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Teriparatide Relies on More than Bone Mineral Density to Reduce Vertebral Fracture Risk in Postmenopausal Women with Osteoporosis

Majority of Effects Linked to Other Factors Related to Bone Strength

NASHVILLE, TENN – A new data analysis of the Fracture Prevention Trial showed that increases in bone mineral density (BMD) account for 30 to 40 percent of the vertebral fracture risk reduction seen with teriparatide.

This work is important because it helps to explain how teriparatide works to prevent fractures. While BMD is a standard measurement used to assess osteoporosis treatment efficacy, the ability of teriparatide to reduce vertebral fracture risk was due in part to BMD, but primarily to improvements in other non-BMD components of bone strength. Understanding these aspects of bone strength will require additional research.

These data, presented today at the 27th Annual Meeting of the American Society for Bone and Mineral Research, provide physicians with new insights into the relationship between changes in BMD and fracture risk reduction with teriparatide.

"These data demonstrate that teriparatide has positive effects on bone strength and fracture risk reduction that go beyond changes in BMD." said study author Dr. Paul Miller MD, Medical Director of the Colorado Center for Bone Research. "While BMD remains the most useful diagnostic tool for identifying patients with osteoporosis and is often used to measure the efficacy of osteoporosis therapy, the ultimate goal for any osteoporosis therapy is to reduce fracture risk. This study gives us an indication that BMD gains do not equal proportional fracture risk reduction."

Methods
The relationship between teriparatide-related increases in lumbar spine BMD and the risk of new vertebral fractures was analyzed by looking at data from the Fracture Prevention Trial. The Fracture Prevention Trial (FPT), a registration trial for FORTEO, was a randomized, double-blinded, placebo controlled study that enrolled 1,637 women with osteoporosis. Subjects were randomized to teriparatide 20 mcg/day (marketed as FORTEO), teriparatide 40 mcg/day or placebo for a median of 19 months.

FORTEO is approved for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men (and postmenopausal women) with a history of osteoporosis-related fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment.

In this analysis, lumbar spine BMD was assessed at baseline and 18 months. Baseline and endpoint lateral spine x-rays were assessed using a visual semiquantitative technique to determine changes in fracture status. Logistic regression analysis was used to model vertebral fracture risk as a function of therapy (placebo or pooled teriparatide), endpoint lumbar spine BMD at 18 months and the interaction with therapy.

Results
This post-hoc analysis found that both baseline BMD and BMD change were contributors to the prediction of fracture risk. The average increase in BMD for teriparatide-treated patients was 0.09 g/cm2. This increase was similar across baseline BMD values. Teriparatide-related increases in BMD accounted for 30 to 41 percent of vertebral fracture risk reduction; the remainder of the risk reduction was due to improvements in other non-BMD determinants of bone strength.

"This study is important because it shows that BMD measurements give us valuable insight, but not the whole story," said Dr. Peiqi Chen, senior research scientist for Eli Lilly and Company, and recipient of ASBMR's Young Investigator Award. "These data tell us that improvements in other components of bone strength play a big role in teriparatide's antifracture efficacy."

Important Safety Information about FORTEO
In two-year studies in rats, FORTEO® caused an increase in the incidence of osteosarcoma, a malignant bone tumor, which was dependent on dose and duration of treatment. Although no case of osteosarcoma has been reported in the patients who received FORTEO in clinical trials, it is not known if humans treated with FORTEO are at increased risk for this cancer.

FORTEO should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. The drug should not be prescribed for patients at increased baseline risk for osteosarcoma, including patients with Paget's

disease of bone or unexplained elevations of alkaline phosphatase, children or growing adults, or those who have had prior external beam or implant radiation therapy involving the skeleton. Additionally, patients with bone metastases or a history of skeletal malignancies, and those with metabolic bone diseases other than osteoporosis, should not receive FORTEO. Patients with high levels of calcium in their blood should not receive FORTEO due to the possibility of increasing their blood levels of calcium.

In clinical trials, the most frequent treatment-related adverse events reported at the 20-microgram (mcg) dose approved for marketing were mild, similar to placebo and generally did not require discontinuation of therapy. Reported adverse events that appeared to be increased by FORTEO treatment were leg cramps and dizziness (2.6 and 8 percent, respectively), compared with placebo (1.3 percent and 5.4 percent, respectively).

FORTEO is supplied in a disposable pen device that can be used for up to 28 days to give once-daily self-administered injections. FORTEO is available in a 20-mcg dose and should be taken for a period of up to 24 months. Lilly has implemented a risk management program that includes comprehensive measures regarding the appropriate use of FORTEO in the target patient population. A Medication Guide explaining the details of the drug to the patient also accompanies the product. FORTEO also has a black box warning in its package insert about the osteosarcoma findings in rats during preclinical testing. For full prescribing information, please visit http://www.forteo.com.

About Osteoporosis
More than 50 percent of all women over the age of 75 are estimated to have osteoporosis, and due to their advanced age, have a high risk of fracture. In fact, most American women over the age of 50 will experience one or more osteoporosis-related fractures during their lifetimes, and women with osteoporosis who have two or more previous fractures have up to a nine times greater risk of future fracture compared with women who have not suffered a previous fracture.

About Lilly
Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at http://www.lilly.com