Pipeline Looks Full of New Osteoporosis Therapies

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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 (PTH [1-84]) has been completed, and a new drug application (NDA) was submitted to the Food and Drug Administration in July 2005. "The latest rumors are that there needs to be little more safety data coming in before that one's going to go much further," she said.

Meanwhile, inhaled-powder and oral forms of PTH are in phase I and phase II trials, and at least one 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."

Oral calcitonin 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. Although 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 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 medication.

There are several new selective estrogen receptor modulators under development, with three—lasofoxifene, bazedoxifene, and arzoxifene—in phase III or beyond. An NDA for lasofoxifene was submitted to the FDA in 2004, but the manufacturer apparently received a nonapprovable letter in September 2005, putting the drug in limbo. An NDA for bazedoxifene has been submitted 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 arzoxifene are expected in 2010.

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, whereas those taking tibolone experienced no average weight gain. A multinational fracture study involving 4,000 women is expected to conclude sometime this year.

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 because it has a higher density than calcium.

Denosumab, or AMG 162, is a monoclonal antibody that seems to lower bone resorption. Currently in a phase III fracture trial on postmenopausal women, it will require two subcutaneous injections per year.

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

In one study, the combination of folate and vitamin B_{12} greatly decreased the incidence of hip fractures, but it involved patients who experienced stroke and hemiplegia. If this combination proves equally efficacious in other populations, it would provide a remarkably inexpensive and safe intervention for osteoporosis. Finally, β-blockers constitute another class of drugs that may have bone effects, but random trials are needed to establish whether they have a place in osteoporosis therapy. ■

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