Novel Antiresorptives Well Tolerated

BY MICHELE G. SULLIVAN
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DESTIN, FLA. — Investigational antiresorptive agents with novel methods of action and dosing regimens may improve patient compliance and persistence, but will not reduce the risk of fracture associated with osteoporosis beyond that seen with current agents.

"The objective of all these drugs is to normalize bone turnover, which we already do extraordinarily well and easily with bisphosphonates," Dr. Michael McClung said at a rheumatology meeting sponsored by the Virginia Commonwealth University.

However, some of the investigational antiresorptives are just as good at increasing bone mineral density as are the bisphosphonates, and may be easier for patients to take, he added.

Denosumab, currently in phase III studies, has shown some promising effects. The agent inhibits the binding of the RANK protein to its ligand. The binding increases the population of osteoclasts and allows them to live longer, inhibiting the binding blocks that process, thus reducing bone turnover.

A phase II study compared different denosumab doses to placebo and to alendronate. It found that denosumab increased bone density as well or better than alendronate, especially at sites greater in cortical bone. Denosumab reduced serum C-telopeptide levels more than did alendronate. Within 3 days of initiating therapy, the levels dropped 80% with all doses of denosumab, compared with 25% with alendronate (N. Engl. J. Med. 2006;354:821-31).

The drug was well tolerated, said Dr. McClung, director of the Oregon Osteoporosis Center, Portland, and principal investigator of the study. There were no injection site reactions or adverse events that increased with dosage, and no observed immune response problems, he said at the meeting, also sponsored by the International Society for Clinical Densitometry and the Alabama Chapter of the Arthritis Foundation. The phase III study is looking at the effects of a 60-mg subcutaneous dose once every 6 months.

Intravenous bisphosphonates given every few months avoid the gastrointestinal side effects and could improve persistence in therapy. They will be especially convenient for nursing home residents, Dr. McClung said.

Ibandronate was recently approved for intravenous dosing of 3 mg every 3 months. A trial showed that bone mineral density and bone turnover marker responses to this dose were similar to those achieved with daily oral dosing of 2.5 mg. There are no fracture data available for the new dosing schedule, but a previous study showed that infusions of 0.5 or 1 mg of ibandronate every 3 months did not persistently suppress markers of bone turnover and did not significantly reduce fracture risk. (Bone 2004;34:890-9).

Intravenous zoledronic acid, already approved in 4-mg doses for the treatment of cancer-related bone diseases, is now being studied for an osteoporosis indication. A phase II study demonstrated that a single dose of 4 mg IV suppressed indices of bone turnover for at least 12 months. A phase III study is exploring yearly infusions of 5 mg IV zoledronic acid for the treatment of osteoporosis.

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DR. McCLUNG

Cathepsin K inhibitors are also being investigated in phase II trials, he said. Cathepsin K is an enzyme required for hydrolysis of the bone matrix, inhibiting the enzyme reduces bone resorption.

Several new selective estrogen receptor modulators are also under investigation. "I don't think anyone has found the magic SERM that is as potent as estrogen on the skeleton, but without the problematic side effects," said Dr. McClung.

Strontium ranelate is an interesting compound being investigated in Europe. The orally administered strontium salt is taken up in bone much the same way as is calcium; however, it is denser than calcium. It has been shown to reduce the risk of vertebral and nonvertebral fracture in older women with osteoporosis. It is available in several counties, but there are no immediate plans to market the drug in the United States.

New anabolic or bone-forming agents are also being studied. Parathyroid hormone 1-84 has been shown to increase bone formation and to reduce the risk of vertebral fractures in women with osteoporosis. The drug is under consideration by the Food and Drug Administration.

In animal studies, an antibody that binds sclerostin, an inhibitor of osteoblast activity, normalized bone mass and the deterioration of bone structure that occurred after estrogen deficiency.

"The availability of new agents will provide important new options for both clinicians and our patients," said Dr. McClung. "Importantly, we may find new combinations of antiresorptive and anabolic agents that provide additive effects and, perhaps, even the cure for osteoporosis." ■

Don't Immediately Switch Bone Agents if BMD Fails to Improve

DESTIN, FLA. — A lack of increase in bone mineral density does not necessarily indicate a failure of antiresorptive therapy for osteoporosis, and is not a reason to switch a patient's drugs, Dr. Michael McClung said at a rheumatology meeting sponsored by the Virginia Commonwealth University.

A sizeable proportion of patients on antiresorptive therapy do not have an increase in their bone mineral density (BMD), and some actually experience a decrease, he said. "Patients need to be told up front that these are not bone density-building drugs—they are designed to prevent bone loss and preserve what is there."

Nor do changes in bone density completely predict future fracture risk, according to a study cited by Dr. McClung, director of the Oregon Osteoporosis Center, Portland. Osteoporosis treatments increase BMD and reduce fracture risk, but even those women with no increase in density experience protection from fracture. "This suggests that most of the reduction in fracture risk is due to something else besides increasing bone density," he said.

Markers of bone turnover are also an imperfect way to predict future fracture risk, Dr. McClung said. Patients who respond usually have quick and observable changes in their markers, but attempting to use markers to monitor treatment response in individual patients is difficult because of the imprecision of current assays.

Nonresponse can only be identified by deterioration of skeletal health while on treatment. This deterioration is usually defined as a true decrease in BMD, but in clinical trials, it's very uncommon. With estrogen or alendronate, nonresponse occurs in less than 3% of patients. In clinical practice however, bone loss may be more common (8%-10%) due to noncompliance, poor bioavailability, and other medical issues that affect bone health.

"Don't overinterpret any changes, or lack of changes, you see when you monitor patients," said Dr. McClung. "The main reason to follow BMD after starting therapy is to identify those patients who continue to lose bone mass. Seeing no change or even a decrease in bone density is a signal to review dosing and compliance, and to take another look at any other medical circumstances that could be affecting bone health."

It is not even possible to monitor treatment response with some agents, like calcitonin, which have very small effects on BMD or markers, Dr. McClung said.

—Michele G. Sullivan

Three-Year Diabetes Initiative Aims to Improve Quality of Care

BY MIRIAM E. TUCKER
Senior Writer

PHILADELPHIA — The American College of Physicians' 3-year diabetes initiative is off and running, Dr. Vincenza Snow said at a press briefing during the college's annual meeting.

The program, announced last year, is funded by a $9.27 million unrestricted educational grant from Denmark-based insulin manufacturer Novo Nordisk. The initiative aims to "increase awareness of the gap between current practice and acceptable standards of diabetes care, provide educational interventions to improve diabetes care, increase physician awareness of what constitutes high-quality, evidence-based care, and recognize medical practices that improve their diabetes care," according to an ACP statement.

To help meet those educational goals, the ACP meeting included 16 educational sessions on diabetes during 23 separate time slots (some were offered twice), compared with 8 topics in 16 sessions offered last year, said Dr. Snow, director of clinical programs and quality of care at ACP, and clinical director of the diabetes initiative.

Another element of the initiative, the new patient guide called "Living with Diabetes," was developed under the guidance of experts in both diabetes and health literacy and a psychologist, based on input from patients, physicians, nurse-educators, pharmacists, and other members of the diabetes "team." Written in English and Spanish, the guide is "conversational and warm. It leaves patients feeling confident and encouraged," said Terry Davis, Ph.D., the psychologist who worked on the guide.

The guide organizes the information based on what's most important to patients. For example, the chapter on food is the longest and is placed at the front, explained Dr. Davis, professor of medicine and pediatrics at Louisiana State University Health Sciences Center, Shreveport.

Another aspect of the initiative, "Closing the Gap," held its first training session at this year's meeting. Nineteen practices from across the country each sent two staff members to participate in intensive quality-improvement training, which they will take back to their practices and use to train their office staff.

Dr. Michael A. Weisz has made ACP's overall "Closing the Gap" program—aimed at training teams of health care providers to improve quality of care for patients with a variety of chronic conditions—central to his tenure as ACP governor for Oklahoma. Five Oklahoma physician practices attended the "Closing the Gap" workshops this year.

"I've been in practice now 18 years, and this is a totally different way of taking care of patients. Rather than focusing on single [patient evaluations], it's a way of focusing on diseases and changing the system of how we do that," said Dr. Weisz, vice chairman of internal medicine and residency program director of the University of Oklahoma in Tulsa.

Physicians shouldn't look at quality improvement as a seismic shift, Dr. Weisz advised. "The idea is to go back and make small changes and see what happens. If something doesn't work, you can make [another] quick change." ■