

## Osteonecrosis of the jaw (ONJ) and bisphosphonates

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Oral bisphosphonates are the most common therapies for women with postmenopausal osteoporosis. Each of the three bisphosphonates approved for treating osteoporosis (alendronate [Fosamax], risedronate [Actonel], and ibandronate [Boniva]) have been documented to prevent bone loss and to decrease the risk of vertebral fractures by about 60%, while both alendronate and risedronate had been demonstrated to reduce the risk of nonspine fractures by 30% to 40% and hip fractures by 40% to 50%.<sup>1</sup> Intravenous bisphosphonates (pamidronate [Aredia] and zoledronic acid [Zometa]) are commonly used to treat patients with cancer-related bone diseases such as multiple myeloma and metastatic breast or prostate cancer. The doses of bisphosphonates used for treating cancer are much higher than are the doses used for osteoporosis. Over the past 4 years, the presence of ONJ has been identified in patients receiving bisphosphonate therapy for cancer and for benign diseases including osteoporosis.<sup>2</sup>

*What is ONJ?* The diagnosis of ONJ is made when exposed bone in the mouth is present for 3 months or more.<sup>3,4</sup> Many patients present with no symptoms, and the diagnosis is made by observing a nonhealing lesion of the jaw following an invasive dental procedure, such as tooth extraction or dental implant. In other patients, pain and swelling in the jaw occurs when the exposed bone becomes secondarily infected. It is important to note that ONJ is not a cause of periodontal bone loss, tooth loss, tooth pain, dental caries, or periodontal disease and is not present in most patients with jaw pain.

*Who gets ONJ?* The great majority of patients who are diagnosed with ONJ have received high-dose intravenous bisphosphonate therapy for cancer-related bone diseases.<sup>2</sup> Cancer patients with recent invasive dental procedures, poor dental health (especially severe periodontal disease), bony abnormalities in the mouth (e.g. mandibular tori), injury to the gums (e.g. from ill-fitting dentures), or who take medications like chemotherapy and prednisone that interfere with tissue healing are more apt to have ONJ. It appears that the risk increases with longer term treatment. Patients without cancer who receive the osteoporosis doses of bisphosphonates have also been diagnosed with ONJ. It is probable that the same risk factors apply to these healthy patients with osteoporosis, although it is unclear whether longer treatment is a risk factor in these patients.

*How often does it occur?* Several studies have suggested that ONJ develops in 2% to 10% of patients receiving intravenous bisphosphonate therapy for cancer, usually after 2 or more years of treatment.<sup>3,4</sup> In healthy adults being treated with bisphosphonates for osteoporosis, the incidence is not known but is estimated to be between 1:60,000 and 1:100,000.<sup>5,6</sup> The risk is higher in patients who have dental procedures exposing the bone. We do not know whether the risk differs among the three approved bisphosphonate drugs. It is important to compare this risk with the benefit of bisphosphonate therapy in women with osteoporosis. A 70-year-old woman whose bone

mineral density is at the threshold for the diagnosis of osteoporosis (T-score  $-2.5$ ) has a risk of experiencing a serious fracture (hip, spine, wrist, or shoulder) of about 2% each year.<sup>7</sup> If she has had a fragility fracture since menopause, her risk is about 3.5% per year, and if she has had a previous spine fracture, her risk is about 8% per year. Since bisphosphonate treatment reduces overall fracture risk by about 50%, the absolute reduction in fracture risk in the three patients described would range from 1% to 4% per year (1 in 25 to 1 in 100). Thus, the benefit of treating women with osteoporosis with bisphosphonates far outweighs the risk of developing ONJ. Since fracture risk reduction has not been observed with bisphosphonate therapy in postmenopausal women who do not have osteoporosis, the risk/benefit ratio cannot be estimated in those patients.

#### *Recommendations to patients.*<sup>3, 4</sup>

For patients in whom bisphosphonates therapy is being considered, it would be appropriate to have any planned invasive dental procedures performed and the lesions healed before beginning treatment. For patients on bisphosphonate therapy for 2 or more years who require nonemergency invasive dental procedures, it is advised to stop therapy for 2 to 3 months and then wait until the lesions have healed before restarting treatment. There is no evidence that discontinuing therapy reduces the risk of ONJ, but there is very little risk in stopping therapy for a few months. There is no justification for these patients to avoid routine dental care such as cleaning, fillings, or placement of crowns or for stopping treatment before routine treatments. On the contrary, it is probably more important for patients on bisphosphonate therapy to receive regular dental care. If a patient receiving a bisphosphonate develops oral lesions consistent with ONJ, stopping therapy is advised (again without evidence of benefit), and referral to an oral surgeon experienced in managing this problem is appropriate.

*Conclusion.* Although ONJ appears to be a potential complication of oral bisphosphonate therapy for osteoporosis, the likelihood of it happening is very small and should not preclude therapy in patients at moderate to high risk of fracture.

#### **References**

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