Five Factors Identify Women At Risk for Hip Fractures

The prediction rule has a 90% sensitivity rate; however, the specificity rate was only 24%.

BY JANE NEFF ROLLINS
Contributing Writer

LOS ANGELES — A prediction rule combining five easily obtainable risk factors distinguishes with high sensitivity women at high risk of developing osteoporotic fractures within the next 3 years, Dr. Idris Guessous reported at the annual meeting of the Society of General Internal Medicine.

The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study was a 3-year, prospective, multicenter study (n = 623) that computed a prediction score using low heel ultrasound stiffness index (SI), older age, fracture history, recent fall, and missed chair test to predict osteoporotic hip fractures and other nonvertebral fractures.

The objective of the study was to compute a prediction rule that would identify women at high risk of osteoporotic fracture in general, or a hip fracture in particular, within the next 3 years, said Dr. Guessous of the University Hospital of Lausanne, Switzerland.

The heel bone ultrasonometer (Lunar Corp., Madison, Wisc.) was chosen because it is simple, inexpensive, noninvasive, and transportable. Of 7,114 Swiss women who responded to a mailed request to participate, 6,174 women between 70 and 85 years old were enrolled. Exclusion criteria included previous hip fracture, bilateral hip replacement, renal failure, and active cancer.

Bone SI was calculated using quantitative ultrasound of the heel, broadband ultrasound attenuation, and speed of sound as the inputs. SI is expressed as a percentage of values obtained by the manufacturer in a young adult population. Osteoporotic fractures were defined as hip, wrist, or arm breaks that occurred spontaneously or secondary to falling from standing height or lower despite a low level of trauma.

The investigators included baseline characteristics (age, weight, height, body mass index), known risk factors for osteoporosis (fracture history, history of maternal hip fracture, current smoking habits, early menopause, surgical menopause), fall (history of recent fall, missed chair test), and SI as parameters to develop a prediction score. The investigators then used bootstrap methods to evaluate the stability of the score, Dr. Guessous said.

Mean follow-up was 2.8 years (17,546 person-years). Five risk factors were independent, significant predictors of the incidence of osteoporotic fractures: age older than 75, SI greater than 78%, history of any prior fracture, history of a fall during the last 12 months, and missed chair test (not being able to rise from a chair three successive times without using one's arms).

The investigators assigned a score to each of the five significant predictors: age, up to 3; SI, up to 7.5; history of fall within past 12 months, 1.5; fracture history, 1; and positive chair test, 1. Thus, the maximum prediction score is 14 points. The cutoff score to discriminate women at high risk of fracture with 90% sensitivity is 4.5. With this cutoff, 1,464 women (23.7%) were considered at low risk of hip fracture (score less than 4.5), and 4,710 (76.3%) were considered at high risk (score at least 4.5). Among these high risk women, 60 (1.3%) experienced an osteoporotic hip fracture. In contrast, 6 (0.4%) of the low risk women experienced such a fracture.

The main limitation of this predictor rule is that at a sensitivity of 90%, the specificity was only 24%. ■

Single-Dose Zoledronic Acid Rapidly Improves Bone Markers

BY NANCY WALSH
New York Bureau

TORONTO — A single intravenous dose of zoledronic acid reduced markers of bone resorption in postmenopausal women more rapidly and to a greater extent than did weekly oral alendronate, Dr. Kenneth Saag reported in a poster session at a world congress on osteoporosis.

Zoledronic acid is the most powerful of the available bisphosphonates, and its long duration of effect now has been shown in a multicenter double-blind trial that randomized 118 women aged 45-79 years to a single infusion of 5 mg zoledronic acid or 70 mg weekly oral alendronate for 24 weeks. Patients receiving IV zoledronic acid also received oral placebo, and those receiving oral alendronate also received IV placebo.

Flulike symptoms led to a greater frequency of adverse events in the zoledronic group than in the alendronate group.

DR. SAAG

In the zoledronic acid group, mean urine cross-linked *N*-telopeptide of type I collagen (NTx) fell from 46.1 to 15.2 nmol bone collagen equivalent (BCE)/mmol creatinine at 1 week, while the level of this marker of bone turnover fell from 45.8 to 35.5 nmol BCE/mmol creatinine in the alendronate group at 1 week. The greater reduction in urine NTx with zoledronic acid was significant and persisted throughout the 24 weeks of the study, according to Dr. Saag of the division of rheumatology, University of Alabama, Birmingham.

Levels of bone-specific alkaline phosphatase (BSAP) also decreased from baseline through week 24 in both groups. While reductions in BSAP levels were significantly greater in the zoledronic acid group at week 12, levels in both groups were within the premenopausal range of 6.2-12.8 ng/mL.

Overall, 91% of patients in the zoledronic acid group and 86% of those in the alendronate group experienced an adverse event. During the first 3 days after drug initiation, flulike symptoms led to a greater frequency of adverse events in the zoledronic acid group than in the alendronate group (64% vs. 37%), but after 3 days the adverse event rates were similar in the two groups, Dr. Saag said.

Serious adverse events were reported by two patients in the zoledronic acid group (one report of osteoarthritis and one of chest pain) and by three patients in the alendronate group (one report of patella fracture and two of osteoarthritis). None of the reports was considered to be related to the treatment.

Patient preferences for the treatments also were analyzed, with study participants expressing a "strong preference" for the single infusion compared with the weekly regimen (66% vs. 20%), Dr. Robert Lindsay noted in another poster session at the meeting, which was sponsored by the International Osteoporosis Foundation.

Even among patients who experienced adverse events during the 3 days after the infusion, 74% expressed an overall preference for the single-dose treatment, according to Dr. Lindsay of the clinical research center, Helen Hayes Hospital, West Haverstraw, N.Y.

The study was funded by Novartis Pharma AG, Basel, Switzerland. ■

Nasal Spray Formulation of Teriparatide Is in the Works

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — A nasal spray formulation of the osteoporosis drug teriparatide has cleared its first scientific hurdle.

Intranasal parathyroid hormone (PTH1-34) demonstrated a similar absorption profile as the approved injectable product, Forteo, in a phase I, pharmacokinetics study, Dr. Gordon Brandt and colleagues reported in a poster at the annual meeting of the American Association of Clinical Endocrinologists.

Twelve healthy men and women, ages 20-40 years, received a 20-mcg injection of teriparatide on day 1, followed by single doses of the nasal spray on 4 subsequent days. Two nasal formulations of teriparatide were evaluated: Formulation No. 1 was given at 200 mcg and 400 mcg, and No. 2 at 500 mcg and 1,000 mcg. Blood samples were taken up to 4 hours post treatment.

The times of maximal drug concentration for teriparatide nasal spray and Forteo were not statistically different, reported Dr. Brandt, executive vice president, clinical research and medical affairs, Nastech Pharmaceutical Co., Bothell, Wash., which sponsored the study.

While Forteo achieves a 50-pg/mL peak blood level after subcutaneous administration, the tested doses of nasal spray delivered up to a 400-pg/mL peak blood level, Dr. Brandt said in an interview. "In this first-in-man study, we administered higher doses than are required, so in subsequent studies we will adjust the doses," he said.

Still, while the bioavailability of Forteo was 95%, that of nasal formulation No. 1 was only 5%-8%, and 12%-15% for No. 2.

Intersubject variability for the nasal sprays was similar to or lower than Forteo, suggesting that intranasal dosing may provide consistent dosing.

There was no nasal irritation with the nasal sprays. Interestingly, two patients developed hypercalcemia after the Forteo injection, whereas there were no reports of hypercalcemia with the nasal spray.

Procter & Gamble has signed an agreement with Nastech to further develop the nasal spray formulation, Dr. Brandt said. The U.S. Food and Drug Administration has put the nasal formulation on a 505(b)(2) regulatory path, which requires only a single noninferiority study of the nasal sprays versus Forteo. The timing of this study has not been announced.

In a separate poster at the meeting, cost and side effects were identified as barriers for patients considering teriparatide.

In a retrospective study of 84 patients who had received a recommendation for teriparatide for severe osteoporosis since 2004, 28 patients (33%) refused the drug primarily because of cost, concerns about subcutaneous injections, or anxiety surrounding the incidence of osteosarcomas in rat studies, Dr. Pauline Camacho and Laurie Bachrach, of Loyola University Health System, Chicago, reported. A 28-day supply of teriparatide averaged $96.50.

Of the 56 patients who tried teriparatide, only 34 took the drug for 1 year. At 1 year, the mean change in bone mineral density of the lumbar spine was 6.9%.

Of the 52 patients who responded to a survey about side effects, 26 reported one or more, mostly lower extremity cramps or fatigue, dizziness, and transient elevation of ionized calcium levels.

Seven patients were nonresponders: One showed no change, and six showed decreases in bone mineral density of the lumbar spine. Three of the patients were later found to have underlying disease processes that explained the poor response. The remaining four claimed good compliance with the drug, Ms. Bachrach, a medical student at the university, said in an interview. ■