

ORIGINAL ARTICLE

Teriparatide or Alendronate in Glucocorticoid-Induced Osteoporosis

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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 μ g 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 (\pm SE) bone mineral density at the lumbar spine had increased more in the teriparatide group than in the alendronate group ($7.2\pm 0.7\%$ vs. $3.4\pm 0.7\%$, $P<0.001$). 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.)

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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 μ g), 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-

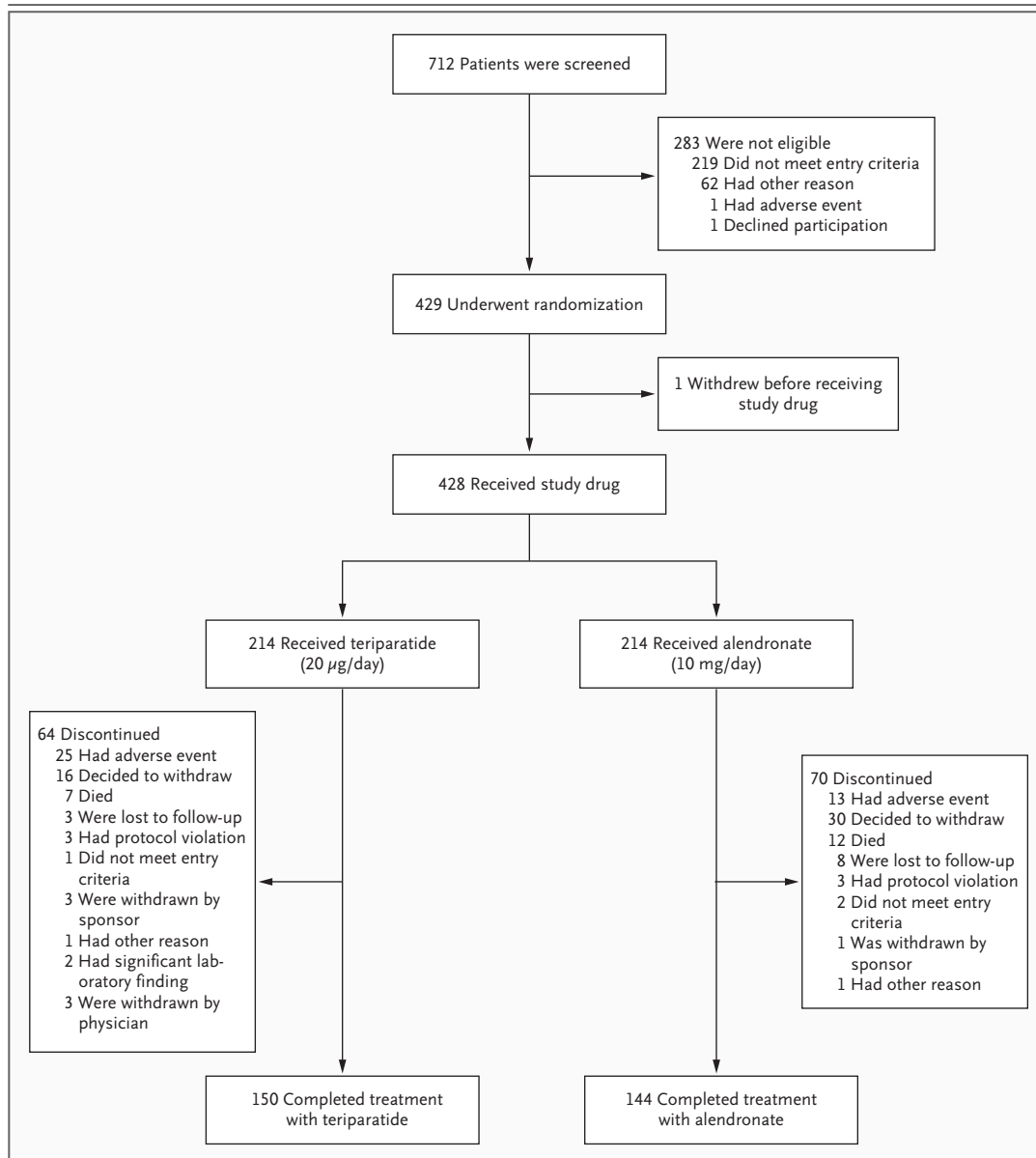


Figure 1. Enrollment and Outcomes.

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/cm ²	0.85±0.13	0.85±0.13
T score	-2.6±0.89	-2.5±0.88
Total hip		
Measurement — g/cm ²	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 \pm 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 pre-defined 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).

(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.

RESULTS

PATIENTS

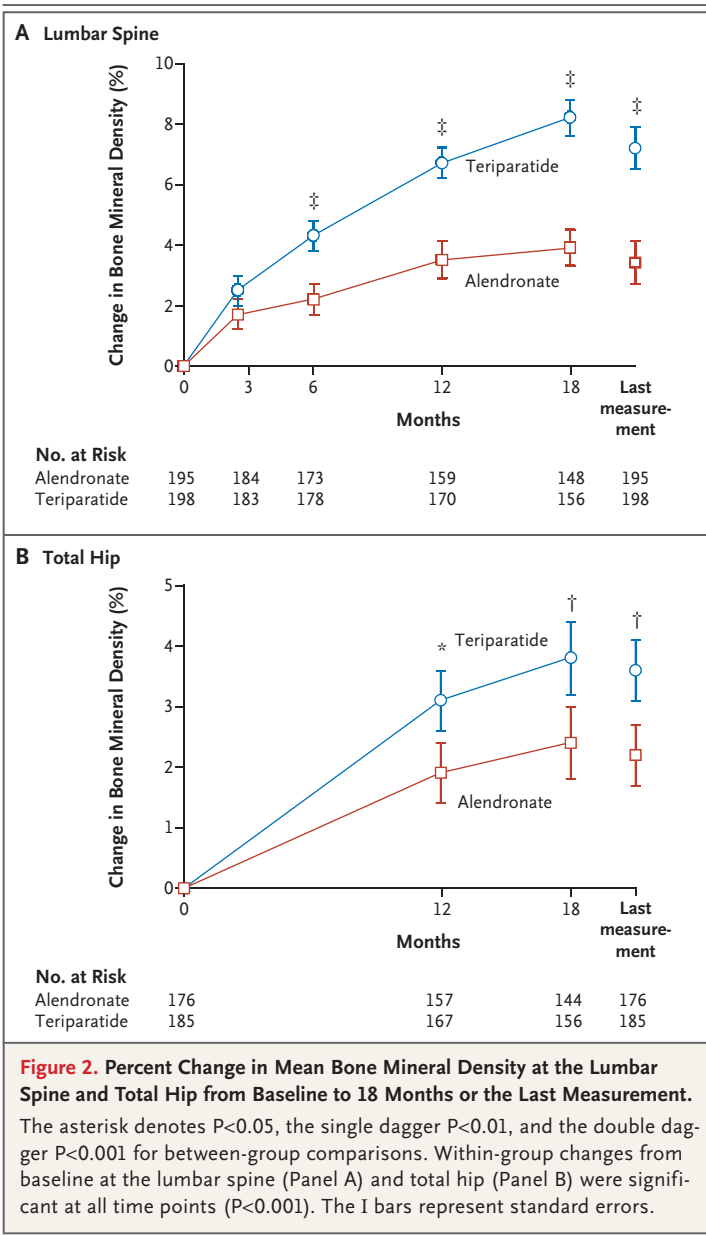
A total of 712 patients (564 women and 148 men) were screened in 12 countries. Of these patients, 429 underwent randomization and 428 began treatment (345 women and 83 men) (Fig. 1). A total of 134 patients discontinued the study prematurely, 70 in the alendronate group (32.7%) and 64 in the teriparatide 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

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-



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

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 base-

line was $3.8\pm 0.6\%$ in the teriparatide group and $2.4\pm 0.6\%$ 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-

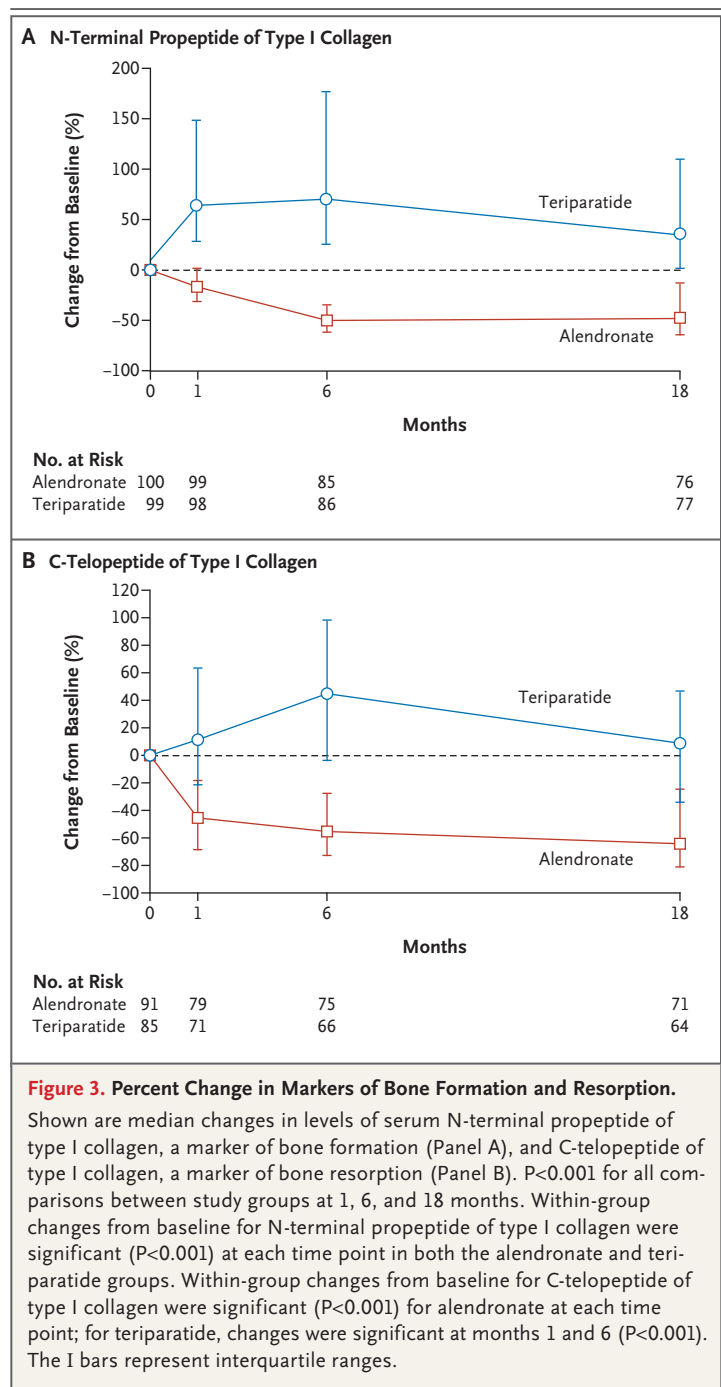
tients in the teriparatide group reported having nausea, insomnia, pharyngitis, and viral infection; more patients in the alendronate group reported having rash, a decrease in weight, sciatica, and asthma. In the teriparatide group, hyperuricemia was reported as an adverse event for three patients, and 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).

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. (%)			
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. (%)			
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.

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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 Goiânia, S. Reumatologia, Goiás — A.C. Ximenes; Complexo Hospitalario Heliópolis, São Paulo — C.A. Zerbini; Hospital Agamenon Magalhães, Recife — F. Bandeira; Hospital Universitario Pedro Hernesto, Rio de Janeiro — G.R.C. Pinheiro; Instituto de Pesquisa Clínica e Assistência Médica, 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. Reumatologia, São Paulo — R.M.R. Pereira; Hospital de Clínicas de Curitiba, Curitiba — S.C. Radominski; Escola Paulista de Medicina, São Paulo — V. Szejnfeld; Hospital de Servidor Público 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; Charité 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. Lingeogowda; 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 Atlas, Caracas — B.R. Losada.

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