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Placebo-Controlled Trials in Osteoporosis — Proceeding with Caution

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Abstract

This article presents one viewpoint on the issues surrounding placebo-controlled trials in osteoporosis. The other Sounding Board article in this issue presents an opposing view. At NEJM.org, in a related interactive feature, the authors of each article give their Point of View about the other article. At NEJM.org, readers can participate in forming community opinion by choosing one of the viewpoints and, if they like, providing their reasons.

Effective treatments are now available to prevent osteoporotic fractures, but the process of approving new agents has been accompanied by a simmering controversy about the ethics of placebo-controlled trials for testing new drugs. This debate is often framed by the simple question of whether people who are highly susceptible to an osteoporotic fracture should be involved in a clinical trial and thereby risk random assignment to a placebo. However, the issue is more complex than this question and centers on multiple concerns that run the gamut from clinical equipoise (i.e., genuine uncertainty over whether or not the treatment will be beneficial) to informed consent to health care accessibility. Notwithstanding this debate, appropriate guidelines to exclude high-risk patients would allow placebo-controlled trials in osteoporosis to benefit some patients and inform investigators.

In the field of osteoporosis, the most prominent example of a well-executed placebo-controlled clinical trial is the Women's Health Initiative, which showed the antifracture efficacy of estrogen and progesterone but also illuminated critically important nonskeletal adverse events.¹ More recently, investigators in a large, randomized, placebo-controlled trial of denosumab, the first of a new class of biologic agents, provided strong evidence of vertebral and nonvertebral antifracture efficacy but also reported unique side effects that have necessitated further study.²

The results of large, randomized, placebo-controlled trials, although convincing, are insufficient to promote universal acceptance of these drugs for the treatment of osteoporosis. In future studies, women at very high risk should not be allowed to enroll in a placebo-controlled trial of a new intervention when standard treatments are known to reduce the risk of a fracture by 30 to 50%. Who are such patients? We would argue that women with a history of a fragility fracture of the hip or spine, a very low bone mineral density (T score less than –2.5), or both should be excluded, even if they express a willingness to participate. Of course, the choice ultimately rests with the individual woman, but high-risk patients must be encouraged to seek conventional therapeutic options. In addition, for such trials, a clinical trial investigator should not recruit his or her own patients who have osteoporosis.

Which women might we consider suitable for enrollment in such randomized trials? We would follow the recommendations of an expert panel that considered it appropriate to enroll patients with low bone mineral density in placebo-controlled trials if they had no history of fragility fractures or if radiologic imaging showed only asymptomatic morphometric vertebral fractures.³ Similarly, patients who had side effects from previous therapies or who did not have a response to conventional therapy might be considered. Inherent in these assumptions is the fact that few pure placebo-controlled trials involve patients with osteoporosis. Virtually all industry- and investigator-originated trials use an add-on approach in which one group receives calcium and vita-min D and another group receives calcium and vitamin D plus the active agent. For example, in another group of the Women's Health Initiative, the use of calcium plus 400 IU of vitamin D was associated with an increase in femoral bone mineral density and a reduction in the risk of hip fracture among older postmenopausal women.⁴ That trial empirically established the standard for a comparison group in studies of osteoporosis treatments.

In other circumstances, placebo-controlled trials inform us about new therapies in patients with a relatively low risk of fracture. The rates of absolute fracture among younger postmenopausal women with moderately reduced bone mass (i.e., T score greater than -2.5) but no previous fractures are low. Trials that enroll these women are often designed to examine rates of bone loss, changes in surrogate indexes (such as biochemical markers of bone turnover), and critical safety indexes. Similarly, the comparison with a placebo-control group is particularly important for newer classes of drugs (e.g., a biologic agent such as denosumab) that would be difficult to contrast with other established drugs or historical control data.

There are certainly alternatives to placebo-controlled trials in osteoporosis. The most common alternatives are noninferiority and superiority trials in which a no-treatment group is replaced by a group that receives an established drug. These trials are much more difficult to carry out and require larger numbers of participants to prove noninferiority for a reduction in fracture risk. For example, in phase 3 fracture studies, 5000 to 8000 patients are generally required to achieve statistical power to assess group differences. In a noninferiority trial for antifracture efficacy, that number would increase and substantially more time would be required to conduct the trial. Furthermore, a trial that used alendronate as a comparison drug would necessitate the inclusion of patients who were at higher risk, since alendronate has not been shown to reduce fractures in women with T scores greater than -2.0.⁵ Ultimately, any trial involving a comparison group would, given its necessarily larger size, result in more fractures over the duration of the trial than would be observed in a placebo-controlled study and, thus, it would offer no ethical advantage over the latter.⁶ Finally, these trials are also complicated by the issue of "assay sensitivity" (i.e., the level of accuracy in comparing a new drug with an established drug when the effect size is relatively small). Notwithstanding these issues, noninferiority studies can test surrogate markers for fracture (e.g., bone mineral density or bone-turnover markers), indexes that reduce the required number of study participants but do not directly address fracture outcomes, the most clinically important end point. However, the matter is complicated because changes in surrogate indexes, including bone mineral density, do not always predict the reduction of fracture risk during treatment.

Alternative approaches to recruitment could be considered; these include allowing patients to be randomly assigned to active drug or placebo if they are already receiving weaker agents such as a selective estrogen-receptor modulator or calcitonin. Another approach might be to improve decision making by subjects who are considering enrollment in clinical trials of new osteoporosis treatments by, for example, using the recently developed fracture risk assessment tool (FRAX) for screening subjects. The FRAX score provides the individual patient, in percentage terms, with an absolute risk of hip fracture or any

osteoporotic fracture over the next 10 years, thereby allowing more informed decision making based on each patient's risk of fracture without active treatment.⁷ For example, in a 65-year-old woman with no fractures or other risk factors but a bone mineral density T score of -2.5, the 10-year probability of a major fracture would be 13% and the 10-year probability of a hip fracture would be 2.8%. During a 3-year, randomized, controlled trial of a drug that would be predicted to reduce fractures by 40%, a total of 4.0% of subjects in a placebo group would sustain a fracture as compared with 2.4% of subjects in the treatment group. Providing these data to potential patients would inform decision making at all levels.

Guidelines from the European Medicines Agency⁸ that are quite similar to older (1994) guidelines from the U.S. Food and Drug Administration⁹ still promote the use of placebo-controlled trials to test new drugs in persons at risk for fractures. With that in mind, we believe that trial design and implementation should not supersede patient welfare or underestimate the potential for harm. To be ethical, the trial design first must answer the question being asked. It should provide potential participants with a high and clear standard of informed consent, including active review by an institutional review board and an independent data and safety monitoring board. Shared decision making must be a centerpiece of this process. The Declaration of Helsinki, which states that placebo trials are permissible when no major harm could be expected to come to trial participants as a result of delaying treatment, remains a major guideline for investigators.⁶ With the use of appropriate guidelines to exclude high-risk patients, placebo-controlled trials of osteoporosis treatments can benefit some patients and can inform investigators and the health care profession in a safe, transparent, and scientific manner.

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