Bisphosphonates: ONJ Bystander or Cause?

BY FRAN LOWRY

CHICAGO — Many people who currently take or who have taken bisphosphonates are being denied essential dental procedures because of undue fears about bisphosphonate-induced osteonecrosis of the jaw, according to a specialist in oral pathology.

"The phenomenon of ONJ seen in patients who happen to be on a bisphosphonate can also be seen in patients who have never had a bisphosphonate, but whether the bisphosphonate is directly responsible for this occurrence has not been scientifically [proved]," said Ellen Eisenberg, D.M.D., head of oral and maxillofacial pathology at the University of Connecticut Health Center in Farmington.

Dr. Eisenberg, a pathologist and a consultant for Novartis, said she is unable to tell the difference between osteonecrosis of the jaw (ONJ) that has occurred in patients treated with radiation for head and neck cancer, in patients treated with intravenous or long-term oral bisphosphonates, or in patients who have not received either treatment.

"If you were to take something like 15 microscopic slides from dead bone of the jaw in such patients and ask me to tell what the difference is amongst them, I can tell you this: They all look the same," she said.

The definitive diagnosis of bisphosphonate-associated ONJ requires exposed bone in the jaw for 8 weeks or longer. Although most cases involve a history of a surgical procedure in the mouth, most typically a tooth extraction, 40% of cases report sudden exposure of bone for no reason.

"The jaw is a high traffic area that is subject to extreme forces, and therefore it is very likely that a patient may not recall a particularly traumatic event. Nevertheless, that trauma occurred, and that preceded the exposure of the bone," Dr. Eisenberg said at the annual Chicago Supportive Oncology Conference.

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DR. EISENBERG

Dr. Eisenberg emphasized that the pathogenesis of ONJ is presumptive, based on the presumed alteration in the dynamic inhibition, resorption, and apposition of bone. "However, we do not know with any scientific certainty that this [presumed alteration] is, indeed, the cause," she said.

Until results from definitive studies show that bisphosphonates, whether oral or intravenous, are indeed the cause of ONJ, it is imperative that any patient about to embark on bisphosphonate therapy get a thorough dental examination, so that any potential sites of infection or inflammatory disease can be eliminated, Dr. Eisenberg said.

Patients who develop ONJ have a host of comorbidities which may be cofactors in play. Right now, it is not scientifically sound to focus on just bisphosphonates as the cause, since there may be other reasons for developing ONJ, she maintained. For instance, patients with metastatic breast cancer or multiple myeloma suffer from widespread disease, with all of its implications, Dr. Eisenberg said.

Even older age can predispose an individual to develop ONJ, she added.

Dr. Eisenberg also suggested that a genetic polymorphism may predispose individuals to develop bisphosphonate-associated ONJ. "This is my suspicion, and it is purely conjecture, but I think that there is a subset of individuals who may be susceptible because their genetic profile predisposes them to the complication," she said.

"What that genetic polymorphism is, I don't know, but we cannot dismiss the fact that only a very small proportion of people actually get ONJ. What is it that makes them vulnerable? Much more work needs to be done before we single out bisphosphonates as the sole cause."

The conference is sponsored by the Journal of Supportive Oncology. The Journal of Supportive Oncology and this news organization are owned by Elsevier. ■

Gene Linked to OA, Nonvertebral Fractures

BY MICHELE G. SULLIVAN

A genetic variant known to affect height and osteoarthritis risk has now been shown to increase the risk of nonvertebral fracture in older women, possibly because of the increased hip axis length seen in those with two copies of the gene.

"Our results suggest that the GDF5 variants target the long bones, since we find an association with hip axis length," lead investigator Dr. Joyce van Meurs said in an interview. "This difference in hip axis length could cause a difference in fracture risk."

Findings from the Rotterdam Study, a prospective population-based cohort of 6,114 individuals aged 55 years and over, showed that women who carried two copies of the gene were 32% more likely to experience nonvertebral fracture during the follow-up period than were noncarriers. Women with one copy of the gene had no increased risk; nor did men, regardless of their genotype, wrote Dr. van Meurs of the Erasmus Medical Centre, Rotterdam, the Netherlands, and her colleagues (Ann. Rheum. Dis. 2008 Nov. 24 [doi:10.1136/ard.2008.099655]).

The Rotterdam Study is an ongoing prospective cohort study that is examining the risks for cardiovascular, neurologic, ophthalmologic, and endocrine diseases in 15,000 subjects aged 45 years and older.

All of those in the genetic study were genotyped for rs143383. The polymorphism lies near the GDF5 gene. Mutations in this area have been linked with skeletal dysplasias, including shortening of the digits, and chondrodysplasias involving joint ankylosis.

In addition to genotyping, the subjects in the Rotterdam study underwent bone mineral density testing and radiologic assessment for osteoarthritis, and were measured for hip axis length and C-telopeptide levels. Fractures were assessed over a 10-year period.

Sixteen percent of the women and 14% of the men were homozygous carriers of rs143383; 48% of both sexes were heterozygous for the variant.

In the men there were no associations between the genotype and osteoarthritis at the hip, knee, or hand; fracture risk; or C-telopeptide levels. However, there were some significant associations among women.

Heterozygous women were 32% less likely to have osteoarthritis of the knee and hand than were noncarriers. Homozygous women were 34% less likely to have knee osteroarthritis and 48% less likely to have hand osteoarthritis than were noncarriers. Women with two copies of the gene also had significantly lower C-telopeptide levels than did noncarriers.

Among women, each copy of the gene was associated with a height increase of 0.55 cm; there was a similar, but nonsignificant, trend in men. The gene was not associated with weight or body mass index in either gender.

Nonvertebral fracture risk also was associated with rs143383 in women, but not in men. Women with two copies of the gene were 32% more likely than were noncarriers to experience a nonvertebral fracture over the follow-up period—a significant difference.

"Neither adjustment nor stratification for height and presence of osteoarthritis had an effect on the association with fracture risk," the authors noted. "This implies that the association is not driven by any of the other observed associations, and genetic variation in the GDF5 gene seems to contribute independently to an increased fracture risk."

The hip axis length in female homozygotes was significantly larger than that of either heterozygotes or noncarriers.

The Rotterdam Study is being funded by the European Union and national grants from the Netherlands. None of the authors declared a financial conflict with regard to the study. ■

All Fractures After 60 Up Mortality

BY MARY ANN MOON

All major low-trauma fractures, not just hip and vertebral fractures, are associated with increased mortality after age 60.

Moreover, even minor fractures—those that do not involve the pelvis, distal femur, proximal tibia, proximal humerus, or three or more ribs—raise mortality risk in the oldest patients, reported Dr. Dana Bliuc of St. Vincent's Hospital, Sydney, and associates.

The researchers assessed outcomes after low-trauma fractures in a population-based study of 4,005 men and women aged 60 years and older who were followed from 1989 through 2007. This population was almost entirely white, so the findings may not be generalizable to other ethnic groups.

A total of 952 women and 343 men sustained at least one low-trauma fracture. Death followed closely in 461 of the women and 197 of the men.

At any age, mortality was consistently higher in subjects who had sustained fractures than in the general population. Mortality was 2-4 times higher than normal for both sexes after hip fracture, approximately 2 times higher after vertebral fracture, approximately 1.5 times higher after major fracture, and approximately 1.3 times higher after minor fracture.

Mortality remained elevated for a full 5 years before returning to normal levels following all fractures. The exception was hip fractures, in which mortality remained high for up to 10 years, the investigators said (JAMA 2009;301:513-21).

Patients who sustained one fracture were at twofold to fourfold higher risk for subsequent fractures, and mortality risk rose the same amount again for another 5 years with every subsequent fracture they sustained.

"Nonhip, nonvertebral fractures, [which are] generally not even considered in these types of studies, not only constituted almost 50% of the fractures studied, but also were associated with 29% of the premature mortality," Dr. Bluic and colleagues wrote.

"This study was not specifically designed to examine the underlying causes of mortality; however, examination of death certificates suggested no difference between causes of death in the fracture group and the general population, with cardiac, respiratory, cerebrovascular, and malignancy being the major causes.

It still remains to be determined exactly what is responsible for the increased mortality following fracture," they added.

This study was supported in part by grants from Amgen Inc., Merck Sharp & Dohme, Sanofi-Aventis, Servier Laboratories, and Novartis. ■