

Treatment Challenges Grow With New Options

BY DAMIAN McNAMARA

EXPERT ANALYSIS FROM THE AMDA - DEDICATED TO LONG TERM CARE MEDICINE ANNUAL MEETING

TAMPA – The treatment of osteoporosis is in flux because of a variety of forces, including a substantial increase in the number of aging patients deemed eligible for treatments, a leading geriatrician said. Just as baby boomers begin reaching senior status, a recently developed tool for assessing people's fracture risk is increasing the number of patients considered suitable for preventive therapy.

Meanwhile, those therapy options are multiplying, and emerging evidence suggests that one, bisphosphonates, is associated with an increased risk for atypical fractures, although the absolute risk appears to be low, Dr. Barbara Messinger-Rapport, said at the meeting.

The assessment tool making a difference is the Web-based Fracture Risk Assessment Tool (FRAX), released by the World Health Organization in 2008. FRAX guides clinicians to consider drug therapy for patients with T scores (deviations from healthy bone density) of -2.5 or lower at the femoral neck or spine, a T score between -1.0 and -2.5 as well as a 3% or higher calculated risk for hip fracture over 10 years, or a 20% or greater risk of major osteoporosis-related fracture.

Even if a person's T score never reaches -2.5 , his or her hip fracture risk can climb to 3% or higher, said Dr. Messinger-Rapport, director of the Center for Geriatric Medicine at the Cleveland Clinic and medical director of the Fairfax Health Care Center Nursing Home, also in Cleveland. "This could widen the number of people who could be put on treatment."

The Web-based Fracture Risk Assessment Tool (FRAX), which was released by the World Health Organization in 2008, 'could widen the number of people who could be put on treatment.'

Bisphosphonates remain the most-common treatment strategy, but optimal duration of therapy, timing of drug holidays, and how age and gender play into risk for adverse events remains unclear, she said.

A newer option, the monoclonal antibody denosumab (Prolia, Amgen), significantly reduced vertebral fractures compared with a placebo in published studies. Administered as a subcutaneous injection every 6 months, denosumab also may be more convenient than agents requiring infusion, Dr. Messinger-Rapport said.

Higher cost is a consideration, however. Wholesale cost of denosumab is approximately \$850 per 60-mg subcutaneous injection. In contrast, generic alendronate costs \$100-\$200/year; brand-name oral bisphosphonate costs up to \$1,000 a year; and zoledronic acid, delivered via intravenous infusion, is about \$1,100 a year, she said.

Denosumab's impact on clinical care is not yet known, Dr. Messinger-Rapport said. She suggested that clinicians consider this agent in high-risk elders, women or men with osteoporosis, men with prostate cancer with androgen deprivation, patients with metastatic prostate or breast cancer, and possibly patients with renal impairment (denosumab clearance is not renal). Also consider denosumab for patients who cannot tolerate a bisphosphonate either orally or by infusion, she added.

Researchers showed a 68% decrease in vertebral fractures, a 40% decline in hip fractures, and a 20% decrease in nonvertebral fractures with denosumab versus placebo in the FREEDOM study of osteoporotic women treated for 36 months (N. Engl. J. Med. 2009;361:756-65). A similar 62% decrease in vertebral

fractures with denosumab, compared with placebo, was observed in a 24-month study of men with androgen deprivation for prostate cancer (N. Engl. J. Med. 2009;361:745-55).

Researchers also have examined reports of atypical femoral fractures associated with bisphosphonate use and found an association. For example, in a study published last year, 17 of 20 atypical femoral fractures occurred in patients taking oral bisphosphonates (N. Engl. J. Med. 2010;363:1848-9). In a New England Journal letter (N. Engl. J. Med. 2010;362:1848-9), the researchers stated that although they found the association, "overall the anti-fracture effects of bisphosphonates far outweigh their potential risks."

More recently, other investigators found an increased risk of subtrochanteric and femoral shaft fractures in women treated for 5 years or more with oral bisphosphonates (JAMA 2011;305:783-9). The authors stated that the absolute risk of the atypical fractures is low, however.

Dr. Messinger-Rapport listed contraindications to bisphosphonates as a prior allergic reaction, vitamin D depletion (less than 30 ng/mL), hypocalcemia, dysphagia, esophageal disorders, and severe gastroesophageal reflux disorder.

A person attending the meeting asked if it is appropriate to continue bisphosphonate therapy after a patient's T score improves. "Yes, even if the T score only improves by a few percentage points," Dr. Messinger-Rapport replied, because there is a disproportionate benefit in terms of fracture risk reduction.

Dr. Messinger-Rapport is a member of the National Osteoporosis Foundation's editorial board.

To watch an interview with Dr. Messinger-Rapport, scan this QR code with a smartphone.



Denosumab Reduces Fracture Incidence at All Risk Levels

BY MIRIAM E. TUCKER

FROM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Denosumab reduced the incidence of new vertebral and hip fractures in postmenopausal women with osteoporosis at both higher and lower risk for fracture, in a post-hoc analysis of data from a 3-year, phase III randomized trial.

The monoclonal antibody denosumab (Prolia) was approved in June 2010 for treatment of postmenopausal women who have a high risk of osteoporotic fractures. In phase II and III trials, denosumab rapidly decreased bone resorption markers and increased bone mineral density at all skeletal sites, compared with placebo, said Dr. S. Boonen of Leuven (Belgium) University and his associates (J. Clin. Endocrinol. Metab. 2011;96 [doi:10.1210/jc.2010-2784]).

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial enrolled 7,808 postmenopausal women aged 60-80 years with osteoporosis to receive either a subcutaneous injection of denosumab (60 mg) or placebo along with daily calcium and vitamin D supplements every 6 months. All subjects had bone mineral density (BMD) T scores of less than -2.5 but not less than -4.0 at the lumbar spine

or total hip. At 36 months, denosumab was associated with reductions of 68% in vertebral fracture and 40% in hip fracture (N. Engl. J. Med. 2009;361:756-65).

The new analysis compared high-risk and low-risk groups within the FREEDOM population. High-risk groups included women with two or more preexisting vertebral fractures of any degree of deformity, or one or more vertebral fractures of moderate or severe deformity, or both; a femoral neck BMD T score of -2.5 or less; or both multiple and/or moderate or severe vertebral deformities and a femoral neck BMD T score of -2.5 or less.

For hip fractures, the higher-risk subgroups included women who were age 75 years or older; had a femoral neck BMD T score of -2.5 or less; or were 75 years or older with a femoral neck BMD T score of -2.5 or less. Women who did not have those specified risk factors were included in the lower-risk subgroups.

Over 3 years, denosumab treatment was equally effective at reducing the risk of new vertebral fractures in women at both higher and lower risk for those types of fractures, similar to the overall FREEDOM population. Compared with placebo, denosumab reduced the incidence of vertebral fracture in the subgroups at higher risk by prevalent vertebral fracture status by 9.2% (16.6%

placebo vs. 7.5% denosumab) among those at risk via baseline femoral neck BMD T score of -2.5 by 6.8% (9.9% vs. 3.1%), and among those with both risk factors by 12.3% (20.1% vs. 8.1%).

The numbers needed to treat to prevent one vertebral fracture in each of these higher-risk subgroups were 11, 15, and 12, respectively, Dr. Boonen and his associates said.

Similar results were seen for the lower-risk groups, including a 4.4% absolute risk reduction in those without prevalent vertebral fracture, 3.7% for those with BMD T score greater than -2.5 , and 4.5% for those with one or both risk factors.

Subgroup results for hip fractures were also consistent with the findings from the overall FREEDOM population, with the same efficacy of denosumab consistent across patients with different levels of risk. Compared with placebo, denosumab significantly reduced hip fracture incidence among those aged 75 years or older by 1.4% (2.3% placebo vs. 0.9% denosumab); those with a baseline femoral neck BMD T score of -2.5 or less by 1.4% (2.8% vs. 1.4%); and by 2.4% among those with both risk factors (4.1% vs. 1.7%).

Overall mortality was lower – but not significantly so – among all the subgroups with denosumab. However, there

was a significantly lower incidence of fatal adverse events with denosumab vs. placebo in the higher-risk group with prevalent vertebral fracture (1.8% vs. 4.9%) and in those with both prevalent vertebral fracture and low femoral neck BMD (1.6% vs. 7.1%). The difference in mortality among the higher-risk subgroups was greater than that of the lower-risk groups, they noted.

"Our analyses highlight the consistency of the antifracture efficacy of denosumab across subjects with differences in a variety of major risk factors for fractures at baseline. Our analyses suggest that denosumab reduces both new vertebral and hip fractures, regardless of the underlying risk and that the higher absolute fracture risk observed in the higher-risk subgroups is associated with greater absolute risk reduction," Dr. Boonen and his associates concluded.

The study was funded by Amgen. Dr. Boonen has received funding for serving as an investigator and as a member of the steering committee for Amgen, as well as consulting and lecture fees. He is also senior clinical investigator of the Fund for Scientific Research in Flanders, Belgium. Four of his coinvestigators are Amgen employees, and the others disclosed relationships with Amgen and several other pharmaceutical companies.