Aromatase Inhibitors All Promote Bone Resorption

Exemestane, letrozole, and anastrozole increased biomarkers of bone turnover about equally.

**ARTICLES BY**

**KERRI WACHTER**

Senior Writer

**Philadelphia** — Steroidal and nonsteroidal aromatase inhibitors appear to have very similar effects on bone metabolism, which result in increased bone turnover, according to data presented at the annual meeting of the American Society for Bone and Mineral Research.

‘Anastrozole, letrozole, and exemestane in this study seem to have similar effects on bone biochemical measurements, and thus bone turnover. ... The increase in bone turnover doesn’t appear to be significantly different with the steroid versus nonsteroidal aromatase inhibitors,’ said Dr. Eugene McCloskey, a senior clinical lecturer in metabolic bone disease at the University of Sheffield in England.

Aromatase inhibitors have been associated with increased bone turnover, particularly in the setting of adjuvant therapy for breast cancer. Some preclinical studies have suggested that there may be differences between the effect of the steroidal (exemestane) and nonsteroidal (letrozole and anastrozole) aromatase inhibitors on bone turnover.

With the Letrozole, Exemestane, and Anastrozolene Pharmacodynamics (LEAP) trial, Dr. McCloskey and his colleagues compared the effects of these three aromatase inhibitors on safety parameters such as serum markers of bone formation and resorption, lipid profiles, and adrenal function in healthy postmenopausal women with normal bone mineral density at the spine and hip.

Letrozole (Femara) is made by Novartis Pharmaceutical Corp., exemestane (Aromasin) by Pfizer Inc., and anastrozole (Arimidex) by AstraZeneca. The study was sponsored by AstraZeneca, and Dr. McCloskey disclosed that he has received research grants from the company.

In the study, healthy postmenopausal women were randomized to receive letrozole (2.5 mg/day), exemestane (25 mg/day), or anastrozole (1 mg/day) once daily for 24 weeks. The women were followed for another 12 weeks after the end of therapy. Overall, 102 women were randomized and 96 were included in this analysis (32 on letrozole, 34 on exemestane, and 30 on anastrozole).

The group showed changes from baseline bone alkaline phosphatase (a formation marker), serum C-telopeptide crosslinks (a marker of resorption), parathyroid hormone, and propeptide of type I procollagen (a marker of formation).

For bone alkaline phosphatase (ALP) all three drugs showed a trend toward increased levels but only exemestane reached statistical significance. However, there was no statistical difference between the three groups.

There was no statistical increase for all three groups in terms of propeptide of type I procollagen (PINP) but no statistical difference between the groups.

Serum C-telopeptide crosslinks (CTX) levels were also increased in all three groups but there was no significant difference between the groups.

To look at these formation and resorption marker increases in more detail, the researchers calculated the uncoupling index, which is a measure of the difference between formation and resorption. To do this, they calculated z scores for the resorption marker (CTX) and formation markers (ALP and PINP). Z scores for formation markers were subtracted from z scores for CTX. The results indicated that resorption generally exceeds formation for all three drugs.

In terms of change in parathyroid hormone (PTH) levels, there was a greater decrease with exemestane than with anastrozole. The difference was statistically significant. It’s unclear whether there are any significant differences between these drugs in terms of fracture rates, Dr. McCloskey noted.

Zoledronic Acid Headed Off Fractures After Liver Transplants

**Philadelphia** — Prophylactic zoledronic acid appears to reduce morbidity associated with bone mineral loss and fractures in patients who have undergone a liver transplant, Dr. Martin Bodingbauer said at the annual meeting of the American Society for Bone and Mineral Research.

Vertebral fractures after liver transplant are linked to substantial morbidity and increased mortality. Fracture rates in the first 12 months after the procedure have been reported to range from 25% to 35%.

‘Bone mineral density measurements do not accurately predict the fracture risk of the transplant patients,’ said Dr. Bodingbauer of the surgery department at the Medical University of Vienna. The etiology of hepatic osteodystrophy is unclear.

In this preliminary study, 96 patients were randomized at the time of transplant to receive treatment with zoledronic acid (eight 4-mg IV infusions in 12 months) along with calcium (1,000 mg/day) and vitamin D (800 IU/day) supplements, or supplements alone.

Of the 96 patients, 47 were randomized to the treatment group and 49 to the control group.

The investigators calculated the uncoupling index, which showed that in general, bone resorption exceeded bone formation for all three agents.

The researchers measured changes from baseline in biochemical parameters such as serum markers of bone formation and resorption, lipid profiles, and adrenal function in healthy postmenopausal women with normal bone mineral density at the spine and hip.

Letrozole (Femara) is made by Novartis Pharmaceutical Corp., exemestane (Aromasin) by Pfizer Inc., and anastrozole (Arimidex) by AstraZeneca. The study was sponsored by AstraZeneca, and Dr. McCloskey disclosed that he has received research grants from the company.

In the study, healthy postmenopausal women were randomized to receive letrozole (2.5 mg/day), exemestane (25 mg/day), or anastrozole (1 mg/day) once daily for 24 weeks. The women were followed for another 12 weeks after the end of therapy. Overall, 102 women were randomized and 96 were included in this analysis (32 on letrozole, 34 on exemestane, and 30 on anastrozole).

The group showed changes from baseline bone alkaline phosphatase (a formation marker), serum C-telopeptide crosslinks (a marker of resorption), parathyroid hormone, and propeptide of type I procollagen (a marker of formation).

For bone alkaline phosphatase (ALP) all three drugs showed a trend toward increased levels but only exemestane reached statistical significance. However, there was no statistical difference between the three groups.

There was no statistical increase for all three groups in terms of propeptide of type I procollagen (PINP) but no statistical difference between the groups.

Serum C-telopeptide crosslinks (CTX) levels were also increased in all three groups but there was no significant difference between the groups.

To look at these formation and resorption marker increases in more detail, the researchers calculated the uncoupling index, which is a measure of the difference between formation and resorption. To do this, they calculated z scores for the resorption marker (CTX) and formation markers (ALP and PINP). Z scores for formation markers were subtracted from z scores for CTX. The results indicated that resorption generally exceeds formation for all three drugs.

In terms of change in parathyroid hormone (PTH) levels, there was a greater decrease with exemestane than with anastrozole. The difference was statistically significant. It’s unclear whether there are any significant differences between these drugs in terms of fracture rates, Dr. McCloskey noted.

**Fractures and Mortality Reduced With Prophylactic Bisphosphonate**

**Note:** Based on a study of liver transplant patients after 2 years of treatment.

Source: Dr. Bodingbauer

**Antiresorptives Reduced Recurrent Hip Fracture**

**Philadelphia** — Antiresorptive therapy reduces the risk of recurrent hip fracture by more than 25%, according to one analysis presented at the annual meeting of the American Society for Bone and Mineral Research.

Patients exposed to bisphosphonate therapy following a first hip fracture had a 26% reduction in recurrent hip fracture (hazard ratio [HR] 0.74), after adjusting for age, sex, comorbidity, and medication, said Dr. Suzanne N. Morin, an internist at the McGill University Health Centre in Montreal.

‘In general, the exposed patients tended to be younger and to have less comorbidities than the nonexposed,’ Dr. Morin said. The antiresorptive-exposed patients were also more likely to take calcium and vitamin D supplements and to use corticosteroids. Bisphosphonates were prescribed the most frequently.

For exposed patients, follow-up began on the day that the prescription for an antiresorptive was filled. Unexposed patients were assigned starting dates that were frequency matched to those of the exposed patients. Mean follow-up was 2.2 years, during which time 9,146 patients died and 992 recurrent fractures occurred. The refraction rate was 2.2 per 100 person-years for the exposed group and 2.9 per 100 person-years for the nonexposed group.

Men were also less likely to have a recurrent hip fracture (HR 0.75). For each 1-year increase in age, the risk increased 3%. The presence of osteoporosis was associated with a twofold increase in the risk of recurrent hip fracture.