CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 21, NO. 7, 2005, 1027–1034

0300-7995
doi:10.1185/030079905X49671

ORIGINAL ARTICLE

The effects of teriparatide on the incidence of back pain in postmenopausal women with osteoporosis*

Harry K. Genant[a], Johan Halse[b], Walter G. Briney[c], Li Xie[d], Emmett V. Glass[d] and John H. Krege[d]

[a] *UCSF-OARG and Synarc Inc., San Francisco, CA, USA*

[b] *Betanien Medical Laboratory, Oslo, Norway*

[c] *Denver Health Medical Center, Denver, CO, USA*

[d] *Eli Lilly and Company, Indianapolis, IN, USA*

Address for correspondence: Dr. John Krege, Eli Lilly and Company, Lilly Corporate Center, Drop Code 6134, Indianapolis, IN 46285, USA. Tel.: +1-317-651-9705; Fax: +1-317-276-5696; email: kregejh@lilly.com

Key words: Back pain – Osteoporosis treatment – Parathyroid hormone – Postmenopausal – Teriparatide

ABSTRACT

Objectives: Back pain is a major cause of suffering, disability, and cost. The risk of developing back pain was assessed following treatment with teriparatide [rh(PTH 1–34)] in postmenopausal women with osteoporosis.

Research design and methods: A secondary analysis of back pain findings from the global, multi-site Fracture Prevention Trial was conducted where postmenopausal women with prevalent vertebral fractures were administered teriparatide 20 μg ($n = 541$) or placebo ($n = 544$) for a median of 19 months. Treatment-emergent back pain data were collected during adverse event monitoring, and spine radiographs were obtained at baseline and study endpoint.

Main outcome measures: The risk of back pain stratified by severity of new or worsening back pain and the risk of back pain associated with both number and severity of new vertebral fractures.

Results: Women randomized to teriparatide 20 μg had a 31% reduced relative risk of moderate or severe back pain (16.5% vs. 11.5%, $P = 0.016$) and a 57% reduced risk of severe back pain (5.2% vs. 2.2%, $P = 0.011$). Compared with placebo, teriparatide-treated patients experienced reduced relative risk of developing back pain associated with findings of: one or more new vertebral fractures by 83% (6.5% vs. 1.1%, $P < 0.001$), two or more new vertebral fractures by 91% (2.5% vs. 0.20%, $P = 0.004$), and one or more new moderate or severe vertebral fractures by 100% (5.1% vs. 0.0%, $P < 0.001$).

Conclusions: Teriparatide-treated women had reduced risk for moderate or severe back pain, severe back pain, and back pain associated with vertebral fractures. The mechanism of the back pain reduction likely includes the reduction both in severity and number of new vertebral fractures.

* Data previously presented at the 25th Annual Meeting of American Society for Bone and Mineral Research. Minneapolis, MN, 19–23 September 2003 and the 68th Annual Scientific Meeting of the American College of Rheumatology, San Antonio, TX, 16–21 October 2004

Introduction

Osteoporosis is a skeletal disease characterized by reduced bone strength leading to increased skeletal fragility and increased risk for bone fracture[1]. Vertebral fractures are the most common fractures occurring in women with osteoporosis[2]. Prevalence of vertebral fracture substantially increases with age with more than 30% of women aged 75 and 50% of women aged 85 and older having sustained a vertebral fracture[3]. Approximately 10% of postmenopausal women with radiographically defined vertebral fractures have chronic symptoms including severe back pain, functional and psychological impairment, kyphosis, and height loss[4].

Back pain and functional limitation significantly increase following a vertebral fracture[2], and chronic back pain is more frequent in patients with multiple fractures[5]. Deformity, disability, and pain that occur in association with vertebral fractures may have profound psychological consequences on patients including increased anxiety, depression, and loss of self-esteem[6]. These consequences contribute to diminished quality of life[7,8]. In 2002, the care of osteoporotic fractures in the United States cost an estimated $17.5 billion[9]. Vertebral fractures account for approximately 25% of annual hospital admissions related to osteoporosis with average hospitalization charges totaling between 50–63% that of hip fractures[10,11]. Recently, annual hospitalization expenditures associated with vertebral fractures were estimated at $500 million in the United States and €377 million in Europe[10,11]. The majority of these costs are associated with the treatment of back pain and back-related disability due to vertebral fractures.

The present study includes secondary analyses from the Fracture Prevention Trial, a randomized double-blinded, placebo-controlled trial of postmenopausal women with osteoporosis conducted to determine the effects of teriparatide [rh(PTH 1–34)] on fracture risk[12]. Compared with placebo, women treated with teriparatide 20 μg had significant reductions in the risk for new vertebral fractures, moderate or severe vertebral fractures, and multiple vertebral fractures[12]. Women randomized to teriparatide 20 μg had a 26% reduced relative risk of any new or worsening back pain (23% vs. 17%, number needed to treat = 17, $P = 0.017$) compared with placebo[12]. This report includes additional secondary analyses of back pain from the Fracture Prevention Trial: First, it was hypothesized that women treated with teriparatide 20 μg had a reduced risk for moderate or severe back pain. Second, the time course of the reduction in back pain was explored. Third, it was hypothesized that women treated with teriparatide 20 μg had a reduced risk for back pain associated with vertebral fractures, multiple vertebral fractures, and more severe vertebral fractures. Finally, analyses of the association of vertebral fracture severity and number of incident vertebral fractures with back pain in the placebo and teriparatide 20 μg groups were conducted.

Methods

Study group

The methods for the Fracture Prevention Trial have previously been published[12]. Briefly, women at least 5 years postmenopausal with previous vertebral fractures were randomized to receive teriparatide 20 μg, teriparatide 40 μg or placebo therapy by once-daily subcutaneous self-injection for a median of 19 months. Patients received daily calcium (1000 mg) and vitamin D (400–1200 IU) supplements. Patients with fewer than 2 moderate vertebral fractures were required to have bone mineral density at the hip or lumbar spine at least 1 standard deviation (SD) below the mean of normal premenopausal white women (age range, 20 to 35 years). Patients were excluded if diagnosed with any disease known to affect bone or calcium metabolism, urolithiasis within 2 years, serum creatinine level greater than 2 mg per deciliter, alcohol or drug abuse, or medication use known to alter bone metabolism within the previous 2 to 24 months depending on the drug. Institutional review board approval was obtained at all study sites and written informed consent was obtained from each patient. The study methods and procedures were conducted according to the ethical standards of the Declaration of Helsinki.

Assessment of back pain

Back pain data were collected during adverse event monitoring at each study visit. Patients were defined as having back pain if they reported new or worsening back pain after initiating study drug. All reports of back pain were recorded on case report forms that included instructions for investigator assignment of adverse event severity as mild, moderate, or severe. Criteria for classification as mild were no change in physical activity with occasional medication use for relief of symptoms. Criteria for moderate included mild disruption in daily physical activities and regular medication use for alleviation of symptoms. Criteria for severe included major disruption in daily physical activities, additional medication use, and further treatment possibly including hospitalization.

Vertebral fracture assessment

Radiographs of the spine were obtained at baseline and at study conclusion. Evaluation of radiographs was performed at a central location (OARG, UCSF) by a

radiologist blinded to treatment-group assignment. Vertebral fracture severity was assessed using a visual semiquantitative grading system[13]. Briefly, a mild fracture was defined as a 20–25% reduction in anterior, middle or posterior vertebral height. Moderate and severe vertebral fractures were defined as a 25–40% reduction and greater than 40% reduction in vertebral height, respectively. Reporting of new vertebral fractures occurred upon identification of a new vertebral deformity. Vertebrae that were scoliotic, fused, or had other anomalies that prevented radiographic assessment were not graded.

Statistical analyses

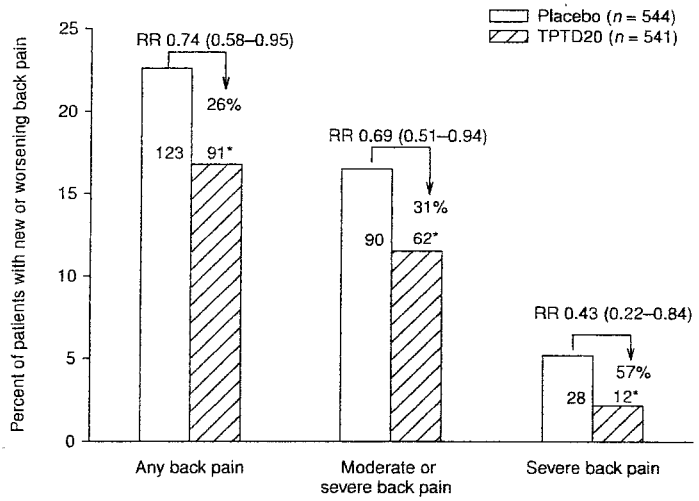
Data from patients randomized to teriparatide 20 µg, the dose now approved for use in humans, or to placebo treatment are presented in this manuscript. Back pain findings for patients randomized to teriparatide 40 µg/day were similar to those reported herein for patients randomized to teriparatide 20 µg.

Characteristics known to increase the risk for osteoporosis-related fractures were examined for between treatment group differences at baseline. Treatment-emergent adverse events of back pain were stratified according to severity and analyzed for between treatment group differences. Analyses including fracture outcomes were performed in patients with adequate radiographs at baseline and study endpoint. Additionally, the incidence of back pain associated with the number of vertebral fractures was examined. All continuous data were analyzed using Student's *t*-test. For categorical data, Pearson's Chi-square test was the common test used in this paper. When analyses involved smaller numbers of patients, both Pearson's Chi-square and Fisher's exact test were performed. These tests gave very similar results, and the Pearson's Chi-square test results were reported. A Cochran Armitage test was performed to examine the trend in back pain incidence with both grade and number of new vertebral fracture. Survival analysis was used to compare the temporal incidence of patients reporting treatment-emergent

Table 1. Baseline demographics of patients randomized in the Fracture Prevention Trial with evaluable radiographs at baseline and study endpoint[12]

	Placebo $N = 448$	TPTD20 $N = 444$	*P*-value
Age (yrs ± SD)	69.0 ± 7.0	69.2 ± 7.0	0.69
Vertebral BMD (g/cm^2 ± SD)	0.8 ± 0.2	0.8 ± 0.2	0.63
Body mass index (kg/m^2 ± SD)	26.7 ± 4.7	26.8 ± 4.2	0.87
> 1 vertebral fracture at baseline (%)	59.4	57.9	0.65
Smokers (%)	18.5	15.8	0.27

TPTD20 = teriparatide 20 µg; BMD = bone mineral density



*$p < 0.05$ vs. placebo RR = Relative Risk, down arrow depicts risk reduction

Figure 1. The relative risk of developing any back pain[12]*, moderate or severe back pain, or severe back pain in teriparatide 20 µg-treated patients*

back pain between treatment groups. All statistical tests were two-sided with a significance level of 0.05 using SAS software, version 8.2 (SAS Institute, Inc., Cary, NC).

Results

Baseline demographics known for women randomized to placebo or teriparatide 20 µg in the Fracture Prevention Trial with radiographs adequate for evaluation at baseline and study endpoint were similar (Table 1)[12].

Back pain

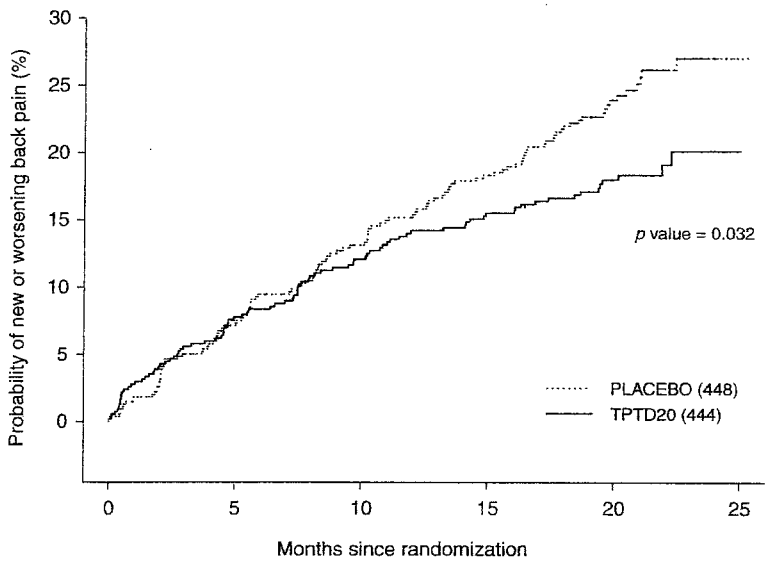
Compared with placebo, the relative risk of developing moderate or severe back pain was reduced 31% ($P = 0.016$) in patients administered teriparatide 20 µg therapy (Figure 1). There was a 57% reduction ($P = 0.011$) in the relative risk of developing severe back pain in teriparatide 20 µg treated patients versus placebo (Figure 1). The probability of experiencing new or worsening back pain in the placebo and teriparatide 20 µg groups appeared to separate after approximately 1 year of therapy with statistically significant ($P = 0.032$) divergence of back pain between groups over the entire time course (Figure 2).

Back pain and vertebral fracture

Follow-up radiographs were available for 448 placebo (82.4%) and 444 teriparatide 20 µg (82.1%) treated patients. Radiographic assessment was not available for all randomized patients due to either their radiographs being not readable or loss to follow-up. Compared with placebo, the relative risk of developing back pain plus one or more vertebral fractures was reduced 83% ($P < 0.001$) in teriparatide 20 µg treated patients (Figure 3). Similarly, among teriparatide 20 µg treated patients the relative risks of developing back pain with a finding of one new vertebral fracture, two or more new vertebral fractures, and one or more new moderate or severe vertebral fractures were reduced 78% ($P = 0.003$), 91% ($P = 0.004$), and 100% ($P < 0.001$), respectively, versus placebo.

Mechanism of teriparatide back pain prevention

The incidence of any back pain ($P < 0.001$) and of severe back pain ($P = 0.03$) significantly increased in placebo-treated women who experienced more severe vertebral fractures (Figure 4). Among placebo-treated patients with no new fracture, or with mild, moderate, and severe new vertebral fractures, 21.1%, 27.3%, 60.7%, and 42.9%, respectively, reported any back pain, with 4.2%, 4.6%, 7.1%, and 21.4%, respectively, reporting severe back pain. Similarly, in placebo-treated women, the incidence of any back pain ($P < 0.001$) and of severe back pain ($P = 0.013$) significantly increased with increasing number of new vertebral fractures (Figure 5). Among placebo patients with 0, 1, and ≥ 2 new vertebral fractures, 21.1%, 42.9%, and 50.0%, respectively, reported back pain, with 4.2%, 4.8% and



*p value from log-rank test for the divergence of back pain between groups over entire time course

Figure 2. Kaplan Meier estimate of the probability of experiencing new or worsening back pain in patients randomized to teriparatide 20 µg or placebo

18.2%, respectively, reporting severe back pain. Thus, in placebo-treated women, back pain and severe back pain incidence increased with increasing new vertebral fracture grade and with increasing number of new vertebral fractures. Among teriparatide-treated patients with no new fracture or with mild new vertebral fractures, 17.3% and 27.8%, respectively, reported any back pain, with 1.9% and 5.6%, respectively, reporting severe back pain (Figure 4). Although these incidences are similar to those observed in the placebo group, no teriparatide 20 µg-treated patients both reported back pain and sustained a new moderate or severe vertebral fracture (Figure 4). The incidence of any back pain ($P = 0.579$) and of severe back pain ($P = 0.083$) did

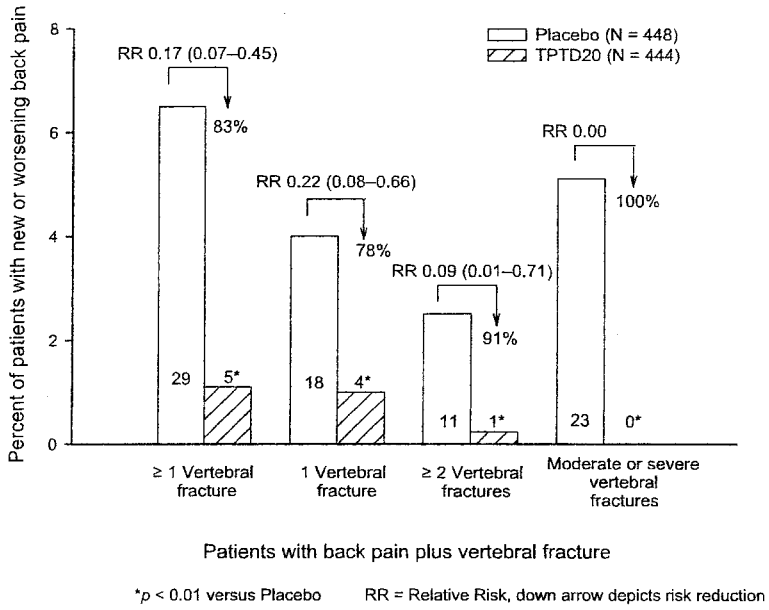


Figure 3. Relative risk of developing new or worsening back pain and a finding of new vertebral fracture in placebo and teriparatide 20 µg-treated patients

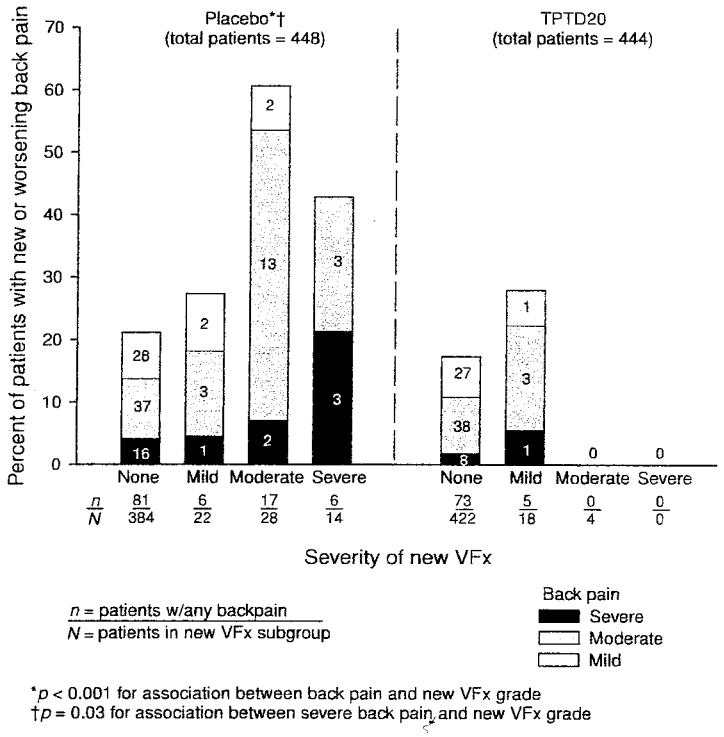


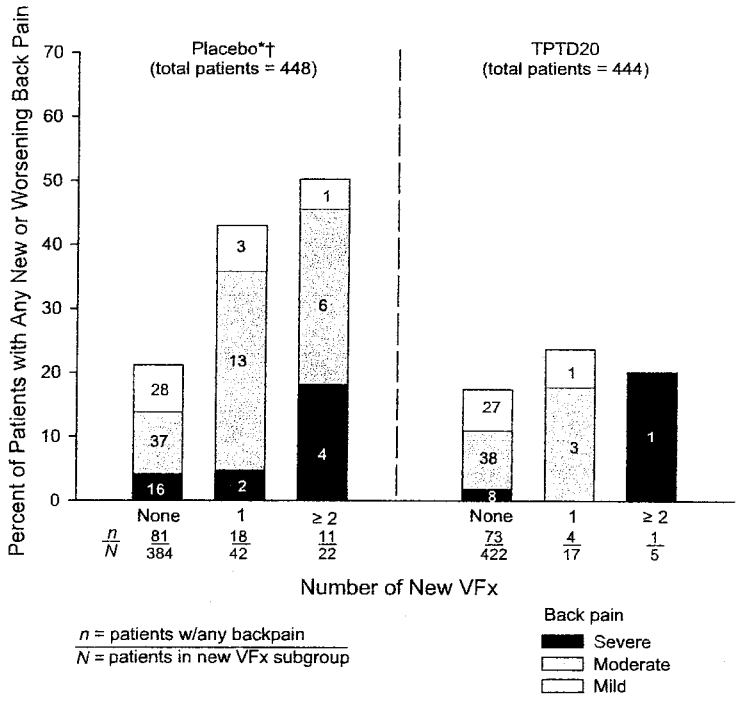
Figure 4. Incidence of back pain stratified by severity of new vertebral fractures in placebo and teriparatide 20 µg-treated patients

not significantly increase in teriparatide-treated women having increasing number of new vertebral fractures (Figure 5). Among teriparatide-treated patients with 0, 1, and ≥ 2 new vertebral fractures, 17.3%, 23.5%, and 20.0%, respectively, reported back pain, and 1.9%, 0% and 20.0%, respectively, reported severe back pain.

Discussion

Neer *et al.* previously reported that back pain occurred in 17% of teriparatide 20 μg-treated patients compared with 23% of placebo-treated patients in the Fracture Prevention Trial[12]. The present report includes new findings that fewer women randomized to teriparatide 20 μg had new or worsening moderate or severe back pain, and severe back pain. Compared with placebo, differences in the incidence of back pain following teriparatide 20 μg treatment were evident after 1 year of therapy. Furthermore, significantly fewer women randomized to teriparatide 20 μg therapy had back pain plus findings of one or more vertebral fractures, multiple vertebral fractures, and moderate or severe vertebral fractures.

Placebo-treated women with increasing severity and number of incident vertebral fractures reported back pain and severe back pain more frequently. These results establish a relationship between increased severity and number of vertebral fractures and back pain. In the Fracture Prevention Trial, as well as in other studies, moderate and severe vertebral fractures are more commonly associated with back pain than are mild vertebral fractures[4,12,14,15]. In addition, our findings in placebo patients are consistent with prior studies that have shown a progressive increase in back pain with number of previous vertebral fracture[15,16]. Prior results from the Fracture Prevention Trial have demonstrated that 19 months treatment with teriparatide 20 μg reduced the incidence of vertebral fractures, multiple vertebral fractures, and moderate or severe vertebral fractures known to progressively increase the risk of back pain. Compared with placebo, teriparatide-treated women had a 65% reduced risk for new vertebral fractures, 90% reduced risk of new moderate or severe vertebral fractures, and 77% reduced risk for multiple new vertebral fractures[12]. Our findings suggest that a mechanism for the reduced risk of back pain in teriparatide-treated women includes prevention of more severe and multiple painful vertebral fractures. Results from preclinical studies have shown that teriparatide accelerates fracture healing in a rat animal model[17]. In patients with vertebral fractures, treatment with



*p <0.001 for association between back pain and number of new VFx
†p =0.013 for association between severe back pain and number of new VFx

Figure 5. Incidence of any new or worsening back pain stratified by number of incident vertebral fractures in placebo and teriparatide 20 μg-treated patients

teriparatide 20 μg may also improve fracture healing thereby contributing to the observed reduction in the relative risk of developing back pain.

Chronic severe back pain arises from changes in both the architecture of vertebrae and in muscles and ligaments providing structural support[5]. Loss of physical function resulting from severe chronic back pain promotes further bone loss favoring the progression of osteoporosis[18]. Teriparatide 20 μg may mitigate this cycle of deterioration by building new bone, and reducing the occurrence of new moderate and severe vertebral fractures, the fractures in the present study associated with back pain in the placebo group.

Although the successful reduction in the incidence of new vertebral fractures by osteoporosis therapies would be anticipated to prevent back pain, this has not been consistently demonstrated in published clinical trials of antiresorptive drugs. Some studies have suggested that calcitonin may have an analgesic effect in the setting of acute back pain due to vertebral fracture[19], however, the primary study reporting fracture data for calcitonin did not include any back pain analyses[20]. Similarly, primary reports from fracture studies comparing alendronate with placebo do not include back pain findings[21–23]. Nevitt *et al.* reported significantly fewer women treated with alendronate in the Fracture Intervention Trial required bed-rest due to back pain and experienced limited activity due to back pain compared with placebo[24]. Also, compared with placebo, women treated with alendronate experienced reductions in the number of days of bed-rest for back pain and days of limited activity due to back pain. These findings were attributed to the reduction of vertebral fractures by alendronate. Importantly, the number of women with back pain or disability due to back pain was not statistically different between treatment groups. Therefore, differences in teriparatide-treated women compared with alendronate-treated women in back pain outcomes might be due to a greater effect of teriparatide on vertebral fracture related back pain prevention relative to alendronate. The results of adverse event monitoring in a randomized double-blinded comparator trial between alendronate and teriparatide showed that significantly ($P = 0.012$) fewer patients treated with teriparatide (5.5%) reported new or worsening back pain compared with patients treated with alendronate (19.2%)[25]. Similar results on back pain were observed in an additional double-blinded placebo-controlled comparator study of teriparatide versus alendronate in postmenopausal women. During this study, fewer patients treated with teriparatide (26%) reported new or worsening back pain compared with patients treated with alendronate (39%) ($P = 0.051$)[26]. Publications from risedronate and raloxifene fracture trials do not include back pain findings[27–30].

Although pain is an important outcome in clinical trials involving women with osteoporosis[31–33], the optimal instrument for assessing pain in clinical trials of osteoporosis drugs is not known. The collection of the back pain data during monitoring of adverse events requires additional comment. In this large randomized and blinded trial, there should have been no bias favoring either group. Directions were provided to investigators to ensure that adverse events were collected in a standard fashion in all patients. As noted in the methods, the results in the teriparatide 20 μg group were similar to those for the teriparatide 40 μg group. Also, the findings from two trials have shown that fewer women randomized to teriparatide compared with alendronate experienced back pain, suggesting consistently reduced back pain in teriparatide-treated patients in these studies. Finally, the biological plausibility of reduced risk for developing back pain should be noted in this trial which showed a 65% reduction in vertebral fracture and a 90% reduction in moderate or severe vertebral fracture risk. Participants in the Fracture Prevention Trial were mostly Caucasian, and as such, generalizations of these findings to women of other racial backgrounds may not be appropriate. Nevertheless, further study in a prospective trial of teriparatide in women at risk of back pain with back pain as a primary endpoint is needed.

In conclusion, postmenopausal women with osteoporosis treated for a median of 19 months with teriparatide experienced significantly reduced risk of developing back pain and risk of developing back pain associated with vertebral fracture. The observed reduction in back pain in our study setting is consistent with the near elimination of moderate and severe vertebral fractures observed in patients treated with teriparatide.

Acknowledgments

Funding was provided by Lilly Research Laboratories. We acknowledge the contributions of the investigators and patients who participated in the Fracture Prevention Trial. Additionally, we acknowledge the contributions of Drs. Gregory Gaich, Bruce Mitlak, and Ouhong Wang. We are grateful to Drs. Peiqi Chen, David Donley and Gerhardt Pohl for their critical review of the manuscript and Mary Ellen Perron for the preparation of the figures.

References

1. Osteoporosis prevention, diagnosis, and therapy. NIH Consensus Statement 2000;17:1-45
2. Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998;128: 793-800

3. Melton III LJ, Lane AW, Cooper C, et al. Prevalence and incidence of vertebral deformities. Osteoporos Int 1993;3:113-9
4. Ettinger B, Black DM, Nevitt MC, et al. Contribution of vertebral deformities to chronic back pain and disability. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1992;7:449-56
5. Mazanec DJ, Podichetty VK, Mompoint A, et al. Vertebral compression fractures: manage aggressively to prevent sequelae. Cleve Clin J Med 2003;70:147-56
6. Gold DT. The nonskeletal consequences of osteoporotic fractures. Psychologic and social outcomes. Rheum Dis Clin North Am 2001;27:255-62
7. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 2000;15:1384-92
8. Silverman SL, Minshall ME, Shen W, et al. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum 2001;44:2611-9
9. Melton III LJ. Adverse outcomes of osteoporotic fractures in the general population. J Bone Miner Res 2003;18:1139-41
10. Gehlbach SH, Burge RT, Puleo E, et al. Hospital care of osteoporosis-related vertebral fractures. Osteoporos Int 2003;14:53-60
11. Finnern HW, Sykes DP. The hospital cost of vertebral fractures in the EU: estimates using national datasets. Osteoporos Int 2003;14:429-36
12. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41
13. Genant HK, Wu CY, van Kuijk C, et al. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48
14. Black DM, Palermo L, Nevitt MC, et al. Defining incident vertebral deformity: a prospective comparison of several approaches. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999;14:90-101
15. Pluijm SM, Tromp AM, Smit JH, et al. Consequences of vertebral deformities in older men and women. J Bone Miner Res 2000;15:1564-72
16. Finsen V. Osteoporosis and back pain among the elderly. Acta Med Scand 1988;223:443-9
17. Nakajima A, Shimoji N, Shiomi K, et al. Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1–34). J Bone Miner Res 2002;17:2038-47
18. Heaney RP. The natural history of vertebral osteoporosis. Is low bone mass an epiphenomenon? Bone 1992;13(Suppl 2):S23-6
19. Silverman SL, Azria M. The analgesic role of calcitonin following osteoporotic fracture. Osteoporos Int 2002;13:858-67
20. Chesnut III CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109:267-76
21. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41
22. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-43
23. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82
24. Nevitt MC, Thompson DE, Black DM, et al. Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. Fracture Intervention Trial Research Group. Arch Intern Med 2000;160:77-85
25. Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002;87:4528-35
26. McClung MR, San Martin J, Miller PD, et al. Teriparatide and alendronate increase bone mass by opposite effects on bone remodeling. Arch Intern Med 2005 [in press]
27. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40
28. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91
29. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52
30. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637-45
31. Cranney A, Tugwell P, Cummings S, et al. Osteoporosis clinical trials endpoints: candidate variables and clinimetric properties. J Rheumatol 1997;24:1222-9
32. Wells G, Cranney A, Shea B, et al. Responsiveness of endpoints in osteoporosis clinical trials. J Rheumatol 1997;24:1230-3
33. OMERACT 3-Workshop report guidelines for osteoporosis trials. J Rheumatol 1997;24:1234-6

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-2999_3, *Accepted for publication*: 29 April 2005
Published Online: 31 May 2005
doi:10.1185/030079905X49671

EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

ROBERT M. NEER, CLAUDE D. ARNAUD, JOSE R. ZANCHETTA, RICHARD PRINCE, GREGORY A. GAICH, JEAN-YVES REGINSTER, ANTHONY B. HODSMAN, ERIK F. ERIKSEN, SOPHIA ISH-SHALOM, HARRY K. GENANT, OUHONG WANG, AND BRUCE H. MITLAK

ABSTRACT

Background Once-daily injections of parathyroid hormone or its amino-terminal fragments increase bone formation and bone mass without causing hypercalcemia, but their effects on fractures are unknown.

Methods We randomly assigned 1637 postmenopausal women with prior vertebral fractures to receive 20 or 40 μg of parathyroid hormone (1-34) or placebo, administered subcutaneously by the women daily. We obtained vertebral radiographs at base line and at the end of the study (median duration of observation, 21 months) and performed serial measurements of bone mass by dual-energy x-ray absorptiometry.

Results New vertebral fractures occurred in 14 percent of the women in the placebo group and in 5 percent and 4 percent, respectively, of the women in the 20-μg and 40-μg parathyroid hormone groups; the respective relative risks of fracture in the 20-μg and 40-μg groups, as compared with the placebo group, were 0.35 and 0.31 (95 percent confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). New nonvertebral fragility fractures occurred in 6 percent of the women in the placebo group and in 3 percent of those in each parathyroid hormone group (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.86]). As compared with placebo, the 20-μg and 40-μg doses of parathyroid hormone increased bone mineral density by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck; the 40-μg dose decreased bone mineral density at the shaft of the radius by 2 more percentage points. Both doses increased total-body bone mineral by 2 to 4 more percentage points than did placebo. Parathyroid hormone had only minor side effects (occasional nausea and headache).

Conclusions Treatment of postmenopausal osteoporosis with parathyroid hormone (1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated. The 40-μg dose increased bone mineral density more than the 20-μg dose but had similar effects on the risk of fracture and was more likely to have side effects. (N Engl J Med 2001;344: 1434-41.)

TREATMENTS for postmenopausal women with osteoporosis include estrogens, selective estrogen-receptor modulators, bisphosphonates, calcitonin, vitamin D, and calcitriol. These treatments reduce bone resorption (and formation) and moderately increase bone density; some agents reduce the risk of fracture, but none routinely restore normal bone mass or strength. Treatments that stimulate bone formation may overcome these limitations.

Parathyroid hormone stimulates bone formation and resorption and can increase or decrease bone mass, depending on the mode of administration. Continuous infusions and daily subcutaneous injections of parathyroid hormone stimulate bone formation similarly but have different effects on bone resorption and bone mass.[1,2] Continuous infusions, which result in a persistent elevation of the serum parathyroid hormone concentration, lead to greater bone resorption than do daily injections, which cause only transient increases in the serum parathyroid hormone concentration.[3]

Parathyroid hormone or its amino-terminal fragments and analogues prevent, arrest, or partially reverse bone loss in animals and humans.[4] In animals, parathyroid hormone induces parallel increases in bone mass and bone strength,[5] suggesting that treatment with parathyroid hormone may provide protection against fractures in humans. We tested this hypothesis in a study of parathyroid hormone (1-34) for the treatment of postmenopausal women with prior vertebral fractures. Parathyroid hormone (1-34) comprises the first 34 amino acids of the hormone and produces its chief biologic effects. The sponsor terminated the study early in order to evaluate the clinical relevance of the finding that osteosarcomas developed in Fisch-

From Massachusetts General Hospital and Harvard Medical School, Boston (R.M.N.); the University of California, San Francisco (C.D.A., H.K.G.); Fundación de Investigaciones Metabólicas, Buenos Aires, Argentina (J.R.Z.); the University of Western Australia and Sir Charles Gairdner Hospital, Perth, Australia (R.P.); Eli Lilly, Indianapolis (G.A.G., O.W., B.H.M.); Polycliniques Universitaires L. Brull, Liege, Belgium (J.-Y.R.); St. Joseph's Health Center, London, Ont., Canada (A.B.H.); Aarhus Amtssygehus, Aarhus, Denmark (E.F.E.); and Rambam Medical Center, Haifa, Israel (S.I.-S.). Address reprint requests to Dr. Mitlak at Eli Lilly, Inc., Lilly Corporate Center, Indianapolis, IN 46285-2680, or at b.mitlak@lilly.com.

Other authors were Dan Mellström, Department of Geriatrics, University of Göteborg, Göteborg, Sweden; Erik S. Oefjord, Bergen Osteoporosesenter, Paradis, Norway; Ewa Marcinowska-Suchowierska, Klinika Chorob Wewnetrznych, Warsaw, Poland; Jorma Salmi, Koskiklinikka, Tampere, Finland; Henk Mulder, Medisch Onderzoekscentrum Gcp, De Bilt, the Netherlands; Johan Halse, Betanien Med Lab, Oslo, Norway; and Andrzej Z. Sawicki, Warszawskie Centrum Osteoporozy, Warsaw, Poland.

er 344 rats during a long-term toxicologic study of parathyroid hormone (1-34). Subsequent evaluation of the clinical data revealed that parathyroid hormone (1-34) was effective in preventing fractures and was well tolerated.

METHODS

Study Subjects

We screened postmenopausal women at 99 centers in 17 countries for enrollment in the study. Women were eligible for enrollment if they were ambulatory, if a period of at least five years had elapsed since menopause, and if they had at least one moderate or two mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine, and an ambulatory status.[6] For women with fewer than two moderate fractures, an additional criterion for enrollment was a value for bone mineral density of the hip or lumbar spine that was at least 1 SD below the mean value in normal premenopausal white women (age range, 20 to 35 years). We excluded women with illnesses that affect bone or calcium metabolism, urolithiasis within the preceding 5 years, impaired hepatic function, a serum creatinine concentration exceeding 2 mg per deciliter (177 μmol per liter), or alcohol or drug abuse, as well as women who had taken drugs that alter bone metabolism within the previous 2 to 24 months (depending on the drug). The study was approved by the ethics committee at each participating center, and all women gave written informed consent.

Treatment Protocol and Follow-up Studies

All enrolled women received daily supplements of 1000 mg of calcium and 400 to 1200 IU of vitamin D. The women gave themselves daily injections of placebo for two weeks and were then randomly assigned to receive placebo or 20 or 40 μg of recombinant human parathyroid hormone (1-34) in a regimen of daily, self-administered injections. We measured serum calcium before and 4 to 6 hours after injection at base line and after 1, 3, 6, 12, 18, and 24 months of treatment, and we measured calcium and creatinine excretion in 24-hour urine specimens at base line and after 1, 6, 12, and 24 months of treatment. All tests of serum and urine samples from an individual woman were performed at one of three laboratories that used identical, cross-calibrated methods of measurement. If the post-injection serum calcium concentration was high or if urinary excretion of calcium exceeded 350 mg (8.8 mmol) per day, and if the increase persisted on repeated testing, the calcium supplement was discontinued permanently or the volume of the injected study drug was halved until the abnormality had disappeared.

All women underwent anteroposterior and lateral radiography of the thoracic and lumbar spine at base line and at the end of the study. Radiologists at a central location who knew the temporal sequence of the radiographs, but not the treatment assignments, graded each woman's vertebrae as normal (i.e., normal height) or as mildly, moderately, or severely deformed (i.e., a decrease in height of approximately 20 to 25 percent, 26 to 40 percent, or more than 40 percent, respectively).[6] A vertebra was not graded if scoliosis, fusion, or another anomaly prevented radiographic assessment. A new vertebral fracture was reported if a normal vertebra became deformed; worsening of preexisting deformities was not analyzed. Nonvertebral fractures were documented by a review of radiographs or radiologic reports and were classified as fragility fractures (the protocol-specified end point) if the associated trauma would not have resulted in the fracture of a normal bone, in the opinion of the local investigator.

We measured the bone mineral density of the lumbar spine, proximal femur, and radius and the total-body bone mineral by dual-energy x-ray absorptiometry with the use of Hologic, Lunar, or Norland equipment. The measurements were analyzed centrally, and the results were not reported to the participating centers. We measured the bone density of the spine at base line and at 12 and 18 months, and at the end of the study in all women (as well as at 3 and 6 months in a subgroup of women); we measured the bone density of the hips (in all women), forearms (in a subgroup), and total body (in a subgroup) at base line, at 12 months, and at the end of the study. Spine and hip values are reported in grams per square centimeter, although they have been converted to standardized units, which eliminate differences in measurements attributable to the manufacturer's calibrations.[7] Measurements of the spine excluded vertebrae with fractures or focal sclerosis. Total-body bone measurements excluded the head in order to avoid dental artifacts. The consistency of serial measurements was assessed with serial measurements of a spine phantom at each center, and the consistency of measurements among centers was assessed with measurements of a standard phantom circulated to all centers. Measurements of the phantoms were used to adjust for minor changes in the performance of the densitometer.[8]

We measured height with a stadiometer at base line and every 12 months; blood counts, serum chemical tests, and urinalysis were performed at base line and at 1, 6, 12, and 24 months. Tests of serum antibodies to parathyroid hormone (1-34), based on the specific binding of radioiodinated parathyroid hormone (1-34), were performed at base line and at 3, 12, and 24 months.

Statistical Analysis

We analyzed data for all women with at least one follow-up visit after enrollment. The rates of side effects and the proportions of women with fractures in the three study groups were compared with the use of Pearson's chi-square test. All laboratory data and bone mineral measurements were evaluated by analysis of variance, with the inclusion of terms for the treatment assignment and country. All statistical tests were two-sided.

RESULTS

Of 9347 women who were screened for the study, 7710 were not eligible or were not interested in participating. The remaining 1637 women were randomly assigned to receive placebo (544 women) or parathyroid hormone (1-34) at a dose of 20 μg per day (541 women) or 40 μg per day (552 women). The base-line characteristics of the women in the three study groups were similar (Table 1). In December 1998, all women were invited to a termination visit because the sponsor had stopped the study. The interval during which women were at risk for vertebral fractures (the period from enrollment to the final radiographic study of the spine) and nonvertebral fractures (the period from enrollment to the final visit) did not differ significantly among the three groups (Table 2 and Table 3, respectively). The cumulative duration of the study treatment in the group that received placebo, the group that received 20 μg of parathyroid hormone (1-34) per day, and the group that received 40 μg per day was 798, 779, and 774 patient-years, respectively, and the mean (±SD) duration of treatment in the three groups was 18±5, 18±6, and 17±6 months, respectively. The average rate of compliance with the regimen of injections, assessed on the basis of returned medication, ranged from 79 to 83 percent at each visit, and the rates did not differ significantly among the three groups.

Vertebral Fractures and Changes in Height

Base-line and follow-up radiographs were available for 1326 of the 1637 women (81 percent); follow-up radiographs were not available for 249 women, and

TABLE 1. BASE-LINE CHARACTERISTICS OF 1637 POSTMENOPAUSAL WOMEN ACCORDING TO WHETHER THEIR SPINAL RADIOGRAPHS WERE ADEQUATE FOR EVALUATION.*

CHARACTERISTIC	WOMEN WITH ADEQUATE RADIOGRAPHS†			WOMEN WITHOUT ADEQUATE RADIOGRAPHS		
	PLACEBO (N=448)	PTH, 20 μg (N=444)	PTH, 40 μg (N=434)	PLACEBO (N=96)	PTH, 20 μg (N=97)	PTH, 40 μg (N=118)
White race (%)	99	99	98	99	98	98
Age (yr)	69±7	69±7	70±7	69±8	71±8	71±7
Years since menopause	21±8	21±9	21±8	21±10	24±9	24±8
Body-mass index‡	26.7±4.7	26.8±4.2	26.6±4.3	26.1±5.0	26.4±4.4	26.5±4.1
Calcium intake (mg/day)	762±433	786±443	757±449	745±460	675±432	758±432
Current smoker (%)	18.5	15.8	14.8	19.8	19.6	20.3
Previous osteoporosis therapy (%)	15	16	13	14	14	14
No. of vertebral fractures	2.3±1.8	2.3±1.8	2.3±1.8	2.6±1.8	2.7±1.7	2.3±1.7
Lumbar-spine BMD (mg/cm²)	820±170	820±170	820±170	810±170	840±160	840±160

*Plus–minus values are means ±SD. PTH denotes parathyroid hormone (1-34), and BMD bone mineral density.

†$P>0.05$ for all comparisons among women with radiographs that could be evaluated.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 2. RADIOGRAPHIC EVIDENCE OF NEW VERTEBRAL FRACTURES.*

VARIABLE	PLACEBO (N=448)	PTH, 20 μg (N=444)	PTH, 40 μg (N=434)
No. of months at risk (randomization to final radiograph)	21±3	21±3	20±4
≥1 Fracture			
No. of women (%)	64 (14)	22 (5)†	19 (4)†
Relative risk (95% CI) vs. placebo	—	0.35 (0.22–0.55)	0.31 (0.19–0.50)
Percent reduction in absolute risk	—	9	10
>1 Fracture			
No. of women (%)	22 (5)	5 (1)†	3 (<1)†
Relative risk (95% CI) vs. placebo	—	0.23 (0.09–0.60)	0.14 (0.04–0.47)
Percent reduction in absolute risk	—	4	4
≥1 Moderate or severe fracture			
No. of women (%)	42 (9)	4 (<1)†	9 (2)†
Relative risk (95% CI) vs. placebo	—	0.10 (0.04–0.27)	0.22 (0.11–0.45)
Percent reduction in absolute risk	—	9	7

*Plus–minus values are means ±SD. PTH denotes parathyroid hormone (1-34), and CI confidence interval.

†$P\leq 0.001$ for the comparison with placebo.

an additional 62 women had pretreatment radiographs that were inadequate for evaluation. Base-line risk factors for new vertebral fractures were similar in the three groups (Table 1), as were serum 25-hydroxyvitamin D concentrations and indexes of bone turnover (data not shown). Of the 1326 women for whom adequate radiographs were available, 105 had one or more new vertebral fractures. As compared with placebo, parathyroid hormone (1-34) at the 20-μg and 40-μg doses reduced the risk of one or more new vertebral fractures by 65 and 69 percent, respectively; the risk of two or more fractures was reduced by 77 and 86 percent, respectively, and the risk of at least one moderate or severe vertebral fracture was reduced by 90 and 78 percent, respectively (Table 2). Treatment with parathyroid hormone (1-34) also reduced the total number of vertebral fractures: the number of fractures per 1000 patient-years of treatment was 136 in the placebo group, 49 in the 20-μg parathyroid hormone group, and 30 in the 40-μg group. With the 20-μg dose, a vertebral fracture was prevented for every 12 patient-years of treatment, and with the 40-μg dose, a vertebral fracture was prevented for every 10 patient-years of treatment.

TABLE 3. NEW NONVERTEBRAL FRACTURES AND NEW NONVERTEBRAL FRAGILITY FRACTURES.*

VARIABLE	PLACEBO (N=544)	PTH, 20 μg (N=541)	PTH, 40 μg (N=552)
No. of months at risk from randomization to last visit	19±5	19±6	18±6
No. of patient-years at risk	857	837	833
≥1 Fracture (no. of women)			
Total	53	34†	32‡
Fragility	30	14‡	14§
Site of fracture (no. of women)			
Hip			
Total	4	2	3
Fragility	4	1	3
Wrist			
Total	13	7	10
Fragility	7	2	3
Ankle			
Total	4	2	2
Fragility	3	1	1
Humerus			
Total	5	4	3
Fragility	2	2	2
Rib			
Total	10	5	5
Fragility	5	3	2
Foot			
Total	4	1	4
Fragility	1	0	3
Pelvis			
Total	3	1	0
Fragility	3	0	0
Other			
Total	16	14	9
Fragility	8	6	3

*Some women had a new fracture at more than one skeletal site or had more than one new fracture at the same site (e.g., in both extremities). The total numbers of nonvertebral fractures in the placebo group and the 20-μg and 40-μg parathyroid hormone groups were 62, 36, and 37, respectively, and the total numbers of nonvertebral fragility fractures were 33, 15, and 17, respectively. Plus–minus values are means ±SD. PTH denotes parathyroid hormone (1-34).

†P=0.04 for the comparison with placebo.

‡P=0.02 for the comparison with placebo.

§P=0.01 for the comparison with placebo.

New or worsening back pain was reported by 23 percent of the women in the placebo group but by only 17 percent and 16 percent of those in the 20-μg and 40-μg parathyroid hormone groups, respectively (P=0.007). These data were consistent with the radiographic findings. Among the 105 women with one or more new vertebral fractures, the mean loss in height was greater in the placebo group (−1.1 cm) than in the 20-μg and 40-μg parathyroid hormone groups (−0.2 and −0.3 cm, respectively; P=0.002). Because most women did not have new vertebral fractures, the overall mean loss in height was small and did not differ significantly among the three groups.

Nonvertebral Fractures

New nonvertebral fractures occurred in 119 women and were considered fragility fractures in 58 (Table 3). Women treated with the 20-μg dose of parathyroid hormone (1-34) and those treated with the 40-μg dose were 35 and 40 percent less likely to have one or more new nonvertebral fractures, respectively, than the women in the placebo group, and were 53 and 54 percent less likely to have one or more new nonvertebral fragility fractures. The absolute risk of one or more nonvertebral fractures was 10 percent in the placebo group and 6 percent in each parathyroid hormone group; the absolute risk of one or more nonvertebral fragility fractures was 6 percent in the placebo group and 3 percent in the two parathyroid hormone groups (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.86]). The cumulative incidence of one or more new nonvertebral fractures or nonvertebral fragility fractures was initially similar in the three study groups; the protective effects of parathyroid hormone treatment became evident after 9 to 12 months (Fig. 1). Although the numbers of women with new nonvertebral fractures at specific skeletal sites were too small to estimate the incidence of each type of fracture, the numbers in the parathyroid hormone groups were generally smaller than — and in no case exceeded — the numbers in the placebo group (Table 3).

Bone Mineral Density and Total-Body Bone Mineral

At base line, bone mineral density was similar among the three groups at all skeletal sites; total-body bone mineral was also similar (Table 4). The mean bone mineral density of the spine was 2.6 SD below the mean value in normal young white women (mean T score, −2.6). Treatment with parathyroid hormone (1-34) resulted in significant dose-dependent increases in the bone mineral density of the spine and hip and in total-body bone mineral (Table 4). The bone mineral density of the shaft of the radius decreased from the base-line values in all three groups; the percent change in the 40-μg group, but not that in the 20-μg group, differed significantly from the percent change in the placebo group (P<0.001). As previously reported by other investigators,[9,10] this difference arose during the first year of treatment; subsequently, the bone mineral density of the radial shaft changed in parallel in all three groups (data not shown). The density of the distal radius did not differ significantly among the three groups.

Adverse Events

There were no significant differences among the three groups with respect to the numbers of deaths and hospitalizations or the numbers of women in whom cardiovascular disorders, urolithiasis, or gout developed during the study. There were no cases of osteosarcoma. Cancer developed in 40 women, with a higher incidence in the placebo group (4 percent) than in the 20-μg and 40-μg parathyroid hormone groups (2 percent in each group; P=0.02 and P=

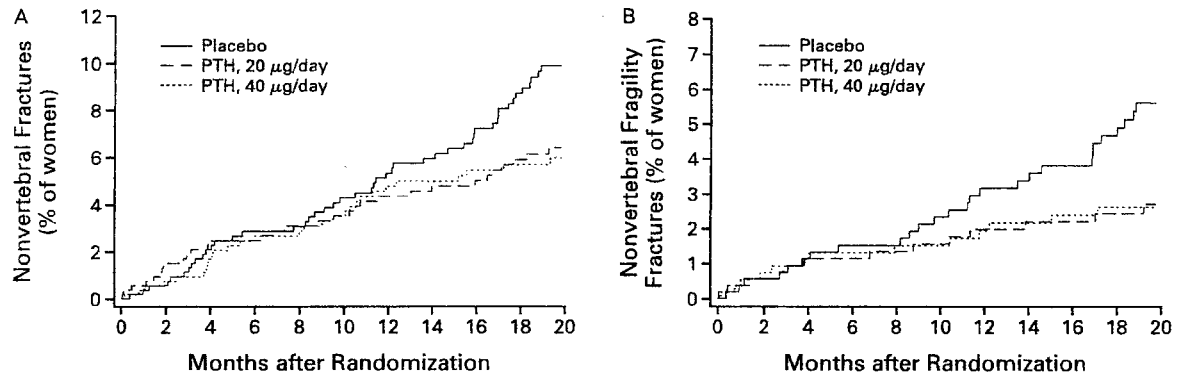


Figure 1. Cumulative Proportion of Women Assigned to Receive Placebo or Parathyroid Hormone (1-34) (PTH) at a Daily Dose of 20 μg or 40 μg Who Had One or More Nonvertebral Fractures (Panel A) and the Cumulative Proportion Who Had One or More Nonvertebral Fragility Fractures (Panel B) during the Study.

For both panels, the respective numbers of women in the placebo group and in the 20-μg and 40-μg PTH groups were 544, 541, and 552 at base line; 497, 492, and 486 at 6 months; 477, 465, and 456 at 12 months; and 404, 400, and 390 at 18 months. P≤0.05 for all pairwise comparisons with placebo, by the log-rank test.

TABLE 4. CHANGE FROM BASE LINE IN BONE MINERAL DENSITY AND TOTAL-BODY BONE MINERAL.*

SKELETAL MEASUREMENT	BASE LINE			LAST VISIT						
	PLACEBO	PTH, 20 μg	PTH, 40 μg	PLACEBO		PTH, 20 μg		P VALUE	PTH, 40 μg		P VALUE
				no. of women	*% change*	*no. of women*	*% change*		*no. of women*	*% change*	
Bone mineral density†											
Lumbar spine	0.82±0.17	0.82±0.17	0.82±0.17	504	1.1±5.5	498	9.7±7.4†	<0.001	497	13.7±9.7	<0.001
Femoral neck	0.64±0.11	0.64±0.11	0.64±0.11	479	−0.7±5.4	479	2.8±5.7†	<0.001	482	5.1±6.7	<0.001
Trochanter	0.57±0.12	0.57±0.12	0.57±0.12	479	−0.2±6.3	479	3.5±6.8†	<0.001	482	4.4±7.5	<0.001
Intertrochanter	0.86±0.16	0.85±0.16	0.85±0.14	257	−1.3±4.5	250	2.6±5.5†	<0.001	254	4.0±6.0	<0.001
Total hip	0.71±0.12	0.70±0.12	0.70±0.11	230	−1.0±4.3	222	2.6±4.9†	<0.001	232	3.6±5.4	<0.001
Distal radius	0.32±0.08	0.31±0.07	0.32±0.07	154	−1.6±8.3	152	−0.1±7.2	0.09	145	−1.5±8.4	0.74
Shaft of radius	0.58±0.11	0.58±0.10	0.59±0.11	154	−1.3±3.3	152	−2.1±4.2	0.09	145	−3.2±4.5	<0.001
Total-body bone mineral‡				140		134		<0.001	131		<0.001
Hologic	1303±263	1250±248	1324±276	61	−1.3±6.5	61	0.6±5.8	—	63	1.0±6.1	—
Lunar	1444±328	1453±293	1481±279	79	0.0±4.8	73	3.1±4.3	—	68	4.5±5.7	—

*Bone mineral density and total-body bone mineral were measured by dual-energy x-ray absorptiometry. PTH denotes parathyroid hormone (1-34). P values are for the comparisons with the placebo group.

†The data for the lumbar spine, femoral neck, trochanter, intertrochanter, and total hip are in standardized units[7] and expressed in grams per square centimeter; the data for the distal radius and shaft of the radius are in grams per square centimeter.

‡Data are expressed in grams. Because manufacturers have not standardized measurements of total-body bone mineral, we report the values according to the instrument used for measurement. Since each woman's total-body bone mineral was measured serially with the same instrument, tests of statistical significance included all data and allowed for an effect of the instrument used.

0.07, respectively). A total of 32 women in the placebo group (6 percent), 35 in the 20-μg parathyroid hormone group (6 percent), and 59 in the 40-μg group (11 percent) withdrew from the study because of an adverse event. Nausea was reported by 18 percent of women taking 40 μg of parathyroid hormone, and headache was reported by 13 percent, whereas only 8 percent of women taking placebo reported each of these symptoms (P<0.001 and P=0.01, respectively); the frequencies of nausea and headache in the lower-dose parathyroid hormone group were similar to those in the placebo group. Nine percent of the women in the 20-μg parathyroid hormone group reported dizziness, and 3 percent reported leg cramps, but these symptoms were reported by only 6 percent and 1 percent of women in the placebo group, respectively (P=0.05 and P=0.02, respectively); the frequencies of dizziness and leg cramps in the 40-μg

parathyroid hormone group were similar to those in the placebo group. Preinjection blood pressure and heart rate, measured at each visit, were unaffected by treatment with parathyroid hormone (1-34).

Because subcutaneous injections of parathyroid hormone (1-34) have the greatest effect on serum calcium during the first four to six hours after injection, we measured serum calcium before and four to six hours after an injection of parathyroid hormone (1-34) at each visit. The preinjection measurements (performed 16 to 24 hours after the previous injection) were usually normal. Mild hypercalcemia (defined as a calcium concentration that exceeded 10.6 mg per deciliter [2.6 mmol per liter]) occurred at least once in 2 percent of the women in the placebo group, 11 percent of those in the 20-μg parathyroid hormone group, and 28 percent of those in the 40-μg group. Of the high serum calcium values, 95 percent were less than 11.2 mg per deciliter (2.80 mmol per liter) in the 20-μg group, and 95 percent were less than 11.8 mg per deciliter (2.95 mmol per liter) in the 40-μg group; in only about one third of the women with high serum calcium concentrations were the values high on retesting, which was usually performed within a few weeks. Women who did not have hypercalcemia during the first six months of treatment seldom had it later. The study protocol required permanently halving the injected dose of medication in women with persistent hypercalcemia after a reduction in calcium intake; this occurred in 3 women in the placebo group (<1 percent), 15 in the 20-μg group (3 percent), and 62 in the 40-μg group (11 percent). Treatment was withdrawn because of repeatedly elevated serum calcium concentrations in one woman in the placebo group, one in the 20-μg group, and nine in the 40-μg group.

Serum 25-hydroxyvitamin D and calcitriol concentrations were similar in the three groups at base line. Serum calcitriol concentrations increased significantly from the base-line values in each parathyroid hormone group and did not change in the placebo group. The mean 24-hour urinary calcium excretion increased slightly during parathyroid hormone (1-34) treatment (by 30 mg [0.75 mmol] per day), but the incidence of hypercalciuria (a value for urinary calcium excretion that exceeded 300 mg [7.5 mmol] per day) did not increase. Serum magnesium concentrations decreased slightly in both parathyroid hormone groups, and serum uric acid concentrations rose by 13 to 20 percent during treatment with parathyroid hormone at a dose of 20 μg per day and by 20 to 25 percent at a dose of 40 μg per day, without clinical sequelae. An average of five weeks after the cessation of treatment, serum calcium, magnesium, and uric acid concentrations had returned to or approached pretreatment values. Serum creatinine concentrations and creatinine clearance were unaffected by parathyroid hormone (1-34) treatment. Circulating antibodies to parathyroid hormone (1-34) developed in 1 woman in the placebo group (<1 percent), 15 women in the 20-μg group (3 percent), and 44 in the 40-μg group (8 percent), but these antibodies had no discernible effects on any of the other measurements.

DISCUSSION

Daily injections of parathyroid hormone (1-34) at a dose of 20 μg and daily injections at a dose of 40 μg increased the bone mineral density of the spine by 9 and 13 percentage points more than did placebo, and reduced the risk of new vertebral fractures by 65 and 69 percent, respectively, as compared with placebo. These benefits exceed those reported for other treatments in similar women. In studies using similar analyses, alendronate (10 mg per day) reduced the risk of new vertebral fractures by 48 percent,[11-13] risedronate (5 mg per day) by 41 percent,[14] an intermittent regimen of cyclical etidronate by 44 percent,[15,16] and raloxifene (60 mg per day) by 30 percent.[17] Estimates of a 40 to 50 percent reduction in the risk of vertebral fractures with estrogen treatment are based on cohort and case–control studies or small placebo-controlled, prospective trials.[18,19] Salmon calcitonin nasal spray has inconsistent effects on the risk of vertebral fractures,[20] and the effects of supplemental calcitriol,[21,22] vitamin D,[23-26] and calcium[27] on this end point cannot be estimated on the basis of the published data.

Daily treatment with parathyroid hormone (1-34) reduced the risk of nonvertebral fractures by 35 percent at the 20-μg dose and by 40 percent at the 40-μg dose and reduced the risk of nonvertebral fragility fractures by 53 and 54 percent, respectively. In similar women, alendronate reduced the risk of nonvertebral fractures by 20 percent,[12] risedronate by 39 percent,[14] and raloxifene by 10 percent.[17] The effects of etidronate[15,16] and calcitonin[20] on the risk of nonvertebral fractures are not known. Vitamin D[23,26] and calcitriol[22] reduced the risk of nonvertebral fractures by 50 to 60 percent in some studies, but the effects of parathyroid hormone in our study are in addition to any effect of vitamin D, since all the women received vitamin D and calcium supplements.

These antifracture benefits make it important to understand the clinical relevance of the osteosarcomas found in rats given parathyroid hormone (1-34) in a standard carcinogenicity bioassay. In that study, the rats were given nearly lifetime daily injections of parathyroid hormone (1-34). The occurrence of osteosarcoma was dose-dependent, and the tumors developed after parathyroid hormone (1-34) had induced osteosclerosis. Parathyroid hormone (1-34) did not increase the incidence of tumors in other tissues in rats, nor were osteosarcomas found in monkeys that had undergone bilateral oophorectomy and then been given daily doses that were 4 to 10 times the maximal dose in humans over a period of 18 months. In stand-

ard tests, parathyroid hormone (1-34) is neither mutagenic nor genotoxic. In prior studies involving a total of nearly 1000 patients, treatment with parathyroid hormone (1-84), parathyroid hormone (1-34), or parathyroid hormone (1-38) for up to three years did not increase the incidence of bone tumors.[28] Osteosarcomas are rare in adults, and chronic primary hyperparathyroidism is not associated with an increased risk of osteosarcoma.[29,30]

In summary, the clinical benefits of parathyroid hormone (1-34) reflect its ability to stimulate bone formation and thereby increase bone mass and strength. This hormone appears to be effective in preventing fractures in postmenopausal women with osteoporosis.

Supported by Eli Lilly.
Dr. Eriksen owns stock in Eli Lilly.

We are indebted to Drs. Hunter Heath III and John T. Potts, Jr., for their comments on the manuscript and to Ms. Michele Y. Hill for editorial assistance and assistance in the preparation of the manuscript.

APPENDIX

The following additional investigators participated in the study: *Argentina* — C.A. Mautalen, Buenos Aires; *Austria* — G. Leb, Astrid Fahricitner, H. Dobnig, Graz; *Belgium* — J.P. Devogelaer, Brussels; J.-M. Kaufman, Ghent; *Canada* — J.P. Brown, Sainte-Foy, Que.; D.A. Hanley, Calgary, Alta.; R.G. Josse, G.A. Hawker, S. Mann, Toronto; W.P. Olszynski, Saskatoon, Sask.; L.G. Ste.-Marie, Montreal; M.O. Al-Daker, Regina, Sask.; C.K. Yuen, Winnipeg, Man.; S. Kaiser, St. John's, Newf.; A.B. Cranney, Ottawa, Ont.; K.G. Siminoski, Edmonton, Alta.; *Czech Republic* — J. Stepan, Prague; O. Topolcan, V. Vyskocil, Plzen-Bory; V. Palicka, Kralove; *Denmark* — L. Hyldstrup, Hvifovre; P. Laurberg, Aalborg, Otto Grove, Varde; H. Beck-Nielsen, Odense; *Finland* — E. Alhava, Kuopio; M. Kormano, Turku; P. Salmela, K. Rontgen, J.E. Heikkinen, Oulu; J. Salmi, Tampere; M. Valimaki, I. Arnala, Helsinki; J. Saltevo, Jyvaskyla; *Hungary* — G. Poor, J. Szuecs, Budapest; L. Gaspar, Szeged; *Israel* — A. Karasik, I. Vered, Tel-Hashomer; E. Segal, Haifa; *Italy* — C. Gennari, Siena; G. Crepaldi, L. Sartori, Padua; A. Pinchera, Pisa; G. Mazzuoli, Rome; M. Passeri, Parma; G. Bianchi, Arenzano; *New Zealand* — N.L. Gilchrist, Canterbury; *Norway* — J.B. Michelsen, Kristiansand; J.A. Falch, Oslo; E. Mohr, Haugesund; S.S. Gudnason, Bergen; U. Syversen, Trondheim; *Poland* — M. Talalaj, P. Kapuscinski, J. Borowicz, E. Sawicka, J. Lesnicki, A. Olak-Popko, Warsaw; T. Miazgowski, J. Ogonowski, S. Czekalski, Szczecin; *Sweden* — S. Ljunghall, K. Larsson, Uppsala; M. Palmer, Orebro; G. Toss, Linkoping; M. Saaf, Stockholm; *United States* — M.A. Bolognese, Gaithersburg, Md.; C. Mckeever, Houston; L. Avioli (deceased), St. Louis; E.S. Orwoll, Portland, Oreg.; M. Greenwald, Palm Springs, Calif.; R.D. Wasnich, Honolulu; S.R. Weiss, San Diego, Calif.; W. Briney, Denver; C. Gallagher, Omaha, Nebr.; O.S. Gluck, Phoenix, Ariz.; M.H. Davidson, Chicago; S.C. English, Billings, Mont.; N.M. Lunde, Arden Hills, Minn.; M.R. Khairi, Indianapolis; J. Rosenstock, Dallas; A.A. Licata, Cleveland; A.L. Burshell, New Orleans; C.E. Lewis, Birmingham, Ala.; A.L. Mulloy, Augusta, Ga.; M.P. Ettinger, Stuart, Fla.; A. Virshup, West Palm Beach, Fla.; S.B. Ward, Philadelphia; N. Wei, Frederick, Md.; J. Stock, Morristown, N.J.; S. Wallach, R. Bockman, New York; C.J. Rosen, Bangor, Me.; C.E. Waud, Worcester, Mass.; R. Marcus, Palo Alto, Calif.; R. Levy, Olympia, Wash.; S.S. Miller, San Antonio, Tex.; S. Songcharoen, Jackson, Miss.; K.D. Schlessel, Willingboro, N.J.; L.M. Cohen, Sarasota, Fla.; V.K. Piziak, Temple, Tex.; S. Scumpia, Austin, Tex.; R.R. Stoltz, Evansville, Ind.

REFERENCES

1. Podbesek R, Edouard C, Meunier PJ, et al. Effects of two treatment regimes with synthetic human parathyroid hormone fragment on bone formation and the tissue balance of trabecular bone in greyhounds. Endocrinology 1983;112:1000-6.
2. Hock JM, Gera I. Effects of continuous and intermittent administration and inhibition of resorption on the anabolic response of bone to parathyroid hormone. J Bone Miner Res 1992;7:65-72.
3. Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: differential effects of intermittent and continuous administration. Endocrinology 1982;110:506-12.
4. Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. Endocr Rev 1993;14:690-709. [Erratum, Endocr Rev 1994;15:261.]
5. Turner CH, Wang T, Hirano T, et al. In primates, treatment with PTH (1-34), LY333334, increases bone strength at trabecular bone sites without compromising the strength of cortical bone. J Bone Miner Res 1999;14: Suppl 1:S414. abstract.
6. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
7. Lu Y, Ye K, Mathur AK, Hui S, Fuerst TP, Genant HK. Comparative calibration without a gold standard. Stat Med 1997;16:1889-905.
8. Lu Y, Mathur AK, Blunt BA, et al. Dual X-ray absorptiometry quality control: comparison of visual examination and process-control charts. J Bone Miner Res 1996;11:626-37.
9. Neer R, Slovik D, Daly M, Lo C, Potts J, Nussbaum S. Treatment of postmenopausal osteoporosis with daily parathyroid hormone plus calcitriol. In: Christiansen C, Overgaard K, eds. Osteoporosis 1990: proceedings of the Third International Symposium on Osteoporosis. Copenhagen, Denmark: Osteopress ApS, 1990:1314-7.
10. Hodsman AB, Steer BM, Fraher LJ, Drost DJ. Bone densitometric and histomorphometric responses to sequential human parathyroid hormone (1-38) and salmon calcitonin in osteoporotic patients. Bone Miner 1991; 14:67-83.
11. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333:1437-43.
12. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.
13. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280: 2077-82.
14. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282:1344-52.
15. Storm T, Thamsborg G, Steiniche T, Genant HK, Sørensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322:1265-71.
16. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323: 73-9.
17. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA 1999;282:637-45. [Erratum, JAMA 1999;282:2124.]
18. Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992;117: 1-9.
19. Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. Lancet 1980;2:1151-4.
20. Chesnut CH, Silverman SL, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures study. Am J Med 2000;109:267-76.
21. Ott SM, Chesnut CH. Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med 1989;110:267-74.
22. Tilyard MW, Spears GFS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992; 326:357-62.
23. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D_3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.
24. Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. Calcif Tissue Int 1992;51:105-10.
25. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124: 400-6.
26. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670-6.
27. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in post-

menopausal women: a randomized controlled trial. Am J Med 1995;98: 331-5.
28. Horwitz M, Stewart A, Greenspan SL. Sequential parathyroid hormone/alendronate therapy for osteoporosis — robbing Peter to pay Paul? J Clin Endocrinol Metab 2000;85:2127-8.
29. Palmer M, Adami HO, Krusemo UB, Ljunghall S. Increased risk of malignant diseases after surgery for primary hyperparathyroidism: a nationwide cohort study. Am J Epidemiol 1988;127:1031-40.
30. Wermers RA, Khosla S, Atkinson EJ, et al. Survival after the diagnosis of hyperparathyroidism: a population-based study. Am J Med 1998;104:115-22.

Anabolic Skeletal Therapy for Osteoporosis

review article

Monica Girotra
Mishaela R. Rubin
John P. Bilezikian

ABSTRACT

Antiresorptive agents for osteoporosis are a cornerstone of therapy, but anabolic drugs have recently widened our therapeutic options. By directly stimulating bone formation, anabolic agents reduce fracture incidence by improving bone qualities besides increasing bone mass. In this article, we review the role of anabolic treatment for osteoporosis. The only anabolic agent currently approved in the United States for osteoporosis, teriparatide (recombinant human parathyroid hormone(1-34)), has clearly emerged as a major approach to selected patients with osteoporosis. Teriparatide increases bone density and bone turnover, improves microarchitecture, and changes bone size. The incidence of vertebral and nonvertebral fractures is reduced. Teriparatide is approved for both postmenopausal women and men with osteoporosis who are at high risk for fracture. Other potential anabolic therapies for osteoporosis, including other forms of parathyroid hormone, strontium ranelate, growth hormone, and insulin-like growth factor-1, are also reviewed in this article. **(Arq Bras Endocrinol Metab 2006;50/4:745-754)**

Keywords: Anabolic agents; Bone quality; Bone mass; Osteoporosis; Teriparatide; Fracture risk

Department of Medicine (MG, MRR & JPB) and Pharmacology (JPB), College of Physicians and Surgeons, Columbia University, New York, NY, USA.

RESUMO

Tratamento Anabólico Ósseo para Osteoporose.
Os agentes anti-reabsortivos são as drogas mais usadas no tratamento da osteoporose, porém os anabólicos recentemente ampliaram nossas opções terapêuticas. Por estimular diretamente a formação, os agentes anabólicos reduzem a incidência de fraturas por melhorar a qualidade óssea, além do aumento da massa óssea. Neste artigo, nós revisaremos o papel do tratamento anabólico para a osteoporose. O único agente anabólico, atualmente aprovado nos Estados Unidos, é o teriparatida (hormônio paratiroidiano recombinante humano), o qual tem sido considerado como a principal abordagem em pacientes selecionados. O teriparatida aumenta a densidade mineral óssea e o *turnover* ósseo, melhorando a microarquitetura, e altera o tamanho do osso. A incidência de fraturas vertebrais e não vertebrais é reduzida. O teriparatida é aprovado tanto para mulheres na pós-menopausa quanto para homens com osteoporose que apresentem alto risco para fraturas. Outras terapias anabólicas potenciais para a osteoporose incluem outras formas de hormônio da paratiróide, ranelato de estrôncio, hormônio de crescimento e IGF1 (*insulin-like growth factor-1*), e serão revisados neste artigo. **(Arq Bras Endocrinol Metab 2006;50/4:745-754)**

Descritores: Agentes anabolizantes; Qualidade óssea; Massa óssea; Osteoporose; Teriparatida; Risco de fraturas

Received in 05/10/06
Accepted in 05/20/06

ANABOLIC AGENTS REPRESENT an important new advance in the therapy of osteoporosis. Until recently, antiresorptive agents were the exclusive pharmacological approach to this disease. They are covered in other articles in this supplement. The anabolic skeletal agents, in contrast to the antiresorptive drugs, influence processes associated with bone formation. By stimulating bone formation to a greater extent and earlier than bone resorption, anabolic agents have the potential to positively affect a number of skeletal properties besides bone density. These include bone size and microarchitecture. They thus have the potential to reconstruct the skeleton, an endpoint not shared by any of the antiresorptives (1). The anabolic agents to be discussed in this review include teriparatide [parathyroid hormone(1-34)], other forms of parathyroid hormone, strontium ranelate, and growth hormone/insulin-like growth factor-1.

PARATHYROID HORMONE AS AN ANABOLIC AGENT

In primary hyperparathyroidism (PHPT), a disorder of chronic, continuous secretion of excess parathyroid hormone (PTH), catabolic effects, primarily at cortical sites such as the distal 1/3 radius, is common. Nevertheless, even in this disorder of chronic PTH secretion, a key property of intermittent PTH administration, namely salutary effects at the cancellous skeleton such as the lumbar spine, can be seen (2). The clinical clue to the utility of PTH as an anabolic skeletal agent came with the recognition that its anabolic potential is seen much more clearly with low dose, intermittent administration. PTH is currently available in many countries as the recombinant human PTH(1-34) fragment known as teriparatide. The full-length molecule, human recombinant PTH(1-84), has been approved for use in some European countries and is under investigation at this time in the United States. Teriparatide leads to a rapid increase in bone formation markers followed sometime thereafter by increases in bone resorption markers. If these markers reflect physiological events, PTH likely initially stimulates processes associated with bone formation (bone modeling) and only later promotes those associated with bone remodeling in which bone resorption predominates. This sequence of events has led to the concept of the "anabolic window," a period of time when the actions of PTH are maximally anabolic (3) (figure 1).

The beneficial effects of teriparatide on bone qualities such as bone density, microarchitecture and bone geometry are seen in the cancellous skeleton (4). At a cortical skeletal site, such as the distal 1/3 radius, PTH typically does not increase bone density. In fact, there may be a small decline in BMD in association with an increase in cortical porosity. However, this does not translate into decreased bone strength because the increased porosity occurs only in the inner one third of bone, where the mechanical effect

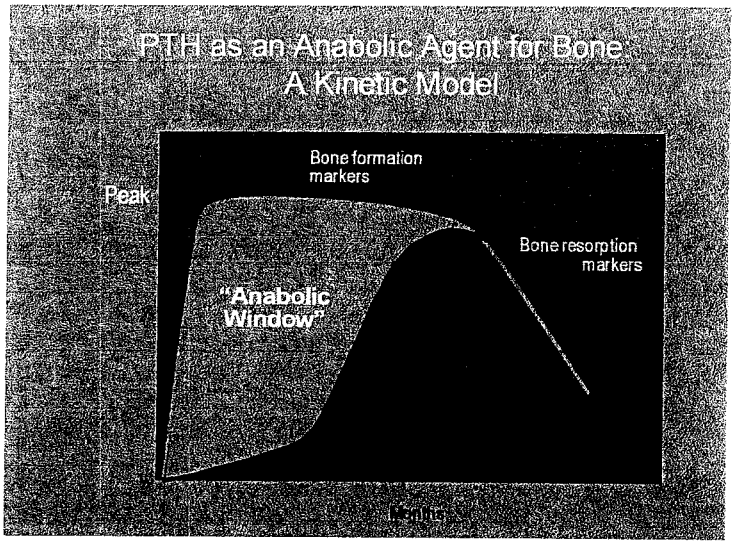


Figure 1. The Anabolic Window. Based upon the difference in kinetics of changes between bone formation and bone resorption markers, an "anabolic window" is formed during which the actions of parathyroid hormone are believed to be maximally anabolic.

is minimal. Even more importantly, other salutary effects of teriparatide at cortical bone, such as changes in bone geometry and microarchitecture, more than compensate for any increase in cortical porosity (5). PTH stimulates periosteal apposition, which leads to increases in cortical area, cortical thickness, and an overall increase in cross-sectional area (5,6). Moreover, microarchitectural changes due to teriparatide are evident at the cortical sites such as the distal 1/3 radius as well. These geometrical and microarchitectural changes strengthen cortical bone despite the small reduction in bone density (7).

INDICATIONS FOR TERIPARATIDE

Teriparatide is used in postmenopausal women and men with osteoporosis who are at high risk for fracture. To help select patients for teriparatide, useful guidelines have been published (1). Patients who have already sustained an osteoporotic fracture are among the highest risk group because the likelihood of sustaining another fracture is very high (8). The T-score itself, even without an osteoporotic fracture, can confer high risk, especially if the T-score is very low (i.e. < -3.0). Patient age is also important as for any T-score, the older the patient the greater the risk. Other potential candidates for teriparatide are patients for whom one might consider a bisphosphonate but who cannot tolerate the drug or who are non-compliant. In addition, patients who fracture while on antiresorptive therapy could be considered to be at high risk and thus candidates for teriparatide. In most countries, teriparatide is approved for a limited period of time, 18–24 months.

TERIPARATIDE AS SINGLE IN POSTMENOPAUSAL OSTEOPOROSIS

In the randomized, double-blind, pivotal clinical trial of, Neer et al., women with severe osteoporosis were treated with subcutaneous injections of placebo, 20 or 40 µg of teriparatide. The average number of fragility fractures per patient was over 2, clearly defining this group as at high risk (9). Over a follow-up period of 21 months, BMD increased by an average of 10–14%. Femoral neck BMD also improved, but more slowly and to a smaller extent (approximately 3%) in comparison to the lumbar spine. At 20 µg of teriparatide, BMD did not change at the distal radius. The most important findings of the teriparatide trial by Neer et al. were reductions in new vertebral fractures by 65% at the 20. The overall incidence of new nonvertebral fractures was reduced by 35% at the 20 µg dose. Hip fracture incidence was not analyzed separately because the study was not sufficiently powered to examine this endpoint. By post-hoc analysis, the reduction in fracture incidence due to teriparatide was not related to the number, severity, or site of previous fractures (10). Further post-hoc analysis of this cohort demonstrated that the fracture risk reduction was largely independent of age and initial BMD (11). In an observational cohort from this trial, fracture reduction was sustained for up to 30 months after teriparatide discontinuation, although many individuals in the original and treatment groups received bisphosphonate therapy during this follow-up period (12).

PTH (1-84) IN POSTMENOPAUSAL OSTEOPOROSIS

PTH(1-84) has been the object of a limited number of studies. In a preliminary clinical trial, preparatory to the definitive clinical trial, subjects were administered placebo, or 1 of 3 doses of PTH(1-84): 50, 75, or 100 µg for 12 months (13). There were time- and dose-related increases in lumbar spine BMD. Similar to the teriparatide studies, bone turnover markers rose quickly. Histomorphometric analyses of bone biopsy specimens confirm an anabolic response to PTH(1-84) with an increase in bone formation and improvements in cancellous architecture (14). In contrast to the study by Neer et al. in which the average number of fragility fractures per study subject was > 2, the incidence of baseline fragility fractures in the phase III PTH(1-84) study was only 19%. Nevertheless, a reduction in new vertebral fracture incidence was seen with PTH(1-84) in women both with and without prior vertebral fractures (15).

TERIPARATIDE IN MEN WITH OSTEOPOROSIS

In the first randomized, controlled trial of teriparatide in men, Kurland et al. randomized 23 men to 400 U/day of teriparatide (equivalent to 25 µg/day) or placebo for 18 months in a double-blinded protocol (16). The men who received teriparatide demonstrated an impressive 13.5% increase in lumbar spine bone density. Hip BMD increased significantly but more slowly and to a smaller extent in comparison to the lumbar spine. Cortical bone density at the distal radius did not change as compared to placebo. Bone turnover markers rose quickly and substantially in the men treated with teriparatide, with bone formation

markers rising and peaking earlier than bone resorption markers. In a larger trial of 437 men that was the counterpart of the pivotal trial of Neer et al. in postmenopausal women, Orwoll et al. (17) followed a protocol that was essentially identical to the study of Neer et al. BMD increased significantly in the 20 µg treatment group by 5.9% at the lumbar spine and by 1.5% at the femoral neck. These increases were independent of gonadal status. The magnitude and time course of BMD increases at the lumbar spine and hip over the 11 months of the study, tracked along the time course seen in the postmenopausal women studied by Neer et al. (9). Although fractures could not be assessed during the short 11-month trial, they were assessed in a follow-up observational period of 30 months. 279 men from the original cohort had lateral thoracic and lumbar spine X-rays 18 months after treatment was stopped. In the combined teriparatide treatment groups (20 µg and 40 µg), the risk of vertebral fracture was reduced by 51% ($p = 0.07$). Significant reductions were seen in the combined group as compared to placebo when only moderate or severe fractures were considered (6.8% vs. 1.1%; $p < 0.02$) (18). As was the case in the observational follow-up period in postmenopausal women, a substantial number of male study subjects in all groups (25–30%) reported use of antiresorptive therapy during the follow-up period. Men treated with placebo utilized antiresorptive therapy to a greater extent than those who were treated with either dose of teriparatide (36% vs. 25%).

SEQUENTIAL AND COMBINATION THERAPY WITH TERIPARATIDE AND AN ANTIRESORPTIVE AGENT

Previous use of an antiresorptive

Many patients who are considered candidates for teriparatide have previously been treated with bisphosphonates or other antiresorptives. Cosman et al. treated postmenopausal women, previously given estrogen for at least 1 year, with teriparatide (19). Increases in vertebral BMD began with no delay and increased in a linear fashion during the entire 3-year study. Ettinger et al. studied the influence of 2 other antiresorptives, raloxifene or alendronate, prior to treatment with teriparatide (20). 59 postmenopausal women with T-scores ≤ -2.0 had been treated for an average of 28 months either with raloxifene or alendronate. Although this was not a prospective clinical trial, in most respects subjects were well matched in terms of age, BMI, and T-scores. Similar to the study of Lindsay et al. for estrogen, raloxifene did not impede the effects of teriparatide to increase BMD rapidly and linearly. In contrast, alendronate was associated with a 6-month delay before BMD in the lumbar spine began to increase. After 18 months, lumbar spine BMD increased by 10.2% in the prior raloxifene-treated group compared to only 4.1% in the prior-alendronate treated subjects ($p < 0.05$). The alendronate-treated group showed an initial decline in hip BMD at 6 months but at 18 months, mean total hip BMD was not different from baseline. During teriparatide treatment, bone markers in prior alendronate patients increased later and peaked at about 1/3 lower levels as compared to prior raloxifene-treated patients.

These results imply that the potency of the antiresorptive to control bone turnover can determine the early response to teriparatide. Cosman et al. have helped to refine this point in a study of teriparatide in postmenopausal women who also had previously received alendronate for the same period of time (21). In contrast to the study of Ettinger et al., their subjects responded to teriparatide with rapid increases in BMD. To account for these differences, it is noteworthy that the baseline bone turnover markers prior to the initiation of teriparatide therapy were markedly different in the 2 studies. In the study by Ettinger et al., bone turnover markers were almost completely suppressed. In comparison, in the study of Cosman et al., bone turnover markers were less suppressed and more in the range that one tends to find in subjects after alendronate therapy. Therefore, it is distinctly possible that it is not so much the specific antiresorptive used prior to teriparatide that dictates the subsequent densitometric response but rather the extent to which bone turnover is reduced. To support this idea, the response to teriparatide has been shown to be a function of the level of baseline bone turnover in subjects not previously treated with any therapy for osteoporosis: the higher the level of turnover, the more robust the densitometric response to teriparatide (16). This may seem counterintuitive, in that teriparatide stimulates bone formation and might be expected to have a greater effect in those with low bone turnover. This may relate to the need for active osteoblasts, primed osteoblasts, or progenitor osteoblast cells that are more receptive to the effects of teriparatide in a high turnover state.

Concurrent use of anabolic and antiresorptive therapy

It is attractive to consider combination therapy with an antiresorptive and PTH as potentially more beneficial than monotherapy given that their mechanisms of action are quite different from each other. If bone

resorption is being inhibited (antiresorptive) while bone formation is being stimulated (anabolic), combination therapy might give better results than with either agent alone. Despite the intuitive appeal of this reasoning, important data to the contrary have been provided by Black et al. (22) and by Finkelstein et al. (23). These 2 groups independently completed trials using a form of PTH alone, alendronate alone, or the combination of a PTH form and alendronate. Black et al. studied postmenopausal women with 100 µg of PTH(1-84). The study of Finkelstein et al. involved men treated with 40 µg of teriparatide. Both studies utilized DXA and QCT to measure areal or volumetric BMD respectively. With either measurement, monotherapy with PTH exceeded densitometric gains with combination therapy or alendronate alone at the lumbar spine. Measurement of trabecular bone by QCT, in fact, showed that combination therapy was associated with substantially smaller increases in BMD than monotherapy with PTH (figure 2). Bone turnover markers followed the expected course for anabolic (increases) or antiresorptive (decreases) therapy alone. However for combination therapy, bone markers followed the course of alendronate, not PTH therapy, with reductions in bone formation and bone resorption markers. This suggests that the impaired response to combination therapy, in comparison to PTH alone, might be due to the dominating effects of the antiresorptive agent on bone dynamics when both drugs are used together.

In a short 6-month clinical trial, Deal et al. have reported that the combination of teriparatide and raloxifene may have more beneficial effects than monotherapy with teriparatide in postmenopausal osteoporosis (24). Bone formation markers increased similarly in both groups. Bone resorption markers, however, were reduced in the combination group. BMD increased to a similar extent in the lumbar spine and femoral neck in both groups, but the increase in total hip BMD was significantly greater in subjects treated with both teriparatide and raloxifene.

Consequences of discontinuing anabolic therapy with PTH

Teriparatide is approved in most countries for a treatment period of 18–24 months. There are obvious concerns regarding the consequences of discontinuing therapy following this relatively short period of time. Some a priori concerns relate to the fact that new bone matrix is not fully mineralized following PTH therapy. Therefore, this new bone matrix could be at risk for resorption if a period of consolidation with an antiresorptive is not used (25).

Published data addressing this concern were initially based on observational trials (22,40-42). These studies, using either bisphosphonate (12,26,27) or estrogen (28,29) therapy following PTH, suggested that antiresorptive treatment may be necessary to maintain densitometric gains achieved during PTH

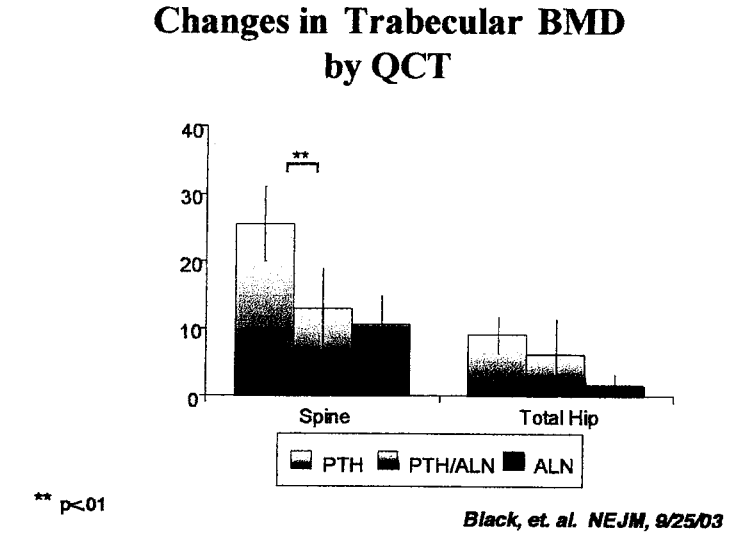


Figure 2. The effect of combination therapy with PTH(1-84) and alendronate on bone density of the lumbar spine. The use of monotherapy with PTH(1-84) is clearly superior in increasing lumbar spine BMD by QCT than combination therapy or monotherapy with alendronate. (Reprinted with permission from (22))

administration. With a stronger experimental design, the PaTH study has provided prospective data in a rigorously controlled, blinded fashion to address this issue (30). Postmenopausal women who had received PTH(1-84) for 12 months were randomly assigned to an additional 12 months of therapy with 10 mg of alendronate daily or placebo. In subjects who received alendronate, there was a further 4.9% gain in lumbar spine BMD while those who received placebo experienced a substantial decline. By QCT analysis, the net increase over 24 months in lumbar spine BMD among those treated with alendronate after PTH(1-84) was 30%. In those who received placebo after PTH(1-84), the net change in bone density was only 13%. There were similar dramatic differences in hip BMD when those who followed PTH with alendronate were compared to those who were treated with placebo (13% vs. 5%). The results of this study establish the importance of following PTH or teriparatide therapy with an antiresorptive.

Fracture efficacy was reported in the 30-month observational cohort following the trial of Neer et al. (12). Subjects were given the option of switching to a bisphosphonate or not taking any further medications following teriparatide. A majority (60%) was treated with antiresorptive therapy after PTH discontinuation. Gains in bone density were maintained in those who chose to begin antiresorptive therapy immediately after teriparatide. Reductions in BMD were progressive throughout the 30-month observational period in subjects who elected not to follow teriparatide with any therapy. In a group who did not begin antiresorptive therapy until 6 months after teriparatide discontinuation, major reductions in BMD were seen during these first 6 months but no further reductions were observed after antiresorptive initiation (26). Despite these densitometric data, the effect of previous therapy with teriparatide and/or subsequent therapy with a bisphosphonate on fracture prevention persisted for as long as 31 months after teriparatide discontinuation. Nonvertebral fragility fractures were reported by proportionately fewer women previously treated with PTH (with or without a bisphosphonate) as compared with those treated with placebo (with or without a bisphosphonate; $p< 0.03$). In a logistic regression model, bisphosphonate use for 12 months or longer was said to add little to overall risk reduction of new vertebral fractures in this post-treatment period. However, it is hard to be sure of this conclusion, as the data were not actually separately analyzed into those who did or did not follow teriparatide treatment with an antiresorptive. Also, the above findings were in an observational study in which participants self-selected for the use of antiresorptive therapy after PTH treatment, making the results even more difficult to interpret. One might anticipate a residual but transient protection against fracture after PTH treatment without follow-up antiresorptive therapy, which could wane over time (45). Additional studies are needed to address fracture outcomes specifically. However, based particularly on the PaTH trial, the importance of following PTH or teriparatide therapy with an antiresorptive to maintain increases in bone mass is clear.

Safety of PTH

Overall, PTH is well tolerated. A toxicity that appears to be unique to animals and not applicable to human subjects is osteosarcoma. The development of osteosarcoma has been seen only in rats that have been given very high doses of either teriparatide or PTH(1-84) for prolonged periods of time (31). It is unlikely that this animal toxicity is related to human skeletal physiology (32,33), but in the United States there is a warning included in the labeling instructions. Tashjian and Gagel have recently summarized our current knowledge of this issue (new reference).

PTH and future considerations

In the future, PTH may be modified for easier and more targeted delivery. Parathyroid hormone-related protein (PTHrP) has also been studied as an anabolic skeletal agent. In a small sample of postmenopausal women, subcutaneous administration of PTHrP resulted in a 4.7% increase in lumbar spine density after only 3 months of treatment (34). Less frequent administration of PTH, such as once weekly, might also be an effective treatment option (35). Cosman et al. have reported on the use of cyclical 3-month courses of teriparatide against a backdrop of continued alendronate use (21). In comparison to regular, uninterrupted teriparatide use, the cyclic administration of teriparatide was associated with similar densitometric gains. Of further interest was the observation that with sequential 3-month cycles of teriparatide, bone formation markers that fell quickly when teriparatide was stopped, were stimulated to the same degree with each cycle. On the other hand, bone resorption markers showed smaller increases with successive cycles. This observation gives credence to the idea that the anabolic window is actually expanded when teriparatide is used in this context (35,36). Most recently, Cosman et al. have shown that during long-term alendronate therapy, a rechallenge with PTH after 12 months off PTH increases bone formation, bone resorption and

BMD to a similar extent as during the first course of PTH administration (37). These data suggest that a future paradigm might be a second course of PTH given 12 months after a first course of therapy in patients who remain at high fracture risk. Apart from forms and ways to administer exogenous PTH, Gowen et al. described an oral calcilytic molecule that antagonizes the parathyroid cell calcium receptor, thus stimulating the endogenous release of PTH (38). This approach could represent a novel endogenous delivery system for intermittent PTH administration.

Strontium ranelate

Animal data with strontium ranelate suggest this compound can both promote bone formation and inhibit bone resorption (39). The exact cellular mechanism of action of strontium ranelate remains unclear. The regulation of bone cell differentiation, namely stimulation of osteoblast proliferation and inhibition of osteoclast formation, and activation of the calcium-sensing receptor have been proposed as possible mechanisms (39,40). It has also been suggested that there is a cation-sensing mechanism distinct from the calcium-sensing receptor that responds to strontium in osteoblasts (41).

Clinical trials support the use of strontium ranelate as a treatment for postmenopausal osteoporosis (42-44). Two recent studies, the Spinal Osteoporosis Therapeutic Intervention (SOTI) (43) and the Treatment of Peripheral Osteoporosis (TROPOS) (44) trials have shown that strontium ranelate reduces vertebral and nonvertebral fractures respectively. In the SOTI trial, 1,649 postmenopausal women with osteoporosis and at least one vertebral fracture were randomized to receive either 2 grams of strontium ranelate per day or placebo for 3 years. Treatment increased lumbar spine and femoral neck BMD, but the true BMD increase is difficult to interpret, even with corrective algorithms. This is because strontium has an atomic number greater than calcium which will weaken x-ray penetration and result in an over-estimation of measured bone mineral density (69). Certainly, the incorporation of the strontium ion into bone is also causing an increase in bone density per se. After making adjustments for the effect of strontium, lumbar spine BMD increased by 6.8% after 3 years. Strontium ranelate reduced vertebral fractures by 49% following the first year of treatment and by 41% at the end of the 3-year study period ($p< 0.001$). Increases in bone formation markers and decreases in bone resorption markers were also observed with strontium treatment, consistent with the idea that the drug both promotes bone formation and inhibits bone resorption. The TROPOS trial, designed in parallel with the SOTI trial, was conducted to determine strontium's effects on nonvertebral fractures. In this study, 5,091 postmenopausal women with osteoporosis were randomized to either 2 grams/day of strontium ranelate or placebo. The relative risk of all nonvertebral fractures was reduced by 16% at 3 years ($p= 0.04$). In a subset of women at high risk for hip fracture (age > 74 years, BMD T score $\leq$ -3), the risk of hip fracture was reduced by 36% ($p= 0.046$). The incidence of vertebral fractures also decreased in these subjects with a 39% risk reduction overall and a 45% risk reduction in the subgroup without prevalent vertebral fractures. Strontium ranelate was well tolerated in both trials with nausea and diarrhea occurring more frequently only during the first three months of therapy. Interestingly, slight reductions in PTH and calcium levels and a slight increase in phosphorus concentrations were observed in the strontium group as compared to placebo. These changes were of no clinical consequence but would be consistent with activation of the calcium-sensing receptor by strontium (44).

GROWTH HORMONE AND INSULIN-LIKE GROWTH FACTOR

The rationale for considering GH and IGF-1 as potential anabolic agents is that both are critical for the acquisition and maintenance of bone mass. Particularly in men, GH and IGF-1 stimulate periosteal apposition, so it is logical to expect both might be effective in human subjects. An added theoretical advantage is salutary effects on muscle strength and coordination, leading potentially to a reduction in falls and fracture rates.

Growth hormone

Most of the studies utilizing GH, however, have been disappointing. Changes in bone mass are minimal in both men (45) and women (46,47). The lack of a beneficial effect with GH on bone mass could be due to the concomitant activation of bone resorption along with formation, so that a net gain does not occur (47,48). Another explanation for a lack of effect could be the relatively short, one year, duration of many of these studies. Recent evidence suggested a delayed and what was ultimately a positive effect of GH on bone. In a double-blind, randomized, placebo-controlled trial, 80 postmenopausal women with osteoporosis on estrogen replacement therapy were administered either placebo, GH 1.0 U/day, or 2.5 U/day for 18 months

(49). Women in both treatment groups continued GH for an additional 18 months. Although there were no significant differences between groups after 3 years, at 4 years, the higher dose of GH resulted in a 14% increase in lumbar spine bone mineral content. These unexpected results conflict with most data on effective osteoporosis therapies in which major increases in bone mass are typically limited to the first three years of therapy. One possible explanation for the "catch-up" bone gain after GH withdrawal might be that the drop in IGF-1 halts GH-stimulated resorption but allows osteoblastic stimulation to persist (50).

IGF-1

IGF-1 promotes chondrocyte and osteoblast differentiation and growth (51). It is also a pivotal factor in the coupling of bone turnover, as it is stored in the skeletal matrix and released during bone resorption (51). When the IGF-1 receptor in bone is knocked out in mice, decreased bone formation and suppressed mineralization ensue (52). Two prospective clinical studies have suggested that low levels of IGF-1 are associated with a greater risk of spine and hip fractures (53,54).

Data on IGF-1 therapy exist for postmenopausal and young women. IGF-1 theoretically is more appealing than GH, because it stimulates bone formation more directly. When elderly women were administered low doses of rhIGF-1, markers of bone formation were differentially stimulated with only a minimal increase in bone resorption (55). Similarly, markers of bone formation increased in short-term trials of young women with anorexia nervosa administered IGF-1 alone (56) or in combination with risedronate (18). A major drawback to the development of IGF-1 as a therapy for osteoporosis is its ubiquitous effect on many organ systems. Similar to GH, potential serious adverse effects could surface with its chronic use.

FUTURE ANABOLIC THERAPIES

Other promising anabolic agents are on the horizon. For example, compounds that might augment the recently identified wnt-signaling pathway, such as inhibitors of sclerostin (57), could yield potentially powerful anabolic effects in the years to come.

CONCLUSIONS

Although antiresorptives remain the mainstay of osteoporosis treatment, the advent of anabolic skeletal agents is changing our approach to therapy. Of the anabolic agents discussed above, parathyroid hormone has clearly emerged as the most promising current treatment. For the first time, a drug is available that not only improves bone density, features of bone turnover, and reduces fracture incidence, but also significantly improves microarchitectural and geometric properties of bone. These changes in bone quality induced by teriparatide are attractive considering the goal of therapy for osteoporosis, namely to improve the basic underlying abnormalities that give rise to skeletal fragility. Recent studies have given insight on the optimal use of this agent, including the importance of subsequent antiresorptive treatment to preserve gains in bone mass incurred during PTH therapy. With the development of additional and more cost-effective therapies, the use of anabolic agents will likely increase in the years to come.

ACKNOWLEDGEMENTS

This project was funded, in part, by NIH grant NIDDK 32333.

REFERENCES

1. Hodsman AB, Bauer DC, Dempster D, Dian L, Hanley DA, Harris ST, et al. Parathyroid hormone and teriparatide for the treatment of Osteoporosis: A review of the evidence and suggested guidelines for its use. **Endocr Rev 2005**;26(5):688-703.
2. Dempster DW, Parisien M, Silverberg SJ, Liang XG, Schnitzer M, Shen V, et al. On the mechanism of cancellous bone preservation in postmenopausal women with mild primary hyperparathyroidism. **J Clin Endocrinol Metab 1999**;84(5):1562-6.
3. Rubin M, Bilezikian J. The anabolic effects of parathyroid hormone therapy. **Clin Geriat Med 2002**;19:415-32.
4. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) (teriparatide) improves both cortical and cancellous bone structure. **J Bone Miner Res 2003**;18(11):1932-41.
5. Burr DB, Hirano T, Turner CH, Hotchkiss C, Brommage R, Hock JM. Intermittently administered human parathyroid hormone(1-34) treatment increases intracortical bone turnover and porosity without reducing bone strength in the humerus of ovariectomized cynomolgus monkeys. **J Bone Miner Res 2001**;16(1):157-65.
6. Parfitt AM. Parathyroid hormone and periosteal bone expansion. **J Bone Miner Res 2002**;17(10):1741-3.
7. Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, et al. Effects of teriparatide (recombinant human parathyroid hormone (1-34)) on cortical bone in postmenopausal women with osteoporosis. **J Bone Miner Res 2003**;18(3):539-43.

8. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. **JAMA 2001**;285(3):320-3.

9. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. **N Engl J Med 2001**;344(19):1434-41.

10. Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. **J Clin Endocrinol Metab 2005**;90(3):1583-7.

11. Marcus R, Wang O, Satterwhite J, Mitlak B. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. **J Bone Miner Res 2003**;18(1):18-23.

12. Prince R, Sipos A, Hossain A, Syversen U, Ish-Shalom S, Marcinowska E, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. **J Bone Miner Res 2005**;20(9):1507-13.

13. Hodsman AB, Hanley DA, Ettinger MP, Bolognese MA, Fox J, Metcalfe AJ, et al. Efficacy and safety of human parathyroid hormone-(1-84) in increasing bone mineral density in postmenopausal osteoporosis. **J Clin Endocrinol Metab 2003**;88(11):5212-20.

14. Fox J, Miller MA, Recker RR, Bare SP, Smith SY, Moreau I. Treatment of postmenopausal osteoporotic women with parathyroid hormone 1-84 for 18 months increases cancellous bone formation and improves cancellous architecture: A study of iliac crest biopsies using histomorphometry and micro computed tomography. **J Musculoskelet Neuronal Interact 2005**;5(4):356-7.

15. Ettinger M, Greenspan S, Marriott TB, Hanley DA, Zanchetta JR, Bone HG 3rd, et al. PTH(1-84) prevents first vertebral fracture in postmenopausal women with osteoporosis: results from the TOP study. **American College of Rheumatology Annual Meeting, 2004**. p. L17.

16. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. **J Clin Endocrinol Metab 2000**;85(9):3069-76.

17. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide (human parathyroid hormone (1-34)) therapy on bone density in men with osteoporosis. **J Bone Miner Res 2003**;18(1):9-17.

18. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. **Osteoporosis Int 2005**;16(5):510-6.

19. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. **J Bone Miner Res 2001**;16(5):925-31.

20. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. **J Bone Miner Res 2004**;19(5):745-51.

21. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendroante. **N Eng J Med 2005**;353:566-75.

22. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. **N Engl J Med 2003**;349(13):1207-15.

23. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. **N Engl J Med 2003**;349(13):1216-26.

24. Deal C, Omizo M, Schwartz EN, Eriksen EF, Cantor P, Wang J, 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):1905-11.

25. Misof BM, Roschger P, Cosman F, Kurland ES, Tesch W, Messmer P, et al. Effects of intermittent parathyroid hormone administration on bone mineralization density in iliac crest biopsies from patients with Osteoporosis: A paired study before and after treatment. **J Clin Endocrinol Metab 2003**;88(3):1150-6.

26. Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. **Arch Intern Med 2004**;164(18):2024-30.

27. Kurland ES, Heller SL, Diamond B, McMahon DJ, Cosman F, Bilezikian JP. The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide (human parathyroid hormone(1-34)). **Osteoporosis Int 2004**;15(12):992-7.

28. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. **Lancet 1997**;350(9077):550-5.

29. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. **J Bone Miner Res 2000**;15(5):944-51.

30. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. **N Engl J Med 2005**;353(6):555-65.

31. Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M. Bone neoplasms in F344 rats given teriparatide (rhPTH(1-34)) are dependent on duration of treatment and dose. **Toxicol Pathol 2004**;32(4):426-38.

32. Jimenez C, Kim W, Al Sagier F, El Naggar A, Sellin R, Berry D, et al. Primary hyperparathyroidism and osteosarcoma: examination of a large osteosarcoma cohort identifies unique characteristics. **J Bone Miner Res 2003**;18(suppl. 2):LB6.

33. Tashjian AH Jr., Gagel RF. Teriparatide (human PTH(1-34)): 2.5 years of experience on the use and safety of the drug for the treatment of osteoporosis. **J Bone Min Res 2006**;21:354-65.

34. Horwitz MJ, Tedesco MB, Gundberg C, Garcia-Ocana A, Stewart AF. Short-term, high-dose parathyroid hormone-related protein as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis. **J Clin Endocrinol Metab 2003**;88(2):569-75.

35. Black DM, Rosen CJ. Parsimony with PTH: Is a single weekly injection of PTH superior to a larger cumulative dose given daily? **J Bone Miner Res 2002**;17(suppl. 1):SA367.

36. Heaney RP, Recker RR. Combination and sequential therapy for osteoporosis. **N Engl J Med 2005**;353(6):624-5.

37. Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Effects of PTH rechallenge 1 year after the first PTH course in patients on long-term alendronate. **27th Annual Meeting of the American Society for Bone and Mineral Research**, Nashville, Tennessee, **2005**. Presentation Number 1079.

38. Gowen M, Stroup GB, Dodds RA, James IE, Votta JB, Smith BR, et al. Antagonizing the parathyroid calcium receptor stimulates parathyroid hormone secretion and bone formation in osteopenic rats. **J Clin Invest 2000**;105(11):1595-604.

39. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. **Calcif Tissue Int 2001**;69(3):121-9.

40. Brown EM. Is the calcium receptor a molecular target for the actions of strontium on bone? **Osteoporos Int 2003**;14(suppl. 3):S25-34.

41. Pi M, Quarles LD. A novel cation-sensing mechanism in osteoblasts is a molecular target for strontium. **J Bone Miner Res 2004**;19(5):862-9.

42. Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis-a 2-year randomized placebo controlled trial. **J Clin Endocrinol Metab 2002**;87(5):2060-6.

43. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. **N Engl J Med 2004**;350(5):459-68.

44. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. **J Clin Endocrinol Metab 2005**;90(5):2816-22.

45. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. **N Engl J Med 1990**;323(1):1-6.

46. Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R. Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. **J Clin Endocrinol Metab 1994**;79(2):470-9.

47. Donahue LR, Rosen CJ. Growth Hormone and Insulin-Like Growth Factor I as therapeutic modalities for age-related Osteoporosis. In: Rosen CJ, Glowacki J, Bilezikian JP. **The aging skeleton**. San Diego: Academic Press, **1999**. pp. 579-84.

48. Ackert-Bicknell C, Rubin J, Zhu L, Fan X, Murphy T, Nanes M, et al. IGF-I Acts as a coupling factor for bone remodeling by regulating osteoprotegerin and RANK ligand in vitro and osteoprotogerin in vivo. **84th Annual Meeting of the Endocrine Society**, San Francisco, CA, **2002**. pp. 3-366.

49. Landin-Wilhelmsen K, Nilsson A, Bosaeus I, Bengtsson BA. Growth hormone increases bone mineral content in postmenopausal osteoporosis: a randomized placebo-controlled trial. **J Bone Miner Res 2003**;18(3):393-405.

50. Rosen CJ, Wuster C. Growth hormone rising: did we quit too quickly? **J Bone Miner Res 2003**;18(3):406-9.

51. Donahue L, Rosen CJ. IGFs and bone. The osteoporosis connection revisited. **Proc Soc Exp Biol Med 1998**;219:1-7.

52. Hurley MM, Okada Y, Sobue T, Zhang XZ, Xiao L, Tanaka Y, et al. The anabolic effect of parathyroid hormone is impaired in bones of Fgf2 null mice. **J Bone Miner Metab 2002**;17(suppl. 1):1061.

53. Sugimoto T, Nishiyama K, Kuribayashi F, Chihara K. Serum levels of insulin-like growth factor (IGF) I, IGF-binding protein (IGFBP)-2, and IGFBP-3 in osteoporotic patients with and without spinal fractures. **J Bone Miner Res 1997**;12(8):1272-9.

54. Bauer DC, Rosen CJ, Cauley J, Cummings SR. Low serum IGF-1 but not IGFBP-3 predicts hip and spine fracture: the study of osteoporotic fracture. **J Bone Miner Res 1998**;23:S561.

55. Ghiron LJ, Thompson JL, Holloway L, Hintz RL, Butterfield GE, Hoffman AR, et al. Effects of recombinant insulin-like growth factor-I and growth hormone on bone turnover in elderly women. **J Bone Miner Res 1995**;10(12):1844-52.

56. Grinspoon S, Baum H, Lee K, Anderson E, Herzog D, Klibanski A. Effects of short-term recombinant human insulin-like growth factor I administration on bone turnover in osteopenic women with anorexia nervosa. **J Clin Endocrinol Metab 1996**;81(11):3864-70.

57. Ott SM. Sclerostin and Wnt signaling-the pathway to bone strength. **J Clin Endocrinol Metab 2005**;90(12):6741-3.

Address for correspondence:

John P. Bilezikian
Department of Medicine
College of Physicians and Surgeons
630 W. 168th Street
New York, NY 10032
Fax: 212-305-6486
E-mail: jpb2@columbia.edu

Effetto della terapia con teriparatide [ormone paratiroideo umano (1-34)] sulla densità ossea in uomini con osteoporosi

ES ORWOLL, WH SCHEELE, S PAUL, S ADAMI, U SYVERSEN, A DIEZ-PEREZ, J-M KAUFMAN, AD CLANCY e GA GAICH

JOURNAL OF BONE AND MINERAL RESEARCH
VOLUME 18, NUMERO 1, 2003; PAGG. 9-17

Edizione italiana a cura di:
OGM - One Global Medicine s.r.l.
Corso Buenos Aires, 37 - 20124 Milano
Tel. 02.20241664 (r.a.) - Fax 02.2043000
Publishing Services & Communication
Traduzione a cura di OGM s.r.l.
OG-07-1225

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 18, Number 1, 2003

Effetto della terapia con teriparatide [ormone paratiroideo umano (1-34)] sulla densità ossea in uomini con osteoporosi

ES Orwoll[1], WH Scheele[2], S Paul[2], S Adami[3], U Syversen[4], A Diez-Perez[5], J-M Kaufman[6], AD Clancy[2], GA Gaich[2]

ABSTRACT

Il teriparatide [rhPTH(1-34)] incrementa la densità minerale ossea e riduce il rischio di fratture vertebrali nelle donne. Abbiamo randomizzato 437 uomini, con densità minerale ossea del rachide o dell'anca superiore pari a 2 DS al di sotto della media calcolata per i maschi adulti giovani, a iniezioni giornaliere di placebo, teriparatide 20 µg o teriparatide 40 µg. Tutti i soggetti hanno ricevuto anche dei supplementi di calcio e vitamina D. Lo studio è stato concluso dopo una durata mediana di 11 mesi a causa del riscontro di osteosarcomi nei ratti nel corso di studi tossicologici di routine. Nel corso del trattamento, all'aumento precoce dei markers biochimici di neoformazione ossea, hanno fatto seguito aumenti degli indici di attività osteoclastica. Dopo 3 mesi di terapia con teriparatide, la densità minerale ossea del rachide è risultata maggiore rispetto ai soggetti trattati con placebo, e alla fine del trattamento è aumentata del 5,9% (20 µg) e del 9,0% (40 µg) rispetto al basale ($p<0.001$ vs placebo per entrambi i confronti). Nei soggetti trattati con teriparatide la densità minerale ossea del collo femorale è aumentata dell'1,5% (20 µg; $p=0,029$) e del 2,9% (40 µg; $p<0,001$), e il contenuto minerale osseo dell'intero scheletro è aumentato dello 0,6% (20 µg; $p=0,021$) e dello 0,9% (40 µg; $p=0,005$) rispetto al basale. Non è stata osservata alcuna variazione della densità minerale ossea radiale nei gruppi di trattamento con teriparatide. Le risposte al trattamento con teriparatide in termini di densità minerale ossea sono risultate simili indipendentemente da stato gonadico, età, densità minerale ossea basale, body mass index, abitudine al fumo o consumo di alcol. I soggetti hanno presentato modificazioni del metabolismo minerale che erano attese. Gli eventi avversi sono risultati simili nei gruppi di trattamento con placebo e teriparatide 20 µg, mentre sono stati più frequenti nel gruppo di trattamento con teriparatide 40 µg. Questo studio dimostra che il trattamento con teriparatide determina un aumento della densità minerale ossea ed è una potenziale utile terapia per l'osteoporosi negli uomini. (J Bone Miner Res 2003;18:9-17).

Parole chiave: teriparatide, osteoporosi, uomini, terapia farmacologica, densità ossea.

INTRODUZIONE

Sebbene si riscontri più frequentemente nelle donne, l'osteoporosi nel sesso maschile rappresenta un importante problema di salute pubblica (1). La densità minerale ossea (BMD) è comunemente bassa negli uomini più anziani ed è strettamente correlata ad un aumentato rischio di fratture (2). Circa il 27% delle fratture dell'anca – la conseguenza più devastante dell'osteoporosi – si verifica nel sesso maschile, e ci si aspetta che questo numero aumenti con l'espansione della popolazione anziana (3). Negli uomini, anche il rischio di andare incontro ad una frattura vertebrale sintomatica aumenta rapidamente con l'avanzare dell'età (4). Il 30% circa degli uomini di razza bianca di età avanzata presenta deformità vertebrali prevalenti (5) e gli uomini colpiti da fratture vertebrali soffrono di varie disabilità, quali dolore e compromissione funzionale (6). Negli uomini già colpiti da una frattura vertebrale, la probabilità di andare incontro a frattura dell'anca è quattro volte superiore a quella della popolazione generale (7).

Negli uomini l'osteoporosi è generalmente idiopatica (8) e sono stati studiati adeguatamente solo pochi trattamenti potenzialmente diretti alla cura di questa condizione. In un ampio trial, la terapia antiriassorbitiva con alendronato ha aumentato la BMD e ha ridotto il rischio di frattura vertebrale negli uomini con osteoporosi (9). Nelle donne in postmenopausa con pregresse fratture vertebrali, il frammento 1-34 dell'ormone paratiroideo originato da DNA ricombinante [rhPTH(1-34)], o teriparatide, aumenta la BMD e riduce l'incidenza di fratture

Drs Orwoll, Diez-Perez, and Kaufman have been consultants for Eli Lilly & Co. Ms Clancy and Dr Scheele, Paul, and Gaich are employees of Eli Lilly & Co. Drs Adami and Syversen have no conflicts of interest.

[1]Oregon Health and Sciences University and Veterans Affairs Medical Center, Portland, Oregon, USA.
[2]Eli Lilly and Company, Indianapolis, Indiana, USA.
[3]Università di Verona, Valeggio sul Minicio (VR), Italia.
[4]University Hospital, Trondheim, Norway.
[5]Hospital del Mar, Barcelona, Spain.
[6]Ghent University Hospital, Ghent, Belgium.

vertebrali e non vertebrali (10). Sebbene le terapie anaboliche negli uomini sono state molto meno studiate, in piccoli trial la terapia con ormone paratiroideo (1-34) ha determinato un aumento della BMD (11-12), suggerendone una sua possibile utilità nel trattamento dell'osteoporosi nell'uomo. In questo studio abbiamo valutato l'utilità del teriparatide in un ampio gruppo di uomini con riduzione della densità minerale ossea maggiore di 2 DS al di sotto della media calcolata per i maschi adulti giovani. Abbiamo inoltre accertato l'influenza esercitata dai livelli di ormoni sessuali, dall'abitudine al fumo e da altri fattori sulla risposta al teriparatide.

MATERIALI E METODI

Soggetti

Gli uomini sono stati reclutati in 37 centri dislocati in 11 Paesi, nell'ambito di cliniche ospedaliere e strutture di assistenza primaria. I soggetti sono stati considerati eleggibili se di età compresa tra 30 e 85 anni, pazienti ambulatoriali, liberi da condizioni croniche disabilitanti diverse dall'osteoporosi, e con BMD del rachide lombare o del femore prossimale (collo o totale) almeno 2 DS al di sotto della media calcolata per gli uomini giovani sani (rachide lombare: 0,871 g/cm^2 per i densitometri della Hologic e 0,980 g/cm^2 per i densitometri della Lunar). Ai ricercatori è stato richiesto di arruolare un ugual numero di soggetti con livello basso e normale di testosterone libero.

Gli uomini con malattie metaboliche ossee secondarie, incluso l'eccesso di glucocorticoidi, sono stati esclusi. Altri motivi di esclusione sono stati: utilizzo di agonisti o antagonisti degli estrogeni, cumarinici e derivati dell'indandione, anticonvulsivi (diversi dalle benzodiazepine), antiacidi contenenti calcio o alluminio, o di qualsiasi altro farmaco in grado di alterare il metabolismo osseo; storia di nefrolitiasi o urolitiasi nei 2 anni precedenti la randomizzazione; sprue, malattia infiammatoria intestinale, sindrome da malassorbimento, o qualsiasi indicazione di scarso assorbimento intestinale del calcio, quale la combinazione di ridotta escrezione urinaria del calcio ed elevato livello sierico di ormone paratiroideo intatto, nell'anno precedente la randomizzazione; funzione renale o epatica significativamente compromessa; abuso di alcol (>6 bicchieri al giorno) o di stupefacenti nell'anno precedente la randomizzazione. I soggetti sono stati esclusi nel caso in cui avessero presentato, nell'anno precedente la randomizzazione, disturbi ossei di origine metabolica diversi dall'osteoporosi primaria, quali morbo di Paget, osteodistrofia renale, osteomalacia o altri disturbi riconosciuti come causa di alterazione del metabolismo osseo.

I livelli sierici di calcio e dell'ormone paratiroideo endogeno, nonché l'escrezione urinaria del calcio nelle 24 ore, erano normali in tutti i soggetti. Sono stati considerati non eleggibili anche gli uomini che avevano ricevuto, nei 6 mesi precedenti, un trattamento per l'osteoporosi con androgeni o altra terapia anabolica steroidea, calcitonina, progestinici, fluoruri, bisfosfonati orali, vitamina D >50.000 UI/settimana, o analoghi del calcitriolo. Tuttavia i pazienti affetti da ipogonadismo, nei quali i dosaggi di androgeni o di altri steroidi anabolici erano stati mantenuti stabili nei 6 mesi precedenti la randomizzazione, sono stati considerati eleggibili e hanno continuato tale terapia durante lo studio. I soggetti con deficit dell'ormone della crescita da qualsiasi causa, inclusi pregressa chirurgia, tumore o radioterapia a livello della ghiandola ipofisaria, non sono stati considerati eleggibili per l'arruolamento. Sono stati esclusi anche gli uomini con sospetto carcinoma o storia di carcinoma (ad eccezione del carcinoma cutaneo) nei 5 anni precedenti la randomizzazione. Gli uomini con alterazioni a livello del rachide lombare di gravità tale da impedire la valutazione della BMD non sono stati considerati eleggibili. Lo studio è stato approvato dai comitati etici di ciascun centro e i pazienti hanno fornito il consenso informato scritto alla partecipazione allo studio.

Trattamento

I soggetti sono stati assegnati (mediante randomizzazione centralizzata a blocchi di tre) al trattamento con placebo, teriparatide 20 μg o teriparatide 40 μg (prodotto mediante tecnologia del DNA ricombinante). La sequenza di randomizzazione è stata generata da una tavola numerica casuale ed è stata stratificata in base alla misurazione iniziale dei livelli di testosterone al mattino (normale vs basso a seconda dell'età del paziente). I ricercatori e i pazienti erano in cieco rispetto all'assegnazione del trattamento.

I pazienti si sono auto-somministrati iniezioni giornaliere sottocute di teriparatide o placebo mediante un apparecchio iniettivo. La valutazione della compliance è stata effettuata mediante il conteggio del numero di dosi non utilizzate restituite nel corso delle visite previste dallo studio. I pazienti hanno ricevuto anche supplementi orali giornalieri di calcio (1000 mg) e vitamina D (400-1200 UI), a partire da almeno 1 mese dopo la randomizzazione. Lo studio era stato originariamente pianificato per una durata di almeno 24 mesi, ma è stato interrotto prima dallo sponsor dal momento che studi tossicologici di routine hanno evidenziato la comparsa di osteosarcomi nei ratti Fischer 344 trattati con teriparatide per quasi tutta la vita (13).

Misurazioni

La BMD è stata valutata utilizzando l'assorbimetria a raggi X a doppia energia (DXA: Hologic o Lunar). Tutte le scansioni sono state revisionate e analizzate a livello centrale, e sono state escluse dall'analisi le vertebre con fratture o artefatti. La BMD del rachide lombare è stata misurata al basale e a 3, 6 e 12 mesi e/o al momento della visita finale. La BMD dell'anca, dell'intero scheletro e quella radiale sono state misurate al basale e a 12 mesi e/o al momento della visita finale. Le misurazioni dell'intero distretto corporeo non hanno incluso il capo.

I marker biochimici di neoformazione ossea [fosfatasi alcalina ossea sierica (ALP ossea), procollagene I carbossiterminale (PICP) sierico] e di riassorbimento [N-telopeptide urinario (NTX), desossipiridinolina libera urinaria (fDPD), e 1,25 diidrossivitamina D [1,25-$(OH)_2$D] sono stati misurati al basale e a 1, 3, 6 e 12 mesi. La ALP ossea è stata misurata mediante dosaggio radioimmunometrico a 2 siti (CV interdosaggio <8%); la PICP è stata misurata mediante dosaggio radioimmunologico all'equilibrio (CV interdosaggio <8%), l'NTX è stato misurato mediante ELISA ad inibizione competitiva (CV interdosaggio <11%), la fDPD è stata misurata mediante dosaggio immunoenzimatico competitivo (CV interdosaggio <13%), e la 1,25-$(OH)_2$D è stata misurata mediante dosaggio di legame radiorecettoriale (CV interdosaggio <10%). La misurazione del calcio nel siero è stata effettuata a 1, 3, 6 e 12 mesi, entro le 4-6 ore successive all'iniezione. I campioni utilizzati per la valutazione dell'escrezione del calcio e della creatinina nelle urine delle 24 ore sono stati misurati al basale e dopo 1, 6 e

TABELLA 1. CARATTERISTICHE DEI SOGGETTI AL BASALE (MEDIA ± DS O PERCENTUALI)

Caratteristica	*Placebo (N = 147)*	*Teriparatide 20 µg (N = 151)*	*Teriparatide 40 µg (N = 139)*
Razza bianca (%)	100	99	99
Età (anni)	59 ± 13	59 ± 13	58 ± 13
Body mass index (kg/m²)	25 ± 4	25 ± 4	25 ± 4
Apporto di calcio (g/die)	0,86 ± 0,57	0,84 ± 0,54	0,80 ± 0,50
Abitudine al fumo (%)	32	30	27
Consumo di alcol (%)	69	76	65
Pregressa terapia per l'osteoporosi (%)	12	15	18
Basso livello di testosterone libero (%)	50	48	49
BMD vertebrale (g/cm²)	0,85 ± 0,14	0,89 ± 0,15	0,87 ± 0,14
T-score			
Rachide lombare	−2,4 ± 1,2	−2,0 ± 1,3	−2,2 ± 1,2
Collo femorale	−2,7 ± 0,8	−2,6 ± 0,8	−2,7 ± 0,8
Anca totale	−1,9 ± 0,8	−1,8 ± 0,8	−1,9 ± 0,9

12 mesi di trattamento. Se i soggetti trattati con teriparatide presentavano un elevato livello sierico di calcio (livello sierico di calcio non corretto ≥2,64 mM) o un'escrezione urinaria del calcio superiore a 350 mg (8,8 mmol)/die, unitamente ad un aumentato rapporto calcio/creatinina nelle urine, è stata effettuata una riduzione o la sospensione della dose del supplemento di calcio, o la dose del farmaco dello studio è stata ridotta della metà secondo il giudizio del ricercatore. Se nel corso di test ripetuti tale aumento risultava costante, la somministrazione del farmaco dello studio è stata interrotta.

La misurazione dei livelli di testosterone libero al basale è stata effettuata su due campioni sierici, e la media dei risultati è stata utilizzata per analisi successive. I livelli di testosterone sono stati confrontati con i valori di riferimento normali in base all'età. La stima del testosterone libero è stata effettuata mediante uno specifico dosaggio radioimmunologico competitivo (CV interdosaggio <16%). I livelli sierici di estradiolo sono stati determinati su campioni prelevati al basale, utilizzando uno specifico dosaggio radioimmunologico sequenziale con doppio anticorpo (CV interdosaggio <10%; limite di rilevamento, 1,4 pg/ml). L'esame emocromocitometrico completo, la valutazione dei parametri biochimici e l'esame delle urine sono stati effettuati al basale, a 6 e 12 mesi, e/o al momento della visita finale. La determinazione dell'ormone paratiroideo intatto (1-84) nel siero è stata effettuata mediante un dosaggio immunoradiometrico validato, al basale e a 12 mesi. Gli anticorpi sierici diretti contro il teriparatide sono stati misurati al basale e dopo 12 mesi mediante dosaggio radioimmunologico indiretto. Gli eventi avversi sono stati registrati ad ogni visita, sulla base delle segnalazioni spontanee dei pazienti. Il consumo di alcol e l'abitudine al fumo sono stati determinati al basale e alla fine dello studio.

Analisi statistica

L'obiettivo primario dello studio è stato quello di determinare le variazioni dal basale alla fine dello studio della BMD del rachide lombare nel corso di 2 anni di trattamento. Gli obiettivi secondari hanno incluso la determinazione delle variazioni dal basale alla fine dello studio della BMD dell'anca totale, del collo femorale, dell'intertrocantere, del trocantere, del radio e dell'intero scheletro, nonché quelle del contenuto minerale osseo (BMC) dell'intero distretto corporeo. I risultati sono stati analizzati su base intention-to-treat con l'ultima osservazione portata al termine al punto finale. Le analisi longitudinali hanno incluso tutti i pazienti con almeno un valore determinato dopo il basale. Le misure continue sono state analizzate mediante ANOVA, includendo termini per trattamento e Paese di appartenenza. Dal momento che la distribuzione dei marker biochimici è risultata altamente asimmetrica, è stato utilizzato l'ANOVA ranked, e le mediane sono state presentate come misura di tendenza centrale. Per le misure categoriali, i trattamenti sono stati confrontati mediante il test χ^2 di Pearson. Tutti i test sono stati di tipo two-tailed con un livello di significatività di 0,05. Per determinare le correlazioni tra le variabili basali (quali caratteristiche demografiche, abitudine al fumo e consumo di alcol, ormoni sessuali, BMD, e marker biochimici di turnover e neoformazione ossei) in relazione alle variazioni dal basale alla fine dello studio della BMD e dei marker biochimici di turnover osseo, sono state effettuate ulteriori analisi esplorative di sottogruppo. Per effettuare le analisi di sottogruppo è stato utilizzato l'ANOVA con trattamento, Paese di appartenenza, sottogruppo e sottogruppo per interazione con il trattamento, e l'interazione è stata testata al livello di significatività di 0,10. Le analisi statistiche sono state effettuate con il SAS v6,09 per MVS.

RISULTATI

Dei 959 uomini selezionati, 437 sono stati considerati eleggibili per l'arruolamento e randomizzati a placebo (147 soggetti) o teriparatide 20 µg/die (151 soggetti) o 40 µg/die (139 soggetti). Le caratteristiche demografiche basali degli uomini sono risultate simili nei tre gruppi dello studio (Tabella 1). Duecentoundici soggetti (49%) presentavano livelli basali di testosterone libero sierico al di sotto dei gruppi di riferimento in relazione all'età. Diciannove uomini stavano ricevendo dosi stabili di androgeni: sette nel gruppo placebo, cinque nel gruppo 20 µg e sette nel gruppo 40 µg.

La durata del trattamento per tutti i pazienti inclusi nell'analisi è variata da 2 a 15 mesi. L'esposizione mediana al trattamento è risultata di 11 mesi, ma leggermente inferiore nei gruppi teriparatide rispetto al gruppo placebo (mediana di 328 giorni per il placebo, di 313 giorni per teriparatide 20 µg e di 302 per teriparatide 40 µg: p=0,046). Trecentoundici (71,2%) soggetti hanno ricevuto teriparatide o placebo per almeno 9 mesi: 114 (77,6%) nel gruppo placebo, 106 (70,2%) nel gruppo teriparatide 20 µg e 91 (65,5%) nel gruppo teriparatide 40 µg. In base al numero degli apparecchi iniettivi restituiti nel corso delle visite

TABELLA 2. VARIAZIONE PERCENTUALE DELLA DENSITÀ E DEL CONTENUTO MINERALE OSSEI DAL BASALE ALLA FINE DELLO STUDIO

	Placebo	*Teriparatide, 20 μg*		*Teriparatide, 40 μg*		
Misurazione scheletrica	*Variazione percentuale (media ± DS)*	*Variazione percentuale (media ± DS)*	*Valore di* p *vs placebo*	*Variazione percentuale (media ± DS)*	*Valore di* p *vs placebo*	*Valore di* p, *teriparatide 20 μg vs 40 μg*
Densità minerale ossea (g/cm²)						
Rachide lombare	0,52 ± 3,90	5,87 ± 4,50	<0,001	9,03 ± 6,46	<0,001	<0,001
Collo femorale	0,31 ± 4,1	1,53 ± 3,95	0,029	2,93 ± 6,34	<0,001	0,023
Trocantere	1,09 ± 3,30	1,33 ± 4,15	NS	2,08 ± 5,32	NS	NS
Intertrocantere	0,61 ± 2,87	1,18 ± 3,09	NS	2,34 ± 4,41	<0,001	0,012
Anca totale	0,54 ± 2,70	1,17 ± 2,94	NS	2,33 ± 4,41	<0,001	0,009
Radio distale	−0,15 ± 1,87	−0,46 ± 2,39	NS	−0,56 ± 2,36	NS	NS
Radio ultradistale	−0,29 ± 3,17	−0,48 ± 3,21	NS	0,22 ± 5,82	NS	NS
Intero corpo	−0,36 ± 2,72	0,40 ± 2,93	NS	0,51 ± 2,43	0,023	NS
Contenuto minerale osseo dell'intero corpo (g)	−0,45 ± 2,75	0,64 ± 3,65	0,021	0,87 ± 3,65	0,005	NS

NS=non significativo.

dello studio, la percentuale media di farmaco assunto in ciascun gruppo di trattamento è stata pari al 79%.

Ottantuno pazienti hanno abbandonato lo studio precocemente (17 nel gruppo placebo, 28 nel gruppo 20 μg e 36 nel gruppo 40 μg). Le interruzioni dello studio sono state dovute nella maggior parte dei casi alla comparsa di eventi avversi (36 pazienti) o in seguito a decisione del paziente (25 pazienti), e sono risultate più frequenti nei gruppi teriparatide. Altre cause di interruzione dello studio sono state: utilizzo di farmaci non consentiti, alterazioni clinicamente rilevanti dei valori di laboratorio, perdita di efficacia dovuta a progressione della malattia, mancata compliance, perdita al follow-up, trasferimenti del paziente, decisione del medico, mancato rispetto di un criterio di inclusione e morte.

BMD e BMC dell'intero corpo

Il trattamento giornaliero con teriparatide 20 μg e 40 μg ha incrementato in modo dose-dipendente la BMD del rachide lombare e del collo femorale (Tabella 2). Anche il BMC dell'intero corpo è aumentato in entrambi i gruppi teriparatide. La BMD del rachide lombare è risultata maggiore nei gruppi teriparatide rispetto al gruppo placebo a partire dal terzo mese (Figura 1). Circa il 40% dei pazienti nel gruppo placebo ha presentato una riduzione netta della BMD del rachide lombare alla fine dello studio, mentre la BMD del rachide lombare si è ridotta del 7,1% dei pazienti nel gruppo teriparatide 20 μg e del 6,2% nel gruppo teriparatide 40 μg. La BMD del rachide lombare è aumentata del 5% o più nel 55% dei pazienti del gruppo 20 μg e nel 71% del gruppo 40 μg, rispetto al 9,8% del gruppo placebo. Alla fine dello studio, la variazione percentuale della BMD dell'anca totale, intertrocanterica e dell'intero corpo osservata nel gruppo 40 μg è risultata maggiore di quella osservata nel gruppo placebo (Tabella 2). I valori della BMD a livello del radio distale e ultradistale non sono risultati differenti tra i gruppi teriparatide e placebo.

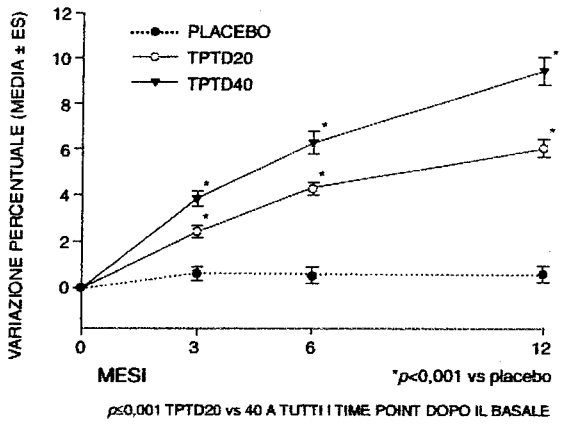


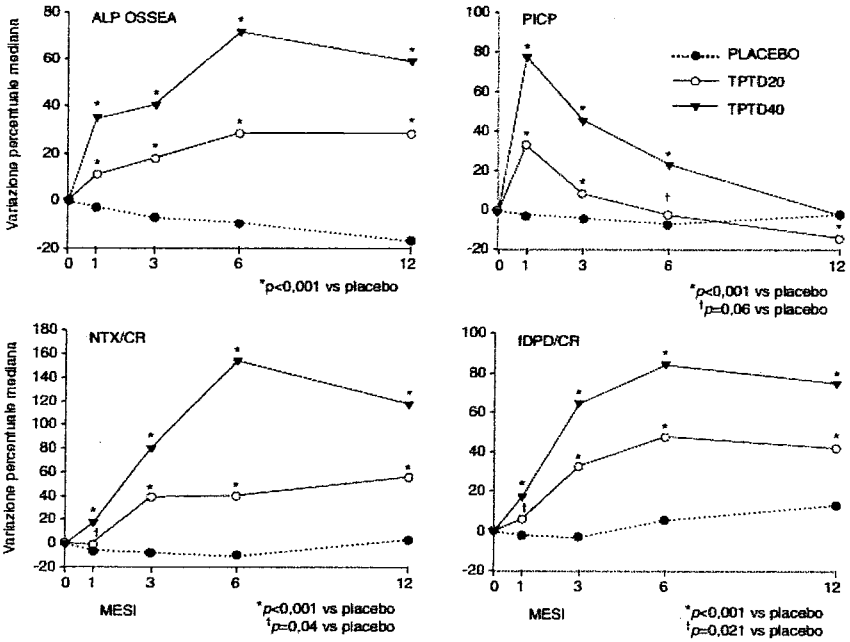
Figura 1. Variazione percentuale (media ± ES) della densità minerale ossea del rachide lombare dal basale alla fine dello studio per i casi osservati a 3, 6 e 12 mesi. TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg.

Marker biochimici di rimodellamento osseo

Il trattamento con teriparatide è risultato associato ad aumenti dose-dipendente degli indici biochimici di neoformazione (ALP ossea, PICP) e di riassorbimento (NTX, fDPD) ossei (Figura 2). I marker dell'attività osteoclastica sono aumentati dopo 1 anno di trattamento con teriparatide (p<0,001), mentre nel gruppo placebo si sono mantenuti stabili (PICP) o sono andati incontro ad una lieve riduzione (ALP ossea). Nei gruppi teriparatide, le concentrazioni della ALP ossea hanno raggiunto il valore massimo dopo 6-12 mesi di terapia e, a 12 mesi, sono risultate aumentate del 29% e del 59% rispetto al valore basale nei gruppi 20 μg e 40 μg, rispettivamente (p<0,001 per entrambi i confronti). I livelli sierici della PICP hanno raggiunto il picco dopo 1 mese di trattamento con teriparatide in entrambi i gruppi 20 μg e 40 μg (p<0,001), per poi ridursi progressivamente nei mesi successivi. I marker di riassorbimento osseo (NTX e fDPD) si sono mantenuti stabili nel gruppo placebo, mentre sono aumentati nei gruppi teriparatide. L'escrezione urinaria sia dell'NTX che della fDPD è risultata maggiore rispetto a quella osservata nel gruppo placebo a partire dal completamento del primo mese di trattamento e si è mantenuta elevata per tutto il corso dello studio.

Metabolismo minerale

Le concentrazioni medie di calcio nel siero, misurate 4-6 ore dopo l'iniezione di teriparatide, sono risultate più elevate nei gruppi teriparatide a tutti i time point (p<0,001 vs placebo; Figura 3). I livelli sierici di calcio sono risultati al di sopra del limite superiore del valore normale (>2,64 mM) nel 6,2% dei



p≤0,001 TPTD20 vs 40 (ALP OSSEA, PICP, NTX/CR, CTX); p<0,01 (FDPD) a tutti i time point dopo il basale

Figura 2. Variazioni percentuali mediane rispetto al basale dei marker biochimici di neoformazione ossea (in alto) e di riassorbimento osseo (in basso), dal basale alla fine dello studio per i casi osservati a 3, 6 e 12 mesi. ALP ossea, fosfatasi alcalina ossea; PICP, procollagene I carbossi-terminale; NTX/CR, rapporto N-telopeptide urinario/creatinina; fDPD/CR, rapporto desossipiridinolina libera/creatinina; TPTD20, teriparatide 20 µg; TPTD40, teriparatide 40 µg.

soggetti trattati con teriparatide 20 µg ($p = 0,003$ vs placebo) e nel 16,8% dei soggetti trattati con teriparatide 40 µg ($p < 0,001$ vs placebo). Quasi tutti questi episodi si sono verificati nelle prime 28 settimane dello studio (89% e 91% nei gruppi 20 µg e 40 µg, rispettivamente). Due pazienti nel gruppo 20 µg ed 8 pazienti nel gruppo 40 µg hanno presentato, in più di un'occasione, elevate concentrazioni sieriche di calcio post-dose. La supplementazione di calcio è stata ridotta in 4 pazienti nel gruppo 20 µg e in 12 pazienti nel gruppo 40 µg per la comparsa di aumento post-dose dei livelli sierici di calcio, di aumento dell'escrezione urinaria delle 24 ore del calcio, o di sintomi quali nausea o cefalea. La dose di teriparatide è stata ridotta da 40 a 20 µg in 7 pazienti. Tre pazienti (2%) nel gruppo 20 µg e sei pazienti (4%) nel gruppo 40 µg hanno abbandonato lo studio a causa dell'aumento dei livelli sierici di calcio dopo l'iniezione del farmaco.

Il trattamento ha determinato un aumento dell'escrezione urinaria media del calcio in tutti i gruppi (20-40 mg/die al di sopra del valore basale; Figura 3), ma l'aumento si è verificato quando si è cominciato a somministrare la supplementazione di calcio e vitamina D all'inizio dello studio e non è aumentata ulteriormente dopo l'inizio della terapia con teriparatide o placebo.

Non vi sono state differenze tra i gruppi di trattamento per quanto riguarda l'incidenza di alterata escrezione urinaria del calcio [>350 mg (8,8 mmol)/24 ore] o alterato rapporto urinario calcio/creatinina (>1,0 mmol calcio/mmol di creatinina).

Le concentrazioni di 1,25-$(OH)_2$D sono aumentate in entrambi i gruppi teriparatide rispetto al gruppo placebo (Figura 4). In entrambi i gruppi teriparatide, la 1,25-$(OH)_2$D ha raggiunto il picco dopo 1 mese ($p<0,001$ vs placebo per entrambi i gruppi teriparatide) e si è mantenuta elevata per tutta la durata dello studio. A partire dal dodicesimo mese, l'ormone paratiroideo intatto (1-84) sierico si è ridotto al di sotto del limite di quantificazione (16 pg/ml) nel 91,9%, nell'89,8% e nell'88,1% dei pazienti nei gruppi placebo, 20 µg e 40 µg, rispettivamente. Nel siero prelevato da 2 pazienti è stata identificata, nel corso di

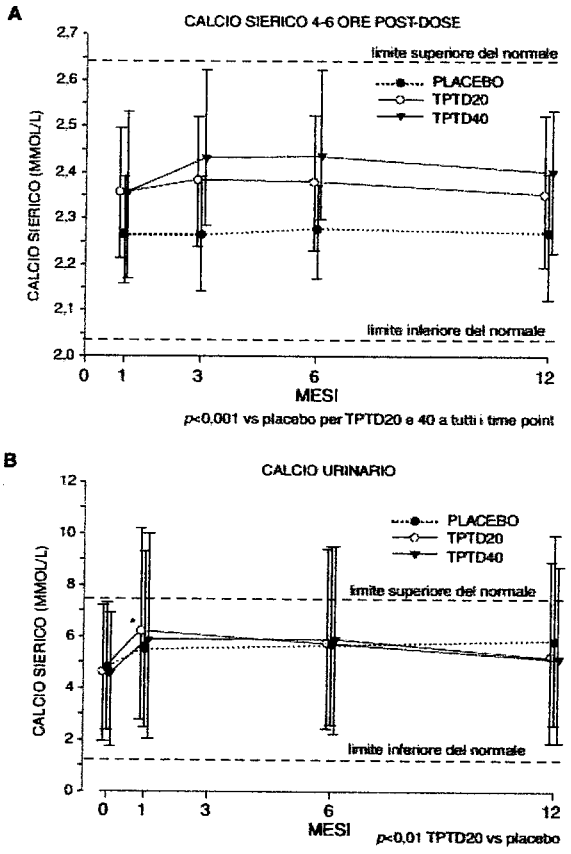


Figura 3. (A) Livelli sierici di calcio (media e 10° e 90° percentile) 4-6 dopo l'iniezione di teriparatide (post-dose) nel corso dello studio. (B) Escrezione urinaria del calcio durante lo studio. Poiché alcuni partecipanti non hanno completato i 12 mesi dello studio, il numero di soggetti inclusi nelle analisi al time point di 12 mesi rappresenta circa la metà di quelli che hanno completato lo studio. TPTD20, teriparatide 20 µg; TPTD40, teriparatide 40 µg.

nuto costante per tutto il periodo di trattamento. Questi risultati sono simili a quelli riportati da Kurland et al. (12), che hanno rilevato aumenti della BMD in uomini con osteoporosi idiopatica trattati con ormone paratiroideo (1-34). In questo studio, il decorso temporale e la magnitudine della variazione della BMD vertebrale sono stati simili a quelli osservati in uno studio sull'impiego del teriparatide nelle donne (10,14). Sebbene la durata della terapia in questo studio sia stata breve (mediana, 11 mesi), gli aumenti della BMD indotti dalla terapia con teriparatide sono risultati superiori a quelli osservati dopo un periodo di 1 anno negli uomini trattati con alendronato (9).

I rapidi aumenti, di tipo dose-dipendente, degli indici biochimici di turnover osseo, simili a quelli riportati in precedenza (12), sono compatibili con una modalità d'azione di tipo anabolico per il teriparatide. Gli aumenti indicano un'attivazione globale del rimodellamento, mentre il rapido e prolungato incremento della BMD durante il trattamento con teriparatide indica un equilibrio nel rimodellamento continuamente positivo in favore della neoformazione ossea. L'incremento precoce della BMD è suggestivo di una rapida stimolazione dell'attività osteoblastica da parte del teriparatide, che verosimilmente si verifica attraverso una stimolazione degli osteoblasti esistenti o un'attivazione di cellule di rivestimento (15). Questa risposta è alquanto differente da quella che si verifica in seguito a terapia antiriassorbitiva, durante la quale si verifica una soppressione dei marker di turnover osseo, che riflette un ridotto rimodellamento osseo (16). Il pattern di risposta della PICP sierica, che è risultato di breve durata e distinto da quello della ALP ossea sierica, supporta l'ipotesi secondo la quale non tutti i marker forniscono informazioni intercambiabili sulla funzione osteoblastica. Le ragioni in grado di spiegare questi pattern di risposta distinti non sono chiare, ma gli effetti del teriparatide sugli osteoblasti sono complessi e possono includere stimolazione di osteoblasti attivi, attivazione delle cellule di rivestimento, reclutamento e differenziazione di precursori osteoblastici, e riduzione dell'apoptosi osteoblastica (12).

I soggetti trattati con teriparatide hanno mostrato le variazioni attese dell'omeostasi minerale, inclusi piccoli aumenti del calcio sierico nelle 4-6 ore successive all'iniezione e aumento dei livelli della 1,25-$(OH)_2$D 1 mese dopo l'inizio della terapia, eventi che indicano un'azione indipendente del teriparatide sul metabolismo minerale. Dopo l'inizio della supplementazione di calcio e vitamina D, il calcio urinario è aumentato in tutti i gruppi, suggerendo che tale supplementazione ha influenzato in misura maggiore l'escrezione del calcio. Il PTH endogeno è stato soppresso al di sotto del limite di quantificazione, sia nel gruppo placebo che nei gruppi teriparatide. Anche Kurland et al. (12) hanno riscontrato che il PTH endogeno si è ridotto del 50% rispetto al basale a 6 mesi in un gruppo di uomini osteoporotici trattati con 400 UI di PTH (1-34) al giorno (equivalenti a circa 25 µg); inoltre tale valore è risultato più basso del 40% dopo 18 mesi di terapia (p=0,05 vs placebo). Tuttavia, Cosman et al. (17) hanno dimostrato che donne in postmenopausa trattate con teriparatide 400 UI al giorno per un periodo fino a 3 anni non hanno avuto alcuna perdita per quanto riguarda la risposta del PTH endogeno.

Circa la metà dei partecipanti ha presentato livelli sierici di testosterone libero al di sotto dei range di riferimento normali in base all'età. Ciononostante, gli aumenti della BMD e dei marker di turnover osseo in risposta al teriparatide sono risultati indipendenti dalle concentrazioni di testosterone ed estradiolo rilevate al basale. Questa osservazione è di notevole significato, dal momento che in alcuni studi *in vitro* e su modelli animali gli steroidi sessuali hanno influenzato la responsività delle cellule osteoblastiche all'ormone paratiroideo (18-20). Negli uomini con osteoporosi vengono frequentemente riscontrati bassi livelli di testosterone e di estrogeni (21), ma secondo quanto emerso da questo studio essi non costituiscono un fattore determinante nella risposta al teriparatide. Inoltre il consumo di alcol e l'invecchiamento, condizioni che sono state associate a riduzione della neoformazione ossea, non hanno ridotto né la stimolazione del rimodellamento osseo né l'aumento della BMD indotto dal teriparatide.

La durata prevista dello studio era di 24 mesi, ma il riscontro di osteosarcomi nei ratti trattati con teriparatide, nel corso di test standard di cancerogenicità, ha portato alla precoce interruzione della somministrazione del farmaco. L'esposizione totale al teriparatide è stata limitata ad una durata mediana di 11 mesi. Un'ampia review ha concluso che il riscontro nei ratti [esposti a dosi giornaliere di PTH(1-34) per la maggior parte della loro vita] non è predittivo di un aumento del rischio negli uomini trattati durante la vita adulta per periodi relativamente brevi (22). Nei primati non umani sottoposti ad ooforectomia bilaterale e trattati per 18 mesi con dosi di teriparatide da 4 a 10 volte superiori la dose massima per l'uomo, non sono stati osservati osteosarcomi. In diversi test standard (il test *in vitro* di mutagenesi batterica con e senza attivazione metabolica, il test del linfoma murino per la mutazione cellulare dei mammiferi, il test di aberrazione cromosomica su cellule ovariche del criceto cinese, e il test di micronucleo *in vivo* nei topi) il teriparatide non è risultato mutageno né genotossico. Non sono stati osservati osteosarcomi in uomini e donne esposti al farmaco nell'ambito di studi clinici per un periodo fino a 18 mesi e successivamente seguiti fino a 3 anni (circa 2500 pazienti) (10,23-26). Inoltre, studi epidemiologici pubblicati non hanno riportato alcun aumento dell'incidenza di osteosarcomi nei pazienti con iperparatiroidismo primario (27,28). Nel corso di un'indagine sullo Swedish Cancer Registry, i ricercatori non hanno riscontrato alcun aumento del rischio di tumori primari dell'osso in 12.644 uomini e donne con storia clinica di adenoma paratiroideo (22).

In generale, la terapia con teriparatide è risultata ben tollerata, in particolare nel gruppo di trattamento del dosaggio di 20 µg. Sebbene si sia verificata la comparsa di ipercalcemia nelle 4-6 ore successive l'iniezione in un piccolo numero di soggetti, tale aumento è stato transitorio, solitamente lieve, e di limitata rilevanza clinica. Nel gruppo di trattamento con dosaggio di 20 µg, l'aumento dei livelli sierici di calcio ha portato ad una riduzione della supplementazione del minerale in soli 4 pazienti (3%) e all'abbandono dello studio in 3 pazienti (2%). In nessuno dei pazienti trattati con la dose di 20 µg è stata necessaria una riduzione della dose di teriparatide. Altri eventi avversi si sono verificati con una frequenza simile nei gruppi placebo e 20 µg. La dose di teriparatide di 40 µg ha determinato variazioni della BMD maggiori rispetto a quella di 20 µg, ma al costo di una maggiore incidenza di eventi avversi. Nei gruppi di trattamento la nausea e la cefalea sono state più frequenti, e per tale ragione in questi gruppi è stata osservata la maggior parte delle interruzioni del trattamento a causa di eventi avversi. Anche l'ipercalcemia è stata più frequentemente riscontrata nei pazienti trattati con la dose di 40 µg e ha portato a riduzioni

21. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: A key role for bioavailable estrogen. J Clin Endocrinol Metab **83:** 2266–2274.
22. Tashjian AH, Chabner BA 2002 Clinical safety of recombinant human parathyroid hormone (1-34) in the treatment of osteoporosis in postmenopausal women and men. J Bone Miner Res **17:**1151–1161.
23. Ste-Marie L-G, Scheele WH, Jasque-Romano S, Schwartz SL, Clancy AD, Myers SL 2001 Bone mineral density changes during an 18 month observational period following discontinuation of recombinant human parathyroid hormone (1-34) treatment of postmenopausal women receiving hormone replacement therapy. Arthritis Rheum 44(Suppl): S257.
24. Kulkarni PM, Gaich GA, Scheele WH 2001 Lumbar spine bone mineral density response rates in a study of recombinant human parathyroid hormone (1-34) compared to alendronate sodium in postmenopausal women with osteoporosis. Arthritis Rheum 44(Suppl):S379.
25. Orwoll E, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A 2001 Brief therapy with recombinant human parathyroid hormone (1-34) increases lumbar spine bone mineral density in men with idiopathic or hypogonadal osteoporosis. J Bone Miner Res **16:**S1;S221.
26. Lindsay R, Scheele WH, Clancy AD, Mitlak B 2001 Incident vertebral fractures during an 18 month observation period following discontinuation of LY333334 [recombinant human parathyroid hormone (1-34), rhPTH (1-34)] use in postmenopausal women with osteoporosis. J Bone Miner Res **16:**S1;S163.
27. Palmer M, Adami HO, Krusemo UB, Ljunghall S 1988 Increased risk of malignant diseases after surgery for primary hyperparathyroidism. A nationwide cohort study. Am J Epidemiol **127:**1031– 1040.
28. Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, O'Fallon WM, Melton LJ III 1998 Survival after the diagnosis of hyperparathyroidism: A population-based study. Am J Med **104:** 115–122.

Address reprint requests to:
Eric Orwoll, MD
Bone and Mineral Research Unit
Oregon Health and Sciences University (CR113)
3181 Sam Jackson Park
Portland, OR 97201, USA

Received in original form February 25, 2002; in revised form July 16, 2002; accepted August 1, 2002.

ORIGINAL ARTICLE

Teriparatide or Alendronate in Glucocorticoid-Induced Osteoporosis

Kenneth G. Saag, M.D., Elizabeth Shane, M.D., Steven Boonen, M.D., Ph.D., Fernando Marín, M.D., David W. Donley, Ph.D., Kathleen A. Taylor, Ph.D., Gail P. Dalsky, Ph.D., and Robert Marcus, M.D.

ABSTRACT

BACKGROUND

Bisphosphonate therapy is the current standard of care for the prevention and treatment of glucocorticoid-induced osteoporosis. Studies of anabolic therapy in patients who are receiving long-term glucocorticoids and are at high risk for fracture are lacking.

METHODS

In an 18-month randomized, double-blind, controlled trial, we compared teriparatide with alendronate in 428 women and men with osteoporosis (ages, 22 to 89 years) who had received glucocorticoids for at least 3 months (prednisone equivalent, 5 mg daily or more). A total of 214 patients received 20 μg of teriparatide once daily, and 214 received 10 mg of alendronate once daily. The primary outcome was the change in bone mineral density at the lumbar spine. Secondary outcomes included changes in bone mineral density at the total hip and in markers of bone turnover, the time to changes in bone mineral density, the incidence of fractures, and safety.

RESULTS

At the last measurement, the mean (±SE) bone mineral density at the lumbar spine had increased more in the teriparatide group than in the alendronate group (7.2±0.7% vs. 3.4±0.7%, P<0.001). A significant difference between the groups was reached by 6 months (P<0.001). At 12 months, bone mineral density at the total hip had increased more in the teriparatide group. Fewer new vertebral fractures occurred in the teriparatide group than in the alendronate group (0.6% vs. 6.1%, P=0.004); the incidence of nonvertebral fractures was similar in the two groups (5.6% vs. 3.7%, P=0.36). Significantly more patients in the teriparatide group had at least one elevated measure of serum calcium.

CONCLUSIONS

Among patients with osteoporosis who were at high risk for fracture, bone mineral density increased more in patients receiving teriparatide than in those receiving alendronate. (ClinicalTrials.gov number, NCT00051558.)

From the University of Alabama at Birmingham, Birmingham (K.G.S.); College of Physicians and Surgeons, Columbia University, New York (E.S.); Katholieke Universiteit Leuven, Leuven, Belgium (S.B.); and Lilly Research Laboratories, Eli Lilly, Indianapolis (F.M., D.W.D., K.A.T., G.P.D., R.M.). Address reprint requests to Dr. Saag at the University of Alabama at Birmingham, FOT 820, 1530 Third Ave. S., Birmingham, AL 35294-3408, or at ksaag@uab.edu.

N Engl J Med 2007;357:2028-39.

SUBSTANTIAL PROGRESS HAS OCCURRED in the understanding of the pathogenesis and prevention of glucocorticoid-induced osteoporosis, the most common cause of secondary osteoporosis.[1-5] However, providing effective treatment remains a challenge.[6] International guidelines currently recommend bisphosphonates for patients who either already have or are at risk for glucocorticoid-induced osteoporosis.[7-17]

Once-daily recombinant human parathyroid hormone (1-34) (teriparatide) stimulates bone formation, increases bone mass, and reduces the risk of vertebral and nonvertebral fractures.[18,19] Teriparatide may be a rational treatment for glucocorticoid-induced osteoporosis because it directly stimulates osteoblastogenesis and inhibits osteoblast apoptosis, thereby counteracting two key mechanisms through which glucocorticoid therapy promotes bone loss.[20,21] Patients with large deficits in bone mineral density are at high risk for fracture and might preferentially benefit from such anabolic therapy.[21] In a study of postmenopausal women with glucocorticoid-induced osteoporosis, treatment with synthetic teriparatide and estrogen significantly increased bone mineral density at the lumbar spine, as compared with estrogen alone.[22] However, no randomized, controlled trials involving patients with glucocorticoid-induced osteoporosis have compared teriparatide with a bisphosphonate. We report the results of the first 18 months of a 36-month prospective trial designed to directly compare the effects of recombinant teriparatide with those of alendronate for the treatment of patients with osteoporosis who have had long-term exposure to glucocorticoids and are at high risk for fracture.

METHODS

STUDY DESIGN AND PATIENTS

In this randomized, double-blind clinical trial, the primary outcome was the change from baseline to 18 months in bone mineral density at the lumbar spine associated with the administration of daily teriparatide (at a dose of 20 μg), as compared with that of daily alendronate (at a dose of 10 mg), in patients with established glucocorticoid-induced osteoporosis. Prespecified secondary outcomes included changes in bone mineral density at the total hip and markers of bone turnover, the time to changes in bone mineral density at the lumbar spine and total hip, the incidence of vertebral and nonvertebral fractures, and adverse events. We report on the results of the first 18 months of the study (primary phase); the 18-month extension phase is in progress.

The protocol committee included academic investigators and physicians employed by Lilly Research Laboratories. Study data were collected by investigators and transmitted to the sponsor, which performed the analyses. All authors participated in the interpretation of the data and the decision to publish the findings, had unrestricted access to the data, were not limited by the sponsor with regard to statements made, and vouch for the veracity and completeness of the data. The first draft of the manuscript was written jointly by Drs. Saag and Marcus.

Ambulatory patients were eligible for enrollment if they met the following criteria: an age of 21 years or more, a history of sustained glucocorticoid therapy, and a T score (the number of standard deviations above or below the mean value in normal adults) for bone mineral density at the lumbar spine or total hip of either −2.0 or less or −1.0 or less in addition to at least one fragility fracture during treatment with glucocorticoids. Sustained glucocorticoid therapy was defined as a mean daily dose of 5 mg or more of prednisone or its equivalent for 3 or more consecutive months immediately preceding the screening visit. Such exposure constitutes a reasonable threshold for long-term use on the basis of international guidelines.[2,11-14,16,17] A fragility fracture was defined as a fracture associated with trauma equivalent to a fall from standing height or less. Men and women were enrolled in North America and South America, but only women were enrolled in Europe.

Patients were excluded if they had fewer than three lumbar vertebrae that could be evaluated on dual energy x-ray absorptiometry, abnormal laboratory values, unresolved skeletal diseases other than glucocorticoid-induced osteoporosis, a history of cancer within 5 years before screening (with the exception of superficial basal-cell or squamous-cell carcinomas of the skin that had been definitively treated), an increased risk of osteosarcoma, gastrointestinal disorders that would be likely to reduce tolerance of oral alendronate, or substantial renal impairment (on the basis of the Cockcroft–Gault formula). Patients were required to have normal thyroid function or to be taking a stable dose of thyroid hormone, with normal levels of thyrotropin. Patients were excluded if they had

received a bisphosphonate for more than 2 weeks within 6 months before enrollment or for more than 2 years within the previous 3 years and for nontrivial exposure to other osteoporosis therapies. The institutional review board at each study site approved the study protocol, and all patients provided written informed consent.

Patients were randomly assigned to receive either injectable teriparatide (Forteo, Eli Lilly) at a daily dose of 20 μg plus an oral placebo or oral alendronate (Fosamax, Merck) at a daily dose of 10 mg plus an injectable placebo. Teriparatide or its placebo was administered by subcutaneous injection by means of a prefilled pen. Alendronate tablets and placebo tablets were overencapsulated to look similar. Patients received the first dose of a study drug at the clinical site. They also received supplementation with calcium carbonate (at a dose of 1000 mg of elemental calcium) and vitamin D (at a dose of 800 IU) to be taken daily throughout the trial. Follow-up evaluations were scheduled at 1, 3, 6, 12, and 18 months. Compliance with the study-drug regimen was assessed by interviewing the patients at each visit and by quantifying the oral and injectable medications that were returned to investigators. The first patient was assigned to receive therapy in December 2002, and the last patient completed the 18-month study period in July 2006.

BONE MINERAL DENSITY

Areal bone mineral density (in grams per square centimeter) of the lumbar spine and total hip was assessed by dual energy x-ray absorptiometry with the use of either Hologic (Hologic) or GE-Lunar (GE Medical Systems) densitometers. Quality assurance, cross-calibration adjustment, and data processing were done centrally by Bio-Imaging Technologies. Scan results were withheld from local investigators unless a patient reached a prespecified safety value of a loss of more than 8% of bone. Lumbar vertebrae that were fractured during the trial were excluded from the calculation of bone mineral density.

FRACTURE

Radiographs of the thoracolumbar spine were obtained at entry, at 18 months or at early discontinuation, and at unscheduled times if there were new or worsening symptoms suggestive of clinical vertebral fracture. Radiographs were assessed in a blinded fashion by an independent reader at Bio-Imaging Technologies for new vertebral fractures. Worsening of a preexisting deformity was not considered a new fracture. Vertebrae were graded individually for compression deformity with the use of semiquantitative criteria.[23,24] Central adjudication of incident nonvertebral fractures was performed through direct examination of radiographs or evaluation of a radiologist's report.

MARKERS OF BONE REMODELING

Markers of bone formation (intact N-terminal propeptide of type I collagen, bone-specific alkaline phosphatase, and C-terminal propeptide of type I collagen) and bone resorption (C-telopeptide of type I collagen) were measured in serum obtained after an overnight fast in a subgroup of 199 patients at 1, 6, and 18 months. Frozen serum samples were shipped to a central laboratory for analysis (Covance Central Laboratory) and run in batches.

ADVERSE EVENTS

Data on adverse events occurring or worsening after administration of the first dose of a study drug were collected throughout the study. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 9.1. In addition to adverse event reports of hypercalcemia and hyperuricemia, we examined total serum calcium concentrations of more than 10.5 mg per deciliter (2.62 mmol per liter) in a sample obtained more than 16 hours after the administration of a study drug; sustained elevated total serum calcium was defined as at least two elevated values at separate study visits. Elevated serum urate was defined as a concentration of more than 9.0 mg per deciliter (535 μmol per liter).

STATISTICAL ANALYSIS

The study had a power of 90% to detect a between-treatment difference of 0.015 g per square centimeter (approximately 2%) in the absolute change in bone mineral density at the lumbar spine from baseline to the last measurement during the first 18 months of therapy, assuming a standard deviation of 0.04 and with the use of a two-sided t-test with an alpha level of 0.05.

Block randomization that was stratified according to sex, investigative site, and previous use of bisphosphonates was used to assign patients to the two study groups in a ratio of approximately 1:1. Analyses were conducted on data from patients who underwent randomization and who received at least one dose of the assigned study drug be-

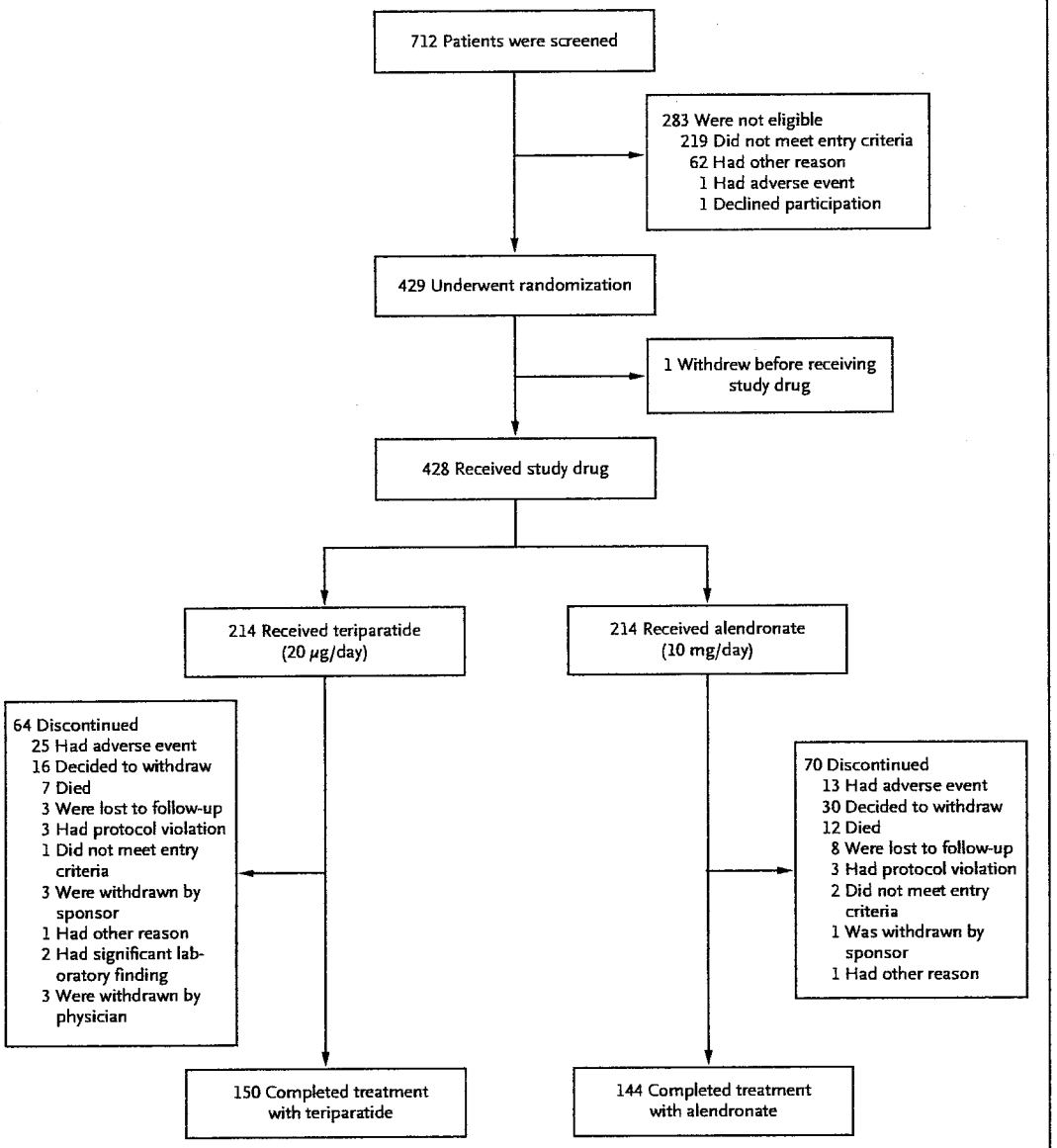


Figure 1. Enrollment and Outcomes.

The four patients who were withdrawn by the sponsor either received less than 50% of a study drug in two consecutive visits or had a decrease of more than 8% in bone mineral density at the lumbar spine or total hip.

tween baseline and completion of the study at 18 months or early discontinuation. For the primary outcome, the change from baseline to the last measurement of bone mineral density at the lumbar spine was examined. Models for continuous variables included fixed effects for the stratification terms and treatment. Analysis of variance was used for continuous variables except for markers of bone turnover, which required nonparametric methods. Categorical variables were compared between study groups with the use of a Cochran–Mantel–Haenszel test stratified according to geographic region or Fisher's exact test.

The effects of treatment on the absolute change in bone mineral density from baseline to 3, 6, 12, and 18 months were assessed with mixed-model repeated measures. Covariates included in the models were the treatment assignment, stratification variables, bone mineral density at the lumbar spine at baseline, time of the visit, and interaction

Table 1. Baseline Characteristics of the Patients.*

Variable	Alendronate (N=214)	Teriparatide (N=214)
Age — yr	57.3±14.0	56.1±13.4
White race — no. (%)†	148 (69.2)	153 (71.5)
Female sex — no. (%)	173 (80.8)	172 (80.4)
Postmenopausal women	143 (82.7)	134 (77.9)
Previous drug therapy — no. (%)		
Bisphosphonate	20 (9.3)	20 (9.3)
Glucocorticoid		
Prednisone equivalent daily dose — mg		
Median	7.8	7.5
Interquartile range	5.0–10.0	5.0–10.0
Duration of therapy — yr‡		
Median	1.2	1.5
Interquartile range	0.3–5.7	0.3–5.2
Previous fracture — no. (%)		
Radiographically confirmed vertebral§	53 (25.4)	62 (30.0)
Any nonvertebral	89 (41.6)	93 (43.5)
Nonvertebral fragility	43 (20.1)	42 (19.6)
Bone mineral density		
Lumbar spine		
Measurement — g/cm²	0.85±0.13	0.85±0.13
T score	−2.6±0.89	−2.5±0.88
Total hip		
Measurement — g/cm²	0.76±0.12	0.74±0.11
T score	−1.9±0.91	−2.0±0.88
Markers of bone remodeling		
No. of patients evaluated	100	99
N-terminal propeptide of type I collagen — μg/liter		
Median	38.8	40.2
Interquartile range	28.6–50.8	28.8–56.8
C-terminal propeptide of type I collagen — μg/liter		
Median	139.5	147.5
Interquartile range	110.5–176.5	122.0–183.0
Bone-specific alkaline phosphatase — μg/liter		
Median	8.8	9.0
Interquartile range	6.8–11.7	6.1–11.4
C-telopeptide of type I collagen — pmol/liter		
Median	3331	3265
Interquartile range	2388–5366	2070–4723

Table 1. (Continued.)

Variable	Alendronate (N=214)	Teriparatide (N=214)
Underlying glucocorticoid-requiring disorders — no. (%)		
Rheumatologic disorders	161 (75.2)	161 (75.2)
Rheumatoid arthritis	111 (51.9)	98 (45.8)
Systemic lupus erythematosus	21 (9.8)	28 (13.1)
Polymyalgia rheumatica	8 (3.7)	10 (4.7)
Vasculitis	3 (1.4)	5 (2.3)
Other rheumatic disorders	18 (8.4)	20 (9.3)
Respiratory disorders	31 (14.5)	29 (13.6)
Inflammatory bowel disease	4 (1.9)	3 (1.4)
Other conditions	18 (8.4)	21 (9.8)

* Plus–minus values are means ±SD. There were no significant differences between the two study groups. The T score is the number of standard deviations below the mean value for bone mineral density in young adults.
† Race was determined by the investigators.
‡ The duration of glucocorticoid therapy was derived on the basis of the time that the patient received the current dose at screening and may thus underestimate the cumulative duration.
§ Values could be determined only for 209 patients in the alendronate group and 207 patients in the teriparatide group who underwent radiography at baseline.

between the visit and treatment. These models were used to analyze percent changes. A predefined gatekeeping strategy controlled the overall type 1 error at an alpha level of 0.05 for testing of the primary objective and, subsequently, for determining the earliest time at which the increase in bone mineral density at the lumbar spine differed significantly between the study groups.[25] Testing of the remaining secondary outcomes was not adjusted for multiple comparisons, and no interim analyses were conducted. All tests were two-sided, and analyses were performed with the use of SAS statistical software, version 8 (SAS Institute).

RESULTS

PATIENTS

A total of 712 patients (564 women and 148 men) were screened in 12 countries. Of these patients, 429 underwent randomization and 428 began treatment (345 women and 83 men) (Fig. 1). A total of 134 patients discontinued the study prematurely, 70 in the alendronate group (32.7%) and 64 in the teriparatide group (29.9%) (P=0.54). Of these patients, 30 in the alendronate group (14.0%) and 16 in the teriparatide group (7.5%) discontinued participation in the study at their own request (P=0.03); 13 patients in the alendronate group (6.1%) and 25 in the teriparatide group (11.7%) discontinued because of an adverse event (P=0.04). There were no significant differences between the alendronate group and the teriparatide group with respect to the rate of adherence to treatment (93.2% and 94.3%, respectively, for oral administration and 97.6% and 98.7%, respectively, for injection).

There were no significant differences between study groups in baseline characteristics (Table 1). In both study groups combined, 115 patients (26.9%) had radiologic evidence of previous vertebral fractures and 182 patients (42.5%) had radiologic evidence of previous nonvertebral fractures.

BONE MINERAL DENSITY

Similar patterns of response to the treatments were observed in analyses of absolute and relative changes in bone mineral density; only relative changes are presented here. (For absolute changes, see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

Lumbar Spine

Patients in the teriparatide group had an increase in the baseline value for bone mineral density at the lumbar spine that was significantly greater than the increase in the alendronate group (Fig. 2A). At the last measurement, patients in the teripara-

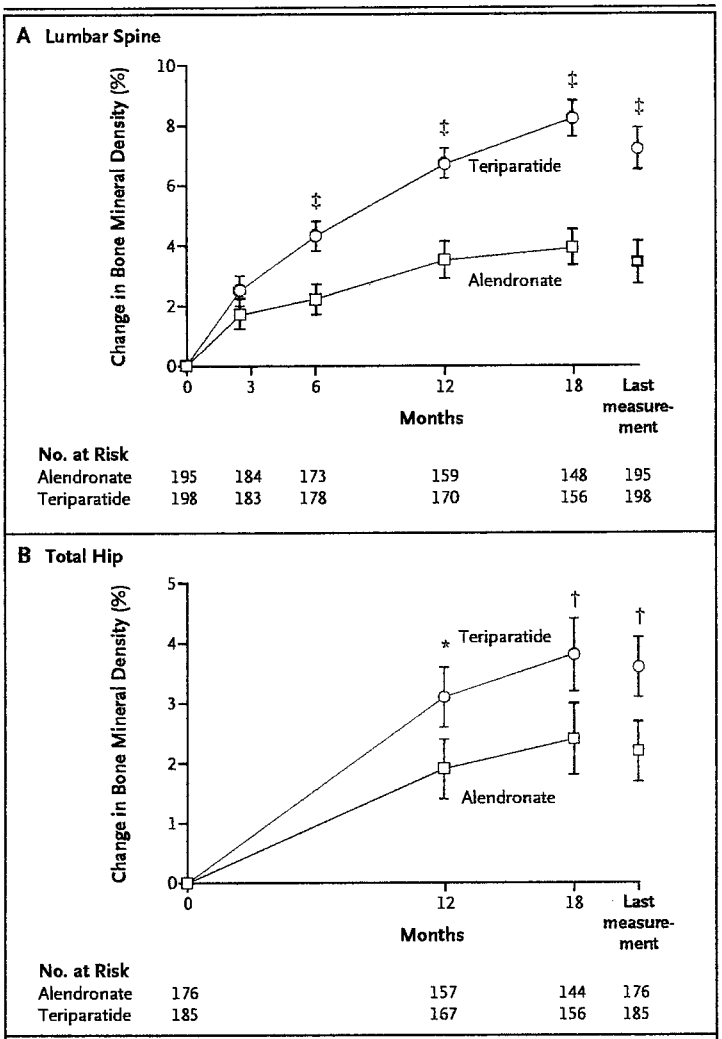


Figure 2. Percent Change in Mean Bone Mineral Density at the Lumbar Spine and Total Hip from Baseline to 18 Months or the Last Measurement.

The asterisk denotes P<0.05, the single dagger P<0.01, and the double dagger P<0.001 for between-group comparisons. Within-group changes from baseline at the lumbar spine (Panel A) and total hip (Panel B) were significant at all time points (P<0.001). The I bars represent standard errors.

tide group had an increase in mean (±SE) bone mineral density at the lumbar spine from baseline that was significantly greater than that of patients in the alendronate group (7.2±0.7% vs. 3.4±0.7%, P<0.001).

Total Hip

Changes from baseline in bone mineral density at the total hip differed significantly between the study groups by 12 months (P=0.01), when the first post-baseline measurement was performed (Fig. 2B). At 18 months, the change from baseline was 3.8±0.6% in the teriparatide group and 2.4±0.6% in the alendronate group, with a between-group difference of 1.4 percentage points (95% confidence interval [CI], 0.4 to 2.4; P=0.005).

MARKERS OF BONE TURNOVER

In the teriparatide group, N-terminal propeptide of type I collagen, a marker of bone formation, and C-telopeptide of type I collagen, a marker of resorption, were increased at 1 month and peaked at 6 months (an increase of 69.8% and 44.8% from baseline, respectively). In the alendronate group, these markers decreased at 1 month and remained suppressed at 18 months (Fig. 3). Levels of C-terminal propeptide of type I collagen and bone-specific alkaline phosphatase significantly increased in the teriparatide group and decreased in the alendronate group (data not shown).

FRACTURES

Eleven patients in the two study groups combined had radiographic evidence of a new vertebral fracture (Table 2). The 10 fractures in the alendronate group involved a mild deformity in four patients, a moderate deformity in two patients, and a severe deformity in four patients; the single fracture in the teriparatide group involved a moderate deformity. On the basis of semiquantitative grading, there was no progression of preexisting vertebral fractures. The number of patients with new nonvertebral fractures did not differ significantly between groups (Table 2).

ADVERSE EVENTS

Safety profiles in the two study groups were similar, with no significant differences in the overall incidence of adverse events, the incidence of serious adverse events, or the incidence of events either leading to withdrawal from the study or considered to be possibly related to a study drug (Table 2). Nineteen subjects died during the study (12 in the alendronate group and 7 in the teriparatide group); 1 patient in the teriparatide group died the day after being withdrawn from the study because of an adverse event. Causes of death included coronary heart disease, congestive heart failure, and systemic infection. Investigators attributed more adverse events to injections in the teriparatide group, including injection-site reactions, headache, and dizziness.

There were some significant differences in specific adverse events between the groups. More pa-

tients in the teriparatide group reported having nausea, insomnia, pharyngitis, and viral infection; more patients in the alendronate group reported having rash, a decrease in weight, sciatica, and asthma. In the teriparatide group, hyperuricemia was reported as an adverse event for three patients, and gout was reported as an adverse event for one patient; no adverse events of hyperuricemia or gout were reported in the alendronate group. More patients in the teriparatide group had a serum urate value of more than 9.0 mg per deciliter (Table 2).

Within-group changes in the serum calcium concentration, as measured before the administration of a study drug, were significant at 1 and 6 months in the alendronate group, with reductions of 0.2 mg per deciliter (0.06 mmol per liter) at 1 month ($P<0.001$) and of 0.1 mg per deciliter (0.03 mmol per liter) at 6 months ($P=0.01$); at 18 months, an increase of 0.1 mg per deciliter (0.03 mmol per liter) was significant in the teriparatide group ($P=0.03$). In the teriparatide group, hypercalcemia was reported as an adverse event for one patient, and no adverse events of hypercalcemia were reported in the alendronate group. A significantly higher proportion of patients in the teriparatide group had at least one serum calcium value of more than 10.5 mg per deciliter (2.62 mmol per liter) before drug administration, but the difference in proportions between the study groups was not significant for sustained elevations (Table 2). There was no significant difference between the study groups in the proportion of patients with a calcium level of more than 11.0 mg per deciliter (2.76 mmol per liter). No patient in either group had a sustained calcium level of 11.0 mg per deciliter or more (data not shown).

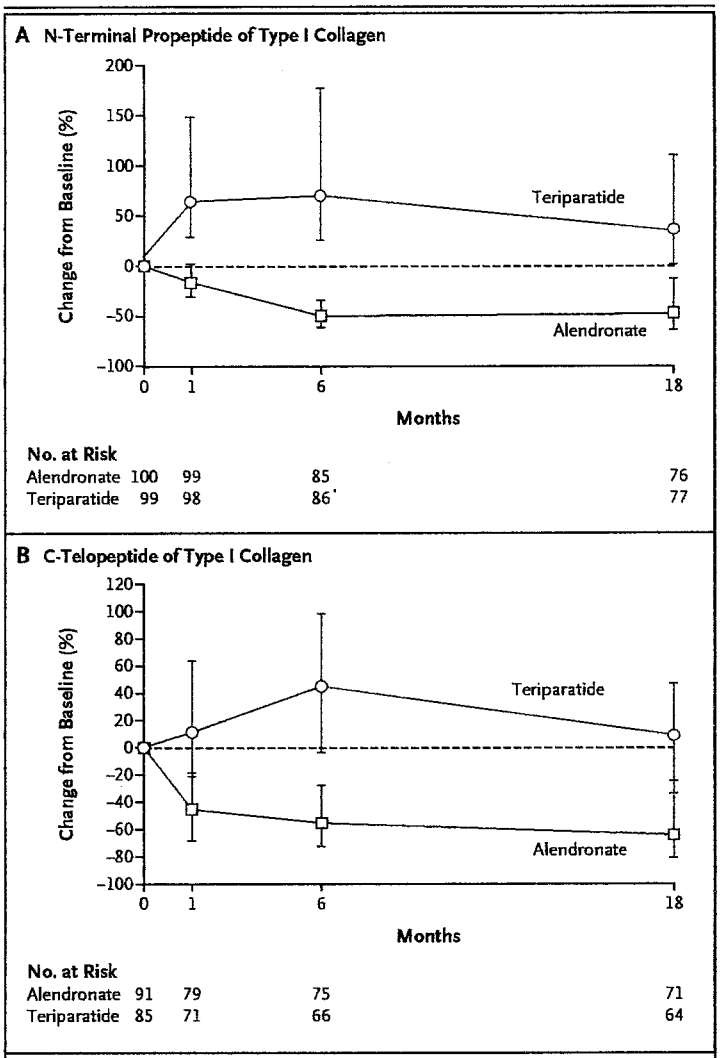


Figure 3. Percent Change in Markers of Bone Formation and Resorption.

Shown are median changes in levels of serum N-terminal propeptide of type I collagen, a marker of bone formation (Panel A), and C-telopeptide of type I collagen, a marker of bone resorption (Panel B). $P<0.001$ for all comparisons between study groups at 1, 6, and 18 months. Within-group changes from baseline for N-terminal propeptide of type I collagen were significant ($P<0.001$) at each time point in both the alendronate and teriparatide groups. Within-group changes from baseline for C-telopeptide of type I collagen were significant ($P<0.001$) for alendronate at each time point; for teriparatide, changes were significant at months 1 and 6 ($P<0.001$). The I bars represent interquartile ranges.

DISCUSSION

In this active-comparator trial, the anabolic agent teriparatide appeared to show significant skeletal benefits in patients with glucocorticoid-induced osteoporosis, as compared with the bisphosphonate alendronate. At 18 months, teriparatide treatment was significantly less likely to be associated with radiographic evidence of new vertebral fractures.

Bisphosphonates are the current standard of care for glucocorticoid-induced osteoporosis.[11-17,26,27] In a recent trial comparing a bisphosphonate with teriparatide in postmenopausal women with osteoporosis, teriparatide therapy was associated with increased areal and volumetric bone mineral density and estimates of bone strength at the lumbar spine, as compared with alendronate.[28,29] Although the time course of changes in markers of bone turnover in our trial resembled that

Table 2. Summary of New Fractures and Clinically Relevant Adverse Events.

Variable	Alendronate (N=214)	Teriparatide (N=214)	P Value
Fractures			
Vertebral — no./total no. (%)*			
Radiographic evidence	10/165 (6.1)	1/171 (0.6)	0.004
Clinical evidence†	3/165 (1.8)	0	0.07
Nonvertebral — no. (%)‡			
Any	8 (3.7)	12 (5.6)	0.36
Nonvertebral fragility	3 (1.4)	5 (2.3)	0.46
Adverse events§			
Adverse event — no. (%)			
Any	170 (79.4)	182 (85.0)	0.11
Possibly related to treatment¶	28 (13.1)	38 (17.8)	0.19
Serious adverse event — no. (%)			
Any	39 (18.2)	45 (21.0)	0.44
Possibly related to treatment¶	2 (0.9)	3 (1.4)	0.66
Event related to injection — no. (%)	14 (6.5)	24 (11.2)	0.09
Gastrointestinal event — no. (%)	70 (32.7)	84 (39.3)	0.15
Nausea	15 (7.0)	30 (14.0)	0.02
Upper abdominal pain	13 (6.1)	11 (5.1)	0.67
Dyspepsia	15 (7.0)	7 (3.3)	0.07
Abdominal pain	9 (4.2)	9 (4.2)	0.96
Gastritis	6 (2.8)	14 (6.5)	0.06
Gastroesophageal reflux disease	6 (2.8)	5 (2.3)	0.81
Dysphagia	3 (1.4)	5 (2.3)	0.44
Musculoskeletal event — no. (%)	77 (36.0)	75 (35.0)	0.89
Back pain	22 (10.3)	18 (8.4)	0.53
Arthralgia	16 (7.5)	17 (7.9)	0.81
Muscle spasm	7 (3.3)	8 (3.7)	0.77
Pain in a limb	7 (3.3)	8 (3.7)	0.75
Musculoskeletal pain	3 (1.4)	6 (2.8)	0.29
Myalgia	5 (2.3)	3 (1.4)	0.49

observed in postmenopausal women, the magnitude of gains in bone mineral density in the teriparatide group was less than that seen previously.[18,28] This differential response may reflect the characteristic ability of glucocorticoids to inhibit osteoblast and osteocyte function profoundly by several mechanisms, including the stimulation of apoptosis.[30]

In our study, patients in the teriparatide group had fewer new vertebral fractures than did patients in the alendronate group, although the overall number of fractures was small. Bisphosphonates have been associated with a reduced incidence of vertebral fractures in this patient population in randomized trials of alendronate,[31,32] in pooled studies of risedronate,[33] and in a nonrandomized, open-label study of ibandronate.[34] Although there were more nonvertebral fractures in the teriparatide group than in the alendronate group in our study, the difference was not significant. In previous studies of teriparatide, there was a reduction in nonvertebral fractures in postmenopausal women with osteoporosis.[18,35]

The strengths of our study included the ran-

Table 2. (Continued.)

Variable	Alendronate (N=214)	Teriparatide (N=214)	P Value
Nervous system event — no. (%)	38 (17.8)	44 (20.6)	0.43
Dizziness	12 (5.6)	15 (7.0)	0.53
Headache	12 (5.6)	16 (7.5)	0.47
Other — no. (%)			
Rash	10 (4.7)	3 (1.4)	0.05
Insomnia	2 (0.9)	11 (5.1)	0.01
Hypercalcemia — no./total no. (%)‖			
At least one serum calcium level >10.5 mg/dl	12/209 (5.7)	38/211 (18.0)	<0.001
Two or more serum calcium levels >10.5 mg/dl	4/196 (2.0)	10/195 (5.1)	0.10
At least one serum calcium level ≥11.0 mg/dl	2/209 (1.0)	8/211 (3.8)	0.06
At least one serum urate level >9.0 mg/dl — no./total no. (%)‖	10/208 (4.8)	17/212 (8.0)	0.18

* Vertebral fractures were defined as deformities in vertebrae that had been seen as normal (grade 0) on baseline radiographs. These deformities included a reduction in anterior, middle, or posterior vertebral height on post-baseline radiographs. Fractures were defined as mild (grade 1, a 20 to 25% reduction), moderate (grade 2, a >25 to 40% reduction), or severe (grade 3, a >40% reduction). Baseline spinal radiographs could not be evaluated for 5 patients in the alendronate group and 7 in the teriparatide group; post-baseline spinal radiographs could not be evaluated for 44 patients in the alendronate group and 36 patients in the teriparatide group.

† Clinical vertebral fractures were recorded when a patient reported having suggestive symptoms; radiographic evidence of a new fracture was validated at the central reading facility. Clinical vertebral fractures are a subgroup of vertebral fractures as seen on radiography.

‡ Nonvertebral fractures were recorded separately from adverse events, unless the fracture met one of the criteria for a serious adverse event. One patient in the alendronate group (whose data are not listed in the table) reported a hip fracture only as an adverse event.

§ Comparisons between the two groups were calculated with the use of a region-stratified Cochran–Mantel–Haenszel test.

¶ The local investigator determined whether the event was related to therapy.

‖ Values refer to patients' laboratory data and not to reports of clinical adverse events. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for urate to micromoles per liter, multiply by 59.48.

domized study design, large sample, and representation of various underlying disorders requiring long-term glucocorticoid therapy.[36,37] However, there were certain limitations. The severity of underlying illnesses contributed to a high discontinuation rate (31.3%), with a resultant rate of radiographic assessment of approximately 80%. The alendronate group used an overencapsulated study drug; nevertheless, the response in bone mineral density was similar to that in previous studies of alendronate.[28,35,38,39] These results suggest that the alendronate used in our study had the expected pharmacodynamics. Although weekly administration of bisphosphonates is now the most commonly used regimen, the fracture rates associated with bisphosphonate therapy were obtained with daily therapy in the previously cited studies. Thus, the daily alendronate used in our study was representative of previous fracture studies. Although our fracture finding was a unique outcome for a randomized study involving patients with glucocorticoid-induced osteoporosis, the study was not statistically powered to assess a reduction in the risk of vertebral fracture and was further limited because paired radiographs (baseline and post-baseline) for the assessment of new vertebral fractures were missing for 92 patients. Finally, we would not have detected transient hypercalcemia after the administration of a study drug, as described in the Fracture Prevention Trial.[18]

The standard of care for patients at risk for glucocorticoid-associated bone loss and osteoporosis includes a choice of antiresorptive agents. However, for patients with established osteoporosis who are at high risk for fracture, more aggressive and expensive therapy may be warranted. Patients in our trial had lower bone mineral density and more prevalent fractures than those in previous trials involving patients with glucocorticoid-induced osteoporosis, which suggests

an even greater need for an efficacious intervention.[7-10,26,31,33]

In our study, teriparatide was associated with greater increases in bone mineral density at the spine and hip and with significantly fewer new vertebral fractures, with no significant differences between groups in the incidence of nonvertebral fractures or serious adverse events. The occurrence of sporadic hypercalcemia was more frequent in the teriparatide group than in the alendronate group. On the basis of the known pathophysiology of glucocorticoid-induced osteoporosis, teriparatide might be considered as a therapeutic strategy for patients at high risk for fracture.

Supported by Eli Lilly.

Dr. Saag reports receiving research grants from Eli Lilly, Merck, Aventis, Amgen, Novartis, Roche, and GlaxoSmithKline, consulting fees from Eli Lilly, Merck, Novartis, Roche, and Amgen, and lecture fees from Novartis and Merck; Dr. Shane, research grants from Novartis, Aventis, Procter & Gamble, and Amgen; Dr. Boonen, research grants from Amgen, Eli Lilly, Novartis, Pfizer, Procter & Gamble, Sanofi-Aventis, and Roche–GlaxoSmithKline, consulting fees from Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, Sanofi-Aventis, and Servier, and lecture fees from Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, Sanofi-Aventis, and Servier; and Drs. Marín, Donley, Taylor, Dalsky, and Marcus, being full-time employees of Eli Lilly and having equity ownership in the company. No other potential conflict of interest relevant to this article was reported.

We thank Javier San Martin, M.D., and Pandurang Kulkarni, Ph.D., for their contributions to the study design, and Mary Ellen Perron and Melinda Rance for their technical assistance.

APPENDIX

In addition to the authors, the following investigators participated in the study: **Argentina:** *Instituto de Investigaciones Metabólicas, Buenos Aires* — J.R. Zanchetta; *Organización Médica de Investigación, Buenos Aires* — G. Tate; *Hospital Ramos Mejía, Buenos Aires* — E. Kerzberg. **Austria:** *Medical University of Graz, Graz* — H. Dobnig; *Wilhelminenspital der Stadt Wien, Vienna* — A. Dunky. **Belgium:** *Cliniques Universitaires St. Luc, Brussels* — J.-P. Devogelaer; *Universitair Ziekenhuis Gent, Ghent* — J.-M. Kaufman. **Brazil:** *Hospital General de Goiania, S. Reumatología, Goias* — A.C. Ximenes; *Complexo Hospitalario Heliopolis, São Paulo* — C.A. Zerbini; *Hospital Agamenon Magalhães, Recife* — F. Bandeira; *Hospital Universitario Pedro Hernesto, Río de Janeiro* — G.R.C. Pinheiro; *Instituto de Pesquisa Clínica e Assistancia Medica, Campiñas, São Paulo* — J.F.M. Neto; *Instituto de Pesquisa Clínica e Medicina Avancada, São Paulo* — M.L. Castro; *Hospital das Clínicas de São Paulo, S. Reumatología, São Paulo* — R.M.R. Pereira; *Hospital de Clínicas de Curitaba, Curitaba* — S.C. Radominski; *Escola Paulista de Medicina, São Paulo* — V. Szejnfeld; *Hospital de Servidor Publico Estadual, São Paulo* — W. Chahade. **Colombia:** *Instituto de Reumatología, Bogotá* — M. Chalem; *Clínica Cayre, Bogotá* — N. Casas; *Unidad Médica Torre Plaza, Medellín* — J.F. Molina. **Denmark:** *Hvidovre Hospital, Endokrinologisk Afd., Hvidovre* — J.-E.B. Jensen; *Aarhus Amtssygehus, Osteoporoseklinikken, Aarhus* — B. Langdahl. **Finland:** *Laakariasema Pulssi, Turku* — T.T. Möttönen; *Heinolan Reumasairaala, Heinola* — M.J. Kauppi. **Germany:** *Orthopädie an der Rennbahn, Frankfurt* — T. Hennigs; *Clinical Research Laboratory, Magdeburg* — R. Möricke; *Charite Campus Benjamin Franklin, Berlin* — D. Felsenberg; *Klinikum der Friedrich Schiller Universität Jena, Jena* — G. Hein. **Mexico:** *Instituto Nacional de la Nutrición, México City* — R. Correa; *Médica Monraz, Guadalajara* — P. de La Peña; *private practice, Guadalajara* — J. Orozco. **Norway:** *Revmatisme Sykehuset Innlandet, Lillehammer* — H. Nygaard. **Puerto Rico:** *Ponce Medical School, Ponce* — E. Barranco; *Radames Sierra Zorita, San Juan* — R. Sierra-Zorita; *private practice, Bayamón* — Y. López. **United States:** *Radiant Research, Dallas* — S.B. Cohen; *Medical Consultants, Muncie, IN* — G. Hughes; *Bone and Joint Hospital Research Department, Oklahoma City* — L. Willis; *Arthritis, Rheumatic and Back Disease Associates, Voorhees, NJ* — S. Solomon; *Indiana University School of Medicine, Indianapolis* — M. Econs; *Vanderbilt University School of Medicine, Nashville* — B. Tanner; *Clinical Research Center of Reading, Reading, PA* — M. Borofsky; *Hunter Holmes McGuire Research Institute, Richmond, VA* — R. Adler; *Mercy Arthritis and Osteoporosis Center, Des Moines, IA* — T. Rooney, C.J. Ronkar; *University of Wisconsin Hospital and Clinics, Madison* — M. Drezner; *Ochsner Clinic Foundation, New Orleans* — A.L. Burshell; *Park Nicollet Clinic, St. Louis Park, MN* — J. Schousboe; *Scott and White Memorial Hospital and Clinic, Temple, TX* — V.K. Piziak; *Puget Sound Medical Investigators, Olympia, WA* — M.W. Layton; *Osteoporosis Research Center, Loma Linda, CA* — D.J. Baylink; *Veterans Affairs Medical Health Care System, Tucson, AZ* — M.J. Maricic; *Center for Rheumatology, Albany, NY* — J. Kremer; *Loyola University School of Medicine, Maywood, IL* — P. Camacho; *Center for Diabetes and Endocrine Care, Hollywood, FL* — S. Lerman; *Oregon Health Sciences University School of Medicine, Portland* — A. Barkhuizen; *Order of Saint Francis Medical Group Clinical Research Center, Peoria, IL* — S. Hippler; *Rheumatology Consultants, Hagerstown, MD* — R. Malamet, S.J. Klein; *State University of New York at Stony Brook, Stony Brook* — B. Gruber; *University of Colorado Health Sciences Center, Aurora* — S. West; *Washington University Medical Center, St. Louis* — R. Civitelli; *Whittier Institute for Diabetes, La Jolla, CA* — G.E. Dailey; *Rheumatology Associates of South Florida, Boca Raton, FL* — J. Forstot; *Intermountain Orthopaedics, Boise, ID* — J.E. Loveless; *New England Research Associates, Trumbull, CT* — G. Gladstein; *Odyssey Research Services, Bismarck, ND* — K. Datz; *Odyssey Research Services, Fargo, ND* — M. Lillestol; *Odyssey Research Services, Jamestown, ND* — V. Lingegowda; *United Osteoporosis Center, Gainesville, FL* — C.P. Recknor; *Clinical Research Center of Connecticut and New York, Danbury, CT* — M. Spiegel, K.B. Miller. **Venezuela:** *Clínica Atias, Caracas* — B.R. Losada.

REFERENCES

1. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002;13:777-87.
2. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004; 19:893-9.
3. Steinbuch M, Youket TE, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. Osteoporos Int 2004;15:323-8.
4. Saag K, Morgan S, Cao X. Osteopenic bone diseases. In: Koopman WJ, Moreland LW, eds. Arthritis and allied conditions: a textbook of rheumatology. 15th ed. Philadelphia: Lippincott, Williams & Wilkins, 2004:2473-541.
5. Gourlay M, Franceschini N, Sheyn Y. Prevention and treatment strategies for glucocorticoid-induced osteoporotic fractures. Clin Rheumatol 2007;26:144-53.
6. Curtis JR, Westfall AO, Allison JJ, et al. Longitudinal patterns in the prevention of osteoporosis in glucocorticoid-treated patients. Arthritis Rheum 2005; 52:2485-94.
7. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced os-

teoporosis. N Engl J Med 1998;339:292-9.
8. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999;42:2309-18.
9. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. J Bone Miner Res 2000;15:1006-13.
10. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int 2001;69:242-7.
11. Adachi JD, Olszynski WP, Hanley DA, et al. Management of corticosteroid-induced osteoporosis. Semin Arthritis Rheum 2000;29:228-51.
12. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update: American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum 2001;44:1496-503.
13. Sambrook PN, Diamond T, Ferris L, et al. Corticosteroid induced osteoporosis: guidelines for treatment. Aust Fam Physician 2001;30:793-6.
14. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: Royal College of Physicians, 2002.
15. Adler RA, Hochberg MC. Suggested guidelines for evaluation and treatment of glucocorticoid-induced osteoporosis for the Department of Veterans Affairs. Arch Intern Med 2003;163:2619-24.
16. Geusens PP, de Nijs RN, Lems WF, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. Ann Rheum Dis 2004;63:324-5.
17. Nawata H, Soen S, Takayanagi R, et al. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). J Bone Miner Metab 2005;23:105-9.
18. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
19. Girotra M, Rubin MR, Bilezikian JP. The use of parathyroid hormone in the treatment of osteoporosis. Rev Endocr Metab Disord 2006;7:113-21.
20. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids: potential mechanisms of their deleterious effects on bone. J Clin Invest 1998;102:274-82.
21. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest 1999;104:439-46.
22. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis: results of a randomized controlled clinical trial. J Clin Invest 1998;102:1627-33.
23. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
24. Genant HK, Jergas M, Palermo L, et al. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. J Bone Miner Res 1996;11:984-96.
25. Westfall PH, Krishen A. Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. J Stat Plann Infer 2001;99:25-40.
26. de Nijs RN, Jacobs JW, Lems WF, et al. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med 2006;355:675-84.
27. van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. Calcif Tissue Int 2006;79:129-37.
28. McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med 2005;165:1762-8. [Erratum, Arch Intern Med 2005;165:2120.]
29. Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. J Bone Miner Res 2007;22:149-57.
30. O'Brien CA, Jia D, Plotkin LI, et al. Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength. Endocrinology 2004;145:1835-41.
31. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001;44:202-11.
32. Sambrook PN, Kotowicz M, Nash P, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. J Bone Miner Res 2003;18:919-24.
33. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000;67:277-85.
34. Ringe JD, Dorst A, Faber H, Ibach K, Sorenson F. Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. Osteoporos Int 2003;14:801-7.
35. Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002;87:4528-35.
36. Mudano A, Allison J, Hill J, Rothermel T, Saag K. Variations in glucocorticoid induced osteoporosis prevention in a managed care cohort. J Rheumatol 2001;28:1298-305.
37. Walsh LJ, Lewis SA, Wong CA, et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. Am J Respir Crit Care Med 2002;166:691-5.
38. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.
39. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis: a double-blind, randomized, controlled trial. Ann Intern Med 1998;128:253-61.

ACP Clinical Practice GUIDELINES

Pharmacologic Treatment of Low Bone Density or Osteoporosis to Prevent Fractures: A Clinical Practice Guideline from the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Paul Shekelle, MD, PhD; Robert Hopkins Jr., MD; Mary Ann Forciea, MD; and Douglas K. Owens, MD, MS, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the available evidence on various pharmacologic treatments to prevent fractures in men and women with low bone density or osteoporosis.

Methods: Published literature on this topic was identified by using MEDLINE (1966 to December 2006), the *ACP Journal Club* database, the Cochrane Central Register of Controlled Trials (no date limits), the Cochrane Database of Systematic Reviews (no date limits), Web sites of the United Kingdom National Institute of Health and Clinical Excellence (no date limits), and the United Kingdom Health Technology Assessment Program (January 1998 to December 2006). Searches were limited to English-language publications and human studies. Keywords for search included terms for osteoporosis, osteopenia, low bone density, and the drugs listed in the key questions. This guideline grades the evidence and recommendations according to the ACP's clinical practice guidelines grading system.

Recommendation 1: *ACP recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures (Grade: strong recommendation; high-quality evidence).*

Recommendation 2: *ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis (Grade: weak recommendation; moderate-quality evidence).*

Recommendation 3: *ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of risk and benefits in individual patients (Grade: strong recommendation; moderate-quality evidence).*

Recommendation 4: *ACP recommends further research to evaluate treatment of osteoporosis in men and women.*

Ann Intern Med. 2008;149:404-415. www.annals.org

For author affiliations, see end of text.

See related article in 5 February 2008 issue (volume 148, pages 197-213).

The National Institutes of Health's consensus conference (1) defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk for fracture. Bone strength reflects the integration of two main features: bone density and bone quality. . . . Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures), and mineralization." Although osteoporosis can affect any bone, the hip, spine, and wrist are most likely to be affected. Osteoporosis affects an estimated 44 million Americans or 55% of people 50 years of age or older. Another 34 million Americans are estimated to have low bone mass, meaning that they are at an increased risk for osteoporosis.

Osteoporosis can be diagnosed by the occurrence of fragility fracture. In patients without fragility fracture, osteoporosis is often diagnosed by low bone density. Dual x-ray absorptiometry (DXA) is the current gold standard test for diagnosing osteoporosis in people without an osteoporotic fracture. Dual x-ray absorptiometry results are scored as standard deviations (SDs) from a young healthy norm (usually female) and reported as T-scores. For example, a T-score of −2 indicates a bone mineral density that is 2 SDs below the comparative norm. The international reference standard for the description of osteoporosis in postmenopausal women and in men age 50 years or older is a femoral neck bone mineral density of 2.5 SD or more below the young female adult mean (2). Low bone density, as measured by DXA, is an imperfect predictor of fracture risk, identifying fewer than half the people who go on to have an osteoporotic fracture. Screening guidelines for women are well established (3), and

See also:

Print
Summary for Patients. 1-46

Web-Only
CME quiz
Conversion of graphics into slides

* This paper, written by Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Paul Shekelle, MD, PhD; Robert Hopkins Jr., MD; Mary Ann Forciea, MD; and Douglas K. Owens, MD, MS, was developed for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP): Douglas K. Owens, MD, MS (*Chair*); Donald E. Casey Jr., MD, MPH, MBA; Paul Dallas, MD; Thomas D. Denberg, MD, PhD; Mary Ann Forciea, MD; Lakshmi Halasyamani, MD; Robert H. Hopkins Jr., MD; William Rodriguez-Cintron, MD; and Paul Shekelle, MD, PhD. Approved by the ACP Board of Regents on 12 May 2008.

the American College of Physicians (ACP) recently published guidelines on screening for men (4).

This guideline presents the available evidence on various pharmacologic treatments to prevent fractures in men and women with low bone density or osteoporosis. Medications used to treat osteoporosis may affect different parts of the skeletal system differently, and efficacy for vertebral fractures does not necessarily imply efficacy for nonvertebral fractures. The target audience for this guideline is all clinicians and the target patient population is all adult men and women with low bone density or osteoporosis. These recommendations are based on the systematic evidence review by MacLean and colleagues (5) and the Agency for Healthcare Research and Quality–sponsored Southern California Evidence-Based Practice Center evidence report (6).

The drugs currently approved for prevention of osteoporosis include alendronate, ibandronate, risedronate, zoledronic acid, estrogen, and raloxifene. The drugs currently approved for treatment of osteoporosis include alendronate, ibandronate, risedronate, calcitonin, teriparatide, zoledronic acid (in postmenopausal women), and raloxifene. Testosterone, pamidronate, and etidronate are not approved by the U.S. Food and Drug Administration for the treatment or prevention of osteoporosis.

Methods

The literature search done by MacLean and colleagues for the systematic review (5) included studies from MEDLINE (1966 to December 2006), the *ACP Journal Club* database, the Cochrane Central Register of Controlled Trials (no date limits), the Cochrane Database of Systematic Reviews (no date limits), Web sites of the United Kingdom National Institute of Health and Clinical Excellence (no date limits), and the United Kingdom Health Technology Assessment Program (January 1998 to December 2006). The reviewers limited their search to English-language publications and human studies. They derived evidence for comparative benefits of various treatments exclusively from randomized, controlled trials, whereas they included evidence from other types of studies for short- and long-term harms.

Two physicians independently abstracted data about study populations, interventions, follow-up, and outcome ascertainment by using a structured form. For each group within a randomized trial, a statistician extracted the sample size and number of persons reporting fractures. Two reviewers, under the supervision of the statistician, independently abstracted information about adverse events. The statistician or the principal investigator resolved disagreements.

This guideline is based on an evaluation of 76 randomized, controlled trials, 4 of which were identified in the updated search, and 24 meta-analyses that were included in the efficacy analyses. The analyses of adverse events included 491 articles, representing 417 randomized trials, 25 other controlled clinical trials, 11 open-label trials, 31 large observational studies, and 9 case reports of osteonecrosis among bisphosphonate users. MacLean and colleagues' background article (5) includes details about the methods used for the systematic evidence review.

Table 1. **The American College of Physicians' Guideline Grading System***

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden OR Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I-recommendation	

* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

The ACP rates the evidence and recommendations by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system with minor modifications (**Table 1**). In addition, the evidence reviewers used predefined criteria to assess the quality of systematic reviews and randomized trials, based on internal and external validity assessments detailed in the Quality of Reporting of Meta-Analyses (QUOROM) statement (7).

The objective of this guideline is to synthesize the evidence for the following questions:

1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone density: bisphosphonates, specifically alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid; calcitonin; estrogen for women; teriparatide; selective estrogen receptor modulators (SERMs), specifically raloxifene and tamoxifen; testosterone for men; vitamins and minerals, specifically vitamin D and calcium; and the combination of calcium plus vitamin D?

2. How does fracture reduction resulting from treatments vary among individuals with different risks for fracture as determined by bone mineral density (borderline, low, or severe), previous fractures (prevention vs. treatment), age, sex, glucocorticoid use, and other factors (such as community-dwelling vs. institutionalized or vitamin D–deficient vs. not)?

3. What are the short- and long-term harms (adverse effects) of these therapies, and do these vary by specific subpopulations?

Comparative Benefits of Drugs versus Placebo in Fracture Reduction

Evidence from 24 meta-analyses (8–30) and 35 additional randomized trials published after the meta-analyses

(31–65) described the effect of 9 of the 14 agents (alendronate, etidronate, risedronate, calcitonin, estrogen, teriparatide, raloxifene, calcium, and vitamin D) on fracture incidence. For 4 agents (ibandronate, pamidronate, zoledronic acid, and tamoxifen), the reviewers found no meta-analyses and instead gathered the evidence from 14 randomized trials (66–79). No studies were found that reported fracture rates for testosterone. Three randomized trials (35, 80, 81) and 1 meta-analysis (82) evaluated the combination of calcium plus vitamin D on fractures.

Bisphosphonates

Good-quality evidence showed that alendronate, etidronate, ibandronate, and risedronate prevent vertebral fractures. In addition, evidence from good-quality studies demonstrated that both alendronate and risedronate prevent nonvertebral and hip fractures. Two large randomized trials showed that zoledronic acid prevents vertebral and nonvertebral fractures in high-risk populations and reduces the risk for hip fracture (67, 74). Ibandronate has not been shown to reduce nonvertebral fractures (68). Of the 6 fairly small trials that looked at vertebral fractures, 1 demonstrated a statistically significant reduction in fractures with pamidronate relative to placebo (0.14 [95% CI, 0.03 to 0.72]) (73). However, after these data were pooled, the pooled risk estimate for fractures for pamidronate relative to placebo was not significant (0.52 [CI, 0.21 to 1.24]) (6).

Calcitonin

Fair-quality evidence shows that calcitonin reduces vertebral fractures (83, 84). Good-quality evidence indicates that calcitonin does not reduce nonvertebral fractures (13, 16).

Estrogen

Good-quality evidence shows that estrogen reduces the incidence of vertebral (29, 85), nonvertebral (86), and hip fractures (85).

Teriparatide

Good-quality evidence shows that teriparatide prevents vertebral fractures. The evidence related to teriparatide preventing nonvertebral fractures is mixed; 1 large randomized trial showed a reduction in nonvertebral fractures (34) but 2 small trials did not (87, 88).

SERMs

Good-quality evidence shows that raloxifene prevents vertebral fractures, but that tamoxifen has no effect on vertebral fractures (89–91). In addition, both raloxifene and tamoxifen had no effect on hip fractures (91). Tamoxifen is not approved by the U.S. Food and Drug Administration for the treatment or prevention of osteoporosis.

Testosterone

No studies reported fracture rates for testosterone.

Calcium and Vitamin D

In the studies evaluated by MacLean and colleagues (5), the evidence for the effect of calcium alone on reduction of fractures is complex. Most studies of pharmacologic agents for osteoporosis include calcium and vitamin D as part of the treatment regimen. Evidence from 1 meta-analysis (27) and several randomized trials (35, 48, 51, 92) showed no significant difference between calcium and placebo in preventing vertebral, nonvertebral, and hip fractures in postmenopausal women. However, nonadherence to therapy may influence this result, and 1 trial with a prespecified analysis of adherent patients found a reduction in fracture risk (48). A recent meta-analysis (82) concluded that the relative risk (RR) for fracture with calcium alone was 0.90 (CI, 0.80 to 1.00), but it did not include a modestly large trial with negative results (35).

MacLean and colleagues (5) included 5 systematic reviews that evaluated vitamin D. Four meta-analyses (8, 21, 24, 28) found that standard vitamin D (D_2, D_3, or 25-hydroxyvitamin [25(OH)]D) did not have any effect on risk for vertebral, nonvertebral, or hip fractures; a fifth (35) showed a statistically significant reduction in the pooled risk for nonvertebral and hip fractures for vitamin D_2 or D_3. In addition, MacLean and colleagues identified 3 meta-analyses (21, 23, 24) that showed that vitamin D analogues [1,25(OH)D and 1(OH)D] significantly reduced the risk for vertebral, nonvertebral, and hip fractures. A meta-analysis published after MacLean and colleagues' review concluded that vitamin D and calcium reduced fractures by 13% (RR, 0.87 [CI, 0.77 to 0.97]) (82).

In summary, for evaluating the comparative benefits of drugs versus placebo in fracture reduction, good-quality evidence shows that alendronate, etidronate, ibandronate, risedronate, calcitonin, teriparatide, and raloxifene prevent vertebral fractures. The reviewers also found good-quality evidence that alendronate and risedronate prevent nonvertebral and hip fractures. No clear evidence demonstrates the appropriate duration of treatment with bisphosphonates; however, bisphosphonate trials ranged from 3 months to 60 months. Good evidence shows that estrogen reduced the incidence of vertebral, nonvertebral, and hip fractures. The effect of calcium alone is less certain. Systematic reviews of the effectiveness of vitamin D and calcium have reached different conclusions, with the most recent systematic review (82) finding a modest reduction in fracture risk.

Comparative Benefits of Drugs within and among Classes in Fracture Reduction

Evidence from 9 randomized trials comparing different bisphosphonates (41, 93–100), 1 study comparing different SERMs (101), and 16 studies with head-to-head comparisons of agents from different classes (31, 32, 35, 37, 42, 50, 64, 98, 100, 102–108) evaluated intermediate outcomes, such as bone mineral density and changes in markers of bone turnover. These studies were too short to detect clinically important differences in fracture incidence.

The 2 head-to-head trials that compared fracture incidence outcomes (risedronate vs. etidronate [97] and raloxifene vs. alendronate [107]) were underpowered and showed no statistically significant differences.

In summary, evidence is insufficient to determine whether one bisphosphonate is superior to another, with the exception that ibandronate did not reduce nonvertebral fractures in a relatively large trial (68). Little evidence comparing drugs from different classes is available.

Benefits of Drugs in Different Risk Groups for Fracture Reduction

Low-Risk Populations

We defined "low risk" as a 10-year risk for osteoporotic fracture (vertebral, nonvertebral, or hip) of up to 2% and a lifetime risk of up to 21%. The reviewers gathered evidence from 4 meta-analyses (14, 15, 28, 107). Summary estimates for alendronate showed a statistically nonsignificant reduction in the risk for vertebral fracture (RR, 0.45 [CI, 0.06 to 3.15]) and nonvertebral fracture (RR, 0.79 [CI, 0.28 to 2.24]) (15). Estrogen did not reduce the risk for vertebral fracture (28) but reduced nonvertebral fractures (28, 109). However, raloxifene and vitamin D did reduce the risk for vertebral fractures (raloxifene RR, 0.53 [CI, 0.35 to 0.79]; vitamin D RR, 0.86 [CI, 0.72 to 1.02]) (28). Evidence from 2 randomized trials did not show any difference between raloxifene and tamoxifen for reducing fractures (63, 101).

Special Populations

Men

Studies showed that risedronate decreased the risk for hip fractures (RR, 0.25 [CI, 0.08 to 0.78]) (56), calcitonin decreased the risk for vertebral fractures (RR, 0.09 [CI, 0.01 to 0.96]) (61), and teriparatide decreased the risk for total fractures (RR, 0.16 [CI, 0.01 to 0.96]) and possibly the risk for vertebral fractures (odds ratio [OR], 0.44 [CI, 0.18 to 1.09]) (44). Evidence is insufficient to evaluate the effect of calcium alone in men (35).

Populations at Increased Risk for Falls

Populations studied included patients with stroke and hemiplegia, Alzheimer disease, a recent hip fracture, or Parkinson disease. Zoledronic acid reduced the risk for vertebral fractures (hazard ratio, 0.54 [CI, 0.32 to 0.92]) and nonvertebral fractures (hazard ratio, 0.73 [CI, 0.55 to 0.98]) in patients with a recent hip fracture (74). In patients with Alzheimer disease, risedronate reduced the risk for nonvertebral fracture (RR, 0.29 [CI, 0.15 to 0.57]) (53) and hip fracture (RR, 0.29 [CI, 0.13 to 0.66]) (58). Risedronate also reduced the risk for hip fracture in patients with stroke (RR, 0.22 [CI, 0.05 to 0.88]) and hemiparesis (RR, 0.25 [CI, 0.08 to 0.78]) (55, 56). In patients with Parkinson disease, alendronate (RR, 0.30 [CI, 0.12 to 0.78]) reduced the risk for hip fracture (57). Vitamin D also reduced the risk for hip fracture in patients with stroke and hemiparesis (RR, 0.12 [CI, 0.02 to 0.90]).

Populations with Renal Insufficiency

One trial (110) showed that alendronate reduced the risk for fractures to a similar degree in patients with and those without reduced renal function.

Populations with Long-Term Glucocorticoid Use

Evidence from 3 studies included in a systematic review (111) showed a possible reduction in vertebral fracture rate with bisphosphonate treatment (112–114). Six additional trials have been published since this systematic review. Three of these randomized trials (115–117) showed that bisphosphonates reduced the fracture rate. Results from 2 studies also showed that risedronate treatment led to a statistically significant reduction in the absolute risk (11%) and RR (70%) of incident radiographic vertebral fractures after 1 year (117) and in vertebral fractures (116). In another trial (115), alendronate was associated with a reduction in the risk for incident radiographic vertebral fractures. However, 3 additional trials showed no significant effect on fracture risk for etidronate (32, 53), from calcium (32), between calcium and a combination of etidronate and calcium (32), or between calcium and pamidronate (103).

To summarize the overall fracture reduction benefits of drug treatments in special populations in different risk groups, a SERM (raloxifene) and vitamin D both reduced the risk for vertebral fracture in low-risk patients. Far fewer men than women have been included in these trials, resulting in less evidence about the effectiveness of treatment in men. In men, risedronate decreased hip fractures and calcitonin decreased vertebral fractures. Teriparatide decreased total fractures and possibly vertebral fractures. In patients with a previous hip fracture, zoledronic acid reduced the risk for vertebral and nonvertebral fractures. Risedronate reduced the hip and nonvertebral fracture risk among patients with Alzheimer disease. Bisphosphonates (risedronate and alendronate) also reduced the clinical and radiographic fracture rate in patients receiving glucocorticoids.

Adverse Effects of Drugs

Bisphosphonates

The most common adverse effects of bisphosphonates are gastrointestinal. Trials reported esophageal ulcerations from all bisphosphonates except zoledronic acid. One trial of etidronate versus placebo showed a statistically significant increase in esophageal ulceration (OR, 1.33 [CI, 1.05 to 1.68]) (118). Mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn) were more common with etidronate in a pooled analysis (OR, 1.33 [CI, 1.21 to 1.46]) (32, 42, 53, 54, 64, 112, 118–128) and with pamidronate (OR, 3.14 [CI, 1.93

to 5.21]) (75, 79, 129–133). Pooled analysis showed no difference in occurrence of mild upper gastrointestinal events between alendronate, ibandronate, risedronate, or zoledronic acid and placebo. However, pooled analysis of head-to-head trials showed a higher risk for mild upper gastrointestinal events with alendronate than with etidronate (OR, 5.89 [CI, 1.61 to 32.7]), calcitonin (OR, 3.42 [CI, 1.79 to 7.00]), or estrogen (OR, 1.57 [CI, 1.00 to 2.46]). The pooled estimate from 3 studies showed that etidronate users were at increased risk for perforations, ulcerations, and gastrointestinal bleeding events (OR, 1.32 [CI, 1.04 to 1.67]) (59, 118, 134), whereas the pooled estimate from 2 studies showed that ibandronate had a lower risk for serious gastrointestinal adverse events (OR, 0.33 [CI, 0.14 to 0.74]) (68, 135). Case reports and case series have documented increased osteonecrosis of the jaw in patients receiving bisphosphonates, but the most cases of osteonecrosis have occurred in patients with cancer who received high doses of intravenous bisphosphonates (136). However, we could not calculate the risk for this event from the available studies. Some studies showed a link between atrial fibrillation and either zoledronic acid or alendronate (5, 137).

Calcitonin

Evidence from randomized trials showed no clinically important serious adverse events associated with the use of calcitonin.

Estrogen

Estrogen was associated with an increased risk for thromboembolic events versus placebo in pooled results from 4 studies (OR, 1.36 [CI, 1.01 to 1.86]) (37, 85, 138, 139). In addition, pooled results for estrogen–progestin also showed a higher risk for thromboembolic events versus placebo (OR, 2.27 [CI, 1.72 to 3.02]) (52, 140, 141). Pooled odds of stroke were increased with estrogen (OR, 1.28 [CI, 1.05 to 1.57]) (83, 138, 139) and combined estrogen–progestin (OR, 1.28 [CI, 1.05 to 1.57]) relative to placebo (52, 140). Women who received estrogen had a lower pooled risk for breast cancer than those who received placebo (OR, 0.79 [CI, 0.66 to 0.93]) (83, 138, 142–144). However, pooled analysis showed that women who received an estrogen–progestin combination had an increased risk for breast cancer (OR, 1.28 [CI, 1.03 to 1.60]) (52, 131, 140). One study showed a lower risk for colon cancer among women who received an estrogen–progestin combination (OR, 0.64 [CI, 0.43 to 0.95]) (85).

Teriparatide

Evidence from randomized trials showed no clinically important serious adverse events associated with the use of teriparatide.

SERMs

Raloxifene increased the pooled risk for pulmonary embolism (OR, 6.26 [CI, 1.55 to 54.80]) (145, 146). In addition, pooled results showed that raloxifene increased the risk for thromboembolic events (OR, 2.08 [CI, 1.47 to 3.02) (145, 147–152) and mild cardiac events, including chest pain, palpitations, tachycardia, and vasodilatation (OR, 1.53 [CI, 1.01 to 2.35]) (147, 149, 152–155).

Testosterone

No trials of testosterone reported adverse events; however, testosterone has well-known side effects.

Calcium and Vitamin D

Evidence from randomized trials showed no clinically important serious adverse events associated with the use of calcium and vitamin D.

To summarize the adverse effects of drugs, estrogen increased the risk for stroke and thromboembolic events; estrogen–progestin increased the risk for stroke and breast cancer; and raloxifene increased the risk for pulmonary embolism, thromboembolic events, and mild cardiac events. Etidronate was associated with increased risk for esophageal ulcerations and, in addition to mild upper gastrointestinal events, increased the risk for perforations, ulcerations, and bleeding events. Alendronate was associated with a higher risk for mild upper gastrointestinal events than were etidronate, calcitonin, and estrogen.

Summary

Good evidence shows that bisphosphonates (alendronate, etidronate, and risedronate) reduce the risk for vertebral, nonvertebral, and hip fractures. Ibandronate reduces vertebral fractures. No clear evidence indicates the appropriate duration of treatment with bisphosphonates; however, bisphosphonate trials ranged from 3 months to 60 months. Estrogen reduces the risk for vertebral, nonvertebral, and hip fractures. Whereas evidence for fracture risk reduction from calcium alone is less clear, it is stronger for vitamin D and calcium in combination (82). Evidence showed a statistically significant reduction in the risk for vertebral fractures from vitamin D analogues [1,25(OH)D and 1(OH)D] but mixed results for nonvertebral and hip fractures.

Oral bisphosphonates increase the risk for such gastrointestinal adverse events as acid reflux. However, pooled analyses showed no differences in occurrence of mild upper gastrointestinal events among alendronate, ibandronate, risedronate, or zoledronic acid versus placebo; however, pooled analyses of 18 trials of etidronate versus placebo indicated an increased risk for mild gastrointestinal events. The evidence linking zoledronic acid infusion with atrial fibrillation is contradictory. Raloxifene increased the pooled risk for pulmonary embolism and thromboembolic events. Estrogen was linked to an increased risk for cerebrovascular and thromboembolic events.

Recommendations

Recommendation 1: ACP recommends that clinicians offer pharmacologic treatment to men and women who have known

osteoporosis and to those who have experienced fragility fractures (Grade: strong recommendation; high-quality evidence).

Good evidence supports the treatment of patients who have osteoporosis to prevent further loss of bone and to reduce the risk for initial or subsequent fracture. Randomized, controlled trials offer good evidence that, compared with placebo, alendronate, ibandronate, risedronate, calcitonin, teriparatide, and raloxifene prevent vertebral fractures. Evidence is also good that teriparatide prevents nonvertebral fractures compared with placebo and that risedronate and alendronate prevent both nonvertebral and hip fractures compared with placebo. Estrogen has been shown to be associated with reduced vertebral, nonvertebral, and hip fractures. The evidence on use of calcium with or without vitamin D is mixed, and the effectiveness is modest. Because most trials of other pharmacologic therapy included their use, we recommend adding calcium and vitamin D to osteoporosis treatment regimens. Evidence is insufficient to determine the appropriate duration of therapy.

Recommendation 2: ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis (Grade: weak recommendation; moderate-quality evidence).

Evidence supports the treatment of selected patients who are at risk for osteoporosis but who do not have a T-score on DXA less than −2.5. Evidence supporting preventive treatment is stronger for patients who are at moderate risk for osteoporosis, which includes patients who have a T-score from −1.5 to −2.5, are receiving glucocorticoids, or are older than 62 years of age.

Factors that increase the risk for osteoporosis in men include age (>70 years), low body weight (body mass index <20 to 25 kg/m^2), weight loss (>10% [compared with the usual young or adult weight or weight loss in recent years]), physical inactivity (no physical activities performed regularly, such as walking, climbing stairs, carrying weights, housework, or gardening), corticosteroid use, and androgen deprivation therapy (4). Risk factors for women include lower body weight, the single best predictor of low bone mineral density; smoking; weight loss; family history; decreased physical activity; alcohol or caffeine use; and low calcium and vitamin D intake (3). In certain circumstances, a single risk factor (for example, androgen deprivation therapy in men) is enough for clinicians to consider pharmacologic treatment.

Research groups are developing calculators, such as the World Health Organization's Fracture Risk Assessment Tool (available at www.shef.ac.uk/FRAX/), to predict the risk for osteoporotic fracture. Such tools will help guide both clinician and patient decisions.

Recommendation 3: ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of the risk and benefits to individual patients (Grade: strong recommendation; moderate-quality evidence).

We recommend that the choice of therapy for patients who are candidates for pharmacologic treatment be guided by judgment of the risks, benefits, and adverse effects of drug options for each individual patient. Table 2 summarizes the benefits and harms of pharmacologic agents for fracture risk. Because good-quality evidence shows that bisphosphonates reduce the risk for vertebral, nonvertebral, and hip fractures, they are reasonable options to consider as first-line therapy, particularly for patients who have a high risk for hip fracture. Evidence from head-to-head trials is insufficient to demonstrate the superiority of one bisphosphonate over another. Alendronate and risedronate have been studied more than other bisphosphonates (Table 2). Ibandronate has not been shown to reduce nonvertebral or hip fractures, which may be an important consideration for some patients. In a recent trial, zoledronic acid administered to patients with a recent hip fracture reduced subsequent fracture and improved survival (74). Of the other agents available for treatment of osteoporosis, estrogen has efficacy for vertebral, nonvertebral, and hip fractures but is associated with other serious risks; calcitonin has not been demonstrated to reduce nonvertebral and hip fractures; and calcium and vitamin D are part of the treatment regimen in most studies of pharmacologic agents for osteoporosis.

Gastrointestinal events are the most common adverse effects associated with bisphosphonate therapy. No evidence was found that bisphosphonates, calcium, vitamin D, calcitonin, or teriparatide differ regarding risk for serious cardiac events. Etidronate is associated with an increased risk for esophageal ulcers, bleeding events, and mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn). Raloxifene is associated with a higher risk for pulmonary embolism, thromboembolic events, and mild cardiac events (including chest pain, palpitations, tachycardia, and vasodilatation). Estrogen is associated with a greater risk for stroke, and the estrogen–progestin combination is associated with a greater probability of stroke and higher odds of breast cancer. In trials, perforations, ulcerations, and bleeding events occurred with all of the bisphosphonates except zoledronic acid.

Recommendation 4: ACP recommends further research to evaluate treatment of osteoporosis in men and women.

Current evidence is mostly concentrated on postmenopausal women; more research on other patient populations, including men, is needed. Comparative effectiveness data on preventing fractures from head-to-head

Table 2. **Summary of Evidence about Drugs and Fracture Risk**

Agent	Effect on Risk and Level of Evidence			Adverse Effects	FDA Approval
	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture		
Bisphosphonates					
Alendronate	↓; strong evidence	↓; strong evidence	↓; strong evidence	Mild upper GI events, esophageal ulcerations, perforations, and bleeding events	Prevention or treatment
Etidronate	↓; strong evidence	↔; fair evidence	↔; strong evidence	Mild upper GI events, esophageal ulcerations, perforations, and bleeding events	Not FDA-approved for prevention or treatment
Ibandronate	↓; strong evidence	↔; strong evidence	Not studied	Esophageal ulcerations, perforations, and bleeding events	Prevention or treatment
Pamidronate	↔; weak evidence	↔; weak evidence	↔; weak evidence	Mild upper GI events, esophageal ulcerations, perforations, and bleeding events	Not FDA-approved for prevention or treatment
Risedronate	↓; strong evidence	↓; strong evidence	↓; strong evidence	Esophageal ulcerations, perforations, and bleeding events	Prevention or treatment
Zoledronic acid	↓; strong evidence	↓; strong evidence	↓; strong evidence	Muscular and joint pain	Prevention
Calcitonin	↓; fair evidence	↔; strong evidence	Not studied	No clinically significant adverse effects	Treatment
Estrogen	↓; strong evidence	↓; strong evidence	↓; strong evidence	Thromboembolic events; cerebrovascular accident, stroke, and breast cancer (when combined with progestin); gynecologic problems (endometrial bleeding); breast abnormalities (pain, tenderness, and fibrocystosis)	Prevention
Teriparatide	↓; strong evidence	↓; fair evidence	↔; weak evidence	No clinically significant adverse effects	Treatment
SERMs					
Raloxifene	↓; strong evidence	↔; strong evidence	↔; strong evidence	Pulmonary embolism, thromboembolic events	Prevention or treatment
Tamoxifen	↔; strong evidence	Not studied	↔; strong evidence	Pulmonary embolism	Not FDA-approved for prevention or treatment
Testosterone	Not studied	Not studied	Not studied	No clinically significant adverse effects	Not FDA-approved for prevention or treatment
Calcium and vitamin D	Modest effect*; strong evidence	Modest effect*; strong evidence	Modest effect*; strong evidence	No clinically significant adverse effects	Over the counter

↓ = decreased; ↔ = no effect; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; SERM = selective estrogen receptor modulator.
* Pooled estimate across fracture sites.

studies with sufficient power to detect differences would be helpful. The association between bisphosphonates and osteonecrosis of the jaw also needs to be studied. Finally, further research is needed on prevention strategies in both men and women and on the appropriate duration of treatment for osteoporosis.

From the American College of Physicians and University of Pennsylvania, Philadelphia, Pennsylvania; Veterans Affairs Greater Los Angeles Healthcare System and RAND, Santa Monica, California; University of Arkansas, Little Rock, Arkansas; and Veterans Affairs Palo Alto Health Care System and Stanford University, Stanford, California.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Grant Support: Financial support for the development of this guideline comes exclusively from the American College of Physicians' operating budget.

Potential Financial Conflicts of Interest: *Employment:* R. Hopkins (University of Arkansas). *Consultancies:* D.K. Owens (GE Healthcare). *Grants received:* V. Snow (Novo Nordisk, United Healthcare Foundation, Centers for Disease Control and Prevention, Atlantic Philanthropies). Any conflict of interest of the Guideline Development Committee group members was declared, discussed, and resolved.

Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Current author addresses are available at www.annals.org.

References

1. **NIH Consensus Development Program.** Osteoporosis Prevention, Diagnosis, and Therapy. Bethesda, MD: National Institutes of Health; 2000. Accessed at http://consensus.nih.gov/2000/2000Osteoporosis111html.htm on 31 July 2008.
2. WHO scientific group on the assessment of osteoporosis at primary health care level. Geneva: World Health Organization; 2007.
3. **U.S. Preventive Services Task Force.** Screening for Osteoporosis in Postmenopausal Women: Recommendations and Rationale. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Accessed at www.ahrq.gov/clinic/3rduspstf/osteoporosis/osteorr.htm on 31 July 2008.
4. **Qaseem A, Snow V, Shekelle P, Hopkins R, Forciea MA, Owens D. Clinical Efficacy Assessment Subcommittee of the American College of Physicians.** Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;148:680-4. [PMID: 18458281]
5. **MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, et al.** Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med. 2008;148:197-213. [PMID: 18087050]
6. **MacLean C, Alexander A, Carter J, Chen S, Desai SB, Grossman J, et al.** Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis. Comparative Effectiveness Review no. 12. (Prepared by the Southern California/RAND Evidence-based Practice Center under contract 290-02-0003). Rockville, MD: Agency for Healthcare Research and Quality; December 2007. Accessed at www.effectivehealthcare.ahrq.gov/reports/final.cfm on 31 July 2008.
7. **Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF.** Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999; 354:1896-900. [PMID: 10584742]
8. **Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL.** Vitamin D and vitamin D analogues for preventing fractures associated with involutional and postmenopausal osteoporosis. Cochrane Database Syst Rev. 2005:CD000227. [PMID: 16034849]
9. **Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B.** Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257-64. [PMID: 15886381]
10. **Boonen S, Laan RF, Barton IP, Watts NB.** Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. Osteoporos Int. 2005;16:1291-8. [PMID: 15986101]
11. **Cranney A, Welch V, Adachi JD, Homik J, Shea B, Suarez-Almazor ME, et al.** Calcitonin for the treatment and prevention of corticosteroid-induced osteoporosis. Cochrane Database Syst Rev. 2000:CD001983. [PMID: 10796457]
12. **Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23:517-23. [PMID: 12202466]
13. **Cranney A, Tugwell P, Zytaruk N, Robinson V, Weaver B, Shea B, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23:540-51. [PMID: 12202469]
14. **Cranney A, Adachi JD, Griffith L, Guyatt G, Krolicki N, Robinson VA, et al.** WITHDRAWN: Etidronate for treating and preventing postmenopausal osteoporosis. Cochrane Database Syst Rev. 2006:CD003376. [PMID: 17636719]
15. **Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev. 2002;23:508-16. [PMID: 12202465]
16. **Kanis JA, McCloskey EV.** Effect of calcitonin on vertebral and other fractures. QJM. 1999;92:143-9. [PMID: 10326073]
17. **Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC Jr, Adami S, et al.** Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. JAMA. 1997;277:1159-64. [PMID: 9087473]
18. **Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE.** Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res. 2005;20:2105-15. [PMID: 16294264]
19. **Nguyen ND, Eisman JA, Nguyen TV.** Anti-hip fracture efficacy of biophosphonates: a Bayesian analysis of clinical trials. J Bone Miner Res. 2006;21:340-9. [PMID: 16526127]
20. **Palmer S, McGregor DO, Strippoli GF.** Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev. 2005: CD005015. [PMID: 15846740]
21. **Papadimitropoulos E, Wells G, Shea B, Gillespie W, Weaver B, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev. 2002;23:560-9. [PMID: 12202471]
22. **Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE.** Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int. 2005;16:468-74. [PMID: 15448985]
23. **Richy F, Ethgen O, Bruyere O, Reginster JY.** Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int. 2004;15: 301-10. [PMID: 14740153]
24. **Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY.** Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int. 2005;76: 176-86. [PMID: 15692726]
25. **Sawka AM, Papaioannou A, Adachi JD, Gafni A, Hanley DA, Thabane L.** Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. BMC Musculoskelet Disord. 2005;6:39. [PMID: 16008835]

26. Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int. 2006;17: 313-6. [PMID: 16217588]
27. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23:552-9. [PMID: 12202470]
28. 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 Technol Assess. 2005;9:1-160. [PMID: 15929857]
29. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. BMC Musculoskelet Disord. 2001;2:7. [PMID: 11716794]
30. Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev. 2002;23:529-39. [PMID: 12202468]
31. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab. 2000;85:720-6. [PMID: 10690882]
32. Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM. Research Committee of the British Thoracic Society. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax. 2004;59:761-8. [PMID: 15333852]
33. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290:1729-38. [PMID: 14519707]
34. Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. J Clin Endocrinol Metab. 2005;90: 1583-7. [PMID: 15613428]
35. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005;365:1621-8. [PMID: 15885294]
36. Greenspan SL, Bhattacharya RK, Sereika SM, Brufsky A, Vogel VG. Prevention of bone loss in survivors of breast cancer: A randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2007;92:131-6. [PMID: 17047022]
37. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA. 2003;289:2525-33. [PMID: 12759324]
38. Hay JE, Malinchoc M, Dickson ER. A controlled trial of calcitonin therapy for the prevention of post-liver transplantation atraumatic fractures in patients with primary biliary cirrhosis and primary sclerosing cholangitis. J Hepatol. 2001; 34:292-8. [PMID: 11281559]
39. Homik J, Cranney A, Shea B, Tugwell P, Wells G, Adachi R, et al. Bisphosphonates for steroid induced osteoporosis. Cochrane Database Syst Rev. 2000: CD001347. [PMID: 10796432]
40. Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric. 2005;8: 251-62. [PMID: 16390757]
41. Hosking D, Adami S, Felsenberg D, Andia JC, Välimäki M, Benhamou L, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Curr Med Res Opin. 2003;19:383-94. [PMID: 13678475]
42. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. Am J Med. 2004;117:549-55. [PMID: 15465502]
43. Kanaji A, Higashi M, Namisato M, Nishio M, Ando K, Yamada H. Effects of risedronate on lumbar bone mineral density, bone resorption, and incidence of vertebral fracture in elderly male patients with leprosy. Lepr Rev. 2006;77:147-53. [PMID: 16895071]
44. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005;16:510-6. [PMID: 15322742]
45. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354: 821-31. [PMID: 16495394]
46. Milgrom C, Finestone A, Novack V, Pereg D, Goldich Y, Kreiss Y, et al. The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone. 2004;35:418-24. [PMID: 15268892]
47. Palomba S, Orio F Jr, Manguso F, Falbo A, Russo T, Tolino A, et al. Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. Osteoporos Int. 2005;16:1141-9. [PMID: 15928801]
48. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006;166:869-75. [PMID: 16636212]
49. Fracture Intervention Trial Research Group. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. Mayo Clin Proc. 2005;80: 343-9. [PMID: 15757015]
50. Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, et al. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. Arch Intern Med. 2004;164:871-9. [PMID: 15111373]
51. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al. Randomized controlled trial of calcium in healthy older women. Am J Med. 2006;119:777-85. [PMID: 16945613]
52. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-33. [PMID: 12117397]
53. Sato S, Ohosone Y, Suwa A, Yasuoka H, Nojima T, Fujii T, et al. Effect of intermittent cyclical etidronate therapy on corticosteroid induced osteoporosis in Japanese patients with connective tissue disease: 3 year followup. J Rheumatol. 2003;30:2673-9. [PMID: 14719212]
54. Sato Y, Honda Y, Iwamoto J. Etidronate for fracture prevention in amyotrophic lateral sclerosis: a randomized controlled trial. Bone. 2006;39:1080-6. [PMID: 16777503]
55. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture after stroke in elderly women. Neurology. 2005;64:811-6. [PMID: 15753414]
56. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med. 2005;165:1743-8. [PMID: 16087822]
57. Sato Y, Iwamoto J, Kanoko T, Satoh K. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: a randomized controlled trial. Mov Disord. 2006;21:924-9. [PMID: 16538619]
58. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med. 2005; 165:1737-42. [PMID: 16087821]
59. Sato Y, Kanoko T, Yasuda H, Satoh K, Iwamoto J. Beneficial effect of etidronate therapy in immobilized hip fracture patients. Am J Phys Med Rehabil. 2004;83:298-303. [PMID: 15024332]
60. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003;32:120-6. [PMID: 12633783]
61. Tóth E, Csupor E, Mészáros S, Ferencz V, Németh L, McCloskey EV, et al. The effect of intranasal salmon calcitonin therapy on bone mineral density in idiopathic male osteoporosis without vertebral fractures—an open label study. Bone. 2005;36:47-51. [PMID: 15664001]
62. Trovas GP, Lyritis GP, Galanos A, Raptou P, Constantelou E. A random-

ized trial of nasal spray salmon calcitonin in men with idiopathic osteoporosis: effects on bone mineral density and bone markers. J Bone Miner Res. 2002;17: 521-7. [PMID: 11874243]

63. **Ushiroyama T, Ikeda A, Sakai M, Higashiyama T, Ueki M.** Effects of the combined use of calcitonin and 1 α-hydroxycholecalciferol on vertebral bone loss and bone turnover in women with postmenopausal osteopenia and osteoporosis: a prospective study of long-term and continuous administration with low dose calcitonin. Maturitas. 2001;40:229-38. [PMID: 11731184]

64. **Wimalawansa SJ.** A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med. 1998;104:219-26. [PMID: 9552083]

65. **Zein CO, Jorgensen RA, Clarke B, Wenger DE, Keach JC, Angulo P, et al.** Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial. Hepatology. 2005;42:762-71. [PMID: 16175618]

66. **Aris RM, Lester GE, Renner JB, Winders A, Denene Blackwood A, Lark RK, et al.** Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. Am J Respir Crit Care Med. 2000;162:941-6. [PMID: 10988110]

67. **Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. HORIZON Pivotal Fracture Trial.** Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809-22. [PMID: 17476007]

68. **Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE).** Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19:1241-9. [PMID: 15231010]

69. **Coco M, Glicklich D, Faugere MC, Burris L, Bognar I, Durkin P, et al.** Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. J Am Soc Nephrol. 2003;14:2669-76. [PMID: 14514747]

70. **Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al.** Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371-88. [PMID: 9747868]

71. **Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, et al.** Effect of ibandronate on bone loss and renal function after kidney transplantation. J Am Soc Nephrol. 2001;12:1530-7. [PMID: 11423583]

72. **Kananen K, Volin L, Laitinen K, Alfthan H, Ruutu T, Välimäki MJ.** Prevention of bone loss after allogeneic stem cell transplantation by calcium, vitamin D, and sex hormone replacement with or without pamidronate. J Clin Endocrinol Metab. 2005;90:3877-85. [PMID: 15797959]

73. **Kim SH, Lim SK, Hahn JS.** Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. Am J Med. 2004;116:524-8. [PMID: 15063813]

74. **Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. HORIZON Recurrent Fracture Trial.** Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799-809. [PMID: 17878149]

75. **Ninkovic M, Love S, Tom BD, Bearcroft PW, Alexander GJ, Compston JE.** Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. J Hepatol. 2002;37:93-100. [PMID: 12076867]

76. **Ravn P, Clemmesen B, Riis BJ, Christiansen C.** The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind, placebo-controlled dose-finding study. Bone. 1996;19:527-33. [PMID: 8922653]

77. **Recker R, Stakkestad JA, Chesnut CH 3rd, Christiansen C, Skag A, Hoiseth A, et al.** Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone. 2004;34:890-9. [PMID: 15121021]

78. **Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al.** Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med. 2002;346:653-61. [PMID: 11870242]

79. **Reid IR, Wattie DJ, Evans MC, Gamble GD, Stapleton JP, Cornish J.** Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis. J Clin Endocrinol Metab. 1994;79:1595-9. [PMID: 7989461]

80. **Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Women's Health Initiative Investigators.** Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669-83. [PMID: 16481635]

81. **Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al.** Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005;330:1003. [PMID: 15860827]

82. **Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A.** Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007; 370:657-66. [PMID: 17720017]

83. **Ishida Y, Kawai S.** Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. Am J Med. 2004;117:549-55. [PMID: 15465502]

84. **Tóth E, Csupor E, Mészáros S, Ferencz V, Németh L, McCloskey EV, et al.** The effect of intranasal salmon calcitonin therapy on bone mineral density in idiopathic male osteoporosis without vertebral fractures—an open label study. Bone. 2005;36:47-51. [PMID: 15664001]

85. **Women's Health Initiative Steering Committee.** Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291:1701-12. [PMID: 15082697]

86. **Homik JE, Cranney A, Shea B, Tugwell P, Wells G, Adachi JD, et al.** A meta-analysis on the use of bisphosphonates in corticosteroid induced osteoporosis. J Rheumatol. 1999;26:1148-57. [PMID: 10332982]

87. **Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al.** Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005;16:510-6. [PMID: 15322742]

88. **Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al.** The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003;18:9-17. [PMID: 12510800]

89. **Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al.** Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282:637-45. [PMID: 10517716]

90. **Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knickerbocker RK, et al.** Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J. Bone Miner Res. 1998;13:1747-54. [PMID: 9797484]

91. **Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al.** Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl. Cancer Inst. 1998;90:1371-88. [PMID: 9747868]

92. **Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B, et al.** Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int. 2007;18:811-8. [PMID: 17473911]

93. **Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SM, et al.** Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab. 2006;91: 2631-7. [PMID: 16636120]

94. **Fukunaga M, Kushida K, Kishimoto H, Shiraki M, Taketani Y, Minaguchi H, et al. Risedronate Phase III Research Group.** A comparison of the effect of risedronate and eridronate on lumbar bone mineral density in Japanese patients with osteoporosis: a randomized controlled trial. Osteoporos Int. 2002;13:971-9. [PMID: 12459940]

95. **Guañabens N, Parés A, Ros I, Alvarez L, Pons F, Caballería L, et al.** Alendronate is more effective than etidronate for increasing bone mass in osteopenic patients with primary biliary cirrhosis. Am J Gastroenterol. 2003;98: 2268-74. [PMID: 14572578]

96. **Iwamoto J, Takeda T, Ichimura S, Uzawa M.** Comparative effects of treatment with eridronate and alendronate on bone resorption, back pain, and activities of daily living in elderly women with vertebral fractures. Keio J Med. 2003; 52:230-5. [PMID: 14748475]

97. **Kushida K, Fukunaga M, Kishimoto H, Shiraki M, Itabashi A, Inoue T,**

et al. A comparison of incidences of vertebral fracture in Japanese patients with involutional osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. J Bone Miner Metab. 2004;22:469-78. [PMID: 15316868]
98. **Muscoso E, Puglisi N, Mamazza C, Lo Giudice F, Testai M, Abbate S, et al.** Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. Eur Rev Med Pharmacol Sci. 2004;8:97-102. [PMID: 15267123]
99. **Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, et al. Fosamax Actonel Comparison Trial Investigators.** Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res. 2005;20:141-51. [PMID: 15619680]
100. **Tauchmanovà L, De Simone G, Muscella T, Orio F, Ricci P, Nappi C, et al.** Effects of various antireabsorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation. Bone Marrow Transplant. 2006;37:81-8. [PMID: 16247420]
101. **Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. National Surgical Adjuvant Breast and Bowel Project (NSABP).** Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295:2727-41. [PMID: 16754727]
102. **Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, et al.** A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87:4528-35. [PMID: 12364430]
103. **Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer JP.** Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. Calcif Tissue Int. 1997;61:266-71. [PMID: 9312195]
104. **Garcia-Delgado I, Prieto S, Gil-Fraguas L, Robles E, Rufilanchas JJ, Hawkins F.** Calcitonin, etidronate, and calcidiol treatment in bone loss after cardiac transplantation. Calcif Tissue Int. 1997;60:155-9. [PMID: 9056163]
105. **Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, et al.** Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. N Engl J Med. 1998;338:485-92. [PMID: 9443925]
106. **Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J, et al.** Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause. 2004;11:405-15. [PMID: 15243278]
107. **Recker RR, Kendler D, Recknor CP, Rooney TW, Lewiecki EM, Urian WH, et al.** Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. Bone. 2007;40:843-51. [PMID: 17182297]
108. **Uchida S, Taniguchi T, Shimizu T, Kakikawa T, Okuyama K, Okaniwa M, et al.** Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. J Bone Miner Metab. 2005;23:382-8. [PMID: 16133688]
109. **Torgerson DJ, Bell-Syer SE.** Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA. 2001;285:2891-7. [PMID: 11401611]
110. **Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, et al.** Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res. 2007;22:503-8. [PMID: 17243862]
111. **Blair MM, Carson DS, Barrington R.** Bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis. J Fam Pract. 2000;49:839-48. [PMID: 11032210]
112. **Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, et al.** Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med. 1997;337:382-7. [PMID: 9241127]
113. **Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al.** Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 1999;42:2309-18. [PMID: 10555025]
114. **Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al.** Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med. 1998;339:292-9. [PMID: 9682041]
115. **Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, et al.** Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum. 2001;44:202-11. [PMID: 11212161]
116. **Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al.** Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res. 2000;15:1006-13. [PMID: 10841169]
117. **Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al.** Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int. 2000;67:277-85. [PMID: 11000340]
118. **van Staa T, Abenhaim L, Cooper C.** Upper gastrointestinal adverse events and cyclical etidronate. Am J Med. 1997;103:462-7. [PMID: 9428828]
119. **Adami S, Bruni V, Bianchini D, Becorpi A, Lombardi P, Campagnoli C, et al.** Prevention of early postmenopausal bone loss with cyclical etidronate. J Endocrinol Invest. 2000;23:310-6. [PMID: 10882149]
120. **Cortet B, Hachulla E, Barron L, Bonvoisin B, Roux C.** Evaluation of the efficacy of etidronate therapy in preventing glucocorticoid-induced bone loss in patients with inflammatory rheumatic diseases. A randomized study. Rev Rhum Engl Ed. 1999;66:214-9. [PMID: 10339777]
121. **Geusens P, Dequeker J, Vanhoof J, Stalmans R, Boonen S, Joly J, et al.** Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. Ann Rheum Dis. 1998;57:724-7. [PMID: 10070271]
122. **Geusens P, Vanhoof J, Joly J, Dequeker J, Nijs J, Rauss J.** Cyclic etidronate increases bone density in the spine and hip in postmenopausal women on chronic corticosteroid treatment. A double-blind controlled study. . Bone. 1997;20:9S.
123. **Heath DA, Bullivant BG, Boiven C, Balena R.** The effects of cyclical etidronate on early postmenopausal bone loss: an open, randomized controlled study. J Clin Densitom. 2000;3:27-33. [PMID: 10745299]
124. **Herd RJ, Balena R, Blake GM, Ryan PJ, Fogelman I.** The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. Am J Med. 1997;103:92-9. [PMID: 9274891]
125. **Meunier PJ, Confavreux E, Tupinon I, Hardouin C, Delmas PD, Balena R.** Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year follow-up). J Clin Endocrinol Metab. 1997;82:2784-91. [PMID: 9284696]
126. **Pitt P, Li F, Todd P, Webber D, Pack S, Moniz C.** A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long-term oral corticosteroid treatment. Thorax. 1998;53:351-6. [PMID: 9708225]
127. **Roux C, Oriente P, Laan R, Hughes RA, Ittner J, Goemaere S, et al.** Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. Ciblos Study Group. J Clin Endocrinol Metab. 1998;83:1128-33. [PMID: 9543129]
128. **Silberstein EB, Schnur W.** Cyclic oral phosphate and etidronate increase femoral and lumbar bone mineral density and reduce lumbar spine fracture rate over three years. J Nucl Med. 1992;33:1-5. [PMID: 1730972]
129. **Brumsen C, Papapoulos SE, Lips P, Geelhoed-Duijvestijn PH, Hamdy NA, Landman JO, et al.** Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. J Bone Miner Res. 2002;17:1057-64. [PMID: 12054161]
130. **Lees B, Garland SW, Walton C, Ross D, Whitehead MI, Stevenson JC.** Role of oral pamidronate in preventing bone loss in postmenopausal women. Osteoporos Int. 1996;6:480-5. [PMID: 9116394]
131. **Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, et al.** Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med. 1992;117:1-9. [PMID: 1534476]
132. **Reid IR, King AR, Alexander CJ, Ibbertson HK.** Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1, 1-bisphosphonate (APD). Lancet. 1988;1:143-6. [PMID: 2892989]
133. **Ryan PJ, Blake GM, Davie M, Haddaway M, Gibson T, Fogelman I.** Intermittent oral disodium pamidronate in established osteoporosis: a 2 year double-masked placebo-controlled study of efficacy and safety. Osteoporos Int. 2000;11:171-6. [PMID: 10793877]

134. **Sato Y, Asoh T, Kaji M, Oizumi K.** Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. J Bone Miner Res. 2000;15:2487-94. [PMID: 11127214]

135. **McClung MR, Wasnich RD, Recker R, Cauley JA, Chesnut CH 3rd, Ensrud KE, et al. Oral Ibandronate Study Group.** Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. J Bone Miner Res. 2004;19:11-8. [PMID: 14753731]

136. **Woo SB, Hellstein JW, Kalmar JR.** Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144:753-61. [PMID: 16702591]

137. **Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM.** Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med. 2008; 168:826-31. [PMID: 18443257]

138. **Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, et al. ESPRIT team.** Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet. 2002; 360:2001-8. [PMID: 12504395]

139. **Mosekilde L, Beck-Nielsen H, Sørensen OH, Nielsen SP, Charles P, Vestergaard P, et al.** Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women—results of the Danish Osteoporosis Prevention Study. Maturitas. 2000;36:181-93. [PMID: 11063900]

140. **Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al.** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280:605-13. [PMID: 9718051]

141. **Recker RR, Davies KM, Dowd RM, Heaney RP.** The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. Ann Intern Med. 1999; 130:897-904. [PMID: 10375338]

142. **Cummings SR, Schwartz AV, Black DM.** Alendronate and atrial fibrillation [Letter]. N Engl J Med. 2007;356:1895-6. [PMID: 17476024]

143. **Notelovitz M, John VA, Good WR.** Effectiveness of Alora estradiol matrix transdermal delivery system in improving lumbar bone mineral density in healthy, postmenopausal women. Menopause. 2002;9:343-53. [PMID: 12218723]

144. **Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, et al. WHI Investigators.** Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006;295:1647-57. [PMID: 16609086]

145. **Grady D, Ettinger B, Moscarelli E, Plouffe L Jr, Sarkar S, Ciaccia A, et al. Multiple Outcomes of Raloxifene Evaluation Investigators.** Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol. 2004;104:837-44. [PMID: 15458908]

146. **Smith MR, Fallon MA, Lee H, Finkelstein JS.** Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab. 2004;89:3841-6. [PMID: 15292315]

147. **Johnston CC Jr, Bjarnason NH, Cohen FJ, Shah A, Lindsay R, Mitlak BH, et al.** Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. Arch Intern Med. 2000; 160:3444-50. [PMID: 11112238]

148. **Jolly EE, Bjarnason NH, Neven P, Plouffe L Jr, Johnston CC Jr, Watts SD, et al.** Prevention of osteoporosis and uterine effects in postmenopausal women taking raloxifene for 5 years. Menopause. 2003;10:337-44. [PMID: 12851517]

149. **Kung AW, Chao HT, Huang KE, Need AG, Tacchakraichana N, Loh FH, et al.** Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women. J Clin Endocrinol Metab. 2003;88:3130-6. [PMID: 12843154]

150. **Meunier PJ, Vignot E, Garnero P, Confavreux E, Paris E, Liu-Leage S, et al.** Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group. Osteoporos Int. 1999;10:330-6. [PMID: 10692984]

151. **Michalská D, Stepan JJ, Basson BR, Pavo I.** The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2006;91:870-7. [PMID: 16352692]

152. **Zheng S, Wu Y, Zhang Z, Yang X, Hui Y, Zhang Y, et al.** Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in postmenopausal women: a randomized clinical trial in Beijing. Chin Med J (Engl). 2003;116:1127-33. [PMID: 12935394]

153. **Draper MW, Flowers DE, Huster WJ, Neild JA, Harper KD, Arnaud C.** A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. J Bone Miner Res. 1996; 11:835-42. [PMID: 8725181]

154. **Johnell O, Scheele WH, Lu Y, Reginster JY, 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;87:985-92. [PMID: 11889149]

155. **Rubin MR, Lee KH, McMahon DJ, Silverberg SJ.** Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2003;88:1174-8. [PMID: 12629102]

Current Author Addresses: Drs. Qaseem and Snow: 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Shekelle: 1776 Main Street, Santa Monica, CA 90401.
Dr. Hopkins: 4301 West Markham Street, Little Rock, AR 72205.
Dr. Forciea: 3615 Chestnut Street, Philadelphia, PA 19104.
Dr. Owens: 117 Encina Commons, Stanford, CA 94305.