Better Bone Biomarkers on the Distant Horizon

BY JEFF EVANS
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BETHESDA, MD. — Fracture will continue to be the primary end point in clinical trials of treatments for osteoporosis until new biomarkers can stand in as surrogates for fracture, according to speakers at a meeting on bone quality.

The large number of factors that need to be tested to validate a single biomarker as a surrogate end point make it unlikely that any single biomarker will adequately predict the risk of fracture, said Henry Bone, M.D., of the Michigan Bone and Mineral Clinic, Detroit. Researchers may need to combine a set of biomarkers into a model to produce the best surrogate.

Many new potential biomarkers of bone quality are being evaluated in small subgroups in clinical trials, but no single study has compared a set of bone quality measurements with bone mineral density (BMD) and radiographs for prediction of fractures and the effect of treatment, Dr. Bone said. "We really haven't considered using combined models integrating a number of different kinds of these intermediate end points or biomarkers."

"For something as complicated as fracture risk, I think this is where we're going to end up—that we use combinations of anatomical and more dynamic measurements in order to explain the effects of treatment," added Steven R. Cummings, M.D., of the California Pacific Medical Center Research Institute in San Francisco.

Surrogate end points, which may be faster and easier to measure than clinical outcomes such as fracture, could allow researchers to speed up clinical trials, enroll fewer patients into studies, and lower the cost of drug development, said Theresa Kehoe, M.D., of the division of metabolic and endocrine drug products at the Food and Drug Administration's Center for Drug Evaluation and Research.

A surrogate end point in a clinical trial is a laboratory or radiologic measurement or physical sign—a biomarker—used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives. The changes induced by a therapy on this surrogate end point are expected to reflect changes in a clinically meaningful end point, such as fracture, Dr. Kehoe said.

In osteoporosis clinical trials involving the prevention of postmenopausal osteoporosis with estrogens, current regulatory practice permits the use of BMD data alone to act as a surrogate end point, Dr. Kehoe said at the meeting, which was sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the American Society for Bone and Mineral Research.

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DR. BONE

But data on the rate of fracture are necessary for clinical trials of the prevention or treatment of postmenopausal osteoporosis with selective estrogen receptor modulators or nonestrogen products. In those trials, Dr. Kehoe said the FDA "tends not to accept" BMD data as a surrogate for prevention of postmenopausal osteoporosis before it has data on the rate of fracture.

BMD is still the primary end point for efficacy in noninferiority trials that compare a once-daily formulation of a drug that has already been approved based on its ability to reduce the rate of fracture with a new formulation of the same drug, she said.

Dr. Kehoe raised additional questions to consider about surrogate end points:

► Should the surrogate show consistent sensitivity and specificity in more than one therapeutic class of drugs? A single negative therapeutic example has the potential to undermine the biological plausibility of the proposed surrogate, she noted.

► What type of fracture should the surrogate be tested against? This could be an asymptomatic morphometric vertebral fracture, which some already consider to be a surrogate for a symptomatic fracture.

► Should the surrogate have equal sensitivity and specificity for mild, moderate, and severe vertebral fractures?

► What sensitivity, specificity, positive and negative predictive values, or other relevant statistics should be required to prove that a surrogate is valid? ■