Osteonecrosis of the Jaw and Bisphosphonates

TO THE EDITOR: Cases of osteonecrosis of the jaw in connection with the use of bisphosphonates were reported in 2003.[1,2] In 2004, the International Myeloma Foundation conducted a Web-based survey to assess the risk factors for osteonecrosis of the jaw. Of 1203 respondents, 904 had myeloma and 299 breast cancer. Both osteonecrosis and suspicious findings, including bone erosions and spurs plus exposed bone, were assessed. Sixty-two patients with myeloma had osteonecrosis of the jaw and 54 had suspicious findings; 13 patients with breast cancer had osteonecrosis and 23 had suspicious findings — a total of 152 patients with either osteonecrosis or suspicious findings. Of the patients with myeloma, 71 percent had received zoledronic acid and 29 percent had received only pamidronate.

Figure 1 displays the cumulative incidence of osteonecrosis of the jaw among patients receiving either zoledronic acid alone or pamidronate alone who responded to the survey. With censoring at 36 months, osteonecrosis of the jaw developed in 10 percent of 211 patients receiving zoledronic acid, as compared with 4 percent of 413 patients receiving pamidronate (P=0.002 by the log-rank test). The earlier onset of osteonecrosis of the jaw among patients receiving zoledronic acid during the first 36 months reflects remarkably well the reported increase in the occurrence of osteonecrosis in the first 36 months after the Food and Drug Administration approved the drug in 2001.

The censored 36-month estimates of osteonecrosis, suspicious findings, or both did not differ between patients with myeloma and those with breast cancer (P>0.50). No other therapies, including corticosteroids and thalidomide, conferred an added risk over time (P>0.50). However, a history of underlying dental problems, such as infection or dental extraction, was present in 81 percent of patients with myeloma and in 69 percent of patients with breast cancer who had osteonecrosis of the jaw, as compared with 33 percent of those without osteonecrosis (P<0.001 and P=0.01, respectively, in a two-sided test). Maxillofacial surgery was a particular problem for patients with osteonecrosis of the jaw, since the surgery resulted in areas of nonhealing bone and soft tissue that were larger than those in patients who did not undergo surgery.

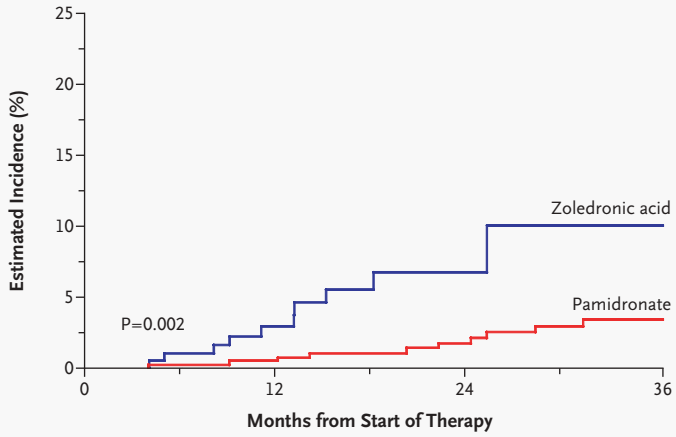

Figure 1. Time to the Onset of Osteonecrosis of the Jaw in Patients with Myeloma Receiving Zoledronic Acid or Pamidronate.

Among patients receiving zoledronic acid, the occurrence of osteonecrosis of the jaw is particularly notable at months 4, 8, 9, 11, 13, 15, and 18. With data censored at 36 months, the estimated incidence among patients receiving zoledronic acid was 10 percent and that among those receiving pamidronate was 4 percent. Without censoring, the mean time to the onset of osteonecrosis among patients receiving zoledronic acid was 18 months, as compared with 6 years for patients receiving pamidronate (P=0.002).

In September 2004, Novartis, the manufacturer of pamidronate (Aredia) and zoledronic acid (Zometa), issued post-marketing guidelines[3] for both drugs in relation to osteonecrosis of the jaw that emphasized a particular risk with surgical intervention. The International Myeloma Foundation is working collaboratively with Novartis to raise awareness and develop enhanced guidelines. The full results of the study were presented to the Food and Drug Administration at an Oncology Drug Advisory Committee meeting held on March 4, 2005.[4]

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TO THE EDITOR: Bisphosphonates are powerful osteoclast inhibitors with antitumor and antiangiogenic properties and a half-life of many years. The use of these drugs significantly reduces skeletal-related events in patients with multiple myeloma and other cancers.[1] However, long-term use can result in suppression of bone turnover and compromised healing of even physiologic microinjuries within bone that occur as a result of day-to-day stresses.[2]

Osteonecrosis of the jaw has been reported recently in patients with cancer who were receiving either pamidronate or zolendronate, or both, and in those receiving alendronate for osteoporosis.[3] Osteonecrosis of the jaw presents as an exposure of the mandible or maxilla that can be either painless or painful. Unlike osteoradionecrosis, osteonecrosis involves the maxilla fairly frequently, and as many as one fifth of cases occur spontaneously. We have seen more than 20 cases of osteonecrosis of the jaw in patients with myeloma at our institution during the past six months, although we had seen very few in previous years; the reasons for this increased incidence are unclear.

Osteonecrosis of the jaw probably results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiologic stress (mastication), iatrogenic trauma (tooth extraction or denture injury), or tooth infection in an environment that is trauma-intense and bacteria-laden. Coexisting factors may include the use of other medications with antiangiogenic properties (such as glucocorticoids, thalidomide, and bortezomib in patients with myeloma), diabetes mellitus, irradiation of the jawbone, peripheral vascular disease, and hyperviscosity syndromes. It is hypothesized that benign sequestration of the lingual mandibular plate in healthy persons results from physiologic trauma to the mucosa, leading to hypovascularity and focal bone death.[4] Interestingly, this site is frequently involved in osteonecrosis.

Radical resection appears to be of limited use in cases of osteonecrosis of the jaw and may be contraindicated; the disease may progress despite surgery and cessation of bisphosphonate therapy.[3] Factors such as underlying disease status, prognosis, extent of the lesion, presence or absence of jaw pain, and presence or absence of infection (not just surface bacterial colonization) should be considered when planning further treatment. Once bone resorption has been curtailed, there may be little benefit in giving lower doses of bisphosphonates, especially in patients receiving long-term bisphosphonate therapy.[5]

In our view, until studies in animals and prospective clinical trials shed more light on this condition, patients should be informed of the risk of osteonecrosis. Dentists and oral surgeons should judiciously remove all dental infections before or within a few weeks of the initiation of bisphosphonate therapy in this high-risk population of patients with cancer. Moreover, among patients receiving bisphosphonates in whom dental infections develop, withdrawal of the drugs until the infection is controlled may be warranted.

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TO THE EDITOR: The main known risk factors for osteonecrosis of the jaw are dental procedures, poor dental hygiene, corticosteroid therapy, and local

radiotherapy. More recently, treatment with bisphosphonates, such as pamidronate and zoledronic acid, was reported to be associated with osteonecrosis of the jaw among cancer patients.[1,2] However, other confounding risk factors for osteonecrosis were also noted in published reports, especially dental procedures during therapy.[3] As a consequence, the manufacturer of zoledronic acid recently modified its U.S. post-marketing and precautions information with the following statement regarding dental care: "While on treatment, these patients should avoid invasive dental procedures, if possible" (www.pharma.us.novartis.com).

We report nine cases of well-documented osteonecrosis of the jaw that occurred in patients who were receiving therapy with zoledronic acid but had not undergone dental procedures. In September 2002, we started using zoledronic acid almost exclusively for skeletal protection in patients with cancer. Zoledronic acid was given every three or four weeks at a dose of 4 mg intravenously during a period of 15 minutes. Between December 2003 and July 2004, nine cases of osteonecrosis of the jaw were diagnosed at our institution (four in patients with multiple myeloma and five in patients with metastatic breast cancer) among 194 patients treated with zoledronic acid. Before receiving zoledronic acid, six patients had been treated first with pamidronate (90 mg every three or four weeks). Eight of the nine patients had biopsy-proven osteonecrosis of the jaw. All the cases were diagnosed while the patients were receiving zoledronic acid. The median duration of treatment with pamidronate was 39 months (range, 4 to 58), with a median cumulative dose of 3060 mg (range, 360 to 5520). For zoledronic acid, the median duration of therapy before the appearance of osteonecrosis was 18 months (range, 4 to 22), and the median cumulative dose was 72 mg (range, 36 to 88).

The percentage of cases of osteonecrosis of the jaw that are associated with zoledronic acid is high in our institution (4.6 percent). Nevertheless, our data confirm other previous reports concerning the possible association between bisphosphonates and osteonecrosis of the jaw. From our observations, it is unclear which bisphosphonate, zoledronic acid or pamidronate, is the causal agent. However, our analysis provides more evidence that further investigations should be performed to determine which patients are at increased risk for osteonecrosis of the jaw, what is the optimal and safe duration of treatment, and what recommendations should be made for the follow-up of patients being treated with bisphosphonates.

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THE ABOVE LETTERS WERE REFERRED TO NOVARTIS PHARMACEUTICALS, THE MANUFACTURER OF PAMIDRONATE AND ZOLEDRONIC ACID, WHICH OFFERS THE FOLLOWING REPLY: The letters published in this issue of the *Journal*, as well as case reports published since 2003,[1-3] underscore the fact that osteonecrosis of the jaw is a concern for cancer patients and their physicians. As the developer of Aredia (pamidronate) and Zometa (zoledronic acid), we have obtained expert advice on how to revise the labels for these two drugs. Our labeling recommends a dental examination to identify and correct predisposing conditions before bisphosphonate treatment is started in patients with potential risk factors, including cancer.[4] This approach may help identify and rectify dental problems before or during treatment so that osteonecrosis of the jaw may be prevented or its progression limited. Patients taking bisphosphonates should avoid invasive dental procedures, if possible. Further, more conservative treatments for osteonecrosis of the jaw may also include systemic antibiotics to control or prevent infection, as well as antimicrobial oral rinses.

Dental surgery may exacerbate osteonecrosis of the jaw in patients in whom the condition has developed during bisphosphonate therapy. No data are available to suggest whether discontinuation of bisphosphonate treatment in patients requiring

dental procedures reduces the risk of osteonecrosis. Collaboration between the oncology and dental communities will be important for gaining better insights into the optimal treatment of patients with osteonecrosis of the jaw.

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