Bone Quality: A Perspective from the Food and Drug Administration

Theresa Kehoe, MD

Corresponding author
Theresa Kehoe, MD
Division of Metabolic and Endocrine Products, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Bldg 22, Rm 3374, Silver Spring, MD 20993-0002, USA.
E-mail: Theresa.Kehoe@fda.hhs.gov

Current Osteoporosis Reports 2006, **4:**76–79
Current Science Inc. ISSN 1544-1873

Osteoporosis, a disease of compromised bone strength, is a leading cause of fracture, morbidity, and mortality. The past 10 years have resulted in the development of new pharmacologic therapies for the treatment of this disease. Most of these agents have been approved for the treatment of osteoporosis based on placebo-controlled fracture trials. However, recent ethical concerns regarding placebo-controlled trials threaten to derail the development of new, possibly better, treatment options. Novel noninvasive imaging technologies may offer greater insight into the pathophysiology and biomechanics of osteoporosis and fracture. Because of these advances, many hope to find a new biomarker that will predict fracture risk better than the current bone density measurements and that ultimately will replace fracture as the primary endpoint for osteoporosis drug registration trials. This paper discusses the perspective of a Food and Drug Administration reviewer regarding the role of surrogate markers as they relate to the quest for new, safe and efficacious treatments for osteoporosis.

Introduction

Osteoporosis is the most common metabolic bone disease in the United States and remains a leading cause of fracture and subsequent disability in older individuals. Although the disease most frequently affects postmenopausal women, both sexes are affected by osteoporosis and subsequent fracture. The 2000 National Institutes of Health (NIH) Consensus Conference on Osteoporosis Prevention, Diagnosis and Therapy defined osteoporosis as a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture [1]. Components of bone strength include bone mineral density (BMD) and bone quality. Currently, the diagnosis of osteoporosis relies on BMD, which is predominantly measured by noninvasive dual x-ray absorptiometry (DXA). It is well recognized that although a decrease in BMD correlates with the risk of fracture, this correlation is insufficient to completely explain the diminution of risk achieved with therapeutic interventions. Other qualities of bone that may play a role in fracture risk are more difficult to define and measure. New mechanisms and methods for exploring bone quality and skeletal integrity are the focus of intensive research investigation. Areas of investigation into the properties of skeletal integrity include (but are not limited to) bone geometry and macrostructure, trabecular and cortical microarchitecture, and material properties and crack propagation. Methods to assess these properties of skeletal integrity are also under investigation. The NIH and the American Society for Bone and Mineral Research (ASBMR) have jointly sponsored several meetings focused on the evolving science of bone quality and skeletal integrity. In addition, the NIH has recently formed the Collaborative Initiative on Bone Strength. The goal of the initiative is to advance the scientific research of bone quality and skeletal integrity in order to foster the development of noninvasive measurements that predict fracture more accurately than BMD. The ultimate aim is to accumulate the data needed to validate biomarkers as surrogate endpoints that will replace fracture as the primary endpoint in osteoporosis drug development trials.

At present, trials for the registration of new drug and biologic products for the treatment of osteoporosis are required to have fracture as the primary endpoint. Of concern is whether the conduct of placebo-controlled fracture trials continues to be ethical. In October 2000, the World Medical Association [2] revised the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* to state, "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." The statement was later revised to clarify that placebo-

controlled trials could be done to determine safety and efficacy in the setting of compelling and sound methodologic reasons, or for a minor condition in which placebo-treated subjects would not be subject to any additional risk of serious or irreversible harm. Even so, this declaration caused great concern regarding the continued use of placebo-controlled trials in osteoporosis drug development. In June 2002, the NIH and ASBMR convened a meeting entitled "Osteoporosis Trials: Ethical Considerations in Study Design" to address concerns regarding the appropriateness of placebo-controlled fracture trials in osteoporosis drug development [3•]. This meeting discussed alternative approaches to the design of clinical trials, including short-term, placebo-controlled trials in high-risk subjects; placebo-controlled trials in low-risk subjects; add-on trials; superiority trials; and use of nonfracture surrogate endpoints. However, the overall opinion at the end of the meeting appeared to be that demonstration of antifracture efficacy would remain essential for acceptance of new therapies.

In follow-up, in September 2002 the US Food and Drug Administration (FDA) convened a public meeting of the Metabolic and Endocrine Advisory Committee, entitled "Standards of Evidence for Approval of Drugs for Prevention and Treatment of Osteoporosis" [4]. The committee was asked to consider the circumstances under which antifracture efficacy should be required for drug approval. A majority of the panel felt that fracture efficacy was needed for drug registration. They also concluded that placebo-controlled trials, with drug or placebo provided as an add-on therapy to calcium and vitamin D, could continue in women with lower short-term fracture risk. To study high-risk subjects, an active control trial would be needed, with superiority, rather than noninferiority, as the endpoint of choice.

Although these two meetings agreed that placebo-controlled fracture trials may continue with lower-risk osteoporotic subjects, conducting such trials has become increasingly difficult as many institutional review boards will not allow the conduct of placebo-controlled fracture trials. Therefore, there may come a time in the not-too-distant future when placebo-controlled fracture trials will no longer be an option and further osteoporosis drug development may be stifled. When considering the value of new measures of bone quality and skeletal integrity and where they fit in the development of new therapies to treat osteoporosis, including supplanting fracture as the primary efficacy endpoint, we need to consider the overall role of surrogate endpoints and the history of surrogate endpoints in osteoporosis drug development.

The Role of Surrogate Endpoints

Surrogate endpoints are a subset of biomarkers. Biomarkers are physical signs or laboratory measurements that occur in association with a pathologic process and have putative diagnostic and/or prognostic utility. The biomarker may qualify for consideration as a surrogate when there is a known, predictive relationship between the magnitude of change in the biomarker and the magnitude of change in the clinical outcome. One frequently used definition of a surrogate endpoint is a laboratory measurement or a physical sign that is used as a substitute for a clinically meaningful endpoint; that is, one that measures directly how a patient feels, functions, or survives [5•]. Basic criteria for defining a surrogate endpoint include the demonstration of both biologic plausibility and adequate validation that the biomarker is independently predictive of benefit. In addition, measurement of the biomarker must be standardized, reproducible, and precise. In the setting of drug development, surrogate biomarkers or endpoints can serve several different but related roles. The surrogate can be used as a marker to identify the disease and risk of interest, allowing for identification of the target population for study or treatment. A surrogate marker can be used for proof of principle or dose setting in early drug development. A surrogate also can be used as an endpoint for assessment of drug efficacy. In this case, the change in the marker must correlate with and predict the change in benefit; that is, it must be validated.

The benefits of relying on surrogates include shorter and smaller trials to show efficacy, thereby reducing the costs of drug development. With these benefits come risks, however. In particular, the use of surrogate endpoints may produce insufficient data to allow adequate risk-benefit assessments. An inadequate risk-benefit relationship may occur as a result of unexpected variations in the association between the change in biomarker and the clinical outcome, or because of unexpected adverse effects of the drug or biologic product that may not be defined in shorter trials that do not assess ultimate clinical outcomes.

When one applies the definition of a surrogate endpoint specifically to osteoporosis drug development, one may think that the ultimate clinical outcome, fracture, is easily defined. However, pivotal trials for osteoporosis drug registration tend to rely on efficacy measures of the reduction of new or worsening morphometric vertebral fractures. These fractures are predominantly asymptomatic for the patient and are noted only on serial spinal x-rays. Therefore, one could consign a morphometric vertebral fracture, a largely asymptomatic radiographic finding, to surrogate status, as it is a laboratory measurement that is used as a substitute for a clinically meaningful endpoint, a clinical fracture. The question of whether a morphometric vertebral fracture is a clinically meaningful endpoint or a surrogate endpoint remains controversial. However, when one begins the process of validation for new potential surrogate endpoints, the status of morphometric vertebral fractures becomes critical, as validation of one surrogate based on another surrogate would be problematic and possibly futile.

The History of Surrogate Endpoints in Osteoporosis Drug Development

In order to understand the reticence in accepting other surrogate endpoints for fracture, one needs to look at the history of surrogate endpoints in osteoporosis drug development. An FDA guidance document for drug therapies used in the prevention and treatment of osteoporosis has existed for over 25 years. (The full history of the osteoporosis guidance has been published previously [6•].) The initial osteoporosis guidance was issued in 1979. At that time, trials were required to be randomized, double-blind, placebo-controlled, and at least 24 months in duration. The first guidance made it clear that it was desirable to provide evidence that a drug used to treat osteoporosis reduced the risk of fractures. However, because of the recognition that study size might be prohibitively large, bone mass measurement was allowed as a primary efficacy endpoint as long as the newly formed bone was of normal quality. If bone quality was not normal, a fracture trial would be needed to demonstrate adequate effectiveness. Methods available to assess bone mass included single-energy photon absorptiometry (SPA) and total body calcium measured by neutron activation analysis. In 1984, injectable salmon calcitonin became the first drug approved for the treatment of postmenopausal osteoporosis. Its approval was based on measurements of total body calcium, with a postmarketing commitment for a definitive fracture study.

An updated osteoporosis guidance document was issued in 1984. Additions included defining the need for calcium and vitamin D supplementation and a discussion of studies needed for the indications of treatment of osteoporosis and prevention of osteoporosis. The guidance also allowed for dual-energy photon absorptiometry (DPA) for analysis of BMD. After the introduction of the 1984 guidance, the science of bone mass measurement continued to evolve and dual-energy x-ray absorptiometry (DXA) became the accepted standard for the diagnosis of osteoporosis.

Even as DXA became the gold standard for osteoporosis diagnosis, the pitfalls in using bone mass measurements as a surrogate endpoint for the registration of new osteoporosis drugs also became apparent. These limitations are best illustrated by the experiences with sodium fluoride and etidronate. In one 4-year study of postmenopausal women, 75 mg of sodium fluoride daily increased lumbar spine BMD an impressive 35%. Despite that significant increase in BMD, however, the number of new vertebral fractures was similar between the treatment and placebo groups, and nonvertebral fractures actually occurred more frequently with the fluoride treatment [7]. Etidronate raised another concern when, despite continued increases in BMD, an apparent loss of fracture efficacy was noted during the third year of the 3-year trial [8]. These events raised the concern that BMD in fact may not be an adequate biomarker for fracture. They also led to questions regarding the appropriate length of fracture trials for drug registration and, ultimately, to revisions in the osteoporosis guidelines.

In 1994, the FDA issued its current Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis [9]. Although these guidelines recognized the scientific advances in the field of bone mass measurements and included DXA and quantitative CT (QCT) as techniques for evaluating skeletal mass, they also acknowledged the difficulty of using bone mass measurements as the primary efficacy endpoint for osteoporosis treatment trials. To that end, the requirement of a 3-year study with fracture assessment as the primary efficacy endpoint was added for all nonestrogen drug products seeking the indication of treatment of osteoporosis. Qualitative and/or established objective (morphometric) criteria were recommended for the assessment of vertebral fractures. As previously noted, some might consider morphometric criteria to define vertebral fractures to be a surrogate endpoint for clinical fracture. The FDA has relied on fracture data from 3-year trials, accompanied by adequate preclinical and clinical bone histomorphometry data, for approval of new drug and biologic products for osteoporosis since the publication of the 1994 guidelines.

Conclusions

The fields of osteoporosis research and osteoporosis drug development continue to move forward. However, we appear to be approaching the point where placebo-controlled fracture trials are no longer considered ethical or practical. Although the 1994 FDA osteoporosis guidance document does allow the use of either placebo or active-drug control for fracture efficacy trials, placebo-controlled studies have become the norm. BMD is an imperfect surrogate for fracture risk, particularly when used to measure changes in bone mass and risk for fracture following treatment. Therefore, new surrogate endpoints for fracture seem increasingly necessary, and the development of such surrogates is an area of great research interest.

When one considers the clinical application of new surrogates for fracture, the initial question is how the surrogate will be used. A new surrogate used to better identify patients at high risk of fracture would be beneficial in the clinical arena so that therapies could be appropriately tailored. In this setting, there are fewer hurdles to scale and less regulatory intervention would be needed. However, if the intent is for the surrogate to replace fracture as the primary endpoint in osteoporosis drug registration trials, then adequate and accepted validation of the surrogate is essential. Generally speaking, the FDA does not have set standards or requirements for surrogate validation. Some questions that must be addressed during the process of validating a new surrogate for fracture include: 1) What type of fracture should the surrogate be tested against? Although radiologically defined (morphometric) vertebral fractures are more prevalent in clinical trials, they could be considered surrogates themselves and may not

adequately represent the primary clinical outcome, clinical fracture. Hip fractures result in the most significant morbidity and mortality but would also require more resources for validation. If morphometric vertebral fractures are ultimately considered clinically relevant, then a follow-up question would be: Should the surrogate have equal sensitivity and specificity for mild, moderate, and severe vertebral fractures? 2) What sensitivity and specificity, positive and negative predictive value, and other relevant statistics would be required to consider a surrogate valid? The most appropriate surrogate would be one for which a threshold could be defined, thus allowing for these statistical considerations. 3) Has the surrogate shown consistent sensitivity and specificity with more than one therapeutic class of drugs (eg, antiresorptive and anabolic agents)? The most appropriate surrogate would be one for which the magnitude of change in the biomarker directly relates to the magnitude of change in the risk of fracture, regardless of therapeutic intervention. If variations in the biomarker directly correlate with reduction in fracture risk for only one class of drugs, then the biologic plausibility ascribed to that biomarker's function as an adequate surrogate may be significantly damaged. The NIH's Collaborative Initiative on Bone Strength provides a unique and important setting for data sharing and analysis as the clinical, research, industry, and regulatory communities strive to continue the advancement of osteoporosis therapies.

As we move forward with the research and testing required to find a valid surrogate for fracture, many questions need to be answered and many issues need to be addressed. At present, fracture trials will continue to be required and these interventional trials may provide an excellent venue for the evaluation and investigation of new biomarkers. There is no real risk in incorporating these endpoints into the clinical trials. Even in the setting of negative or unfavorable data, fracture outcomes remain the primary endpoints for approval and such data will continue to be important for surrogate validation.

Disclaimer

The views expressed in this paper are those of the author and should not be construed as representing the official position of the Food and Drug Administration.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy: **Osteoporosis prevention, diagnosis, and therapy [review].** *JAMA* 2001, **285:**785–795.
2. **World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects.** *JAMA* 2000, **284:**3043–3045.
3.• Capron A, Donaldson S, Raisz LG, Swift S: **Osteoporosis panel summary.** *J Bone Miner Res* 2003, **18:**1160–1162.

This article summarizes a collection of articles in the *Journal of Bone and Mineral Research* that encapsulates the presentations and discussions from the June, 2002, National Institutes of Health conference on study design and ethical considerations for osteoporosis drug development trials.

4. US Food and Drug Administration, Center for Drug Evaluation and Research: *Endocrinologic and Metabolic Drugs Advisory Committee meeting documents.* Silver Spring, MD, September 25, 2002. http://www.fda.gov/ohrms/dockets/ac/cder02.htm#EndocrinologicMetabolicDrugs. Accessed January 21, 2006.
5.• Temple RJ: **A regulatory authority's opinion about surrogate endpoints.** In *Clinical Measurement in Drug Evaluation*. Edited by Nimmo WS and Tucker GT. New York: John Wiley & Sons; 1995:3–22.

This chapter provides an overview of surrogate endpoints in the drug approval process. It focuses mainly on endpoints related to cardiovascular outcomes.

6.• Colman EG: **The Food And Drug Administration's osteoporosis guidance document: past, present, and future.** *J Bone Miner Res* 2003, **18:**1125–1128.

This article provides a comprehensive history of the FDA's guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of osteoporosis.

7. Riggs BL, Hodgon SF, O'Fallon WM, et al.: **Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis.** *N Engl J Med* 1990, **322:**802–809.
8. Harris ST, Watts NB, Jackson RD, et al.: **Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy.** *Am J Med* 1993, **95:**557–567.
9. US Food and Drug Administration, Center for Drug Evaluation and Research, **Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis.** http://www.fda.gov/Cder/guidance/osteo.pdf.