

Osteoporosis Challenges Grow With Tx 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 Web-based Fracture Risk Assessment Tool (FRAX), released by the World Health Organization in 2008, 'could widen the number of people who could be put on treatment.'

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."

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 \$850/60-mg subcutaneous injection. In contrast, generic alen-

dronate costs \$100-\$200/year; brand-name oral bisphosphonate costs up to \$1,000/year; and zoledronic acid, delivered via intravenous infusion, is approximately \$1,100/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 de-

privation, 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 asso-

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References: 1. Fuchs GS, Mikkelsen S, Knudsen TK, Kappelgaard A-M. Ease of use and acceptability of a new pen device for the administration of growth hormone therapy in pediatric patients: an open-label, uncontrolled usability test. *Clin Ther.* 2009;31:2906-2914. 2. Norditropin® FlexPro® [Instructions for Use]. Princeton, NJ: Novo Nordisk Inc; 2010. 3. Data on file. PDS290 pen-injector for Norditropin® SimpleXx® container closure system: comparison to Norditropin NordiFlex®, Princeton, NJ: Novo Nordisk Inc; 2009.

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ciated 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 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. Messenger-Rapport listed the 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. Messenger-Rapport replied, because there is a disproportionate benefit in terms of fracture risk reduction.

Dr. Messenger-Rapport has disclosed that she is a member of the editorial board for the National Osteoporosis Foundation. ■

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



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Indications and Usage

Norditropin® (somatropin [rDNA origin] injection) is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone, the treatment of children with short stature associated with Noonan syndrome or Turner syndrome, the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2-4 years, and for the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) who meet either of the following two criteria: 1. Adult Onset: Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or 2. Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Important Safety Information

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure as increased mortality may occur.

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients. Norditropin® is not indicated for the treatment of patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Somatropin should not be used or should be discontinued with any evidence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence. In childhood cancer survivors, an increased risk of a second neoplasm, particularly meningiomas in patients treated with radiation to the head for their first neoplasm, has been reported in patients treated with somatropin.

Somatropin should not be used in patients with active proliferative or severe non-proliferative diabetic retinopathy, for growth promotion in pediatric patients with closed epiphyses, or in patients with known hypersensitivity to somatropin or any of its excipients.

Somatropin may decrease insulin sensitivity particularly at higher doses in susceptible patients. Glucose levels should be monitored periodically, including close monitoring of patients with preexisting diabetes or glucose intolerance. Doses of anti-hyperglycemic drugs (insulin or oral agents) may require adjustment for patients with diabetes on somatropin therapy.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting, usually occurring within the first eight (8) weeks after initiation of somatropin therapy, has been reported in a small number of patients. In all reported cases, rapid resolution has occurred after therapy cessation or a reduction of dose. Fundoscopic examination should be performed routinely before and during somatropin therapy. If papilledema is observed, somatropin treatment should be discontinued.

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Periodic thyroid function tests are recommended and thyroid hormone replacement therapy should be initiated or adjusted as needed.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or with rapid growth. Onset of a limp or complaints of hip or knee pain in somatropin patients should be carefully evaluated. Rapid growth may also result in progression of preexisting scoliosis. Patients with a history of scoliosis or skeletal abnormalities, which may be present in untreated Noonan, Turner or Prader-Willi syndrome, should be monitored.

Patients with Turner Syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. Somatropin may also increase the risk of IH in Turner patients. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

Congenital heart disease is an inherent component of Noonan syndrome. Though a clinical study in Noonan syndrome reported no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography), the safety of Norditropin® in children with Noonan syndrome and significant cardiac disease is not known.

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain.

Other somatropin-related adverse reactions include injection site reactions/rashes, lipoatrophy and headaches. Subcutaneous injection of somatropin at the same site repeatedly may result in tissue atrophy and can be avoided by rotating the injection site.

Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in adipose/hepatic tissue, and may significantly impact the metabolism of cortisol and cortisone. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy, especially with cortisone acetate and prednisone, for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses.

Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine) as limited published data suggest somatropin may alter clearance of these compounds.

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal.

The safety and effectiveness of Norditropin® in patients age 65 years and older has not been evaluated in clinical studies. Elderly patients may be more sensitive to the actions of somatropin and may be more prone to develop adverse reactions.

Please see Brief Summary of Prescribing Information on the following pages.

norditropin®
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