

Pharmacovigilance and reporting of bisphosphonate use and osteonecrosis of the jaw

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Concerned groups need better coordination when it comes to reporting serious adverse drug reactions.

Osteonecrosis of the jaw (ONJ) is a unique and potentially serious adverse drug reaction. A weakened state of bone structure due to cell death (necrosis), ONJ can affect the structural integrity of the mandible, maxilla, or teeth.¹ Patients with ONJ can develop gum inflammation and infection, loss of tooth stabilization, and painful lesions in the gums that can eventually expose weakened jaw bones.³ There is no treatment for

this condition, and most therapy aims at simply curtailing it. In some cases, oral surgery is recommended to remove the necrosed bone.³ This toxicity has been reported specifically with the bisphosphonates zoledronic acid (Zometa) and pamidronate (Aredia).

Cases reported

Between 2001 and 2003, 107 patients with ONJ received care from dental professionals. In late 2003 and 2004, peer-reviewed case series were published. By 2006, safety databases maintained by the US Food and Drug Administration (FDA), the manufacturer (Novartis), and the Research on Adverse Drug Events And Reports (RADAR) project included information on 3,061 total cases of ONJ.¹⁻⁸ In 2004 and 2005, the manufacturer reported an incidence estimate of 0.8 ONJ cases per 1,000 person-years of intravenous bisphosphonate therapy,² whereas academic investigators reported 22 ONJ cases per 1,000 person-years.^{9,10}

The RADAR project reviewed databases maintained by pharmacovigilance departments of the manufacturers of bisphosphonates, the FDA Adverse Event Reporting System, the peer-reviewed literature, medical records, and case reports submitted to the International Myeloma Foundation in response to a Web-based survey.

Case series information was initially obtained from healthcare providers. The first nine cases of bisphosphonate-associated ONJ were spontaneously reported to the FDA by healthcare providers in 2002. In 2004, four oral surgeons independently reported to the FDA information on 107 cancer patients with bisphosphonate-associated ONJ seen in their referral dental practices in California, Florida, and New York. These case series were subsequently published as peer-reviewed articles between 2003 and 2004.³

Subsequently, descriptions of this adverse drug reaction were reported with increasing frequency to the manufacturers and the FDA; by 2006, 3,061 total cases were included in safety databases maintained by the FDA and the manufacturer of intravenous bisphosphonates. These reports indicated that the earliest case was associated with pamidronate and had occurred in 1989; in 2004, 391 cases had occurred.

In 2004, 75 patients with breast cancer or multiple myeloma and bisphosphonate-associated ONJ reported to the International Myeloma Foundation that they had been diagnosed with this toxicity. The manufacturer sponsored investigators at M. D. Anderson Cancer Center to review records of all bisphosphonate-treated

Fast Facts

INTRAVENOUSLY ADMINISTERED BISPHOSPHONATES are approved by the US Food and Drug Administration for treatment of hypercalcemia of malignancy, osteoporosis, Paget's disease, and metastatic bone disease of multiple myeloma, breast, lung, and prostate cancers. Bisphosphonates target these conditions by inhibiting osteoclast reabsorption of bone.² These drugs have several modes of tumor suppression, including tumor cell apoptosis, inhibition of tumor extracellular matrix adhesion, and inhibition of tumor invasion.² Two of the most common commercially available intravenous bisphosphonates are pamidronate (Aredia) and zoledronic acid (Zometa).

breast cancer and multiple myeloma patients at that institution. The search identified 16 cases of bisphosphonate-associated ONJ. Also, in 2005, the manufacturer identified 16 cases of bisphosphonate-associated reactions among adverse event reports contained in its industry-sponsored clinical trials database.⁴

Recommendations

Our findings show that the high incidence of ONJ concurrent with bisphosphonate treatment attracted attention among many independent pharmacovigilance groups. Nevertheless, the effort to identify this serious toxicity, although widespread and energetic, was uncoordinated. It is important to increase collaboration among oncologists and dental and oral health professionals in order to greatly improve the effectiveness of reporting adverse drug reactions.

When safety concerns were first reported to the FDA by oral surgeons in 2003, the FDA had already received spontaneous reports from other healthcare providers describing almost 300 cases of ONJ. This finding suggests that despite the relative rapidity with which ONJ was recognized and reported as an adverse drug reaction, a more organized pharmacovigilance approach may result in an even more expedient identification of the problem.

In 2004, an expert panel convened by Novartis recommended that patients on intravenous bisphosphonates be educated on maintaining excellent oral hygiene to reduce the risk of infection. Among the recommendations for patients:

- Aggressively manage oral infections with non-surgical means;
- Have a dental examination prior to initiating bisphosphonate therapy;
- Complete any necessary dental procedures (eg, tooth extraction) prior to initiating bisphosphonate therapy;
- Practice good oral hygiene and minimize jaw trauma;
- Undergo regular dental evaluations during therapy.

If an oncologist is told that a patient has exposed bone or notices exposed bone during routine examination of the mouth, the patient should be referred to an oral surgeon or dentist immediately.

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