Can we discern optimal long-term osteoporosis treatment for women?

The use of osteoporosis drugs in sequence—rather than a single agent for a long time—may be the most effective management strategy

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In a recent systematic review, Fink and colleagues attempted to summarize the published evidence of the efficacy and safety of long-term (> 3 years) therapy for osteoporosis.[1] Unfortunately, they arrived at very limited and tentative conclusions because, as they point out, of the paucity of such evidence.

Why long-term studies stop short

Only 3 of the several tens of placebo-controlled fracture end-point studies (about 58 trials and observational studies) that Fink and colleagues reviewed evaluated treatment for more than 3 years. The nonavailability of longer-term studies is the direct consequence of a requirement by regulatory agencies for a 3-year fracture end-point study in order to register a new drug for osteoporosis. Hence, longer, placebo-controlled studies do not benefit the industry sponsor, and enrolling patients with osteoporosis or who are at high risk for fracture in any, much less long, placebo-controlled trials is now considered to be unethical.

The author reports receiving honorarium and consulting fees from Amgen.

What the authors did observe

From this limited set of information with which to evaluate, Fink and colleagues observed that long-term therapy with raloxifene reduces the risk of vertebral fractures but is associated with thromboembolic complications. In addition, treatment for more than 3 years with bisphosphonates reduces the risk of vertebral and nonvertebral fractures but may increase risk of rare adverse events (including femoral shaft fractures with atypical radiographic features).

The bisphosphonate holiday. The authors refer to the even more limited evidence about the effects of discontinuing bisphosphonate therapy. Unlike the rapid loss of bone mass density (BMD) and fracture protection upon stopping estrogen or denosumab, the offset of these treatment benefits is slower when bisphosphonates are discontinued. This, coupled with concern about increasing risk with long-term bisphosphonate therapy, led to the confusing concept of a "bisphosphonate holiday." While recommendations to consider temporary discontinuation of bisphosphonates in patients at low risk for fracture have been made by expert panels,[2] very little information exists about the benefits/risks of this strategy, how long the treatment interruption should be, or how to decide when and with what to restart therapy.

Unfortunately, overall, Fink and colleagues' observations provide little practical guidance for clinicians.

What we can learn from longer term and recent studies of ideal treatment

Since we have no "cure" for osteoporosis, and since the benefits of therapy, including protection from fractures, abate upon stopping treatment (as they do when we stop treating hypertension or diabetes), very long term if not lifelong management is required for patients with osteoporosis. Persistent or even greater reduction of fracture risk with treatment up to 10 years, compared with the rate of fracture in the placebo or treated group during the first 3 years of the study, has been observed with zoledronate and denosumab.[3-5] Denosumab was not included in the systematic review by Fink and colleagues since the pivotal fracture trial with that agent was placebo-controlled for only 3 years.[6]

Sequential drug treatment may be best. Fink and colleagues also did

not consider new evidence, which suggests that the use of osteoporosis drugs in sequence—rather than a single agent for a long time—may be the most effective management strategy.[7,8]

More consideration should be given to the use of estrogen and raloxifene in younger postmenopausal women at risk for vertebral but not hip fracture.

Only treat high-risk patients. Using osteoporosis therapies to only treat patients at high risk for fracture will optimize the benefit:risk ratio and cost-effectiveness of therapy.

Bisphosphonate holidays may not be as important as once thought. BMD and fracture risk reduction does not improve after 5 years of bisphosphonate therapy, and longer treatment may increase the risk of atypical fractures, while switching to another agent can increase BMD and perhaps mitigate the safety concern, suggesting that there is little justification for continuous use of bisphosphonates for more than 5 years, thereby minimizing the importance of a bisphosphonate holiday.

Hip BMD may serve as indicator for treatment decisions. Recent evidence indicating that the change in hip BMD with treatment or the level of hip BMD achieved on treatment correlates with fracture risk reduction may provide a useful clinical target to guide treatment decisions.[9,10]

Because we have a lack of pristine evidence does not mean that we shouldn't treat osteoporosis; we have to do the best we can with the limited evidence we have. Therapy must be individualized, for we are not just treating osteoporosis, we are treating patients with osteoporosis. ●

References

1. Fink HA, MacDonald R, Forte ML, et al. Long-term drug therapy and drug discontinuations and holidays for osteoporosis fracture prevention: a systematic review. *Ann Intern Med*. 2019;171:37-50.
2. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2016;31:16-35.
3. Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. 2015;30:934-944.
4. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;5:513-523.
5. Ferrari S, Butler PW, Kendler DL, et al. Further nonvertebral fracture reduction beyond 3 years for up to 10 years of denosumab treatment. *J Clin Endocrinol Metab*. 2019;104:3450-3461.
6. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.
7. Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. *J Bone Miner Res*. 2017;32:198-202.
8. Hanley DA, McClung MR, Davison KS, et al; Writing Group for the Western Osteoporosis Alliance. Western Osteoporosis Alliance Clinical Practice Series: evaluating the balance of benefits and risks of long-term osteoporosis therapies. *Am J Med*. 2017;130:862.e1-862.e7.
9. Bouxsein ML, Eastell R, Lui LY, et al; FNIH Bone Quality Project. Change in bone density and reduction in fracture risk: a meta-regression of published trials. *J Bone Miner Res*. 2019;34:632-642.
10. Ferrari S, Libanati C, Lin CJF, et al. Relationship between bone mineral density T-score and nonvertebral fracture risk over 10 years of denosumab treatment. *J Bone Miner Res*. 2019;34:1033-1040.