PPI Therapy, Hip Fracture Risk Raises Concerns

BY SARAH PRESSMAN LOVINGER
Contributing Writer

Hip fracture risk was increased with long-term use of proton pump inhibitors in a study published recently in the Journal of the American Medical Association, and the findings have led to concerns and questions among both patients who take these frequently prescribed drugs and physicians.

Dr. Yu-Xiao Yang of the division of gastroenterology at the University of Pennsylvania and his colleagues analyzed data on 1.8 million patients in the General Practice Research Database, a national database of patients in the United Kingdom, to assess a possible association between proton pump inhibitor (PPI) therapy and the risk of hip fracture (JAMA 2006;296:2947-53).

The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI use was significantly increased at 1.44 (95% confidence interval [CI], 1.30-1.59; *P* less than .001). In addition, patients who were prescribed long-term, high-dose PPI therapy had a markedly increased risk of hip fracture, with an AOR of 2.65 (95% CI, 1.80-3.90; *P* less than .001).

Dr. Colin W. Howden, professor of gastroenterology at Northwestern University in Chicago, said the study does indicate that PPIs increase the risk of hip fracture, but he urged physicians and patients to avoid becoming overly concerned about the findings. "The risk needs to be put in context," he said.

All patients were at least 50 years old and had no documented hip fracture before the study started or during the first year of follow-up; all started follow-up between May 1987 and March 2003. The cohort included 192,028 people who had received at least one prescription for a PPI during the follow-up period; 187,686 people who received at least one prescription for a histamine$_2$ receptor antagonist (H_2RA) during the follow-up period but had not used a PPI; and 1.4 million people who had no documented use of either a PPI or H_2RA, and were thus classified as acid-suppression nonusers.

The authors matched cases of those who had a hip fracture during the study period with controls who did not have a hip fracture. Cases and matched controls were similar in terms of sex, year of birth, and both the calendar period and the duration of follow-up before the index date.

The results revealed that 13,556 incident hip fractures—10,834 among acid-suppression nonusers and 2,722 among PPI users—occurred during the study period. These hip fracture cases were matched with a total of 135,386 controls.

In addition to the increased adjusted odds ratio for hip fracture after more than 1 year of PPI use, the data also showed that the strength of the association between hip fracture and PPI use increased with each cumulative year of use. The AOR was 1.22 for 1 year of PPI therapy (95% CI, 1.15-1.30), 1.41 for 2 years (95% CI, 1.28-1.56), 1.54 for 3 years (95% CI, 1.37-1.73), and 1.59 for 4 years (95% CI, 1.39-1.80), with *P* less than .001 for all comparisons.

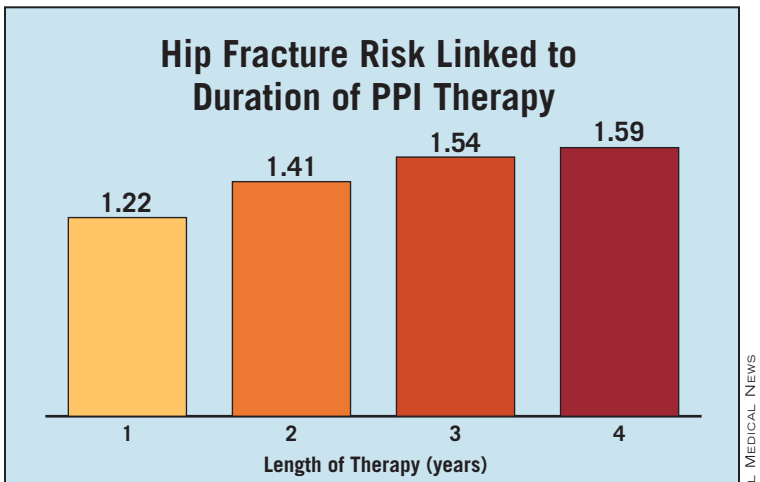
Dr. Howden commented that this study should remind physicians to review their patients' medication lists, particularly those of older patients who are at higher risk for hip fractures. "The bottom line is that if [patients need] to be on a PPI for a valid reason, they should be on a PPI," he said. Clinicians who are concerned about the hip fracture risk in patients who may not need to take a PPI continually could discontinue the drug and see how the patient fares.

The study did not determine the mechanism behind the increased risk of hip fracture in PPI users, but the authors noted that these drugs may decrease calcium absorption via induction of hypochlorhydria, and may also reduce bone resorption by inhibiting the osteoclastic proton transport system.

Currently, there are no guidelines for intensifying osteoporosis screening in patients on long-term PPI therapy or for initiating drug therapy to counteract osteoporosis in this patient population.

Until specific guidelines are published, physicians should consider the needs of individual patients and make diagnostic and treatment recommendations accordingly. Dr. Howden cautions against taking an alarmist approach to this study.

Dr. George Sachs, professor of medicine and physiology at the University of California, Los Angeles, agrees that the study shows only a small excess risk of hip fracture. These medications have only a small effect on stomach pH levels and hence calcium absorption, according to Dr. Sachs. Increasing calcium supplements or milk intake is the best method of decreasing the risk of hip fracture. "I think if [doctors] have concerns, they can always tell their patients to take extra calcium," he said. ■



Note: Adjusted odds ratios based on an analysis of 1.8 million patients in the United Kingdom's General Practice Research Database.
Source: Journal of the American Medical Association

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Obesity May Not Protect Against Bone Loss After All

BY PATRICE WENDLING
Chicago Bureau

VERONA, ITALY — Contrary to conventional wisdom, obese patients may not be protected against osteoporosis and could present with significant bone loss, new data show.

In a study of 233 morbidly obese patients, 34% showed a significant decrease in bone mineral density at the lumbar spine with a median T score of –1.98 (range –1.1 to –4.2), Dr. Carlo Lubrano and his colleagues reported in a poster at a joint meeting of the Italian Association of Clinical Endocrinologists and the American Association of Clinical Endocrinologists.

Low bone mass is defined as a bone density at the spine or hip between 1.0 and 2.4 standard deviations below the average for healthy young adults, which translates to a T score of –1 to –2.5, according to the World Health Organization. Bone density 2.5 standard deviations or more below the young adult mean is categorized as osteoporosis.

The 195 women and 38 men in the study had an average body mass index of 37 kg/m^2 and a mean age of 44 years. Bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry.

Overall, 31.5% of the women showed a median BMD of 0.971 g/cm^2 and a median T score of –1.93 (range –1.0 to –4.2). Among the male population, 45% showed a modification in BMD with a median lumbar BMD of 0.93 g/cm^2 and a median T score of –1.85 (range –1.3 to –2.6), wrote the investigators from the University of Rome La Sapienza.

Few data are available on potential skeletal modifications in patients affected by severe obesity. It had been thought that, although obese patients are often affected by hypertension, dyslipidemia, impaired glucose metabolism, and an increase in cardiovascular diseases, obesity might protect the skeleton against osteoporosis. Recent evidence suggests that obesity may actually weaken the skeleton and increase the risk of fractures.

Given their findings, the authors concluded that a "specific and careful characterization of skeletal metabolism might be useful in both female and male obese subjects." ■

Zoledronic Acid Found to Shield Bones From Aromatase Inhibitors

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Twice-yearly intravenous zoledronic acid started simultaneously with aromatase inhibitor therapy in postmenopausal women with hormone receptor–positive early-stage breast cancer shows promise as a means of preventing bone loss and even building bone, according to the 2-year results of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST).

Z-FAST is an ongoing open-label multicenter randomized trial involving 600 U.S. and Canadian women receiving up to 5 years of adjuvant letrozole (Femara) as part of the treatment of hormone receptor–positive early breast cancer. Participants were randomized to up-front 15-minute infusions of 4 mg of zoledronic acid every 6 months or to the delayed start of bisphosphonate until after a clinical fracture occurred or a patient's bone mineral density (BMD) T score dropped to below 2. Through 24 months, 12.7% of patients in the delayed group had initiated zoledronic acid, Dr. Adam M. Brufsky reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Z-FAST was designed to determine whether up-front zoledronic acid is the superior strategy for prevention of aromatase inhibitor–associated bone loss and fractures. The recently published 1-year Z-FAST results (J. Clin. Oncol. 2006 Dec. 11 [Epubdoi 10.1200/JCO.2005.05.3744]) showed up-front therapy protected against bone loss while the delayed strategy did not.

At 2 years, the gap in efficacy has widened. The mean increase in BMD at the lumbar spine was 3.1% with up-front zoledronic acid, compared with a mean 2.9% decline with delayed therapy. The mean increase in total hip BMD was 1.4% with up-front therapy, vs. a 3.2% drop with delayed therapy. Markers of bone turnover were continuously suppressed in the up-front therapy arm over 24 months, according to Dr. Brufsky of the University of Pittsburgh.

The incidence of clinical fractures through 24 months was 4.3% in the up-front therapy group and 4.0% in the delayed treatment arm. Two cases of renal impairment have occurred in the up-front therapy group, both believed related to zoledronic acid. No cases of osteonecrosis of the jaw have occurred in the 600-patient study.

Dr. Brufsky is a consultant to and member of the speakers' bureau for Z-FAST sponsor Novartis Pharmaceuticals. ■