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).

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.

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 patients 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 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 nonvertebral fragility fracture. The reason for taking glucocorticoids was rheumatologic disease in 75% of each group.

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

DR. GRAF

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. ■

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_3 supplementation after malab-

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