Commentary

Ethical challenges raised by osteoporosis-related clinical trials

Maryam Mirahmad[1], Sayed Mahmoud Sajjadi-Jazi[2], Fariba Asghari[3], Bagher Larijani[4*]

1. Researcher, Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
2. Associate Professor, Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
3. Professor, Medical Ethics and History of Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran.
4. Professor, Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.

Keywords: *Osteoporosis; Placebo; Trial design; Ethics.*

Introduction:

Low bone mineral density (BMD), which mainly encompasses osteoporosis and osteopenia, is a chronic bone metabolic condition characterized by impaired bone microstructure and reduced bone mass. This condition elevates the risk of fractures in different parts of the body, resulting in a substantial economic, societal, and health burden. It is projected that the global prevalence of hip fractures is expected to increase by 240% for women and 310% for men by 2050 (1, 2).

In recent decades, there have been significant advancements in both the availability of novel medications for treating osteoporosis and our understanding of the disease's pathogenesis. In the late 1980s, treatment options for postmenopausal women with osteoporosis were limited to estrogen replacement or, perhaps, calcitonin, in addition to calcium and vitamin D supplementation (3).

However, there are now multiple effective treatment choices available for preventing and managing osteoporosis. At least five bisphosphonate agents, alongside biologic medicines, parathyroid hormone therapy, hormone replacement therapy, parathyroid hormone-related protein analogs, and selective est-

****Corresponding Author***
Bagher Larijani

Address: *Shariati Hospital, Jalal-e-Al-e-Ahmad Hwy., Tehran, Iran.*
Postal Code*: 1411713135*
Tel: *(+98) 21 88 22 00 38*
Email: *emrc@tums.ac.ir*

Received: *25 Feb 2023*
Accepted: *10 May 2023*
Published: *2 Dec 2023*

Citation to this article:
Mirahmad M, Sajjadi-Jazi M, Asghari F, Larijani B. Ethical challenges raised by osteoporosis-related clinical trials. J Med Ethics Hist Med. 2023; 16: 7.

-rogen receptor modulators, have demonstrated their efficacy in managing osteoporosis (4).

The first osteoporosis therapy was authorized more than four decades ago. Since then, numerous innovative therapies have been developed, and safety concerns have been raised. Furthermore, a general regulatory approach is followed in the development of osteoporosis treatments (5).

To promote osteoporosis-related clinical trials and translate their results into recommendations for patient care, it is crucial to gain a better understanding of clinical trial design. In the following section, we will discuss general perspectives on the ethical aspects of clinical trial design. Additionally, our aim is to address the ethical considerations of conducting placebo-controlled clinical trials when there is a proven effective therapy for osteoporosis

Active control or placebo?

The selection of control groups in clinical trials is a crucial and challenging factor to obtain interpretable results, as the effects associated with the control group serve as a baseline for assessing the efficacy of the proposed intervention assigned to the investigational arm.

Randomizing participants to a treatment arm is recommended because it enhances the likelihood that both measured and unmeasured parameters affecting the outcome will be properly distributed across the research arms. The presence of a control group ensures that the study's findings accurately reflect the impact of applied therapies rather than the natural course of the disease (6). However, the use of placebos as controls in clinical trials raises substantial ethical concerns.

Over the years, two main groups have emerged, one supporting the active-control arm and the other defending the placebo arm. Representatives from both sides have requested modifications to placebo regulation from drug authorities, presenting ethical and methodological justifications for their respective views (7).

Supporting rationale in favor of placebo-controlled trials

Some experts believe that placebo-controlled clinical trials are methodologically superior to studies with an active control arm due to the following reasons (8):

1- One of the most well-known concepts in medical ethics is the idea that 'bad design is bad ethics.' A methodological drawback associated with active-controlled designs, such as equivalent trials or non-inferiority trials, is their poor assay sensitivity in distinguishing effective therapies from ineffective

or less effective therapies. Historically, this has been a point of contention for proponents of placebo-controlled trials, as it can lead to an erroneous conclusion of efficacy (9).

2- Another argument in favor of the placebo-control design is that it typically requires a smaller sample size, leading to reduced drug development costs and fewer individuals being exposed to potential risks (10).

3- In some cases, patients enrolled in the placebo group of a placebo arm show no negative health effects and may even experience improvements (11).

4- Alternative trial designs, such as superiority trials, may raise the approval threshold for novel treatments, particularly when the novel treatment's advantages lie in factors like ease of administration (which can enhance treatment compliance) or improved tolerability (which might be perceived as increased efficacy) rather than higher absolute effectiveness (12).

Arguments against placebo-controlled trials

Supporters of active-control trials reject the rationale behind placebo-controlled studies (8).

1- Advocates of active-control trials argue that there is no justification for exposing study participants to additional risk, danger, or discomfort when a verified effective therapy for the disease already exists. According to the Declaration of Helsinki, in every clinical study, all patients, including those in the control group, must be ensured that they receive the best therapeutic approach (13).

2- Placebo-controlled trials violate the equipoise principle as placebos are less effective than standard treatment. In contrast, active-controlled studies provide a comparison of the therapy, whether it is superior, inferior, or equivalent to standard therapies, while also aligning with the principle of equipoise.(7,14)

3- Advocates of active-control, counter utilitarian ethics by stressing the significance of the deontological principle, which claims that the physician's commitment to protect his patients surpasses the gain of data for society.

Specific aspects related to osteoporosis clinical trials

The preference for long-term placebo-controlled trials in osteoporosis is currently under debate. Fractures are rare events, and clinical trials must enroll a large number of patients to ensure a sufficient number of fractures for statistical analysis (15). For example, in the largest randomized clinical trial that included Teriparatide in the treatment arm, only two hip fractures were

recorded throughout the entire course of the trial (16).

Furthermore, there is a consensus that conducting placebo-controlled studies is not ethically justifiable when an available treatment option exists that reduces the risk of death or serious complications. However, in cases where the adverse consequences of a disease are modest or infrequent, many believe it may be ethically acceptable to forego a beneficial therapy. In the context of osteoporosis, vertebral and hip fractures have significant health implications, such as the need for surgery, long-term physical impairment, and a high risk of mortality (17).

Results from placebo-controlled trials have confirmed that the use of available medications like bisphosphonates can reduce the risk of osteoporotic fractures by up to 50% compared to a placebo (18-20).

There is a widespread consensus that established and beneficial therapies should not be discontinued when conducting a placebo-controlled trial would expose individuals to an increased risk of death or irreversible morbidity (21). Some argue that, given the availability of effective treatments for osteoporosis, women at very high risk of fractures should not be included in future placebo-controlled trials. Exclusion criteria could be defined as women with low BMD (T score less than -2.5), those with a history of fragility spine or hip fractures, or both. Certainly, patients should make their own decision, but high-risk patients should be encouraged to consider standard treatments (22). A panel of experts recommended that patients with low BMD could be included in placebo-controlled clinical trials related to osteoporosis if they have no history of fragility fractures or if only asymptomatic morphometric vertebral fractures are identified in radiologic imaging (23).

From another perspective, the practice of excluding patients with the highest fracture risk from placebo-controlled trials implicitly recognizes that untreated osteoporosis carries the potential for significant consequences, which therapeutic options can mitigate. This approach addresses concerns about adverse outcomes in patients receiving placebos, rather than solely focusing on negative consequences (17).

In response to concerns raised by regulatory agencies such as the Food and Drug Administration (FDA), a clinical trial guidance was published in late 2009 by a consortium of U.S. osteoporosis societies. This guidance endorsed placebo-controlled trials for the registration of novel therapeutics, with a focus on vertebral or non-vertebral fracture endpoints, and considered them

ethically appropriate. There was a consensus that such trials could be shortened to approximately 1.5 to 2 years to demonstrate effectiveness. Subsequently, there would be a minimum five-year period to provide evidence of safety and sustained reduction in the fracture risk. If it is demonstrated that a particular treatment reduced the risk of fractures, dose regimens and other indications can be defined using bone turnover markers (BTMs) in conjunction with BMD, except for corticosteroid-induced osteoporosis (23).

Alternatives like superiority and non-inferiority trials

Multiple strategies have been suggested for placebo-controlled trials of osteoporosis. These include experiments on patients with osteopenia, who are not currently eligible to receive treatment; add-on trial designs, in which novel therapy or placebo is added to the standard treatment; and clinical trials with "informed refusal", in which participants are either unable to tolerate standard treatment, decline currently available therapies, or gain no benefit from them (24).

All of these alternate designs have drawbacks. Generalizing the data from people with osteopenia to those with osteoporosis may not be valid. The clinical relevance of add-on studies may be limited. Informed-refusal clinical trials commonly involve researchers with an inherent conflict of interest. It is possible that the same physicians who recommend the currently available and approved treatment to patients enroll them for a clinical trial requiring refusal of such treatment. These studies may also face other challenges in enrollment and maintaining the adherence of patients, since the participants are individuals who have previously refused or are unable to take prescribed treatment (17, 25).

The development of novel effective therapies for osteoporosis has led to the belief that placebo-controlled studies are no longer necessary, and superiority or non-inferiority studies should be considered instead. These designs have their advantages and limitations. In such designs, the absolute efficacy of the target agent will remain uncertain. In addition, these alternatives require large sample sizes, thus the cost of research will increase significantly. Another justification opposing employing superiority trials is that novel treatments offering benefits other than efficacy, like reduced price and improved safety profile or tolerability, may be rejected using this research method. This might potentially be overcome if such parameters are specified as the primary outcome

measure (26, 27). Non-inferiority trials are typically conducted to demonstrate that the target treatments are not less effective than active controls by more than the equivalence margin. However, these trial designs may also encounter various challenges (28). First, choosing the margin of non-inferiority unequivocally remains a challenging issue. Second, the following prerequisites must be fully validated: an appropriate active comparator should be chosen. This comparator should be widely recognized and should have shown apparent anti-fracture efficacy in osteoporosis under circumstances similar to those in the clinical trial analyzing the novel chemical entity. The magnitude of the comparator's impact must be coherent across surveys.

Conclusion

Considering the severe disability resulting from fractures, the increased risk of death due to this disability, and the complex and risky nature of fracture fixation in the elderly, assigning participants to the placebo group without any treatment is ethically unjustifiable. With the increasing development of new drugs that effectively reduce fractures in osteoporosis, it is no longer ethical to evaluate new drugs in placebo-controlled clinical trials. While designing trials with active treatment groups may present methodological and operational difficulties and may not reveal the net effect of the new drug, these challenges do not justify the use of placebo control groups in clinical trials with fracture endpoints. Moreover, even valid informed consent cannot ethically justify the conduct of such trials.

Placebo-controlled trials should be restricted to those with alternative endpoints, such as BMD and BTMs. Clinical trials with bone fracture endpoints should include an active control group, or if feasible based on the mechanism of effect, adopt an add-on design. While it is theoretically possible to conduct a study with a control group comprising individuals who do not tolerate any active drugs, the limited number of potential participants raises concerns about obtaining valid informed consent, particularly when the research teams may have a conflict of interest.

Acknowledgements & Funding

There is no Acknowledgements and funding.

Conflict of Interests

There are no competing interests to declare.

References:

1. Gullberg B, Johnell O, Kanis J. World-wide projections for hip fracture. Osteoporosis international. 1997; 7(5): 407-13.

2. Shen Y, Huang X, Wu J, Lin X, Zhou X, Zhu Z, et al. The Global burden of osteoporosis, low bone mass, and its related fracture in 204 countries and territories, 1990-2019. Front Endocrinol (Lausanne). 2022; 13: 882241.

3. Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. Lancet Diabetes Endocrinol. 2017; 5(11): 898-907.

4. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019; 30(1): 3-44.

5. Kehoe T, Blind E, Janssen H. Regulatory aspects of the development of drugs for metabolic bone diseases - FDA and EMA perspective. Br J Clin Pharmacol. 2019; 85(6): 1208-12.

6. Vallotton MB. Council for international organizations of medical sciences perspectives: protecting persons through international ethics guidelines. International Journal of Integrated Care. 2010;10(5).

7. Skierka AS, Michels KB. Ethical principles and placebo-controlled trials-interpretation and implementation of the Declaration of Helsinki's placebo paragraph in medical research. BMC Med Ethics. 2018; 19(1): 24.

8. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials—a middle ground. Mass Medical Soc; 2001, p, 915-9.

9. Group ICoHEW. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice. CFR & ICH Guidelines. 1997.

10. Miller FG, Brody H. What makes placebo-controlled trials unethical? The American Journal of Bioethics. 2002; 2(2): 3-9.

11. Iolascon G, Moretti A. What are the efficacy and safety of pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D? A Cochrane review summary with commentary. J Musculoskelet Neuronal Interact. 2022; 22(1): 1-4.

12. Howick J. Questioning the methodologic superiority of 'placebo' over 'active' controlled trials. Am J Bioeth. 2009; 9(9): 34-48.

13. Association WM. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 310(20): 2191-4.

14. Michels KB, Rothman KJ. Update on unethical use of placebos in randomised trials. Bioethics. 2003; 17(2): 188-204.

15. Heaney RP. Evidence-based medicine and common sense: practical and ethical issues in clinical trials for osteoporosis. International Journal of Clinical Rheumatology. 2007; 2(1): 105.

16. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016; 316(7): 722-33.

17. Stein CM, Ray WA. The ethics of placebo in studies with sracture end points in osteoporosis. New England Journal of Medicine. 2010;363(14):1367-70.

18. Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health technology assessment (Winchester, England). 2005; 9(22): 1-160.

19. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C, et al. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocrine Reviews. 2002; 23(4): 570-8.

20. Byun JH, Jang S, Lee S, Park S, Yoon HK, Yoon BH, et al. The efficacy of bisphosphonates for prevention of osteoporotic fracture: an update meta-analysis. J Bone Metab. 2017; 24(1): 37-49.

21. World medical association. declaration of Helsinki, ethical principles for medical research involving human subjects. 52 nd WMA general assembly, Edinburgh, Scotland. 2000.

22. Rosen CJ, Khosla S. Placebo-controlled trials in osteoporosis — proceeding with Caution. New England Journal of Medicine. 2010; 363(14): 1365-7.

23. Silverman SL, Cummings SR, Watts NB, for the consensus panel of the ASBMR I, NOF. recommendations for the clinical evaluation of agents for treatment of osteoporosis: consensus of an expert panel representing the American society for bone and mineral research (ASBMR), the International

society for clinical densitometry (ISCD), and the national osteoporosis foundation (NOF). Journal of Bone and Mineral Research. 2008; 23(1): 159-65.

24. Brody BA, Dickey N, Ellenberg SS, Heaney RP, Levine RJ, O'brien RL, et al. Is the use of placebo controls ethically permissible in clinical trials of agents intended to reduce fractures in osteoporosis? Journal of Bone and Mineral Research. 2003; 18(6): 1105-9.

25. Tanne JH. FDA puts restrictions on an institutional review board after secret investigation. British Medical Journal Publishing Group. 2009.

26. Batra S, Howick J. Empirical evidence against placebo controls. J Med Ethics. 2017.

27. Krol FJ, Hagin M, Vieta E, Harazi R, Lotan A, Strous RD, et al. Placebo-To be or not to be? are there really alternatives to placebo-controlled trials? European Neuropsychopharmacology. 2020; 32: 1-11.

28. Delmas PD, Calvo G, Boers M, Abadie E, Avouac B, Kahan A, et al. The use of placebo-controlled and non-inferiority trials for the evaluation of new drugs in the treatment of postmenopausal osteoporosis. Osteoporos Int. 2002; 13(1): 1-5.