Osteoporosis Therapy Pipeline Is Chock Full

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San Francisco — “It’s a pretty exciting time for drug development in osteoporosis,” Dr. Deborah Sellmeyer said at a meeting on osteoporosis sponsored by the University of California, San Francisco. While joking that her information was “sourced from Google and rumor and various investment brochures,” Dr. Sellmeyer, director of the Center for Osteoporosis at the university, listed some of the osteoporosis drugs in the pipeline.

A fracture trial for a full-length version of parathyroid hormone 1-34 (PTH) has been completed, and a new drug application (NDA) was submitted to the Food and Drug Administration in July 2005. Meanwhile, inhaled powder and oral forms of PTH are in phase I and phase II trials, and at least one oral form of PTH analogue is in phase III.

“Everyone’s looking for the magic combination that will be able to replicate the PTH skeletal effect and get rid of the hypercalcemic effect,” Dr. Sellmeyer said.

Oral calcium preparations are in phase I and phase II. And low-dose and ultralow-dose estrogen remain fertile areas of research. The hope is that these preparations will replicate the beneficial bone effects of estrogen while avoiding its harmful vascular effects. While two low-dose patches and one low-dose pill have already been approved for the prevention of osteoporosis and for the treatment of vasomotor symptoms, no fracture data are yet available.

Zoledronic acid, a once-a-year intravenous bisphosphonate, is currently approved for hypercalcemia of malignancy and is now in a phase III trial to determine whether it prevents osteoporotic fractures. This agent is likely to benefit people who cannot tolerate oral bisphosphonates, people in assisted-living situations, and people who have difficulty remembering to take medications.

There are several new selective estrogen receptor modulators under development, with three—lasofoxifene, bazedoxifene, and azoloxifene—in phase III or beyond. An NDA for losoxifene was submitted to the FDA in 2004, but the manufacturer apparently received a nonapprovable letter for the drug, putting the drug in limbo. An NDA for bazedoxifene was submitted in 2006 for the prevention of osteoporosis, and an NDA is planned for 2007 for a combination of bazedoxifene and estrogen for osteoporosis treatment and possible premenopausal use. Results from a phase III trial of azoloxifene are not yet available.

Tibolone is a drug that “likes every steroid receptor it ever met,” in Dr. Sellmeyer’s words. Its three metabolites separately have affinities for estrogen, progesterone, and androgen receptors. A recently completed 24-month prevention trial in 90 women showed no difference in vaginal spotting between tibolone and placebo. Interestingly, the women taking placebo experienced a 12% weight gain, while the women taking tibolone experienced no average weight gain. A multinational fracture study involving 4,000 women is expected to conclude sometime in 2006.

It’s been known for decades that strontium improves bone mineral density (BMD), but it was never developed for osteoporosis prevention or treatment because it’s a nonpatentable chemical element. Recently, however, a proprietary formulation of strontium—strontium ranelate—has shown some promise. A granular form has already been approved for use in Europe and the United Kingdom, and a once-a-day pill finished a phase I trial in September 2005. Strontium ranelate is likely to complicate interpretation of BMD testing, since it improves bone mineral density.

Denosumab, also known as AMG 162, is a monoclonal antibody that appears to decrease bone resorption. Currently in a phase III fracture trial on postmenopausal women, denosumab will require two subcutaneous injections per year.

Isorbidone mononitrate, long used for the pain of angina, appears to improve several bone markers in postmenopausal women. A BMD trial is currently underway.

J-blockers constitute another class of drugs that may well have bone effects. Most epidemiologic studies associate use of J-blockers with increases in BMD and decreases in fractures. Randomized trials are needed to determine whether J-blockers actually have a place in osteoporosis prevention or treatment. Finally, there are several new agents with presumably unrelated mechanisms of action in the pipeline. Among them are selective androgen receptor modulators, cathepsin K inhibitors, and calcyltics. All are in early-phase studies for osteoporosis.

About a third of the anastrozole patients had not reached 5 years of follow-up, however. They were categorized as “not recorded” in Dr. Coleman’s analysis.

In a discussion of the trial, Dr. Julie Gralow, of the University of Washington, Seattle, excluded the 27 tumors that started out with normal BMD, from a recallulation of the data. When she looked only at patients for whom 5-year data were available, she found that 53% of the women who started with normal BMD became osteoporotic on anastrozole. That anastrozole caused bone loss was no surprise to Dr. Coleman and his coinvestigators. The 9,366-patient ATAC trial reported that the aromatase inhibitor was more effective than tamoxifen at preventing breast cancer recurrences and had fewer side effects overall. Fractures were an exception, however. Proving in 11% of women on anastrozole but in only 7.7% of those on tamoxifen (Lancet 2005;365:60-2).

“Anastrozole suppresses postmenopausal estradiol levels by about 97%, so one would anticipate it would have an effect on bone health,” Dr. Coleman said, noting that the bone-loss study was planned when the trial was designed.

Tamoxifen increases estradiol levels and was associated with significantly less bone loss for 86 women in the other arm of the study. Their average BMD loss was just 2.8% in the lumbar spine and 0.7% in the hip.

Despite greater bone loss with anastrozole, he said its “superior efficacy and better overall tolerability, compared with tamoxifen” would continue to give anastrozole the advantage in a risk-benefit analysis.

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