FPIN's Clinical Inquiries

Combination Therapy for Postmenopausal Osteoporosis

HEATHER TAGLIARINO JONES, MD, Swedish Medical Center, Seattle, Washington

ELLEN HOWARD, MLS, University of Washington Health Science Libraries, Seattle, Washington

Am Fam Physician. 2010 Feb 15;81(4):439-440.

Clinical Question

Is combination therapy, other than with calcium and vitamin D, effective for the treatment of postmenopausal osteoporosis?

Evidence-Based Answer

There is insufficient evidence to recommend combination therapy for the routine management of postmenopausal osteoporosis. (Strength of Recommendation [SOR]: C, based on expert opinion). Combination therapy with parathyroid hormone (PTH) and a bisphosphonate is less effective than treatment with PTH alone, and should not be used. (SOR: C, based on a randomized trial using disease-oriented end points). However, combination therapy with raloxifene (Evista) and a bisphosphonate or PTH, and sequential treatment with PTH followed by alendronate (Fosamax) have been shown to increase bone mineral density (BMD) more than single-agent therapy and may be considered in patients with severe or refractory postmenopausal osteoporosis. (SOR: C, based on expert opinion).

Evidence Summary

Many studies have looked at the effectiveness of combination therapies in treating post-menopausal osteoporosis. To date, no studies have had sufficient power or duration to detect effects on fracture incidence. Instead, studies have been limited to disease-oriented surrogate measures of fracture risk, including BMD and markers of bone turnover.[1]

In a randomized controlled trial (RCT) of 331 postmenopausal women with osteoporosis, participants received 10 mg alendronate daily, 60 mg raloxifene daily, a combination of alendronate and raloxifene, or placebo.[2] After one year, the increase in lumbar spine BMD in the combination therapy group (5.3 percent) was not significantly different from the alendronate group (4.3 percent; $P = .10$), but was significantly greater than the raloxifene group (2.1 percent; $P < .001$). The combination therapy group also had a greater increase in BMD at the femoral neck (3.7 percent) than the alendronate group (2.7 percent; $P = .02$) and the raloxifene group (1.7 percent; $P < .0001$).

In a double-blind trial of 238 postmenopausal women with low BMD, patients were randomized to receive alendronate, PTH, or both for one year.[3] Volumetric density of trabecular bone at the spine, measured by quantitative computed tomography, increased by 25.5 percent in the PTH group, 10.5

percent in the alendronate group, and 12.9 percent in the combination therapy group. In a study of sequential treatment, 66 postmenopausal women with osteoporosis were treated with PTH for one year followed by alendronate for one year.[4] The results showed an increase in vertebral BMD of 11.3 ± 5.7 percent for the group receiving 50 mcg of PTH and 14.6 ± 7.9 percent for the group receiving 100 mcg of PTH. There was no comparison group, but previous RCTs of alendronate alone reported much lower increases in vertebral BMD.[5]

A six-month, double-blind, placebo-controlled trial of 137 postmenopausal women with osteoporosis compared combination therapy of raloxifene and PTH with PTH alone.[6] The group treated with PTH alone had an increase of 5.19 ± 0.67 percent in BMD at the lumbar spine, but no significant change at the femoral neck or total hip. Compared with PTH alone, the combination therapy group showed an increase in BMD of 6.19 ± 0.65 percent at the lumbar spine (P = .28); 2.23 ± 0.64 percent at the femoral neck (P = .19); and 2.31 ± 0.56 percent at the total hip (P = .04).

No drug-drug interactions have been reported with combination therapy for osteoporosis. However, the use of multiple medications for a single indication increases the risk of adverse effects, and data on long-term safety are lacking.[7]

Recommendations from Others

In revised guidelines published in 2003, the American Association of Clinical Endocrinologists recommends against combining medications for the prevention or treatment of postmenopausal osteoporosis until the effect on fracture risk is understood.[8] The U.S. Surgeon General's 2004 report on osteoporosis states that combination therapy should be reserved for patients who have experienced a fracture while on monotherapy; those who start out with very low BMD and a history of multiple fractures; and those with very low BMD who continue to lose bone mass while on monotherapy.[9]

Address correspondence to Heather Tagliarino Jones, MD, at heatherj18@hotmail.com. Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Mauck KF, Clarke BL. Diagnosis, screening, prevention, and treatment of osteoporosis. *Mayo Clin Proc*. 2006;81(5):662–672.
2. Johnell O, Scheele WH, Lu Y, Reginster J, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2002;87(3):985–992.
3. Black DM, Greenspan SL, Ensrud KE, et al., for the PaTH Study Investigators. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med*. 2003;349(13):1207–1215.

4. Rittmaster RS, Bolognese M, Ettinger MP, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab*. 2000;85(6):2129–2134.
5. Chaiamnuay S, Saag KG. Postmenopausal osteoporosis. What have we learned since the introduction of bisphosphonates? *Rev Endocr Metab Disord*. 2006;7(1–2):101–112.
6. Deal C, Omizo M, Schwartz EN, et al. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. *J Bone Miner Res*. 2005;20(11):1905–1911.
7. Crandall C. Combination treatment of osteoporosis: a clinical review. *J Womens Health Gend Based Med*. 2002;11(3):211–224.
8. Hodgson SF, Watts NB, Bilezikian JP, et al., for the AACE Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003 [published correction appears in *Endocr Pract*. 2004;10(1):90]. *Endocr Pract*. 2003;9(6):544–564.
9. U.S. Department of Health and Human Services. Office of the Surgeon General. Bone health and osteoporosis: a report of the Surgeon General; 2004. http://www.surgeongeneral.gov/library/bonehealth. Accessed June 15, 2007.