Reports of Adverse Events From Bone Drugs Prompt Caution

Bridget M. Kuehn

In 2003, CASE REPORTS OF A RARE BUT serious condition occurring in patients taking bisphosphonates to prevent breakdown of bone began surfacing. Since then, reports of more than 2000 cases of this adverse event, osteonecrosis of the jaw, have spurred letters of caution from the manufacturer to physicians and dentists, revisions to the labels of some of the products, and recommendations from the US Food and Drug Administration (FDA).

Although most cases have occurred in patients receiving high-dose intravenous formulations of the drugs as part of cancer treatment, some have occurred in patients taking popular oral bisphosphonates to treat or prevent osteoporosis, suggesting that the problem may be a class effect. Scientists from the FDA have also recently identified another type of adverse event, severe bone, joint, or muscle pain associated with oral formulations.

Some professional groups of physicians and dentists are taking steps to prevent osteonecrosis of the jaw in patients who take these drugs. But many unanswered questions remain about the role of bisphosphonates in these adverse events, how best to prevent such problems, as well as the degree of risk associated with the drugs.

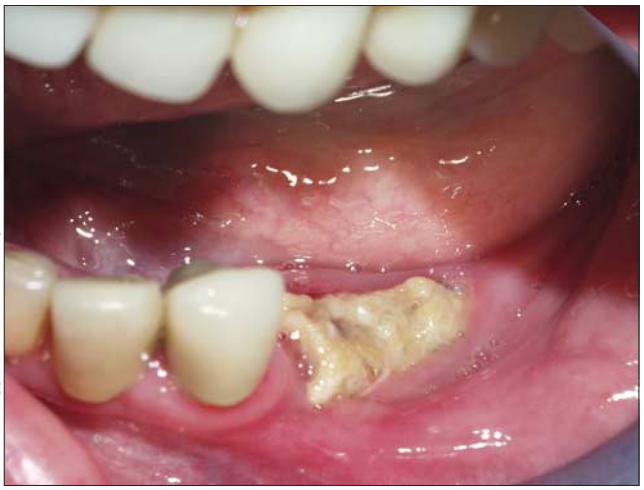
AN EMERGING PICTURE

Patients who develop bisphosphonate-associated jaw osteonecrosis present with such symptoms as sensations of heaviness or numbness in the jaw, pain, swelling, infection, loose teeth, and exposed bone, according to a panel of oral health and physician experts convened in June 2004 by Novartis, the maker of the intravenous bisphosphonates zoledronic acid and pamidronate. Although randomized, prospective clinical trials designed to establish the frequency of these adverse events will be needed to provide a more accurate risk assessment, data on the frequency of problems in patients taking bisphosphonates are beginning to emerge.

Novartis has received 2400 adverse event reports of osteonecrosis and/or osteomyelitis of the jaw. The company estimates that between 2.5 million and 3 million individuals have taken zoledronic acid or pamidronate. Geoffrey M. Cook, executive director of global public affairs for Novartis Oncology, said the company is supporting research on osteonecrosis and bisphosphonates. These projects include a 10-year retrospective review of the charts of 4000 patients with cancer who were treated with bisphosphonates at M.D. Anderson Cancer Center in Houston and a patient registry developed in conjunction with the Southwest Oncology Group, a clinical trials network headquartered at the University of Michigan in Ann Arbor. Additionally, several ongoing clinical trials of zoledronic acid as a treatment for osteoporosis or other bone disorders include osteonecrosis as an end point.

A recent systematic review of 368 published reports of bisphosphonate-associated jaw osteonecrosis found that 94% of the cases occurred in patients with multiple myeloma and metastatic carcinoma to the skeleton who were receiving intravenous bisphosphonates (Woo SB et al. *Ann Intern Med.* 2006;144:753-761). Woo and colleagues estimated that the prevalence of osteonecrosis of the jaw is 6% to10% in patients with cancer taking bisphosphonates, but said that the risk associated with taking bisphosphonates for osteoporosis is unknown.

The researchers also found that trauma to the jaw bone seems to be a major risk factor. In 60% of the reported cases, patients developed the



Salvatore Ruggiero, DMD, MD/Long Island Jewish Medical Center

Exposed bone in the mouth of a patient with osteonecrosis of the jaw. This rare condition has been reported in more than 2000 patients taking bisphosphonates to prevent bone loss. These cases have occurred primarily in patients with cancer taking intravenous formulations.

problem after dental surgery, and the other 40% were likely related to damage caused by dentures, other trauma to the jaw, or infection.

Salvatore Ruggiero, DMD, MD, chief of the division of oral and maxillofacial surgery at Long Island Jewish Medical Center, in New Hyde Park, NY, and colleagues have documented 159 cases of jaw osteonecrosis in patients taking bisphosphonates, 25 of whom took oral formulations. Taking more potent bisphosphonates or taking the drugs for longer periods appears to be associated with the greatest risk, he said.

PAIN SYNDROME

Some patients taking some oral bisphosphonates have reported severe and sometimes incapacitating bone, joint, or muscle pain, FDA officials reported in a letter to the *Archives of Internal Medicine* in February 2005 (Wysowski DK and Chang JT. *Arch Intern Med*. 2005;165:346-347). Between November 2002 and September 2005, the FDA received 118 reports of a severe pain syndrome in patients taking alendronate. Six reports of the pain syndrome were associated with risedronate use and were reported between September 1998 and June 2003. These reports suggest this pain syndrome may represent a class affect, according to the letter. Clinical trials of oral bisphosphonates also revealed a higher frequency of musculoskeletal pain in those taking the drugs than those taking a placebo, according to the FDA.

The pain syndrome has not yet been clearly defined, and data on the frequency of this adverse event were not included in the drugs labeling, according to FDA officials. However, the labels of these drugs now include adverse event warnings about musculoskeletal pain, in addition to warnings about osteonecrosis of the jaw and the more common gastrointestinal tract problems associated with these drugs.

FDA officials suspect the pain syndrome may be a more common adverse effect than has been documented and that it may have a broad range of presentations from mild to severe. "Underreporting of pain is probably considerable because of its subjective nature and because physicians may attribute pain to osteoporosis," Wysowski and Chang note in the letter to the *Archives of Internal Medicine*. They recommend patients report such pain to their physicians, and suggest that physicians consider discontinuing bisphosphonate therapy in patients who experience severe pain.

OVERSUPRESSION?

While the etiology of the pain syndrome remains a mystery, scientists hypothesize that osteonecrosis of the jaw in patients taking these drugs may be the result of oversuppression of osteoclasts. These cells break down existing bone, including damaged or diseased bone, as part of the constant remodeling that occurs in healthy bone. Bisphosphonates, both oral and intravenous formulations, appear to slow bone loss by inhibiting the activity of osteoclasts. However, Woo and colleagues hypothesize that oversuppression of the osteoclasts may allow damaged bone to accumulate in the jaw and lead to osteonecrosis. In patients experiencing trauma or an infection in the jaw, in particular, the suppressed osteoclasts may be unable to meet the demands for repair.

The FDA has required changes to the labeling of bisphosphonate drugs to reflect the possible risk of osteonecrosis. The labels for alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid posted on the FDA Web site, http://www.fda.gov/, all note reports of osteonecrosis of the jaw.

PREVENTION EMPHASIZED

For now, the FDA, the drugs' manufacturers, and professional groups are urging physicians and dentists to take precautions to prevent jaw osteonecrosis, particularly in patients receiving intravenous bisphosphonates. The labeling for intravenous zoledronic acid and pamidronate required by the FDA recommends that patients with cancer, patients who have received chemotherapy or corticosteroids, and those with poor oral hygiene should receive a dental examination and any appropriate preventive dental procedures before initiating treatment with these drugs. Once patients are taking bisphosphonates, the labels suggest avoiding invasive dental procedures if possible.

However, the recommendations are less clear when dental surgery cannot be avoided. There are no data on whether discontinuing the drug might aid healing, according to the label. In these cases, physicians are advised to weigh the risks and benefits for the patient.

For patients taking oral bisphosphonates, the risk of osteonecrosis appears to be small and related to duration of treatment. But a paucity of data has led to varying recommendations on how physicians should manage these risks.

"I think you have a lot more leeway with the orals," said Ruggiero. He said he would not be concerned about a surgical procedure such as a tooth extraction in a patient who has taken oral bisphosphonates for 2 years, but he would be worried about such a procedure in patients who have been on the drug 5 to 10 years. In such individuals, physicians should consider a break in bisphosphonate therapy to reduce the risk, he said.

"I think [physicians] need to be aware this is a potential problem with oral bisphosphonates, though the risk is probably small and related to exposure over many years," he said.

Kenneth G. Saag, MD, director of the Center for Education and Research on Therapeutics of Musculoskeletal Disorders at the University of Alabama at Birmingham, was more cautious about the usefulness of a break in bisphosphonate treatment, noting the drugs are retained in the bones for months or years and no washout period has been established. "I'm not sure stopping has any merit, given that the level of risk [of developing this complication] is probably 1 in 1000," he said.

He said he and his colleagues are advising patients who are starting bisphosphonates and plan to undergo

dental work to have such procedures completed before initiating the drug. He does not think patients who need an invasive dental procedure and have been on bisphosphonates for years should stop taking the drug, unless their physician has another reason to recommend a drug "holiday." The value of drug holidays for patients who have taken oral bisphosphonates for long periods is currently being debated by scientists because some believe that suppressing bone remodeling over many years may eventually weaken a patient's bones.

Woo and colleagues note "there is no published evidence to support or oppose discontinuation of bisphosphonate therapy once osteonecrosis develops, or before required dental surgery." However, there have been some anecdotal reports of healing and recovery in patients with osteonecrosis several months after they stop taking the drugs.

Given the paucity of data on risks associated with oral bisphosphonates, Saag said he and his colleagues worry that paranoia may be getting ahead of the science. The oral medications have been on market for a decade and the number of reports of osteonecrosis in patients taking oral bisphosphonates "is low and the absolute risk minimal," he said. "I'm a strong advocate of getting more data." □

Rare Disease Research Gets Boost

Tracy Hampton, PhD

WHILE SCIENTISTS WHO STUDY conditions such as cancer, heart disease, or stroke can present alarming statistics to highlight a need for funding for their research, those who study rare diseases can find it hard to compete for research dollars. But rare does not mean unimportant, according to the National Institutes of Health (NIH), which announced it will devote $71 million to launch the first clinical studies of its Rare Diseases Clinical Research Network.

More than 20 studies are expected to open in the next few months at about 50 sites in the United States and other countries.

Coordinated primarily by the Office of Rare Diseases and the National Center for Research Resources at the NIH, the network will consist of a central data and technology coordinating center and 10 research consortia charged with investigating a variety of the approximately 6000 rare diseases identified to date. The program has the potential to improve diagnosis and treatment of numerous rare disorders and to provide researchers with a better understanding of the diseases' characteristics and progression.

Rare diseases, defined as diseases or conditions affecting fewer than 200 000 individuals each in the United States, affect an estimated 25 million Americans. The 10 research consortia will study a range of diseases including Angelman, Rett, and Prader-Willi syndromes; myelodysplastic syndrome and other bone marrow failure conditions; lymphangioleiomyomatosis and other rare lung diseases;

Rare Diseases Consortium Studies Currently Recruiting Participants

Consortium	Study Name
Urea Cycle Disorders Consortium	Longitudinal Study of Urea Cycle Disorders
Angelman, Rett, and Prader-Willi Syndromes Consortium	Rett Syndrome Natural History Study Angelman Syndrome Natural History Study
Consortium for Clinical Investigation of Neurological Channelopathies	Episodic Ataxia Syndrome: Genotype-Phenotype Correlation and Longitudinal Study Nondystrophic Myotonias: Genotype-Phenotype Correlation and Longitudinal Study
Bone Marrow Failure Disease Consortium	Screening Protocol and Longitudinal Study of Bone Marrow Failure Syndromes and Cytopenias Phase 1/2 Trial of Sirolimus (Rapamune) and Cyclosporine in Patients With Refractory Aplastic Anemia Phase 1 Study of Revlimid in Combination with Azacitidine in Patients With Advanced Myelodysplastic Syndrome
Vasculitis Clinical Research Consortium	Longitudinal Protocol for Giant Cell Arteritis Longitudinal Protocol for Takayasu's Arteritis Longitudinal Protocol for Polyarteritis Nodosa Longitudinal Protocol for Wegener's Granulomatosis and Microscopic Polyangiitis Longitudinal Protocol for Churg-Strauss Syndrome
Genetic Diseases of Mucociliary Clearance Consortium	Rare Genetic Disorders of the Airways: Cross-sectional Comparison of Clinical Features, and Development of Novel Screening and Genetic Tests

Source: Rare Diseases Clinical Research Network (http://rarediseasesnetwork.epi.usf.edu/study-overview.htm). Accessed May 30, 2006.

The Rare Diseases Clinical Research Network is enrolling patients in more than a dozen studies on certain rare disorders. Trials for other rare conditions are expected to begin in the near future.