patients receiving high doses of antiresorptive therapy [2].

The International Task Force on ONJ (herein referred to as The Task Force) defines ONJ as:

1. Presence of exposed bone in the maxillofacial region which does not heal within 8 weeks after identification by a health care provider;
2. Exposure to an antiresorptive agent (bisphosphonate or denosumab), and;
3. No history of radiation therapy to the craniofacial region.

The Task Force did not include antiangiogenic agents in the definition of ONJ as there are insufficient data confirming a

This article was written on behalf of the International Osteonecrosis of the Jaw Task Force. A full list of the members of this body can be found at the end of the article.

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causal relationship between antiangiogenic agents and the development of ONJ at this time. However, the Task Force plans to address this in more detail as greater evidence becomes available [2].

Diagnosis

A number of conditions can present with pain and local oral symptoms and require exclusion prior to confirming the diagnosis of osteonecrosis of the jaw (Table 1).

ONJ may remain asymptomatic for long periods ranging from weeks to several months or even years [3]. A number of imaging modalities are available to clarify the diagnosis and assist with staging. These include plain films, CT, MRI, bone scanning, and positron emission tomography [2].

Staging

Ruggerio and colleagues have developed a valuable clinical staging system which has been adopted by the International Task Force [4] (Table 2). Stage 1 disease is described as the presence of exposed bone in asymptomatic patients with no evidence of significant adjacent or regional soft tissue inflammation or infection. Stage 2 disease is characterized by exposed bone in the oral cavity in association with pain, soft tissue swelling, or secondary infection. Stage 3 disease is characterized by exposed bone in association with pain, soft tissue swelling, or infection as well as a pathologic fracture or an extraoral fistula or oral antral fistula or evidence radiographically of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus [2].

Individuals with bone pain and radiographic features of osteosclerosis on antiresorptive therapy may present with an early prodromal phase of ONJ. This has been defined as stage 0 ONJ by AAOMS. Approximately, 50 % of individuals with such lesions do not progress to develop clinical ONJ with exposed bone and therefore the Task Force agreed not to include reference to a pre-clinical stage or stage 0 ONJ until further prospective data are available [3].

Table 1 Causes of odontalgia to be excluded prior to considering presence of early prodromal phase of ONJ

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

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Table 2 Staging

The staging of ONJ as recommended by the International Task Force is summarized below [2]:
Stage 1 – exposed bone in the oral cavity
Stage 2 – exposed bone in the oral cavity in association with infection and/or inflammation
Stage 3 – exposed bone in the oral cavity with infection or inflammation as well as a pathologic fracture or fistula or evidence of osteolysis extending to the inferior border of the mandible or sinus floor

Frequency of ONJ

The frequency of ONJ in osteoporosis patients with oral or intravenous amino bisphosphonate therapy has been estimated to be between 0.01 and 0.001 % and may be only slightly higher than the incidence seen in the general population of less than 0.001 % [2].

In osteoporosis patients, data evaluating the incidence and prevalence of ONJ are limited and of low quality. The information available consists largely of case reports, retrospective observational studies, or retrospective cohort studies from pooled data obtained from insurance or health care databases [2]. National surveys of dental and oral surgery practices have also been reported [5–7].

The incidence of ONJ in patients on oral bisphosphonates for osteoporosis has been estimated at 1.04–69 per 100,000 patient-years [6–9]. With IV bisphosphonate therapy in osteoporosis patients, the incidence of ONJ ranges from 0 to 90 per 100,000 patient-years [10, 11]. With the use of denosumab in osteoporosis patients, the incidence ranges from 0 to 30.2 per 100,000 patient years [12–14]. The frequency of ONJ in osteoporosis patients receiving low doses of bisphosphonates or denosumab therapy appears to be very low, ranging from 0.15 to less than 0.001 % person-years of exposure [15–18].

In oncology patients, the prevalence of ONJ is significantly higher and has been evaluated prospectively in individuals being treated with zoledronic acid 4 mg monthly or denosumab 120 mg monthly [19]. Three clinical trials with an identical design allowed pooling of data and compared denosumab to zoledronic acid in the prevention of skeletal-related events (pathologic fracture, radiation therapy to bone, surgery to bone, and spinal cord compression) [19]. Patients with breast cancer, prostate cancer, multiple myeloma, or solid tumors with bone metastasis were enrolled in the study. Five thousand seven hundred and twenty-three patients were

evaluated and there were 89 ONJ cases in total, 52 in the denosumab arm, and 37 in the zoledronic acid-treated arm. The difference between the two groups was not statistically significant. The incidence in the denosumab arm was 1.8 % vs. 1.3 % in the zoledronic acid arm [20]. The ONJ lesions in the denosumab-treated patients had a faster resolution time. The benefit of high-dose antiresorptive therapy was estimated to outweigh the risk of ONJ by a factor of 17.

Risk factors for osteonecrosis of the jaw

A number of risk factors have been identified for the development of ONJ. Aminobisphosphonates are an important contributory factor and in oncology patients the risk of ONJ appears to be related to both dose and duration of aminobisphosphonate exposure [21]. Individuals with metastatic bone disease or multiple myeloma receiving oncology doses of aminobisphosphonates or denosumab have a higher incidence of osteonecrosis of the jaw [2].

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial, the incidence of ONJ in the placebo group was the same as the incidence of ONJ in the treated group, with only one case seen in each group [11].

In the four additional randomized controlled trials of zoledronic acid in individuals with osteoporosis or metabolic bone disease, the adverse event database was searched for possible ONJ cases and no additional cases were identified with the incidence of adjudicated ONJ being <1 in 14,200 patient treatment years [18].

Other risk factors for ONJ include: dentoalveolar surgery, periodontal disease, trauma, and poorly fitting dentures [22]. Glucocorticoid therapy is associated with an increased risk of ONJ. This may be due to multiple factors including inhibition of osteoblast function and increased osteoblast and osteocyte apoptosis. Other effects of glucocorticoids that may contribute to the increase in risk of ONJ include increased bone resorption, immunosuppression, impaired wound healing and increased risk of local infection [19]. Vitamin D deficiency has also been identified as a possible risk factor [23]. Age is an important risk factor, as is obesity and tobacco consumption [21].

Pathophysiology

The pathophysiology of ONJ is not well understood and appears to be multifactorial. Suppression of bone remodelling may contribute to the development of osteonecrosis and result in inadequate osteoclast activity to allow healing of the extraction socket [24, 25]. Infection is a major factor in the development of ONJ. Polymorphonuclear leukocytes and aggregates of bacteria are almost always seen in the ONJ tissue [2, 26, 27]. Bacteria stimulate bone resorption and contribute to bone necrosis. Bacteria can increase bone resorption through the production of local cytokines, resulting in osteolysis locally. The damaged oral mucosa can contribute to infection, and infection can contribute to further mucosal damage. Bisphosphonates may also activate the gamma delta T-cells and impair the immune response to infection [28–30]. Denosumab may impact monocyte function and this may also be a contributing factor to the development of ONJ [2]. Bisphosphonates may have antiangiogenic effects [28–30]; in addition, treatment of cancer with tyrosine kinase inhibitors and monoclonal antibodies to vascular endothelial growth factor has also been associated with the development of ONJ alone or in combination with bisphosphonates and denosumab therapy [31, 32]. Lastly, genetic predisposition may enhance the risk of ONJ in certain individuals who have polymorphisms in the farnesyl pyrophosphate synthase gene or cytochrome P450 CYP2C8 genes [33–37].

Prevention of ONJ

Emphasis on optimal oral hygiene and treatment of local infection has been effective in decreasing the risk of ONJ [38–42]. Antimicrobial mouth rinses before and after oral surgery are also of value [40, 43].

The International Task Force recommends that oncology patients requiring high doses of intravenous bisphosphonates or of denosumab should have dental radiographs before the initiation of antiresorptive therapy. Any dental disease which requires intervention should be addressed prior to proceeding with high-dose antiresorptive therapy [2]. At this time, there is no evidence that interrupting antiresorptive therapy in patients who require a dental procedure will reduce the risk of ONJ or the progression of the ONJ lesions. It is recognized that bisphosphonates have long-term skeletal retention, and stopping bisphosphonate therapy will not have a significant immediate impact on bone remodeling. However, since bisphosphonate uptake is increased at sites of local bone injury,withholding antiresorptive therapy following oral surgery may reduce the local deposition of bisphosphonate in the mandible and maxilla. The International Task Force therefore recommends that, in individuals at high risk of ONJ including those with malignancy receiving high-dose bisphosphonate or denosumab therapy, as well as those with significant risk factors for ONJ, interruption of antiresorptive therapy following the surgical procedure should be considered until the surgical site heals. This may require several weeks of observation.

In determining the suitability of interruption of antiresorptive therapy, the medical practitioner, in consultation with the dental practitioner, will assess the risks of ONJ in comparison to the risks of skeletal-related events in oncology patients.

In those with osteoporosis or metabolic bone disease, the risk of a fragility fracture will need to be weighed against the risk of ONJ. If the risk of fragility fracture is low or moderate, interruption of bisphosphonate therapy or denosumab therapy may be appropriate until the surgical site heals. If, however, the risk of fragility fracture is high and the risk of ONJ is also significant, then consideration may be given to switching therapy to teriparatide in the absence of contraindications. Teriparatide has been associated with enhanced bone healing in published case reports in individuals with osteoporosis without contraindications to therapy, but further studies are required to confirm its efficacy [44–51].

Management of ONJ

The International Task Force recommends that management is determined on the basis of the stage of ONJ, as well as the size of the lesions. For stages 1, 2, and 3, it is essential to improve oral hygiene and actively treat existing dental and periodontal disease. Antibiotic mouth rinses and systemic antibiotic therapy play an important role in the management of ONJ [2]. Teriparatide may be considered in those who do not have contraindications, such as a history of skeletal radiation. Individuals with stage 3 disease may be considered for surgery with osteotomy of the affected area [2]. A number of reports have been published over the past few years, confirming success with surgical management of ONJ lesions. The International Task Force recommends that a full thickness mucoperiosteal flap is elevated and extended, to reveal the entire area of the exposed bone and beyond to disease-free margins. The affected bone can be resected to reach healthy-appearing bleeding bone. It is advised that sharp edges are smoothed, and primary soft tissue closure is achieved in a tension-free manner [2, 52–54]. Other therapies currently being evaluated include low-level laser therapy [55, 56], platelet-derived growth factor applied locally [57], and hyperbaric oxygen in combination with surgery [58].

Future research directions

The pathophysiology of ONJ requires further clarification and would be greatly aided by development of suitable animal models, but differences in bone composition and bone remodeling between animals and humans have limited progress in this area. The cellular mechanisms involved in oral wound healing in the presence of antiresorptive drug therapy also need further research. The impact of bisphosphonates and denosumab on other cells in the bone marrow such as macrophages requires further study. The diagnostic and prognostic factors for ONJ need to be further refined. Inclusion of Stage 0 ONJ may result in overdiagnosis of the condition and could explain the significantly higher incidence of the condition in certain regions such as Asia. Prospective studies of patients at risk for ONJ should provide insight into clinically useful predictors of ONJ.

Conclusion

Osteonecrosis of the jaw is an uncommon condition associated with multiple factors contributing to its pathophysiology. As our understanding of the pathophysiology increases, it is anticipated that effective preventive and treatment regimens will be developed for both the osteoporosis and the oncology patient population. It is recognized that in most cases, the benefits of antiresorptive therapy far outweigh the potential risk of ONJ. We may be able to further improve the risk-benefit ratio by reviewing current treatment approaches to osteoporosis and malignancy with skeletal metastasis using lower doses of antiresorptive therapy and emphasizing good oral hygiene with judicious use of antimicrobial mouth rinses and aggressive management of oral infection. The use of teriparatide in the treatment of ONJ requires further study. In addition, monoclonal antibodies to sclerostin may prove to be an effective treatment approach and further research will enable us to expand therapeutic options for this potentially debilitating condition.

Compliance with ethical standards

Conflicts of interest I, Dr. Aliya Khan would like to declare that I am a member of the advisory board with Amgen and Lilly. I have received honorarium from Amgen and Lilly. I am currently participating in a clinical trial with Amgen and Merck; I have recently completed a clinical trial for NPS pharmaceuticals.

I, Dr. Archie Morrison would like to confirm that I have no conflicts of interest.

I, Dr. Angela Cheung would like to declare that I received honoraria and grants (to institution) from Amgen and Eli Lilly.

I, Dr. Juliet Compston would like to confirm that I have no conflicts of interest.

I, Dr. Waleed Hashem would like to confirm that I have no conflicts of interest.

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