Oral Osteoporosis Therapy Choices Are Expanding

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Bisphosphonates remain the prime oral therapies for osteoporosis, but some competing agents might alter medical practice, Dr. Steven T. Harris said at a meeting on diabetes and endocrinology that was sponsored by the University of California, San Francisco.

More liberal use of vitamin D and a new indication for the selective estrogen receptor modifier raloxifene (Evista) give these agents a higher clinical profile, said Dr. Harris of the university. Investigational oral therapies that soon are likely to play a role in osteoporosis treatment include the monoclonal antibody denosumab and the new bisphosphonate zoledronic acid (Reclast).

► **Vitamin D.** Institute of Medicine recommendations in 1997 that adults get 200-600 IU a day of vitamin D (depending on age) now are widely considered to be inadequate. The minimum probably should be 800-1,000 IU a day for adults, and it's almost impossible to overdose on vitamin D, he noted.

Experts have urged clinicians to keep patients' 25-hydroxyvitamin D levels up to 30 ng/mL or higher, so "we ought to be a little more generous in our D supplementation than we have been historically," he said.

'We ought to be a little more generous in our D supplementation.'

DR. HARRIS

Multiple studies in recent years have reported associations between vitamin D insufficiency and an increase in a variety of immune diseases and malignancies including osteoarthritis, multiple sclerosis, fibromyalgia, type 1 diabetes, and cardiovascular disease.

Dr. Harris changed his practice toward greater emphasis on vitamin D supplementation after a recent study showed that half of osteoporotic patients on prescription therapies had vitamin D insufficiency regardless of where they lived (J. Clin. Endocrinol. Metab. 2005;90:3215-24).

► **Raloxifene.** Approved for the prevention or treatment of osteoporosis, raloxifene has been shown to decrease the incidence of vertebral fractures in women with preexisting vertebral fractures or low bone density. It does not affect the risk of nonvertebral or hip fractures and so "does not compete terribly well with other osteoporosis treatment options," Dr. Harris said.

Three other studies report that raloxifene decreases the risk of estrogen receptor–positive invasive breast cancer (but not estrogen receptor–negative tumors or ductal carcinoma in situ). "It's almost certain that sometime this year Evista is going to be approved by the Food and Drug Administration to reduce the risk of breast cancer."

That added indication might boost raloxifene's use for some osteoporotic patients, though that remains to be seen.

► **Denosumab.** One subcutaneous injection of this experimental monoclonal antibody greatly decreases bone resorption almost immediately, a recent study suggests. One injection every 6 months produced bone density improvements similar to gains seen in patients treated weekly with the oral bisphosphonate alendronate (N. Engl. J. Med. 2006;354:821-31).

A large clinical trial is studying denosumab for osteoporosis. No data on fracture prevention are available yet.

► **Zoledronic acid.** A 15-minute intravenous infusion of 5 mg zoledronic acid once yearly for 3 years in lieu of oral therapy significantly reduced vertebral, nonvertebral, and hip fractures in a study of 7,736 postmenopausal women randomized to the drug or placebo, according to preliminary results reported at a 2006 conference. Zoledronic acid is not approved to treat osteoporosis but is indicated for treatment of patients with hypercalcemia of malignancy, multiple myeloma, Paget's disease of bone, or bone metastases from solid tumors. Dr. Harris predicted the drug would win approval for osteoporosis, and he said he believes it is unlikely to prove more effective than oral therapies but could offer an alternative for osteoporotic patients who can't or won't take oral medication. ■

Confirm Osteoporosis by Bone Biopsy Before Treatment in Advanced CKD

BY BARBARA J. RUTLEDGE
Contributing Writer

TAMPA — Diagnosis of osteoporosis in patients with advanced chronic kidney disease cannot be accomplished simply on the basis of T score or bone fragility, Dr. Paul Miller said at the annual meeting of the International Society for Clinical Densitometry.

"People with more severe chronic kidney disease can have a whole host of metabolic bone diseases that mimic osteoporosis, either by bone density criteria or fractures, and yet may not be osteoporosis," said Dr. Miller, medical director of a bone research center in Lakewood, Colo.

Patients with advanced chronic kidney disease (CKD) are at increased risk for osteoporosis, resulting from a variety of factors. Chronic heparin use and steroid use may be risk factors for patients on dialysis. In transplant patients, the use of calcineurin inhibitors can cause high bone turnover, increasing bone fragility.

Hypogonadism, hyperprolactinemia, poor nutrition, vitamin D deficiency, and hyperparathyroidism are other osteoporosis risk factors in CKD patients. They may be more likely than others to develop forms of osteoporosis that could be treated effectively by bisphosphonates, said Dr. Miller.

However, CKD patients are also at risk for other bone metabolic diseases, including osteitis fibrosa cystica, osteomalacia, and adynamic bone disease. Bisphosphonates may be contraindicated in patients with severe adynamic bone disease or osteomalacia. "We don't have data, but it doesn't make sense to try to use drugs that reduce bone turnover to try to improve bone strength when you already have a low bone-turnover disease such as adynamic bone disease or osteomalacia," he said.

It doesn't make sense ...to use drugs that reduce bone turnover ... when you have a low bone-turnover disease such as adynamic bone disease or osteomalacia.

Renal impairment is associated with increased fracture risk, even in patients without severe renal disease. A recent analysis of data from the Study of Osteoporotic Fractures cohort showed that age-related reduction in renal function that causes mild to moderate renal impairment is associated with increased hip fracture risk in older women (Arch. Intern. Med. 2007;167:133-9).

Diagnosis of osteoporosis in CKD patients must exclude other causes of low bone mineral density (BMD) or fragility fractures. The latter can be seen in transplant recipients and in patients with severe hyperparathyroidism, adynamic bone disease, or osteomalacia.

Severe adynamic bone disease and osteomalacia are considered to have low prevalence in CKD before stage 5 disease, according to Dr. Miller, and mild secondary hyperparathyroidism in that patient population does not cause fractures. Therefore, if the biochemical profile does not suggest severe hyperparathyroidism or other renal bone disease, low T scores based on the World Health Organization criteria or fragility fractures should be sufficient for the diagnosis of osteoporosis in patients with stage 1-4 CKD, he said.

For patients with stage 5 CKD who have low BMD or fragility fractures, a double tetracycline-labeled bone biopsy is necessary to rule out other causes of metabolic bone disease and confirm a diagnosis of osteoporosis.

Caution is advised for bisphosphonate treatment of advanced CKD patients, said Dr. Miller. Labeling recommendations for bisphosphonates exclude patients with creatinine clearance under 35 mL/min, largely because of a lack of data about bisphosphonates in CKD patients. ■

Warn Osteoporotic Patients That T Scores Can Mislead

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — A plateau in bone mineral density improvement while on antiresorptive therapy for osteoporosis does not mean the treatment has stopped working, Dr. Steven T. Harris said at a diabetes update sponsored by the University of California, San Francisco.

One should explain this to patients at the start of therapy to avoid disappointment or worse when their T scores stop rising, he said.

The most important clinical objective is to prevent fractures, not to produce changes in surrogate markers like bone mineral density or biochemical markers of bone turnover, he emphasized.The risk of fracture declines significantly despite a slight improvement in T score or even no change in T score in the first year on antiresorptive medication because of improvements in bone quality. The fracture protection continues while the patient is on therapy, despite no further changes in bone mineral density.

Antiresorptive agents such as bisphosphonates, selective estrogen receptor modifiers, calcitonin, and estrogen decrease bone resorption and bone formation. This typically produces an increase in bone mineral density in the first year of therapy and a smaller increase the second year, which is then followed by a plateau. Despite the plateau, fracture protection continues.

"It is the rule, not the exception, that bone density goes up a little, then stabilizes. That is not nonresponse. That does not mean you have to change the therapy. That does not mean that your patients are not taking their medications. This is physiology in action," Dr. Harris said.

Many patients logically assume that if a T score of –3.2 won them a diagnosis of osteoporosis, for example, then the goal of therapy is to get the T score back to zero, which is why it is important to explain this possiblity early on.

Findings from studies of the bisphosphonates risedronate and alendronate, for example, show that therapy increases spinal bone density 5%-8% and hip bone density by 3%-5% after 3 years in osteoporotic women. Those are "not terribly impressive" numbers until you look at the fracture protection, he said, noting that the drugs reduced the incidence of vertebral fractures by 40%-65% and the incidence of hip fractures by 40%-60%. ■