

Longterm Reduction of Back Pain Risk in Women with Osteoporosis Treated with Teriparatide Compared with Alendronate

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ABSTRACT. Objective. To compare the effects on back pain of teriparatide versus alendronate, we analyzed the reporting of back pain in a head to head comparator trial and a followup study.

Methods. In the comparator trial, women were randomized to receive either daily self-injected teriparatide 40 µg plus an oral placebo (n = 73), or daily oral alendronate 10 mg plus self-injected placebo (n = 73). Treatment was for a median 14 months. After completion of the comparator trial, 72% of these patients enrolled in a nontreatment followup study. Adverse events were recorded at each comparator trial visit and followup study visit, and the incidence of new or worsening back pain in each group was compared.

Results. During the comparator trial, compared with women randomized to alendronate 10 mg, women randomized to teriparatide 40 µg had reduced risk for any back pain (relative risk 0.27, 95% CI 0.09–0.82) and moderate or severe back pain (relative risk 0.19, 95% CI 0.04–0.86). The differences in the reporting of back pain between the teriparatide treated women and the alendronate treated women were sustained during an interval including the comparator trial plus 18 additional months. During an interval including the comparator trial plus 30 additional months, teriparatide treated patients had numerically fewer occurrences of back pain and moderate or severe back pain.

Conclusion. Compared with women randomized to alendronate 10 mg, women randomized to teriparatide 40 µg had reduced risk of back pain during the trial and 2.5 years of followup. (J Rheumatol 2005;32:1556–62)

Key Indexing Terms:

BACK PAIN OSTEOPOROSIS BONE FORMATION TERIPARATIDE ALENDRONATE

More than 75 million people in the United States, Europe, and Japan are affected by osteoporosis¹. The US National Institutes of Health defines osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture². The World Health Organization (WHO) operationally defines osteoporosis as a bone density 2.5 standard deviations below the mean for young Caucasian adult women³. Chronic back pain may occur in patients with osteoporosis who have vertebral fractures⁴. Patients with vertebral fractures are more likely to

have back pain, more back pain related days of bed rest, diminished physical capabilities, kyphosis, and increased mortality⁴⁻⁷. The consequences of osteoporotic vertebral fractures — back pain, physical deformity, and functional disability — may profoundly affect the psychological well being and quality of life of the patient⁸⁻¹⁰. An estimated 8 million women and 2 million men in the US have osteoporosis. Less than half of those patients with osteoporotic vertebral fractures have been diagnosed^{1,11}. Of those patients with clinically diagnosed vertebral deformities, about one-quarter are hospitalized at an annual cost of about \$500 million in the US and E 377 million in Europe¹²⁻¹⁴.

Treatments with teriparatide, an anabolic agent, and with alendronate, an antiresorptive agent, have proven efficacy in reducing the risk of new vertebral fractures in large trials of postmenopausal women with osteoporosis and previous vertebral fractures. Patients treated with teriparatide 20 or 40 µg/day also had a similarly reduced risk for new or worsening back pain compared with placebo treated patients (p = 0.007)¹⁵. In a head to head comparator trial, patients treated with teriparatide 40 µg/day had reduced risk for new or worsening back pain (p = 0.012) compared with patients treated with alendronate 10 mg/day¹⁶. We report additional back pain analyses from the comparator trial and a followup study.

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MATERIALS AND METHODS

Patients. Postmenopausal women with osteoporosis (n = 146) participated in a global, multicenter, double blind, parallel, randomized trial designed to compare increases in vertebral bone mineral density (BMD) and differences in bone turnover following treatment with teriparatide [recombinant human parathyroid hormone (1-34)] 40 µg once-daily injection, or treatment with alendronate sodium 10 mg oral capsule per day. All women received once-daily oral supplementation with calcium (1000 mg) and vitamin D (400 to 1200 IU). Additional details of the methods for this comparator trial are published¹⁶.

After completing the comparator trial, 72% of patients elected to participate in a multicenter, multinational, post-therapy safety and efficacy followup study. This analysis includes data collected at visits during the comparator trial and during 30 months of additional observation. Study visits were at baseline, 1, 3, 6 and 12 months, and endpoint. Followup study visits were scheduled for baseline and 6, 18, and 30 months after completion of the comparator trial. Treatment and observation periods are depicted in Figure 1. Participating investigators and patients in the followup study were not blinded to the patient's prior treatment with teriparatide or alendronate. Patients who enrolled in the followup study were allowed to take treatments for osteoporosis prescribed by their physicians. Table 1 presents osteoporosis drug use during the followup study; 46.7% of patients were treated with bisphosphonates and 23.8% of patients were treated with selective estrogen receptor modulators (SERM) during this period.

Assessment of adverse events. An adverse event was any undesirable experience or unanticipated benefit without regard to treatment group assignment, causality, or seriousness. At each study visit, patients were questioned regarding the occurrence of adverse events, and all adverse events were recorded on the case report form. Women were not queried specifically regarding back pain. Women reporting new or worsening back pain after starting study drug were defined as having back pain. The investigator assessed the severity of adverse events, including back pain, as mild,

moderate, or severe. A mild adverse event was defined as one involving no change in physical activity with occasional medication use for relief of pain symptoms. Criteria for a moderate adverse event included mild disruptions in daily physical activities and regular medication use for alleviation of pain. Criteria for a severe adverse event included major disruption in normal daily activities, additional medication use and treatment for pain, and/or hospitalization.

Statistical analysis. Treatment-emergent adverse back pain events were stratified according to severity and analyzed for between-group differences. All categorical data were analyzed using Pearson's chi-square test and all continuous data using Student's t test. A multivariate Cox proportional hazard model was used to compute the relative risk of back pain after adjusting for baseline lumbar spine BMD. Analyses of back pain incidence compared the alendronate 10 mg and teriparatide 40 µg groups on the basis of time to first new or worsening back pain using a log-rank test. The cumulative incidence of treatment-emergent back pain was calculated using the Kaplan-Meier method. All statistical tests were 2 sided with a significance level of 0.05 using SAS software, version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics. Two hundred sixty-five women were screened and 149 women were randomized to treatment. Three women withdrew before treatment. Seventy-three women were randomized to teriparatide 40 µg/day subcutaneous injection plus oral placebo. Seventy-three women were randomized to alendronate sodium 10 mg/day oral capsule plus placebo injection (Figure 2). The median duration of observation during the comparator trial was 15.4 months. The median duration of observation during the

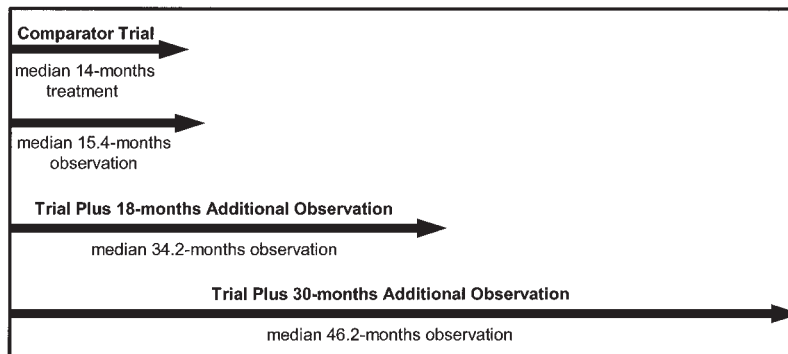


Figure 1. Comparator trial treatment and observation periods; trial plus additional observation periods.

Table 1. Patients taking any osteoporosis drug for any duration from end of the comparator trial to the 30 month followup visit.

Patients taking	Alendronate 10 mg (N = 53), n (%)	Teriparatide 40 µg (N = 52), n (%)	p
Any osteoporosis treatment	37 (69.8)	38 (73)	0.711
Bisphosphonates	23 (43.4)	26 (50)	0.498
Calcitonin	2 (3.8)	—	0.157
Hormone replacement therapy	3 (5.7)	4 (7.7)	0.676
Progestin/androgen	3 (5.7)	2 (3.9)	0.663
Selective estrogen receptor modulators	13 (24.5)	12 (23)	0.861
Multiple osteoporosis treatment	6 (11.3)	5 (9.6)	0.775

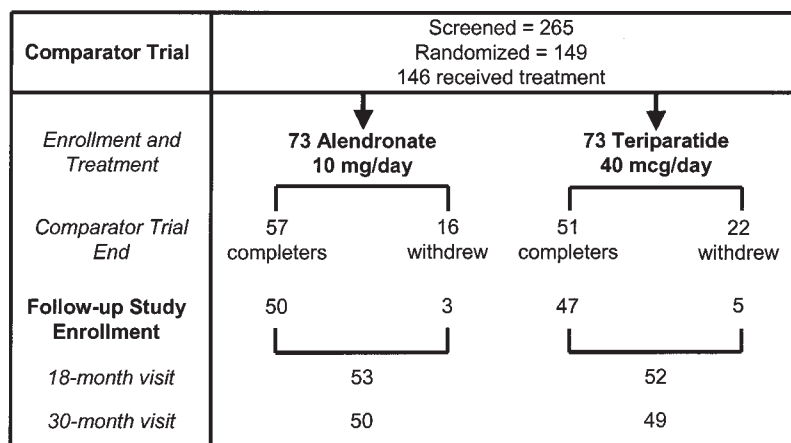


Figure 2. Number of patients enrolled during the comparator trial (alendronate vs teriparatide) and during the followup study.

comparator trial plus an additional 18 months' observation was 34.3 months. The median duration of observation during the comparator trial plus an additional 30 months' observation was 46.2 months (Figure 1).

There were no significant differences between groups in baseline characteristics (Table 2A). The majority of patients were Caucasian (82%), followed by Hispanic origin (16%), and Asian origin (1%). After the comparator trial, 53 patients previously treated with alendronate and 52 previously treated with teriparatide enrolled in the followup study (Figure 2). There were no significant between-group differences in baseline characteristics among women who enrolled in the followup study (Table 2B).

During the first 18 months of additional observation, 66% of the patients previously treated with alendronate and 69% of patients previously treated with teriparatide used an

osteoporosis treatment. Of the subjects who returned after 30 months of additional observation, 70% of those previously treated with alendronate and 73% of patients previously treated with teriparatide had used an osteoporosis treatment. There were no significant between-group differences in the number of patients receiving any osteoporosis treatments or any specific type of osteoporosis treatment at any followup visit (Table 1).

Back pain. Back pain results during the comparator trial are presented in Table 3. The results of back pain reported during the comparator trial plus 18 months and during the comparator trial plus 30 months of additional observation are shown in Table 4. Compared with women treated with alendronate, fewer women randomized to teriparatide reported back pain during the comparator trial (5.5% vs 19.2%; relative risk 0.27, 95% CI 0.09–0.82). During the comparator

Table 2. A. Baseline characteristics of women enrolled in the comparator trial. B. Baseline characteristics of women from the comparator trial subsequently enrolled in the followup study.

A	Alendronate 10 mg, N = 73	Teriparatide 40 µg, N = 73	p
Age, yrs	65 ± 9	66 ± 8	0.43
Vertebral BMD, g/cm ²	0.795 ± 0.12	0.797 ± 0.11	0.92
Body mass index, kg/m ²	24.4 ± 3.5	23.9 ± 4.5	0.45
Years past menopause	19 ± 10	18 ± 9	0.58
Dietary calcium intake, g/day	620 ± 340	700 ± 380	0.18
PTH (1-34), pmol/l	3.3 ± 1.0	3.1 ± 1.1	0.27
B	Alendronate 10 mg, N = 53	Teriparatide 40 µg, N = 52	p
Age, yrs	65 ± 8	66 ± 7	0.52
Vertebral BMD, g/cm ²	0.769 ± 0.10	0.761 ± 0.11	0.78
Body mass index, kg/m ²	24.5 ± 3.4	23.8 ± 4.6	0.36
Post menopause, yrs	20 ± 10	17 ± 8	0.15
Dietary calcium intake, g/day	620 ± 350	670 ± 390	0.48
PTH (1-34), pmol/l	3.4 ± 1.0	3.3 ± 1.2	0.64

BMD: bone mineral density; PTH (1-34): human recombinant parathyroid hormone.

Table 3. Number of patients reporting back pain during the comparator trial.

	Alendronate 10 mg (N = 73), n (%)	Teriparatide 40 µg (N = 73), n (%)	Relative Risk* (95% CI)
Back pain	14 (19.2)	4 (5.5)	0.27 (0.09–0.82)
Moderate or severe back pain	10 (13.7)	2 (2.7)	0.19 (0.04–0.86)
Severe back pain	2 (2.7)	1 (1.4)	0.51 (0.05–5.64)

* Relative risk is based on the Cox proportional hazard model with treatment as a model effect after adjusting for baseline lumbar spine BMD.

Table 4. Back pain during comparator trial plus 18 months additional observation and 30 months additional observation.

	Alendronate 10 mg (N = 53), n (%)	Teriparatide 40 µg (N = 52), n (%)	Relative Risk* (95% CI)
Comparator trial plus 18 months			
Back pain	15 (28.3)	5 (9.6)	0.31 (0.11–0.84)
Moderate or severe back pain	10 (18.9)	2 (3.9)	0.19 (0.04–0.89)
Severe back pain	3 (5.7)	1 (1.9)	0.34 (0.04–3.30)
Comparator trial plus 30 months			
Back pain	15 (28.3)	8 (15.4)	0.49 (0.21–1.16)
Moderate or severe back pain	10 (18.9)	3 (5.8)	0.30 (0.08–1.08)
Severe back pain	3 (5.7)	1 (1.9)	0.34 (0.04–3.30)

* Relative risk is based on the Cox proportional hazard model with treatment as a model effect after adjusting for baseline lumbar spine BMD.

trial plus 18 months of additional observation, fewer women in the teriparatide group reported back pain compared with women in the alendronate group (9.6% vs 28.3%; relative risk 0.31, 95% CI 0.11–0.84). During the comparator trial plus 30 months of additional observation, back pain occurred in fewer teriparatide treated patients (15.4% vs 28.3%; relative risk 0.49, 95% CI 0.21–1.16). The cumulative incidence of reported back pain across all observation periods separated after about 3 months of treatment (Figure 3A). The cumulative incidence of back pain was significantly lower in the teriparatide treated women during the comparator trial ($p = 0.022$), and during the comparator trial plus 18 months of additional observation ($p = 0.014$); however, this difference showed a trend away from significance during the comparator trial plus 30 months of additional observation ($p = 0.09$).

Moderate or severe back pain. Moderate or severe back pain results during the comparator trial are presented in Table 3, and the results of moderate or severe back pain reported during the comparator trial plus 18 months of additional observation and during the comparator trial plus 30 months of additional observation are shown in Table 4. Compared with women treated with alendronate, fewer women randomized to teriparatide reported moderate or severe back pain during the comparator trial (2.7% vs 13.7%; relative risk 0.19, 95% CI 0.04–0.86). During the trial plus 18 months of additional observation, fewer women in the teriparatide group reported moderate or severe back pain compared with women in the alendronate group (3.9% vs 18.9%; relative risk 0.19, 95%

CI 0.04–0.89). During the comparator trial plus 30 months of additional observation, fewer women in the teriparatide group reported moderate or severe back pain compared with women in the alendronate group (5.8% vs 18.9%; relative risk 0.30, 95% CI 0.08–1.08).

The cumulative incidence of reported moderate or severe back pain across all observation periods shows an initial separation after about 3 months of treatment (Figure 3B). The cumulative incidence of moderate or severe back pain was significantly lower in teriparatide treated women during the comparator trial ($p = 0.018$), during the comparator trial plus 18 months of additional observation ($p = 0.015$), and during the comparator trial plus 30 months of additional observation ($p = 0.04$). The number of women reporting severe back pain was small during all observation periods (Table 3, Table 4) and did not show significant differences.

DISCUSSION

In this trial, significantly fewer women treated with teriparatide compared with alendronate reported back pain or moderate or severe back pain. The difference in reported back pain between the groups was sustained during longterm additional observation. The mechanism for the back pain reduction in teriparatide treated compared with alendronate treated women is unknown. The 2 agents have essentially opposite effects on bone turnover. Teriparatide increases bone remodeling and stimulates bone formation, while alendronate suppresses bone remodeling and prevents bone loss¹⁷. Both teriparatide and alendronate reduce the

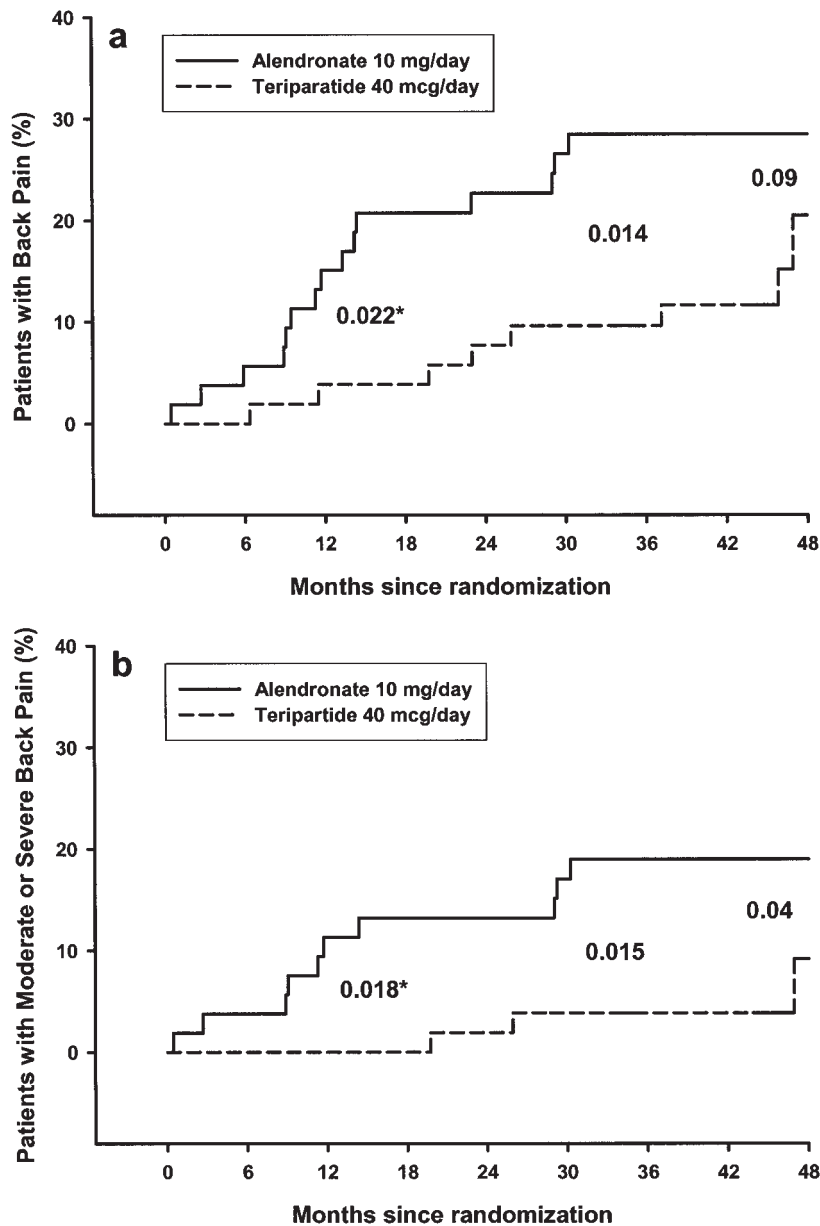


Figure 3. A. Back pain during the comparator trial and at 18 and 30 month followup. B. Moderate or severe back pain during the comparator trial and at 18 and 30 month followup visits. *Log-rank p values at the end of the comparator trial, and at 18 and 30 month followup visits (median 15.4, 34.3, and 46.2 months after randomization).

risk for new vertebral fractures. Women with prevalent vertebral fractures treated with teriparatide 20 µg/day for a median 19 months had a 65% reduced risk for new vertebral fractures, compared with placebo; women treated with teriparatide 40 µg/day had a 69% reduced risk for new vertebral fractures, compared with placebo. The risk of new vertebral fractures graded as moderate or severe was reduced by 90% for the teriparatide 20 µg group and by 78% for the teriparatide 40 µg group¹⁵. Treatment with alendronate 5 mg/day for 2 years and then alendronate 10 mg/day for one year reduced the risk of new vertebral fractures by 47%¹¹,

but the effects of alendronate on new moderate or severe vertebral fractures have not been published. A possible mechanism for the differences in back pain between the 2 groups may be differences in vertebral fracture efficacy of the 2 drugs, but because our study did not include radiographs of the spine, this hypothesis is not testable. However, in indirect support of this hypothesis, significantly fewer ($p = 0.042$) nonvertebral fractures occurred in the teriparatide group (4.1%) than in the alendronate group (13.7%) during the comparator trial¹⁶.

Published trials of antiresorptive drugs do not consistent-

ly include observations of reductions in back pain. The primary publications of the alendronate fracture trials did not include any mention of back pain^{11,18,19}. However, Nevitt, *et al*²⁰ reported an analysis of back pain data in patients taking alendronate compared with placebo, collected using a back pain questionnaire in the FIT-1 trial¹¹. There were no statistically significant differences between treatment groups in the number of patients with back pain or increases in back related disability between baseline and study end. However, significantly fewer women treated with alendronate required bed rest for back pain, and there was a trend for fewer women treated with alendronate to limit their activity because of back pain. The primary publications reporting the results of the risedronate fracture trials do not contain any mention of back pain²¹⁻²³. The primary publication of the raloxifene fracture trial results does not include any reference to back pain²⁴. Nasal calcitonin is commonly believed to have an analgesic effect after acute vertebral fracture²⁵, but the primary publication of the fracture data for this drug does not contain any mention of back pain²⁶.

Limitations and strengths. The absence of vertebral radiographs during the study limits the ability to determine the relationship between episodes of back pain and the occurrence of vertebral fractures. The collection of back pain data during monitoring of adverse events requires additional comment. Randomization, blinding, and standard directions for recording adverse events during the comparator trial should have prevented systematic bias in favor of either treatment group. The followup study was not blinded, patients were no longer taking study drug, and it is unlikely that investigators would have a bias toward reporting back pain in either the previously alendronate treated or previously teriparatide treated groups. Notably, use of other bone drugs during the followup study was similar between the 2 groups. Nevertheless, a prospective trial of teriparatide in women at risk of back pain with back pain ascertainment as the endpoint is needed. This trial should include assessments of quality of life and analgesic consumption.

The teriparatide 40 µg/day dose administered during the comparator trial is higher than the approved 20 µg/day dose. However, a similarly reduced incidence of back pain compared with placebo was observed in both 20 and 40 µg groups in a large placebo controlled trial¹⁵. Also, another recent comparator trial showed reduced back pain incidence in patients randomized to teriparatide 20 µg/day compared with women randomized to alendronate 10 mg/day²⁷.

In conclusion, fewer women randomized to teriparatide 40 µg/day experienced back pain and moderate or severe back pain compared with women randomized to alendronate 10 mg/day during the comparator trial. After stopping study drug, the differences in back pain incidence between the groups were sustained during a longterm followup study.

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