# Osteonecrosis of the jaw and its implications for osteoporosis therapies

**KIRTAN GANDA** BSc, MB BS, FRACP
**MARKUS J. SEIBEL** MD, PhD, FRACP

*Osteonecrosis of the jaw (ONJ) is a rare adverse event related to the use of antiresorptive therapies in patients with osteoporosis. However, the benefits of treatment outweigh the risk of developing ONJ.*

**Key points**

- **The frequency of osteonecrosis of the jaw (ONJ) is one in 10,000 to 100,000 patients treated with antiresorptive therapy for osteoporosis.**
- **Risk factors for ONJ include the duration and dose of antiresorptive therapy, poor dental hygiene, corticosteroid use and invasive dental procedures.**
- **The benefit of preventing an osteoporotic fracture often far outweighs the small risk of ONJ.**
- **In the setting of osteoporosis, most cases of ONJ are mild and represent delayed mucosal repair for which no specific treatment is required.**

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Dr Ganda is a Consultant Endocrinologist in the Department of Endocrinology and Metabolism, Concord Hospital, Sydney; and Clinical Lecturer at the Concord Clinical School, The University of Sydney. Professor Seibel is a Professor and Chair of Endocrinology at The University of Sydney; Head of the Department of Endocrinology and Metabolism, Concord Hospital, Sydney; and Director of the Bone Research Program, ANZAC Research Institute, Sydney, NSW.



Antiresorptive treatment-associated osteonecrosis of the jaw (ONJ) was first reported in 2003 in patients treated with intravenous bisphosphonates in the setting of malignancy.[1] Most cases occur in patients with cancer and skeletal metastases, but ONJ has occasionally been observed among patients treated with antiresorptive agents for osteoporosis.

Although ONJ is a rare event in patients with osteoporosis, reports of such cases have found great attention in the general media with often exaggerated or even erroneous claims. As a result, patients with osteoporosis are often seriously but inappropriately concerned about ONJ and GPs have a crucial role in allaying these exaggerated fears of ONJ in those who require antiresorptive therapy.

This article aims to assist medical practitioners to confidently initiate and maintain treatment in patients with osteoporosis, thereby avoiding delays or failure to treat.

## Definition of antiresorptive treatment-associated ONJ

Antiresorptive treatment-associated ONJ is defined as the presence of exposed bone in the mandibular or maxillary region for more than eight weeks in the setting of current or past antiresorptive therapy and in the absence of previous radiation to the craniofacial region.[2] Affected patients may have associated pain.

## Pathogenesis of ONJ

The pathogenesis of ONJ remains unclear. However, multiple factors are thought to play a role, including periodontal disease,[3] corticosteroid treatment, infection, trauma, reduced bone remodelling and impaired angiogenesis. A potential mechanism for bisphosphonate-associated ONJ has been described.[4] It is thought that after a tooth

extraction, the resultant mucosal defect stimulates the release of inflammatory cytokines and proteases from the periodontal tissue. The proteases then release bisphosphonates from the local bone environment, which in turn may inhibit angiogenesis, delay the formation of granulation tissue and inhibit mucosal tissue repair. This allows the persistence of bacterial infection, which supports the development and further progression of osteonecrosis (see Figure).[5]

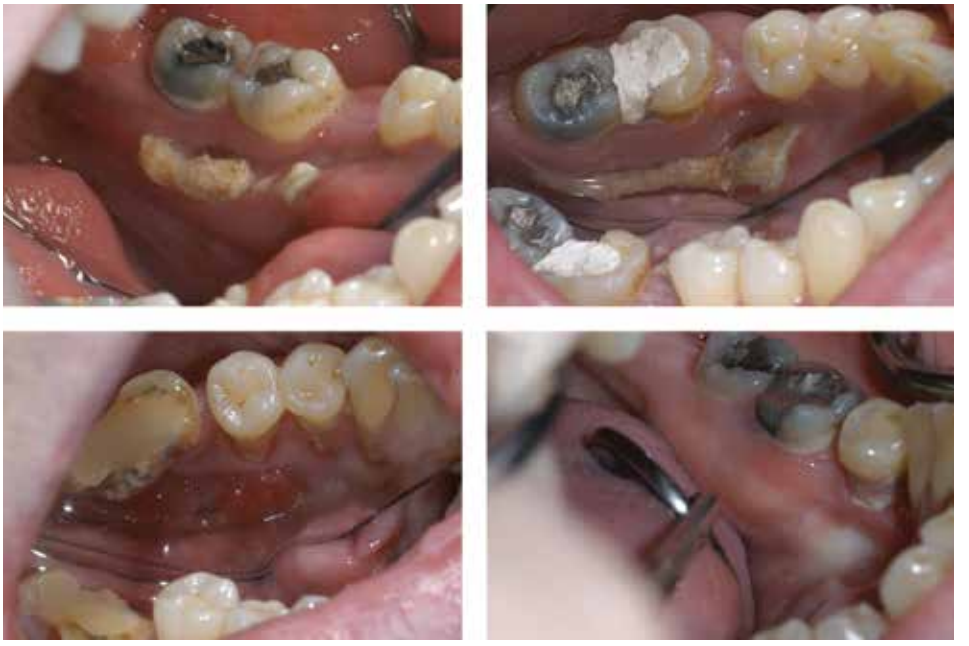

**Figure. A 52-year-old man with osteonecrosis of the jaw after therapy with intravenous zoledronic acid. a (top left). A 1.5 cm area of exposed bone on lingual aspect of mandible after a dental extraction. b (top right). Extension of area of exposed bone at 13-month follow up. c (bottom left). At 46-month follow up, there is partial soft tissue closure after debridement of bone. d (bottom right). Complete soft tissue closure.**

Reproduced with permission from: Watters AL, et al. Oral Surg Oral Med Oral Pathol Oral Radiol 2013; 115; 192-200.[5]

## Frequency of ONJ

The frequency of ONJ has been estimated based mostly on case series and retrospective analyses. In patients treated with antiresorptive therapies for osteoporosis, the frequency of ONJ is about one in 10,000 to 100,000. However, the individual risk of ONJ varies greatly and is determined not only by the amount and duration of bisphosphonate exposure but also by other factors such as poor dental hygiene (pre-existing dental or periodontal disease), corticosteroid use, smoking, alcohol use, previous radiotherapy and invasive dental procedures, such as extractions and poor fitting dental appliances.

The risk of developing ONJ is significantly higher (1 to 10%) in patients with cancer receiving antiresorptive therapy for skeletal metastasis compared with those with osteoporosis. This is thought to be due to:

- the much higher drug doses used in these patients
- the corticosteroids used as part of their cancer treatment regimen
- other, less well-defined factors including poor dental hygiene.

Guidelines have been developed to prevent ONJ in patients with cancer.[6]

The very low risk of ONJ associated with osteoporosis therapy must be weighed up against the significant benefits of this treatment. Modern antiresorptive agents, such as intravenous bisphosphonates (e.g. zoledronic acid) or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. denosumab), reduce the risk of osteoporotic fractures by up to 70%. In absolute terms, the number needed to treat to prevent one fracture varies from 10 to 30, depending on the baseline risk of fracture. On the other hand, the 'number needed to harm' (i.e. to develop one case of ONJ) is 10,000 to 100,000. These numbers clearly favour osteoporosis treatment, which, if withheld, can result in catastrophic fractures and immense cost to both the patient and society.

## Osteoporosis medications and the risk of ONJ

ONJ has been reported among patients treated with bisphosphonates (i.e. alendronate, risedronate, zoledronic acid and pamidronate) and the RANKL inhibitor, denosumab.[7] ONJ has not been reported in patients treated with raloxifene, strontium ranelate or teriparatide. In fact, teriparatide has been used to treat patients with ONJ, although only a few case reports are available and the efficacy of this intervention remains unclear.[8] Currently, there is an ongoing Australian randomised controlled trial of teriparatide to treat patients with cancer-associated ONJ but results are not available yet.

## Management

### Before initiating antiresorptive therapy

Clear doctor–patient communication of the low risk of ONJ is essential once the decision to initiate antiresorptive therapy has been made. Details about the patient's previous dental visit and the need for extractions in the near future should be acquired. If a dental extraction is pending, it is recommended that antiresorptive therapy be started after the extraction site and socket has healed (usually four to six weeks). Patients, particularly those at higher risk of ONJ because of corticosteroid use or poor dental hygiene, should be encouraged to inform their dentist that they are taking antiresorptive therapy for osteoporosis. Furthermore, patients should be encouraged to undergo regular dental visits and practice good oral hygiene; however, a dental examination is not required before starting antiresorptive therapy for osteoporosis.[9]

### During antiresorptive therapy

Patients receiving ongoing antiresorptive therapy who require a tooth extraction should be advised of the low risk of ONJ. The American Dental Association does not recommend stopping treatment with antiresorptive agents before an invasive dental procedure.[9] Therefore, there is no need to cease therapy because the risk of an osteoporotic fracture often outweighs the very low risk of ONJ. Although some experts recommend ceasing treatment before and after the extraction, there are no data to support this recommendation.

If ONJ does occur while a patient is taking antiresorptive therapy, management by a dental specialist is recommended. This usually includes appropriate pain management as well as infection control with oral antimicrobial rinses and/or systemic antibiotic therapy. Surgical treatment is sometimes required to minimise soft tissue trauma (e.g. by removing sharp bone edges and loose bony segments). Whether or not antiresorptive therapy should be ceased will depend on the indication for treatment; however, consideration should be given to treatment cessation until healing has taken place. Of note, in the setting of osteoporosis, most cases of ONJ are mild and represent delayed mucosal repair for which no specific treatment is required. Severe cases of ONJ requiring antibiotics and surgery are rare.

Any confirmed case of ONJ associated with antiresorptive treatment should be reported to the manufacturer and the respective health authorities.

## Conclusion

ONJ is a rare and sometimes serious adverse event associated with antiresorptive therapy for osteoporosis management. Clinicians and patients should be clear about the fact that the benefits of antiresorptive therapy for osteoporosis and the associated fracture risk reduction far outweigh the potential risk of ONJ. **ET**

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