Parathyroid hormone (1-84) plus alendronate was not better than monotherapy with either agent in postmenopausal osteoporosis

Black DM, Greenspan SL, Ensrud KE, et al. **The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis.** N Engl J Med. 2003;349:1207-15.

QUESTION

In postmenopausal women with osteoporosis, is parathyroid hormone (1-84) (PTH) plus alendronate more effective than monotherapy with either agent for increasing bone mineral density (BMD)?

DESIGN

Randomized {allocation concealed*}†, blinded (clinicians, patients, data collectors, data analysts, and outcome assessors),* controlled trial with 12-month follow-up.

SETTING

4 clinical centers in the United States.

PATIENTS

238 postmenopausal women 55 to 85 years of age (mean age 70 y) who had osteoporosis defined as a T score < –2.5 for BMD at the femoral neck, total hip, or spine; or a T score < –2.0 at one of these sites and age ≥ 65 years, history of postmenopausal fracture, or maternal history of hip fracture. Exclusion criteria included treatment with bisphosphonates for > 12 months or for > 4 weeks in the previous 12 months and use of medications known to affect bone metabolism. Follow-up was 95%.

INTERVENTION

Patients were allocated to PTH, 100 µg/d (n = 119); alendronate, 10 mg/d (n = 60); or both (combination, n = 59) for 12 months.

MAIN OUTCOME MEASURES

Areal BMD (the amount of mineral in a 2-dimensional projection divided by the area) measured at the hip, lumbar spine (L1 to L4), and distal one third of the radius; and volumetric BMD and bone geometry in trabecular and cortical compartments assessed at the spine (L1 and L2) and hip, at baseline and at 12 months.

MAIN RESULTS

Analysis was by intention to treat. Increase in total hip areal BMD was greater in the combination group than in the PTH group (Table). Decrease in areal BMD at the distal one third of the radius was greater in the PTH group than in the combination group (Table). Increase in volumetric BMD at the trabecular spine was lower in the combination group than in the PTH group (Table). Decrease in volumetric density of cortical bone at the total hip was greater in the PTH group than in the combination group (Table). Cortical volume at the femoral neck increased in the PTH group but not in the combination group (Table). The combination group did not differ from the alendronate group for any outcomes.

CONCLUSION

In postmenopausal women with osteoporosis, parathyroid hormone (1-84) plus alendronate was not better than monotherapy with either agent for increasing bone mineral density.

Source of funding: National Institute of Arthritis and Musculoskeletal and Skin Disorders.

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*See Glossary.

†Information provided by author.

Combination therapy with parathyroid hormone (1-84) (PTH) plus alendronate vs PTH alone in postmenopausal women with osteoporosis at 12 months‡

Outcomes	Bone site	Mean percentage change from baseline		Difference between groups (95% CI)
		Combination	PTH	
Areal bone mineral density (BMD)	Total hip	1.9	0.3	1.6% (0.3 to 2.9)
	Radius (distal one third)	–1.1	–3.4	–2.3% (–3.5 to –1.2)
Volumetric BMD	Trabecular spine	12.9	25.5	12.6% (2.8 to 22.4)
Volumetric density of cortical bone	Total hip	0.1	–1.7	–1.8% (–3.0 to –0.7)
Cortical volume	Femoral neck	–0.6	3.4	4.0% (0.1 to 7.9)

‡CI defined in Glossary.

COMMENTARY

Alendronate inhibits bone resorption, increases BMD, and reduces fracture risk in men and women with osteoporosis (1–3). PTH administered daily stimulates bone formation and increases BMD in both men and postmenopausal women with osteoporosis (4, 5). PTH also reduces fracture risk in postmenopausal women (6). The different mechanisms of action of PTH and alendronate led to the plausible hypothesis that the combination of these agents would lead to a greater increase in BMD than either agent alone. This hypothesis was tested in the studies by Black and colleagues and Finkelstein and colleagues. Of note, in the study by Finkelstein and colleagues PTH was started after 6 months, so that men in the combination group had already received alendronate for 6 months when PTH began.

In both studies, areal BMD was assessed using dual-energy x-ray absorptiometry (DEXA) and volumetric BMD was assessed with quantitative computed tomography. Areal BMD—the amount of mineral in a 2-dimensional projection divided by the area—can sometimes be misleading because it is influenced by the size of the bone: Areal BMD measurements tend to overestimate the true BMD in larger patients and underestimate the true BMD in smaller patients. Volumetric BMD measures the average concentration of mineral in a defined volume. Volumetric BMD takes into account bone size and can also distinguish between trabecular and cortical bone.

In interpreting the results, it is helpful to evaluate the effects separately for cortical and trabecular bone. In both studies, the volumetric BMD of the spine (which is trabecular bone) increased more in the PTH group than in the combination group. This shows that alendronate impairs the anabolic activity of PTH on trabecular bone. Black and colleagues found that areal BMD at the hip (which consists of cortical bone) remained unchanged in the PTH group and increased in both the alendronate and combination groups. When cortical volume at the hip was evaluated, PTH increased cortical volume at the femoral neck (bone size) and alendronate impaired this effect. In the longer

(continued on page 63)

Parathyroid hormone (1-34) alone was better than parathyroid hormone plus alendronate in men with osteoporosis

Finkelstein JS, Hayes A, Hunzelman JL, et al. **The effects of parathyroid hormone, alendronate, or both in men with osteoporosis.** N Engl J Med. 2003;349:1216-26.

QUESTION

In men 46 to 85 years of age with osteoporosis, is parathyroid hormone (1-34) (PTH) plus alendronate more effective than monotherapy with either agent for increasing bone mineral density (BMD) at the lumbar spine?

DESIGN

Randomized (unclear allocation concealment*), blinded (outcome assessors),* controlled trial with 30-month follow-up.

SETTING

Massachusetts General Hospital in Boston, Massachusetts, USA.

PATIENTS

83 men 46 to 85 years of age who had osteoporosis (defined as BMD of the lumbar spine that was ≥ 2 standard deviations below the mean value of young, normal men). Exclusion criteria included disorders or use of medications known to affect bone metabolism, nephrolithiasis, active peptic ulcer disease, and severe reflux esophagitis. 73 men (mean age 58 y) with follow-up BMD measurements were included in the analysis.

INTERVENTION

Men were stratified by age (< 65 vs ≥ 65 y) and BMD (> vs < 2 standard deviations below the mean for the man's age) and allocated to subcutaneous injections of PTH, 40 µg/d (n = 20); alendronate tablets, 10 mg/d (n = 28); or both (n = 25). Alendronate therapy was begun at the baseline visit and continued for 30 months. PTH therapy was begun at the 6-month visit and continued for 24 months.

MAIN OUTCOME MEASURES

Change from baseline in BMD of the lumbar spine.

MAIN RESULTS

Analysis was by intention to treat. Increase in BMD at the lumbar spine was greater in the PTH-alone group than in the alendronate-alone or combination groups (Table). The increase in BMD at the lumbar spine was also greater in the combination group than in the alendronate-alone group (Table).

CONCLUSION

In men 46 to 85 years of age with osteoporosis, parathyroid hormone (1-34) (PTH) alone was more effective than PTH plus alendronate or alendronate alone for increasing bone mineral density at the lumbar spine.

Source of funding: National Institutes of Health.

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*See Glossary.

Combination therapy with parathyroid hormone (1-34) (PTH) plus alendronate vs monotherapy with either agent in men with osteoporosis at 30 months

Outcome	Comparisons	Mean percentage†	*P* value
Increase from baseline in bone mineral density at the lumber spine	Combination vs PTH	14.8 vs 18.1	<0.001
	Combination vs alendronate	14.8 vs 7.9	<0.001
	PTH vs alendronate	18.1 vs 7.9	<0.001

COMMENTARY *(continued from page 62)*

study by Finkelstein and colleagues, increase in areal BMD at the Finkelstein and colleagues, increase in areal BMD at the femoral neck was greater in the PTH group than in the combination and alendronate groups. These data show that alendronate impairs the effect of PTH even in cortical bone.

How might alendronate attenuate the action of PTH? A probable explanation is that alendronate inhibits bone turnover, which impairs the anabolic action of PTH. PTH enhances the function and lifespan of mature osteoblasts (7). If bone resorption and bone formation are reduced, which is what happens with alendronate therapy, a decrease in mature osteoblasts occurs, decreasing the effectiveness of PTH.

How should we apply the results of these studies to our patients? First, it is important to remember that while BMD is a strong predictor of future fracture, it is still a surrogate outcome. Using BMD as a surrogate for fracture is always problematic, and this may be particularly true with PTH. PTH has complex effects on trabecular and cortical bone that may not be captured by areal BMD measurements. Furthermore, PTH may reduce fractures by improving bone micro-architecture, which will not be reflected in BMD measurements.

Despite this limitation, these studies have implications for treatment of men and women with osteoporosis. First, because of the cost and need for daily subcutaneous injections, physicians should consider PTH only in patients with severe osteoporosis. Second, if a physician is contemplating PTH treatment in a previously untreated patient, the data, based on BMD outcomes, suggest that PTH should be used alone—not in combination with—alendronate or by inference another bisphosphonate. What about patients who are already receiving bisphosphonate therapy? Whereas no definitive answer exists in these studies or elsewhere, one approach might be to stop bisphosphonate when starting PTH therapy. Clearly, the efficacy of this method needs to be tested in further clinical trials with fracture as the primary outcome.

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