

# Osteoporosis Rx Approval Opens Options to Men

BY JEFF EVANS  
Senior Writer

The Food and Drug Administration's recent approval of yearly zoledronic acid infusions for treating low bone mass in men with osteoporosis will give providers a treatment option for men other than oral weekly therapy, according to Dr. Nelson Watts.

The agency's decision brings the total number of indications for the intravenous formulation of zoledronic acid (Reclast) to three, including the treatment of postmenopausal osteoporosis (as well as the reduction of new clinical fractures in patients who have experienced a recent low-trauma hip fracture) and the treatment of Paget's disease of bone. It is the only osteoporosis treatment that has been approved for the reduction of fractures of the hip, vertebrae, and other nonvertebral bones.

The other drugs approved to increase bone mass in men with

osteoporosis—alendronate (Fosamax) and risedronate (Actonel)—“represent very good therapeutic choices with...evidence in women for spine, hip, and nonvertebral fracture reduction,” said Dr. Watts, director of the University of Cincinnati Bone Health and Osteoporosis Center, which was one of the centers that participated in a randomized, double-blind trial that formed the basis for the

FDA's decision. Dr. Watts is a paid consultant to Novartis Pharmaceutical Corp., which manufactures Reclast and is on the company's speakers bureau.

Intravenous dosing would be medically indicated for men in three categories: those who can't tolerate an oral agent because of upper GI problems, those with lower GI problems that interfere with drug absorption, and those who can't remember to take an oral agent.

“We don't have fracture reduction data in men with any of these agents in terms of a pre-planned primary end point [but] there's no real reason to feel that



**IV dosing is indicated for men with upper or lower GI problems and for those who forget to take pills.**

DR. WATTS

bisphosphonates work any differently for osteoporosis in men than they do in women,” Dr. Watts said in an interview.

During the 2-year Novartis-sponsored trial, 153 osteoporotic men received a 15-minute infusion of zoledronic acid once per year, and 148 other osteoporotic men received weekly oral alendronate. Those who were treated with zoledronic acid increased their lumbar spine bone mineral density by a mean of 6.1% over

2 years. This change in BMD was similar to the 6.2% increase in the alendronate group. Each patient in the study received 1,000 mg calcium and 800-1,000 IU of vitamin D each day. The men had a mean age of 64 years (range of 25-86 years). Some had significant osteoporosis secondary to hypogonadism.

In the trial, signs and symptoms of an acute phase reaction occurred in some patients in the first 3 days following the zoledronic acid infusion. Treatment with zoledronic acid was associated with myalgia (17.1%) fever (15.7%), fatigue (12.4%), arthralgia (11.1%), pain (10.5%), chills (9.8%), headache (9.8%), influenza-like illness (8.5%), malaise (5.2%), and back pain (3.3%). No patients developed osteonecrosis of the jaw. There was one death in each group; the two groups had similar rates of serious adverse events.

The FDA has “generally felt” that drugs with proven antifracture efficacy in postmenopausal

women can be approved, on the basis of noninferiority “bridging” studies without fracture data, for new dosing regimens or for new populations such as glucocorticoid users or men, Dr. Watts noted. That is why studies in those circumstances have been smaller and not powered to detect a reduction in fractures.

“The lack of the fracture data doesn't concern me particularly in this population because of the really robust fracture reduction data that we've seen in postmenopausal women,” he said.

Zoledronic acid is available as a 5-mg dose in a 100-mL ready-to-infuse solution. It has been used by more than 164,000 patients since the FDA approved it in 2007, according to Novartis.

“Intravenous Reclast compares in price with the cost of a year's therapy with a brand name oral preparation. Medicare has generally covered this for postmenopausal women, and in some states it's already covering it for men,” Dr. Watts said. ■

## Optimal TSH Levels in Thyroid Cancer Patients Requires a Tailored Approach

BY BRUCE JANCIN  
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CHICAGO — An individually tailored approach to providing thyroid hormone replacement in thyroid cancer patients should be guided by the findings of several key studies, according to endocrinologist Giuseppe Barbesino.

The evidence at hand doesn't permit sweeping generalizations about what the target TSH level should be, said Dr. Barbesino of Harvard University, Boston.

He said his thinking was influenced by a study led by Dr. Jacqueline Jonklaas of Georgetown University, Washington. She and her colleagues analyzed a prospective multicenter registry and showed for the first time that it isn't necessary to drive TSH levels below 0.1 mU/L to improve overall survival in patients with stage II thyroid cancer. Survival can be improved in such patients with moderate TSH suppression in the range of 0.1 to less than 0.5 mU/L (Thyroid 2006;16:1229-42).

That's important because aggressive TSH suppression to less than 0.1 mU/L in patients with differentiated thyroid cancer carries several downsides. It is associated with an increased risk of new-onset atrial fibrillation, an increase in left ventricular mass index and other echocardiographic abnormalities, and some as-yet-inconclusive evidence suggesting increased risks of cardiovascular mortality, fracture, and decreased bone mineral density, Dr. Barbesino said at a satellite symposium held in conjunction with the annual meeting of the American Thyroid Association.

The abnormalities of cardiac structure and function associated with TSH suppression in thyroid cancer patients are subtle, and their clinical significance remains unclear. But researchers at

the University of Cagliari (Italy) have shown that these abnormalities—including left ventricular posterior wall thickening, increased intraventricular septum thickness, increased left ventricular end-diastolic dimension, and an associated diminished exercise tolerance—are reversible by titrating the levothyroxine dose down to the minimum still capable of inducing TSH suppression (J. Clin. Endocrinol. Metab. 2000;85:159-64).

It remains an open question as to whether TSH suppression with levothyroxine reduces bone mineral density and increases fracture risk, Dr. Barbesino said at the symposium supported by Abbott Laboratories, maker of a test for TSH.

He suggested reserving aggressive TSH suppression to less than 0.1 mU/L for patients with high-risk stage III-IV or incurable tumors, since that approach has been shown to improve overall survival. Consider a target level of 0.1 to less than 0.5 mU/L in patients with low-risk tumors prior to restaging, and in patients with high-risk tumors who have had several years with no disease activity, particularly if the patients are over age 60, when the increased risk of atrial fibrillation associated with aggressive TSH suppression is likely to be most damaging.

Reserve mild TSH suppression to 0.5 to less than 2.5 mU/L for patients with microcarcinomas or tumors deemed low risk following negative restaging. Dr. Barbesino said he tries to avoid TSH levels of 2.5 mU/L or more in thyroid cancer patients. He is especially careful to keep levels under 5.0 mU/L because values above that are associated with rapid growth of metastases.

He disclosed having received honoraria from Genzyme Corp., maker of Thyrogen (thyrotropin alfa for injection). ■

## Consider Diabetes Drug Withdrawal in the Elderly

BY MICHELE G.  
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Weaning or reducing diabetes medications in elderly nursing home residents is possible and may reduce the risk of hypoglycemic events that can cause cognitive impairment, cardiac arrhythmias, and even death, a small Swedish study has concluded.

Blood glucose remained stable in the intervention patients by 3 and 6 months. Glucose levels also decreased slightly in patients in a comparator group that continued antidiabetes medications during the study period, Dr. Peter Sjoblom of the Soderkoping (Sweden) Primary Health Care Center and colleagues reported.

They noted the effect of diabetes medication continuation, or withdrawal/reduction in 98 patients (mean age 84 years). Patients with hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels at 6% or higher at baseline (66) stayed on their medication, whereas those with HbA<sub>1c</sub> levels below 6% (32) were placed in the intervention group. Of these, 10 took oral antidiabetic drugs, 17 needed insulin injections, and 5 were on a combination regimen (Diab. Res. Clin. Pract. 2008;82:197-202).

Before intervention, the frequency of hypoglycemia was assessed by measuring the interventions groups' glucose levels 4 times each day for 3 days. There were 31 episodes of hypoglycemia (mean blood glucose level of 72 mg/dL or lower), of which about half (17) were at night.

Frequency varied with the antidiabetic regimen: 40% of patients on oral drugs alone had at least one hypoglycemic event, as did 75% of those on injected insulin and 100% of those on combination regimens.

After the baseline glucose measurements, oral drugs were withdrawn, as was insulin in patients taking 20 U/day or less. Insulin was cut by half in those taking more than 20 U/day.

At 3 months, 24 patients (76%) had been successfully weaned from their medication. Hyperglycemia (plasma glucose of at least 16 mmol/L) occurred in four patients; their medications were restored. Two patients were withdrawn from the trial due to relatives' concern, and two died from causes unrelated to diabetes.

The study was funded by local and regional governmental grants.

The authors said they had no conflicts of interest. ■