

## **Risk Factors for Bisphosphonate Associated Jaw Osteonecrosis**

*Summarized by Jon Giles, M.D.*

Gastrointestinal complications, including esophageal mucosal ulceration, are the most frequent complications of bisphosphonate therapy, commonly used to treat osteoporosis, metabolic bone diseases (such as Paget's disease), multiple myeloma, and to inhibit metastatic solid tumor progression. Recent case reports have emphasized a less frequent complication of bisphosphonate therapy: osteonecrosis of the jaws. However, due to its rarity, little is known about the epidemiology of this potentially troublesome complication. Here, Woo et al. (*Ann Intern Med* 2006; 144: 753) report the findings of a systematic review of published case reports and case series of jaw osteonecrosis associated with bisphosphonate therapy.

**Methods** Published case reports and case series of bisphosphonate associated jaw osteonecrosis were identified from MEDLINE and PubMed and abstracts from the American Society of Clinical Oncology. Data on epidemiology and risk factors was synthesized from the compiled publications.

**Results** 368 unique cases of bisphosphonate associated jaw osteonecrosis were identified from 30 publications. No publications prior to 2003 were identified. Most cases involved the mandible only (65%). One third of lesions were painless. Sixty percent of cases occurred after dental surgery, with the remaining occurring often in the setting of denture wear or in areas in which minor localized oral trauma was common.

Ninety four percent of cases occurred in conjunction with intravenous therapy with the aminobisphosphonates pamidronate or zoledronic acid. The non-aminobisphosphonate, clodronate, was not associated with any published reports of jaw osteonecrosis. Most (85%) of cases occurred in the setting of multiple myeloma or metastatic cancer. Only 4.1% of cases (15 reported patients) occurred in patients treated for osteoporosis (most of who were treated with oral bisphosphonates).

The risk of jaw osteonecrosis increased with duration of exposure to intravenous bisphosphonate, with the median time of exposure until the development of jaw osteonecrosis of 22 to 39 months. The earliest report of bisphosphonate associated jaw osteonecrosis occurred after 4 months of treatment. The cumulative hazard of jaw osteonecrosis was higher in patients treated with zoledronic acid compared to those treated with pamidronate (21% vs. 4% at 3 years, respectively).

**Conclusions** The strongest association of bisphosphonate use and jaw osteonecrosis occurred in patients treated with intravenous bisphosphonates of the amino-bisphosphonate class (pamidronate and zoledronic acid) and mostly in those receiving these drugs for malignancy. Dental surgery and/or physical trauma to the jaw were precipitating events in many cases.

**Editorial Comment** This systematic review is helpful in placing the risk of jaw osteonecrosis, a rare but potentially serious outcome, into perspective. In particular, the risk appears to be exceedingly low in those receiving oral therapy for osteoporosis treatment and prevention. In general, the dose of intravenous bisphosphonate is much higher when used for malignancy than

when used for osteoporosis, and thus, may represent a dose effect. However, oral users for osteoporosis are not immune from this outcome, and thus diligence on the part of prescribers for this outcome is warranted. The severity of osteonecrosis was not addressed in this publication, and thus it is possible that low grade and/or reversible osteonecrosis (i.e. not severe enough to warrant publishing as a case report) may be occurring more frequently in users of oral bisphosphonates.

The association with dental surgery and oral trauma is interesting and should warrant some consideration prior to the use of these agents in patients planning dental surgery. The half-life of these agents is very long, and thus attempting to “wash-out” a long-standing bisphosphonate prior to dental surgery is not practical. Whether temporary discontinuation of bisphosphonates prior to significant dental surgery would be effective at reducing the risk of jaw osteonecrosis has not been studied. However, given the rarity of the outcome among oral users, it is likely not advisable to routinely discontinue the drug in these patients in this circumstance.