

# Compare Drugs for Steroid-Induced Osteoporosis

## Head-to-head trials back options in treatment to allay 'skeletal cruelty'

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS

SAN FRANCISCO – Physicians know that corticosteroids are bad for bones. So bad that rheumatologist Jonathan D. Graf calls them “a case of skeletal cruelty.”

Given the bad reputation of chronic steroid use when it comes to bone health, one might expect physicians to be aware of the medical evidence for choosing a drug to prevent or treat glucocorticoid-induced osteoporosis. Many physicians may be unaware of the evidence, however, judging by a poll Dr. Graf conducted at a meeting on osteoporosis sponsored by the University of California, San Francisco.

Nearly everyone present believed that there have been no comparative head-to-head studies of different medications to manage glucocorticoid-induced osteoporosis.

In reality, two of the approved drugs for managing glucocorticoid-induced osteoporosis – alendronate and risedronate – were shown to be effective in only placebo-controlled trials. But two others – zoledronic acid and teriparatide – showed some advantages over risedronate or alendronate, respectively, in head-to-head comparisons, said Dr. Graf of San Francisco General Hospital.

► **Alendronate:** A 48-week study randomized 477 patients who were taking at least 7.5 mg/day of prednisone (or the equivalent) to treatment with alendronate 5 mg/day or 10 mg/day or placebo. The 10-mg alendronate group showed significantly improved lumbar bone mineral density at 48 weeks compared with the placebo group. Bone density benefits were less impressive but statistically significant for the femoral neck, trochanter, and total body compared with placebo (N. Engl. J. Med. 1998;339:292-9).

The bone density improvements on 10 mg alendronate were seen in all subgroups of patients but especially in postmenopausal women who were not taking estrogen. The risk for fractures did not differ significantly between groups for the cohort as a whole, but postmenopausal women had a significantly lower risk of fracture if they were on 10 mg alendronate, compared with placebo (4% vs. 13%).

In an extension study that followed 208 of the pa-

tients on their same regimens for another 12 months, the difference in fracture risk became significant for the cohort as a whole at 2 years: 1% in the alendronate groups and 7% on placebo. All patients in the extension study received calcium and vitamin D supplementation (Arthritis Rheum. 2001;44:202-11).

► **Risedronate:** Two separate multicenter, double-blind studies randomized patients to 2.5 mg/day or 5 mg/day risedronate or placebo, and all received calcium and vitamin D supplementation.

In one study of 224 adults starting long-term glucocorticoid therapy, patients on risedronate maintained or improved bone mineral density, which decreased significantly in patients on placebo. There was a trend toward a lower rate of new vertebral fractures at 1 year on risedronate 5 mg (6%) than on placebo (17%), but the difference was not statistically significant (Arthritis Rheum. 1999;42:2309-18).

In a separate study of 290 adults who already had been using at least 7.5 mg/day of prednisone for at least 6 months, the rate of new vertebral fractures was significantly lower at 1 year in the combined risedronate groups (5%), compared with the placebo group (15%), while rates of adverse events did not differ significantly. The risedronate groups also showed significantly higher bone mineral density at the hip and spine, compared with the placebo group (J. Bone Miner. Res. 2000;15:1006-13).

► **Zoledronic acid:** A multicenter double-blind, double-dummy trial randomized 833 patients who were on steroid therapy to either a single intravenous infusion of 5 mg zoledronic acid or oral risedronate 5 mg/day. The cohort was “very representative of patients

that I see” in practice, Dr. Graf said. Most were on 7.5 mg/day or more of prednisone daily, mostly for rheumatologic disorders.

Patients receiving zoledronic acid showed significantly better bone density at the lumbar spine after 1 year, compared with patients on risedronate (Lancet 2009;373:1253-63). The advantage was true both for preventing osteoporosis in “new” steroid users (less than 3 months use) and for treating chronic steroid users (more than 3 months).

“There are a whole bunch of issues with toxicity with zoledronic acid, compared with the other bisphosphonates, and there are cost issues and infusion issues,” Dr.

Graf said. “Whether or not you should use it in your practice is your choice, but I think you have to be aware of the fact that this drug has been studied head to head.”

The study did not assess fracture risk. “Clinically speaking, we really don’t know if this improves fracture risk, but we do know that there is a superior effect on bone mineral density,” he said.

► **Teriparatide:** A 3-year double-blinded trial randomized 428 adults who had been on the equivalent of 5 mg/day of prednisone for at least 3 months to treatment with 20 mcg/day of teriparatide or 10 mg/day of alendronate. These

**Consider teriparatide for patients with the most severe cases, or those at highest risk for fracture.**

DR. GRAF

were high-risk patients with baseline bone mineral density T scores of less than -2.0 or less than -1.0 with a history of fragility fracture. In all, 20% in each group had a history of non-vertebral fragility fracture. The reason for taking glucocorticoids was rheumatologic disease in 75% of each group.

A quarter of patients in each group dropped out of the study. In intent-to-treat analyses, bone mineral densities were higher in the teriparatide group than in those on alendronate at 18 months or at 36 months. A highly significant difference emerged in radiographically identified vertebral fractures in the teriparatide group (1%), compared with the alendronate group (6%) at the interim 18-month analysis (N. Engl. J. Med. 2007;357:2028-39).

By 36 months, the teriparatide group showed significantly lower rates of radiographic vertebral fractures (2%) and clinical vertebral fractures (0%), compared with the alendronate group (8% and 12%). No significant differences in nonvertebral fractures were seen at either time point.

“So, this primarily is of clinical benefit in the spine,” Dr. Graf said, “but the overall rate of clinical fractures is low in both groups.”

He suggested that clinicians consider teriparatide for patients with the most severe glucocorticoid-induced osteoporosis or patients at highest risk for fracture, such as those with previous fragility fractures.

► **Denosumab:** Although this drug is not yet approved for managing glucocorticoid-induced osteoporosis, a subgroup analysis from phase II trial data on 218 patients who were taking either glucocorticoids or bisphosphonates showed that adding denosumab significantly improved lumbar bone mineral density “on top of what you would normally see from the bisphosphonate,” Dr. Graf said (Ann. Rheum. Dis. 2010;69:872-5).

Dr. Graf said he has no conflicts of interest. ■



**Patients on zoledronic acid showed significantly better bone density at the lumbar spine after 1 year than did patients on risedronate, but there are toxicity issues with zoledronic acid.**

## Be Alert for Significant Bone Loss After Bariatric Surgery

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS SPONSORED BY THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

SAN FRANCISCO – Bariatric surgery can be beneficial for obese people, but it also can lead to significant bone loss.

The limited data so far suggest that decreased bone mineral density after bariatric surgery is a real problem that increases the risk for fracture, Dr. Anne Schafer said at a meeting on osteoporosis sponsored by the University of California, San Francisco.

The extent of bone loss within a year after the most common bariatric surgery, Roux-en-Y gastric bypass, can be equivalent to “what you would expect in the first 5 years of menopause” in some women, said Dr. Schafer of the division of endocrinology at the University of California, San Francisco.

A 2011 study not yet published by the Mayo Clinic, Rochester, Minn., compared fracture rates in 277 patients undergoing bariatric surgery with local age- and sex-matched fracture rates. The surgeries occurred in 1985-2004, and 94% were gastric bypasses. The retrospective chart study found 138 fractures in 82 patients

since the surgery, with a standardized incidence ratio of 2.1 for any fracture and 1.9 for fractures of the hip, spine, wrist, or arm after bariatric surgery, she said.

Dr. Schafer incorporated her own clinical experience with recommendations from the Endocrine Society and from Tufts University in advising clinicians to take the following steps in managing patients undergoing bariatric surgery.

Prior to surgery, check serum 25-hydroxyvitamin D (25[OH]D) levels and prescribe preoperative treatment to augment vitamin D in patients with low levels. After surgery, all patients should take two multivitamins per day to make

sure their micronutrient needs are met.

After malabsorptive bariatric surgery, such as gastric bypass, patients also should take calcium supplements, although there are not enough data to pinpoint the best dose or to identify which patients might most need the calcium, Dr. Schafer said. She recommended 1,200-2,000 mg/day (preferably in citrate form) after malabsorptive surgery and possibly after restrictive bariatric surgery such as adjustable gastric banding.

Based on the preoperative vitamin D level, prescribe 800-2,000 IU/day of vitamin D<sub>3</sub> supplementation after malab-

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sorptive surgery and possibly after restrictive bariatric surgery. “I’ve had people who need more” than that dose range, she added.

For postoperative surveillance, check calcium homeostasis laboratory tests every 6 months for the first 2 years and then annually after malabsorptive surgery and possibly after any bariatric surgery. The tests include calcium, albumin, phosphate, creatinine, 25(OH)D, and parathyroid hormone.

If the parathyroid hormone level is high, but the 25(OH)D level is low, treat with vitamin D supplementation. If the parathyroid hormone level is high and the 25(OH)D level is ideal, check the patient’s 24-hour urinary calcium, and if that is low, increase calcium intake.

Because some of the etiology of bariatric surgery–induced bone loss may be the preferential loss of lean mass over fat mass, or changes in fat distribution, encourage patients to consume protein and to exercise, she said.

The Endocrine Society recommends dual-energy x-ray absorptiometry

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(DXA) at baseline and annually in people who are undergoing malabsorptive bariatric surgery. No data show that such monitoring actually improves outcomes, “but I do think that you should consider it for any people who can fit on the DXA scan before the operation,” Dr. Schafer said. The weight limit for the scanner is approximately 275-350 pounds.

Dr. Schafer also said that she advises a DXA scan 1-2 years postoperatively. Incorporate those results into “your clinical judgment and other risk factors like age or prior history of fractures to set up an individualized plan for monitoring bone density from there.”

In general, high body mass index has been associated with high bone mineral density, and either voluntary or involuntary weight loss is associated with bone loss and increased fracture risk. Bariatric surgery leads to loss of bone mass for multiple reasons, she said, including nutritional deficiencies from malabsorption, the body’s signals about decreased skeletal loading with weight loss, and changes in fat-secreted hormone.

Most of the data on bone loss after bariatric surgery is for Roux-en-Y gastric bypass, which induces early and sustained increases in bone turnover and decreases in bone mineral density. Fewer data are available on other procedures, but a handful of studies suggest that another malabsorptive procedure, biliopancreatic diversion, may produce effects similar to those of gastric bypass, and that adjustable gastric banding may

have less of an impact on bone, she said.

For gastric bypass, one study of 15 patients reported an 8% decrease in total hip bone mineral density within 9 months (J. Clin. Endocrinol. Metab. 2004;89:1061-5). Femoral neck bone density decreased by 9% within 1 year of gastric bypass in a separate study of 23 patients (J. Clin. Endocrinol. Metab. 2008;93:3735-40). A third study of 42 patients reported a 7% decrease in spine bone density and a 10% decrease in total hip bone density a year after gastric bypass (Obes. Surg. 2009;19:41-6).

Vitamin D deficiency can be a prob-

lem after bariatric surgery because many patients have low vitamin D levels before surgery, some of the surgeries are designed to create malabsorption, and patients eat less food and different kinds of food after surgery. In the worst cases, patients may develop secondary hyperparathyroidism or bone loss, and there have been case reports of osteomalacia.

All the studies used DXA scans to assess bone density after bariatric surgery, but DXA assessment may be biased in the setting of marked weight loss because of changes in soft tissue surrounding the bones. The informal con-

sensus among experts is that the bone density losses reported by studies are real, “but we need nonbiased methods of assessing bone mineral density” for future studies of bariatric surgery’s effects, she said.

Dr. Schafer said that she has no disclosures.

To watch an interview with Dr. Schafer, scan the QR code or visit [www.rheumatologynews.com](http://www.rheumatologynews.com).



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