Manage Patients on Glucocorticoids Differently

BY KERRI WACHTER

DENVER — People on long-term glucocorticoids have a significant risk for fracture at relatively high bone mineral density T scores. As a result, physicians need to rethink their management of this population.

"In glucocorticoid osteoporosis, the fracture risk seems to take off quite dramatically somewhere around T scores of –1.5," Dr. Philip Sambrook said during a clinical roundtable session on glucocorticoid-induced osteoporosis at the annual meeting of the American Society for Bone and Mineral Research. "Most of the guidelines around the world are now suggesting that the intervention threshold [for those on glucocorticoids] should be [a T score of] about –1.5."

Patients on glucocorticoids typically have midline fractures of the vertebrae, where the bone just collapses in the middle of the vertebra.

"This is different from the anterior wedge fracture that occurs most commonly in postmenopausal women with osteoporosis," noted Dr. Nancy Lane, who also participated in the roundtable session. This is because there are some differences in how bones become fragile in the presence of glucocorticoids. "A number of studies have shown that patients on glucocorticoids, for the most part, tend to fracture at bone densities that are greater than [those of] postmenopausal women with osteoporosis."

Dr. Lane and her colleagues have followed bone density in mice that were exposed to moderate doses of glucocorticoids. They found that most of the bone loss occurred very quickly. At roughly a month (28 days), there was a 20% loss in trabecular vertebral bone mineral density (BMD) as measured by quantitative CT, a 3-D means of assessing bone volume. However, during days 28-56 there was little additional loss of bone mass. "Upon giving the mice glucocorticoids, we found that bone resorption went up very quickly," said Dr. Lane, who is the director of the center for healthy aging at the University of California, Davis. By day 7, there was nearly a doubling in bone turnover as measured by CTx, a C-terminal telopeptide of type I collagen, which is a serum marker of bone resorption.

In addition, they found very little change in serum levels of osteocalcin (a biomarker of bone formation) for the first 7 days. Osteocalcin levels then began to decline. "It looks like glucocorticoids also change osteocyte gene expression," she said.

Thus, with glucocorticoids, bone formation goes down and bone resorption goes up. "I always say that bone doesn't have a chance in the presence of glucocorticoids," said Dr. Lane.

Dr. Sambrook, who heads the bone and joint group at the Kolling Institute of Medical Research of Royal North Shore Hospital in Sydney, presented cases that "really illustrate the type of patients that we often struggle with."

Patient No. 1

A 66-year-old woman was recently diagnosed with polymyalgia rheumatica. She had been started on 25 mg/day prednisone and the disease activity lessened in response. Her history included chronic atopic dermatitis and hypothyroidism. She had no other medical problems. There was no family history of hip fracture. She did not smoke or drink. She had a slightly early menopause but had not used hormone therapy. She reported consuming one or two servings of dairy products daily. She also considered herself to be physically active, although she had no formal exercise program.

As part of her work-up, she had a spine x-ray, which showed a vertebral deformity (compression). BMD measurements showed modest osteopenia (T scores of –1.5 at the spine and –1.6 at the hip). She had normal levels of calcium and parathyroid hormone (PTH). Her vitamin D level was equivocal, however. Her thyroid function was normal.

This patient had modest osteopenia at the time of her diagnosis. Once she was started on glucocorticoids, her T scores could have fallen rapidly and then stabilized over time, without treatment for bone loss, said Dr. Sambrook. "As she becomes established on glucocorticoids, she will perhaps not lose that much bone," but she's at risk of fracture.

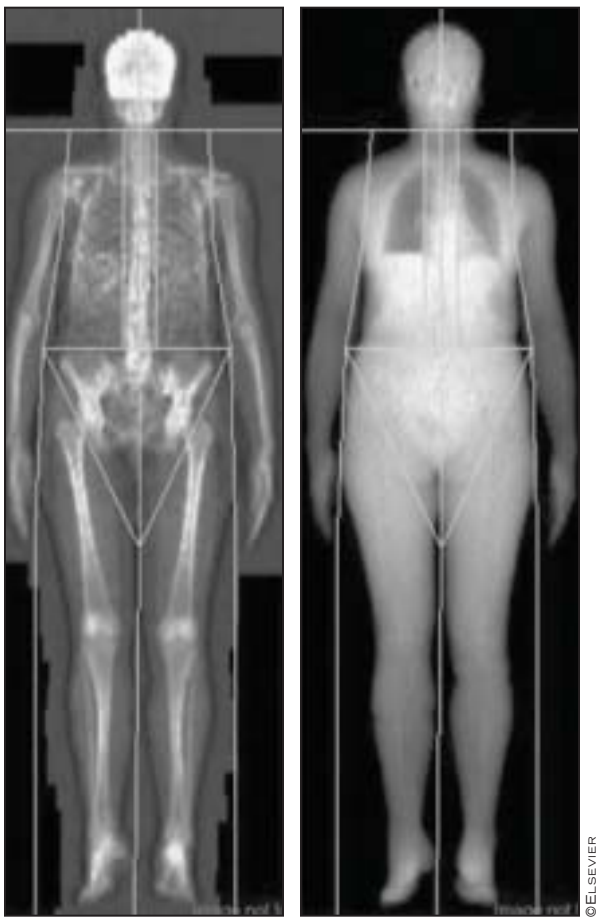
So, when clinical trial data are interpreted, it's important to keep two clinical scenarios in mind: prevention (when initial rapid loss of bone is to be avoided) and treatment (when the patient is on chronic glucocorticoids and may not be losing a lot of bone but is still at risk for fracture).

"Most of us would believe that vitamin D [plus] calcium is an adjunctive therapy," said Dr. Sambrook. The data appear to back that up. In a 1996 trial, patients with glucocorticoid osteoporosis were randomized to 50,000 U/week of vitamin D plus 1,000 mg/day of calcium, or placebo. Both groups lost bone at the spine quite rapidly, although there was a trend for patients on vitamin D and calcium to do slightly better (J. Rheumatol. 1996;23:995-1000).

Bisphosphonates do appear to improve bone density in these patients. In another study, researchers demonstrated that daily alendronate increases bone density in patients who receive glucocorticoid therapy, compared with those on placebo (N. Engl. J. Med. 1998;339:292-9). Similar results have been demonstrated with etidronate, risedronate, and zoledronic acid.

Dr. Sambrook recommended that the patient receive calcium and vitamin D supplementation. Also, "we would primarily give her bisphosphonates until prednisone is discontinued" and possibly beyond, depending on her overall fracture risk after prednisone treatment. It's also important to think about trying to minimize the dose of prednisone.

The woman returned for x-ray of the spine 2 years later. Her bone density was stable, although she had developed mild esophageal symptoms. On endoscopy, these were attributed to esophagitis. She was still taking low-dose prednisone, so she was switched to a different bisphosphonate.



Dual-energy x-ray absorptiometry provides "areal" BMD (g/cm^2) and is currently the diagnostic standard for osteoporosis (T score of –2.5 or below) in bone densitometry. DXA of the whole body can provide information on total and regional BMD (left) and body composition (fat and muscle mass) (right).

Patient No. 2

A 24-year-old woman has had systemic lupus erythematosus for 3 years, and the disease has become severe over that time. Her SLE complications have included encephalitis, vasculitis, renal involvement, and deep vein thrombosis. She had no family history of osteoporosis. She did not consume much dietary calcium, although she claimed to get adequate sun exposure. She had been on an oral contraceptive since the age of 17. Her appetite and weight were average and stable.

At the time of her presentation, she had been on prednisone for 6 months, with dosages averaging 25-50 mg daily. However, the recent onset of renal complications required increasing the dose to 75 mg daily. She was also taking an antimalaria drug. Her vitamin D level was equivocal and needed to be addressed. She had normal calcium and PTH levels and normal thyroid function. However, her spine T score was –1.4 and her hip T score was –1.0.

The concern to Dr. Sambrook was the effect of bisphosphonates on the fetal development. Although the patient was not pregnant at the start of therapy, she might have become so intentionally or unintentionally. Bisphosphonates are classified as pregnancy category C drugs by the U.S. Food and Drug Administration, meaning that they are contraindicated in pregnancy.

"The reports that have been published so far have generally not identified any developmental or bone density abnormalities," in association with prenatal exposure to bisphosphonates, Dr. Sambrook noted. Some reports have identified lower birth weight, lower gestational age at birth, and higher rates of spontaneous abortion with exposure to bisphosphonates.

"These have to be interpreted in context. These women are already ill—otherwise they wouldn't be on steroids—and that's going to affect those types of outcomes," he cautioned.

In animal studies, in which pregnant animals have been subjected to 10 times the recommended human bisphosphonate dose, maternal toxicity, growth retardation, and fetal loss have been reported.

"But these are very high doses. What do we see in real life?" Dr. Sambrook asked.

In a study from Canada published this year, researchers followed 21 women who were exposed to bisphosphonates either during or less than 3 months before pregnancy, and then compared them with matched control women. Outcomes were similar between the two groups, suggesting that preconceptional and first-trimester use of bisphosphonates may not pose substantial fetal risks (Bone 2009;44:428-30).

"These data are fairly reassuring in terms of the safety in patients treated prior to becoming pregnant or … if they become pregnant while on bisphosphonates," he said. However, bisphosphonates should be stopped as soon as it's known that a patient is pregnant, if not prior to her becoming pregnant.

One approach to managing this patient is to simply watch her and measure BMD in 12 months. Another is to use a bisphosphonate in conjunction with vitamin D and calcium supplementation. Risedronate might be the better choice, given its quicker onset and offset of action, he said.

"As long as she stayed on prednisone, I might not be as aggressive as with postmenopausal women," Dr. Sambrook noted. If the prednisone dose was decreased, he said that he might consider stopping bisphosphonate treatment.

Dr. Lane and Dr. Sambrook both reported significant financial relationships with several pharmaceutical companies. ■