

Randomized Teriparatide [Human Parathyroid Hormone (PTH) 1–34] Once-Weekly Efficacy Research (TOWER) Trial for Examining the Reduction in New Vertebral Fractures in Subjects with Primary Osteoporosis and High Fracture Risk

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Context: Weekly teriparatide injection at a dose of 56.5 μg has been shown to increase bone mineral density.

Objective: A phase 3 study was conducted to determine the efficacy of once-weekly teriparatide injection for reducing the incidence of vertebral fractures in patients with osteoporosis.

Design and Setting: In this randomized, multicenter, double-blind, placebo-controlled trial conducted in Japan, the incidence of morphological vertebral fractures by radiographs was assessed.

Patients: Subjects were 578 Japanese patients between the ages of 65 and 95 yr who had prevalent vertebral fracture.

Intervention: Subjects were randomly assigned to receive once-weekly sc injections of teriparatide (56.5 μg) or placebo for 72 wk.

Main Outcome Measure: The primary endpoint was the incidence of new vertebral fracture.

Results: Once-weekly injections of teriparatide reduced the risk of new vertebral fracture with a cumulative incidence of 3.1% in the teriparatide group, compared with 14.5% in the placebo group ($P < 0.01$), and a relative risk of 0.20 (95% confidence interval, 0.09 to 0.45). At 72 wk, teriparatide administration increased bone mineral density by 6.4, 3.0, and 2.3% at the lumbar spine, the total hip, and the femoral neck, respectively, compared with the placebo ($P < 0.01$). Adverse events (AE) and the dropout rates by AE were more frequently experienced in the teriparatide group, but AE were generally mild and tolerable.

Conclusion: Weekly sc administration of teriparatide at a dose of 56.5 μg may provide another option of anabolic treatments in patients with osteoporosis at higher fracture risk. (*J Clin Endocrinol Metab* 97: 3097–3106, 2012)

Osteoporosis is a skeletal disease characterized by compromised bone strength and, consequently, susceptibility to fracture (1). Daily teriparatide injection at a dose of 20 μg is one of the most potent pharmacological treatments currently available for patients with primary osteoporosis, including men (2) and postmenopausal women (3). Teriparatide produces increased bone formation and bone mineral density (BMD) (4) through improved microarchitecture in both trabecular and cortical bone by increasing the rate of bone formation so that it exceeds the rate of resorption (5–8).

Once-weekly injection of teriparatide has also been shown to increase BMD in patients with osteoporosis by increasing bone formation in a phase 2 study (9), and it is thought to be a potential anabolic treatment option for osteoporosis. However, the efficacy of once-weekly teriparatide injection on the risk of fracture in patients with primary osteoporosis has not been examined. Thus, we conducted the Teriparatide Once-Weekly Efficacy Research (TOWER) trial for 72 wk to determine whether once-weekly teriparatide injection would reduce the risk of vertebral fracture in subjects with primary osteoporosis, including older men and postmenopausal women.

Subjects and Methods

Study design

This was a randomized, multicenter, double-blind, placebo-controlled trial conducted in Japan. Subjects were randomly assigned to receive weekly sc injections of teriparatide 56.5 μg or placebo for 72 wk. All subjects received daily oral supplements of calcium 610 mg, vitamin D 400 IU, and magnesium 30 mg (Calcichew D₃; Daiichi Sankyo Healthcare, Tokyo, Japan).

All participants and physicians were blinded to group assignment; teriparatide and placebo were indistinguishable from each other at administration. A central randomization was conducted using the computed minimization method to balance for age, gender, and the number of vertebral fractures. The primary endpoint for the study was the incidence of new vertebral fracture.

This study was jointly designed by the sponsor (Asahi Kasei Pharma Corporation) and the steering committee (including T.Nakam., T.Su., M.S., and Y.N.). The sponsor had responsibility for data collection and quality control. An independent data and safety monitoring board (DSMB), including H.Y., monitored study conduct and safety. Radiographic assessments were performed by the committee of T. Nakan., H.K., and M.I. BMD data assessments were performed by H.H., T.S., and M.F. Study data were periodically consulted for the DSMB. T.F. oversaw the preparation of the manuscript. Analyses for publication were the joint responsibility of the sponsor and the steering committee. All authors contributed to the manuscript and agreed on the final version.

Subjects

Generally healthy men and postmenopausal women between 65 and 95 yr of age were eligible for the study if they had one to

five vertebral fractures with low BMD (young adult mean $\leq 80\%$; T-score ≤ -1.67) at the lumbar spine (L2 to L4), femoral neck, total hip, or distal radius measured by dual-energy x-ray absorptiometry or the right second metacarpal bone measured by radiometry.

All subjects were counseled about the effectiveness and availability of alternative treatments for osteoporosis. Subjects were excluded if they had diseases other than osteoporosis that may affect bone metabolism and decrease BMD, conditions that could reduce vertebral bone strength and interfere with bone mineral densitometry shown by lumbar radiographs, or were users of orthotics covering the whole range of the thoracic and lumbar areas. Additional exclusion criteria were serum calcium levels of 11.0 mg/dl or greater; evidence of serious kidney, liver, or heart disease, or other conditions judged to be inadequate for participation in the trial; risk for osteosarcoma, such as Paget's disease of the bone; a history of malignancy of the bone, exostoses, prior external beam, or implant radiation therapy; or serum alkaline phosphatase levels more than twice the upper limit of the standard. Subjects who had taken bisphosphonates within the past 52 wk or calcitonin, activated form of vitamin D₃, vitamin K, estrogen, selective estrogen-receptor modulators, ipriflavone, or anabolic steroids within the past 8 wk were also excluded.

This trial was conducted in compliance with the ethical principles stated in the Declaration of Helsinki and Good Clinical Practice. The trial was approved by the institutional review boards at each site, and all subjects provided written informed consent before enrollment in the trial.

Efficacy endpoints

The primary endpoint was the incidence of new, radiographically confirmed vertebral fractures (Th4 to L4) in men and women receiving once-weekly sc injections of teriparatide 56.5 μg or placebo for 72 wk. Secondary endpoints included the incidence of clinical vertebral and nonvertebral fractures; changes from baseline in BMD at the lumbar spine (L2 to L4), total hip, and femoral neck; and differences in changes from baseline in the levels of biochemical markers of bone formation and bone resorption between the teriparatide and placebo groups.

Efficacy measures

Lateral spine radiographs were obtained at screening, baseline, and 24, 48, and 72 wk. To identify morphometric vertebral fracture, the vertebral bodies from Th4 to L4 were assessed using both the semiquantitative (SQ) methodology as previously reported (10) and quantitative methods by an independent committee of three experts who were blinded to treatment. Quantitative assessment of prevalent vertebral fracture at baseline was defined as a 20% or greater reduction in the vertebral height in any of the anterior, posterior, or central vertebral heights, or from corresponding values in the adjacent upper or lower vertebra. An incident fracture was identified by SQ methodology as an increase of at least one grade. A quantitative morphometry (QM) assessment was also used to confirm the fracture, which was defined as a 20% or greater decrease from baseline of vertebral height in any of the anterior, posterior, or central vertebral heights. In cases of disagreement between the two methodologies, a binary SQ assessment was conducted by independent experts to adjudicate the discordant result. In addition, all prevalent and incident fractures were confirmed by three experts. New

vertebral fracture was defined as a vertebral fracture that was normal (SQ grade 0) at baseline. Exacerbations in deformity of preexisting vertebral fractures were not counted as new vertebral fracture. Clinical fracture was defined as a fracture confirmed on radiographs with clinically evident symptoms such as pain at the vertebral or nonvertebral region. Clinical fractures were initially identified by physicians at each site and confirmed by radiographs. Clinical fragility fractures were defined as the clinical vertebral fracture and clinical nonvertebral fracture, excluding those that were pathological in nature or sustained after significant trauma (e.g. motor vehicle accident, or a fall from a height higher than standing height).

The BMD of the lumbar spine and hip was measured using dual-energy x-ray absorptiometry at baseline and at 24, 48, and 72 wk. Lumbar spine and total hip BMD were analyzed for subjects who were at institutions where these measurements were available. Lumbar spine BMD was measured in 292 subjects, and the hip in 340 subjects. QDR (Hologic, Bedford, MA) and DPX (GE Healthcare, Fairfield, CT) were used in this trial. The densitometry data were reviewed by an independent committee of experts who were blinded to treatment.

Serum and urine samples were obtained under nonfasting conditions before injection of teriparatide or placebo and stored in the refrigerator at the temperature of -20°C . The measurements were performed centrally in a single batch at a validated institution (Mitsubishi Chemical Medience, Tokyo, Japan). Concentrations of osteocalcin, procollagen type I amino-terminal propeptide (P1NP), and calcium were measured in serum samples at baseline and at 4, 12, 24, 48, and 72 wk. Concentrations of urinary cross-linked N-telopeptide of type I collagen (u-NTX) and calcium were also measured at the same time points. Osteocalcin was measured by immunoradiometric assay (BGP-IRMA Mitsubishi; Mitsubishi Chemical Medience); P1NP was measured by RIA (Orion Diagnostica, Espoo, Finland); and u-NTX was measured by enzyme-linked immunoassay (Osteomark; Inverness Medical Innovations Inc., Waltham, MA).

Adverse events

Safety was assessed by recording all adverse events (AE), serious AE (SAE), and AE that led to withdrawal from the study by physical examination, regular hematological monitoring, blood-chemical measurements, and urinary examinations. Physicians at each site reported all AE, which were then coded using preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA, version 13.0).

Statistical analysis

This study was designed to be powered at 90% to detect a 60% reduction in new vertebral fractures in the teriparatide group, assuming an incidence of 14% in the placebo group at 72 wk and a 15% subject discontinuation rate. All efficacy analyses were conducted on the intention-to-treat population. The intention-to-treat population comprised all patients who received at least one dose and who had not been excluded for noncompliance with the eligibility criteria (stipulated in advance in the protocol) or because randomized data were unavailable.

The primary analysis was conducted to test the superiority of teriparatide treatment to placebo in time to the first diagnosis of new vertebral fracture using a log-rank test. The cumulative incidence of new vertebral fracture at 72 wk was calculated by the Kaplan-Meier method, and between-group differences were dis-

played with confidence interval (CI) by Greenwood's variance. An unadjusted Cox regression model was used to estimate the relative risk and CI of new vertebral fracture. Other bone fracture assessment criteria (clinical fracture, clinical fragility fracture, clinical fragility nonvertebral fracture, and clinical fragility spinal fracture) were also similarly analyzed. Incidences of new vertebral fractures between the two groups were assessed every 24 wk by Fisher's exact test, and the 95% CI were calculated ($\alpha = 0.05$).

A between-group comparison was performed for BMD by applying the paired *t* test to the percentage changes from baseline. For the bone turnover markers, the comparison was performed by applying the Wilcoxon test to the percentage changes from baseline. No multiplicity adjustment was performed for any items. Safety analyses included all subjects who received at least one dose of a study drug. Between-group analyses were performed by Fisher's exact test in the incidences of all AE, SAE, death, events resulting in discontinuation from the study, and SAE of cardiopathy and neoplasms. The significance level was set at $P < 0.05$, and 95% CI values were shown.

Results

Subjects

A total of 809 subjects were screened at 65 study sites in Japan (Fig. 1). Of these, 601 subjects were enrolled, and 578 were randomly assigned to two groups—290 subjects to teriparatide and 288 to placebo. Efficacy analyses were performed for the 572 subjects who received more than one dose of test agent and provided at least one set of data before and after dosing—286 in the teriparatide group and 286 in the placebo group (Table 1). No substantial differences were observed in the baseline background factors between the two groups. The mean age of the subjects was 75.3 yr, and the mean T scores for BMD at the start of treatment were -2.7 for the lumbar spine, -2.1 for the total hip, and -2.4 for the femoral neck. In 35 patients in the placebo group and 29 in the teriparatide group, a fracture was identified by a physician on-site, but the expert committee subsequently determined that no fracture was present using SQ and QM methods. At 72 wk, 442 (76.5%) subjects completed the study—200 (70.0%) in the teriparatide group and 242 (84.0%) in the placebo group. Ninety subjects discontinued the study in the teriparatide group and 46 in the placebo group. No differences were observed between the two groups in the baseline demographics of the subjects who discontinued or completed the study.

Fractures

The cumulative incidence of new morphometric vertebral fractures by Kaplan-Meier estimation was 3.1% in the teriparatide group and 14.5% in the placebo group ($P < 0.01$; log-rank test) (Fig. 2). The risk of new morphometric fracture was significantly reduced in the teripa-

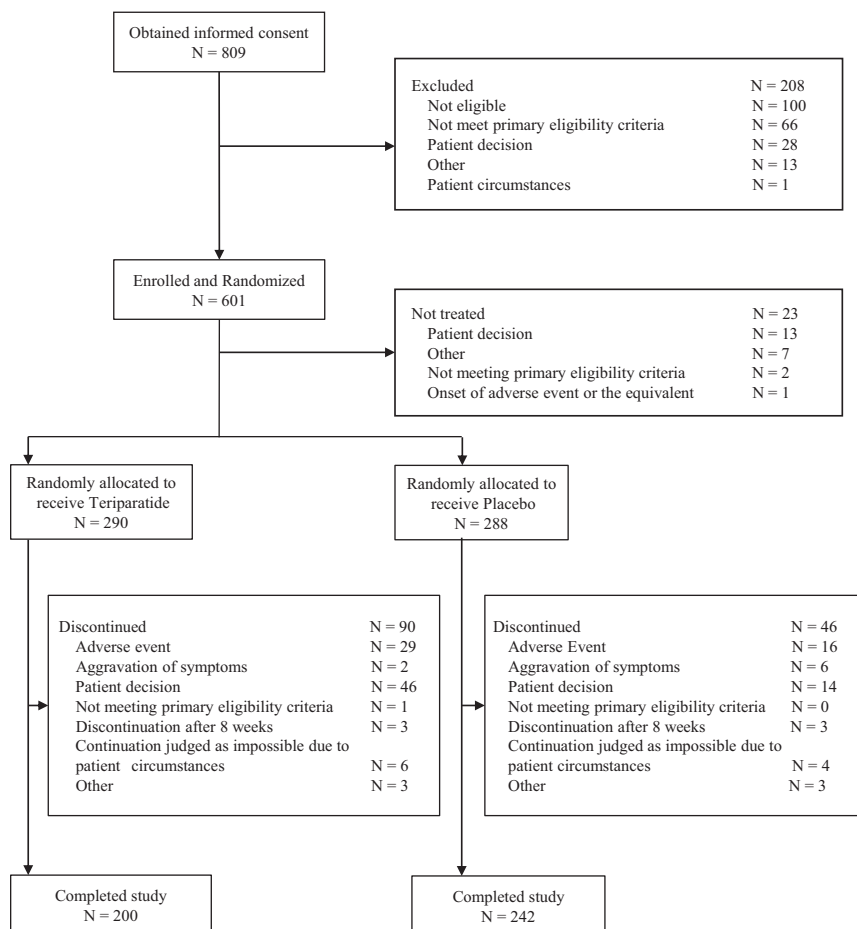


FIG. 1. Trial profile.

teriparatide group (relative risk, 0.20; 95% CI, 0.09 to 0.45; $P < 0.01$) (Fig. 2A). The incidences of new vertebral fractures were consistent every 24 wk in the placebo group at 5.0, 5.1, and 5.3%, respectively (Fig. 2B). In contrast, the incidences in the teriparatide group were 2.3, 0.9, and 0.0%, respectively. The differences were significant after the first 24 wk. The incidences of clinical fragility fracture in the teriparatide and placebo group were 3.6 and 9.9% at 72 wk, respectively ($P < 0.01$). The divergence of the incidences appeared to start at 24 wk (Fig. 2C).

In female patients, the incidences of new morphometric vertebral fracture in the teriparatide and placebo group were 2.8 and 14.1%, respectively (relative risk, 0.18; 95% CI, 0.08 to 0.44) (Table 2). The risk of clinical fragility vertebral fracture in the teriparatide group was significantly reduced by 73% for all patients and by 78% for female patients. The risk of clinical fragility fracture was also significantly reduced in the teriparatide group. However, the incidences of clinical nonvertebral fracture in the teriparatide and placebo groups were 4.7 and 5.5%, respectively, and the difference was not significant. The incidences of clinical fragility nonvertebral fracture or clin-

ical fracture also did not significantly differ between the groups.

BMD and bone markers

BMD increases from baseline in the teriparatide group at 72 wk were 6.7% (95% CI, 5.7 to 7.7) in the lumbar spine, 3.1% (95% CI, 2.1 to 4.0) in the total hip, and 1.8% (95% CI, 0.8 to 2.8) in the femoral neck. The respective values in the placebo group were 0.3% (95% CI, -0.5 to 1.1) in the lumbar spine, 0.1% (95% CI, -0.7 to 0.8) in the total hip, and -0.5% (95% CI, -1.6 to 0.3) in the femoral neck. The differences between the two groups were significant from 24 wk (Fig. 3, A and B). In female patients, BMD increases from baseline in the teriparatide group at 72 wk were 6.7% (95% CI, 5.7 to 7.7) in the lumbar spine, 2.9% (95% CI, 2.0 to 3.9) in the total hip, and 1.8% (95% CI, 0.8 to 2.9) in the femoral neck. The respective values in the placebo group were 0.3% (95% CI, -0.5 to 1.1), 0.1% (95% CI, -0.7 to 0.9), and -0.6% (95% CI, -1.6 to 0.4). The differences between the two groups were also significant from 24 wk.

Serum osteocalcin levels remained constant in the placebo group. In the teriparatide group, however, serum osteocalcin levels significantly increased from baseline by 24.6% on average at 4 wk and gradually declined thereafter, maintaining significantly higher levels at 48 wk (Fig. 3C). The differences from the placebo group were significant at 4, 12, 24, and 48 wk. Serum P1NP levels in the teriparatide group increased by 15.1% at 4 wk and were significantly higher than the placebo group until 12 wk, then significantly lower than placebo from 48 wk (Fig. 3D). u-NTX levels in the placebo group tended to increase, but the values in the teriparatide group significantly decreased from baseline by 12.2% on average at 48 wk (Fig. 3E). The differences between the two groups were significant at 48 and 72 wk. Corrected serum calcium levels did not differ between the groups throughout the study period (Fig. 3F). The numbers of the cases with corrected serum calcium levels of more than 10.4 mg/dl during the trial period were nine in the teriparatide group and 12 in the placebo group, respectively. The highest values of corrected serum calcium levels observed during the period were 11.6 mg/dl in the teriparatide group and 12.1 mg/dl

TABLE 1. Baseline subject characteristics

Variable	Placebo (n = 286)	Teriparatide (n = 286)
Age (yr)	75.5 ± 5.8 [75.4 ± 5.9]	75.1 ± 5.8 [75.0 ± 5.8]
Sex (male/female)	10/276	13/273
Years since menopause	25.3 ± 6.9 (n = 276)	25.6 ± 6.7 (n = 273)
Height (cm)	147.55 ± 6.32 [147.08 ± 5.82]	147.95 ± 6.36 [147.45 ± 5.89]
Weight (kg)	50.58 ± 8.05 [49.62 ± 8.03]	50.58 ± 7.55 [50.37 ± 7.52]
Body mass index (kg/m ²)	22.82 ± 3.36 [22.91 ± 3.31]	23.12 ± 3.22 [23.18 ± 3.25]
Prevalent vertebral fractures, n (%)		
0	35 (12.2) [34 (12.3)]	29 (10.1) [29 (10.6)]
1	119 (41.6) [116 (42.0)]	115 (40.2) [112 (41.0)]
2–3	100 (35.0) [97 (35.1)]	100 (35.0) [91 (33.3)]
≥4	32 (11.2) [29 (10.5)]	42 (14.7) [41 (15.0)]
Lumbar spine BMD T score	−2.6 ± 0.9 (n = 162) [−2.6 ± 0.9 (n = 160)]	−2.7 ± 0.9 (n = 158) [−2.7 ± 0.9 (n = 151)]
Total hip BMD T score	−2.1 ± 0.9 (n = 182) [−2.1 ± 0.9 (n = 176)]	−2.1 ± 1.0 (n = 186) [−2.1 ± 1.0 (n = 177)]
Femoral neck BMD T score	−2.4 ± 0.8 (n = 183) [−2.5 ± 0.8 (n = 177)]	−2.4 ± 0.7 (n = 186) [−2.4 ± 0.7 (n = 177)]
Serum osteocalcin (ng/ml)	8.0 ± 2.9 (n = 286) [8.0 ± 2.9 (n = 276)]	8.1 ± 3.1 (n = 282) [8.2 ± 3.1 (n = 269)]
Serum P1NP (μg/liter)	51.5 ± 20.2 (n = 286) [51.9 ± 20.2 (n = 276)]	53.8 ± 24.4 (n = 282) [54.2 ± 24.6 (n = 269)]
u-NTX (nmol BCE/mmol Cr)	42.7 ± 23.1 (n = 286) [43.2 ± 23.3 (n = 276)]	43.8 ± 25.2 (n = 282) [44.0 ± 25.4 (n = 269)]

Data are expressed as mean ± SD, unless otherwise stated. There were no significant differences between groups. Brackets indicate data for females only. BCE, Bone collagen equivalents; Cr, creatinine.

in the placebo group. Average urinary calcium concentrations tended to decrease in the teriparatide group compared with the placebo group during the study period.

Adverse events

The safety data for the 578 subjects assigned to the two treatment groups (290 teriparatide, and 288 placebo) were analyzed. No differences were found between the placebo and teriparatide groups in the frequencies of any AE, deaths, or SAE (Table 3). AE leading to death were: cardiac disorders (two subjects) and gallbladder cancer (one subject) in the teriparatide group; and cerebellar hemorrhage, stage 4 stomach cancer, congestive heart failure, aortic valve insufficiency, and acute myocardial infarction (one subject each) in the placebo group. No differences were found between the teriparatide and placebo groups in the frequency of SAE such as cardiac disorders and neoplasms including benign, malignant, and unspecified types.

The AE that were more numerous in the teriparatide group than in the placebo group were nausea ($P < 0.01$), headache ($P = 0.03$), abdominal discomfort ($P = 0.03$), and vomiting ($P = 0.02$). These events occurred and

ceased mainly within 12 h after injection, and they were generally mild, tolerable, and amenable to treatment. The subjects who discontinued the study due to AE were more frequently found in the teriparatide group (19.3%) than in the placebo group (6.6%; $P < 0.01$). There were 16, seven, and six subjects with nausea, malaise, and vomiting, respectively, in the teriparatide group and one subject each in the placebo group.

Discussion

Treatment with once-weekly injection of teriparatide at a dose of 56.5 μg for 72 wk significantly decreased the risk of new vertebral fracture in subjects with primary osteoporosis. Relative to placebo, teriparatide injection reduced the risk of new vertebral fracture by 80% in older men and postmenopausal women at least 65 yr of age. The risk reduction for women only was 82%, which was also significant.

The reduction in the risk of new vertebral fracture in postmenopausal patients with osteoporosis at high fracture risk by daily teriparatide injection has been confirmed

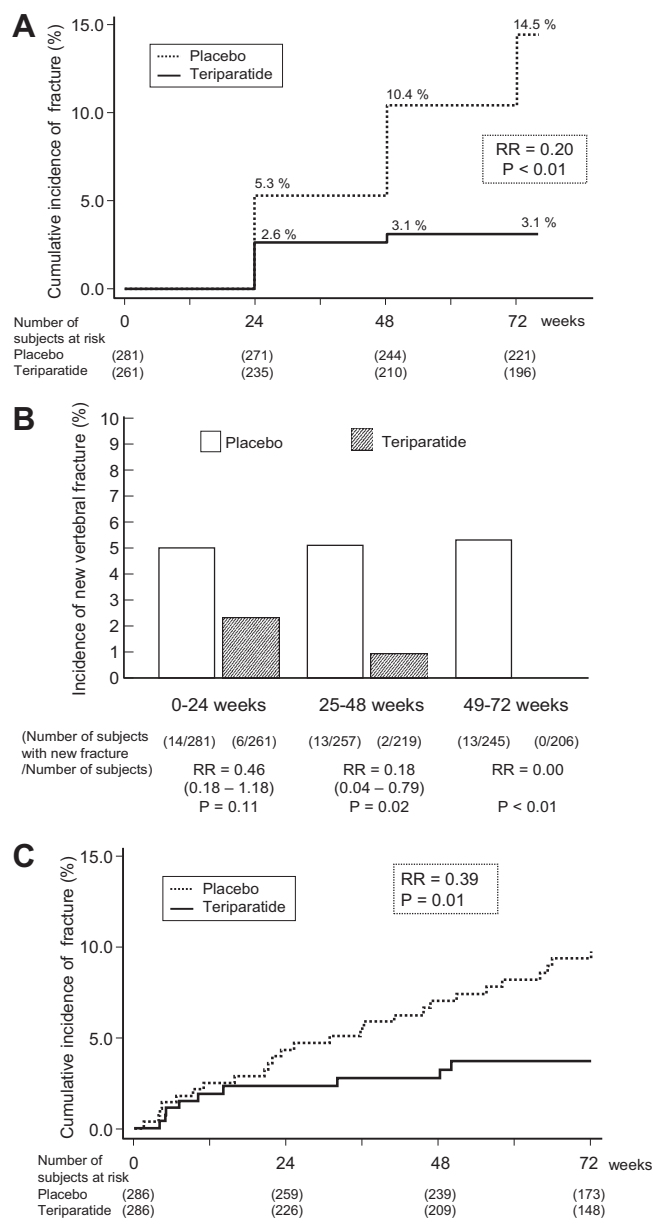


FIG. 2. Incidence of new fractures during the 72-wk study period was confirmed by radiology. A, Kaplan-Meier method, statistical significance assessed by a log-rank test. RR, Relative risk. B, Incidence values of new vertebral fractures assessed every 24 wk by Fisher's exact test. 95% CI is presented for the results of fracture incidences. C, Incidences of clinical fragility fracture in the teriparatide group were significantly reduced compared with placebo.

in the previous study (3, 11, 12). In the Fracture Prevention Trial (FPT) (3, 11), doses of 20 and 40 $\mu\text{g}/\text{d}$ teriparatide reduced the risk of new vertebral fracture by 65 and 69%, respectively, when assessed by visual SQ assessment over a median of 19 months (3). The risk reduction reassessed by the combination of SQ and QM methodology, applied in the FPT, was reportedly 84% in the regimen of daily injection (12). In the present study, we found that weekly teriparatide injection was also effective in reducing the risk in patients with primary osteoporosis with high fracture risk. The average age of the subjects was 75 yr in our study

and 69 yr in the FPT. In the present study, nominal reductions in clinical fractures and clinical fragility nonvertebral fractures were apparently less in the teriparatide group than in the placebo group, but the study was not powered to detect statistical differences in the incidences of these fractures.

Improvements in BMD at the lumbar spine, total hip, and femoral neck by daily and weekly teriparatide injections have been observed in the previous studies (2–4, 9, 13). The differences in the mean values of the changes from baseline between the groups in this study were 6.4, 3.0, and 2.3% at the lumbar, total hip, and femoral neck, respectively, at 72 wk. In the previous study using doses of 100 IU (28.2 μg)/wk and 200 IU (56.5 μg)/wk teriparatide injection, BMD at the lumbar spine increased from baseline by 3.6 and 8.1%, respectively, in 48 wk (9). However, in a study where subjects received injections of 100 $\mu\text{g}/\text{d}$ PTH (1–84) for 1 month followed by the same dose administered weekly for 11 months, there were minimum changes in BMD (14). Thus, the action of weekly injection of teriparatide and PTH (1–84) on BMD may depend on the molar doses of injection.

The changes in bone markers in this study were in contrast to those observed with 20 $\mu\text{g}/\text{d}$ teriparatide injections (3, 4, 15–23) where marked increases in serum osteocalcin and P1NP concentrations were consistently observed from 1 to 6 months and then declined. These increases in bone formation markers were associated with increases in bone resorption markers. In the previous study with weekly teriparatide injection at a dose of 56.5 μg , serum alkaline phosphatase concentrations increased in 4 wk, and urinary deoxypyridinoline and hydroxyproline levels decreased (9). The bone marker data in the present and previous studies of weekly teriparatide injection compatibly indicate that the 56.5- μg dose increased bone formation in 4 wk, declining in 24 wk, maintaining increase in serum osteocalcin level until 72 wk. A reduction of bone resorption activity was unexpectedly apparent at 48 wk and thereafter. The reason for a reduction in bone resorption by weekly teriparatide injection is not clear. Subcutaneously injected teriparatide seems to disappear in serum within 6 h (24), and endogenous intact PTH is suppressed during and after teriparatide injection (25). Thus, it is anticipated that the reduction in serum intact PTH 7 d after previous teriparatide injection may cumulatively contribute to the reduction in bone resorption markers after 6 months of weekly teriparatide injection. Another explanation may be related to an increase in serum Dickkopf-1 due to teriparatide injection (26). Dickkopf-1 was not measured in this study.

The unique action of 56.5 $\mu\text{g}/\text{wk}$ teriparatide injection to increase bone formation and decrease bone resorption

TABLE 2. Effect of once-weekly teriparatide treatment on incidence of fracture at 72 wk

Type of fracture	Placebo, % (n)	Teriparatide, % (n)	Difference in rates (95% CI)	Relative risk (95% CI)	Log-rank P value
New morphometric vertebral fracture	14.5 (37) [14.1 (35)]	3.1 (7) [2.8 (6)]	11.4 (6.5 to 16.2) [11.4 (6.5 to 16.2)]	0.20 (0.09 to 0.45) [0.18 (0.08 to 0.44)]	<0.01 [<0.01]
Clinical fragility vertebral fracture	6.6 (17) [6.5 (16)]	1.6 (4) [1.3 (3)]	5.0 (1.5 to 8.4) [5.2 (1.8 to 8.6)]	0.27 (0.09 to 0.80) [0.22 (0.06 to 0.74)]	0.01 [<0.01]
Clinical fragility fracture	9.9 (26) [9.8 (25)]	3.6 (8) [3.4 (6)]	6.2 (1.9 to 10.5) [6.4 (2.0 to 10.7)]	0.37 (0.18 to 0.82) [0.36 (0.16 to 0.80)]	0.01 [<0.01]
Clinical fracture	11.4 (30) [11.0 (29)]	6.5 (16) [5.9 (14)]	4.9 (−0.1 to 9.8) [5.1 (0.1 to 10.0)]	0.60 (0.33 to 1.11) [0.57 (0.30 to 1.09)]	0.10 [0.08]
Clinical nonvertebral fracture	5.7 (15) [5.5 (14)]	5.3 (13) [4.7 (11)]	0.4 (−3.6 to 4.4) [0.8 (−3.1 to 4.7)]	0.98 (0.47 to 2.07) [0.90 (0.41 to 1.99)]	0.96 [0.80]
Clinical fragility nonvertebral fracture	3.8 (10) [3.9 (10)]	2.4 (6) [2.2 (5)]	1.3 (−1.7 to 4.3) [1.7 (−1.3 to 4.8)]	0.67 (0.24 to 1.84) [0.57 (0.19 to 1.66)]	0.43 [0.29]

95% CI values were presented for the results of fracture incidences. Brackets indicate data for females only.

may be related to the substantial increases in BMD and marked reduction in the risk of vertebral fracture. It may be implied that increased bone formation with suppressed bone resorption is beneficial not only to increase bone

mass, but also to increase the stability of the structure, consequently further strengthening the fragile bone in subjects with osteoporosis. Reduced bone resorption concomitant with increased bone formation by weekly teripa-

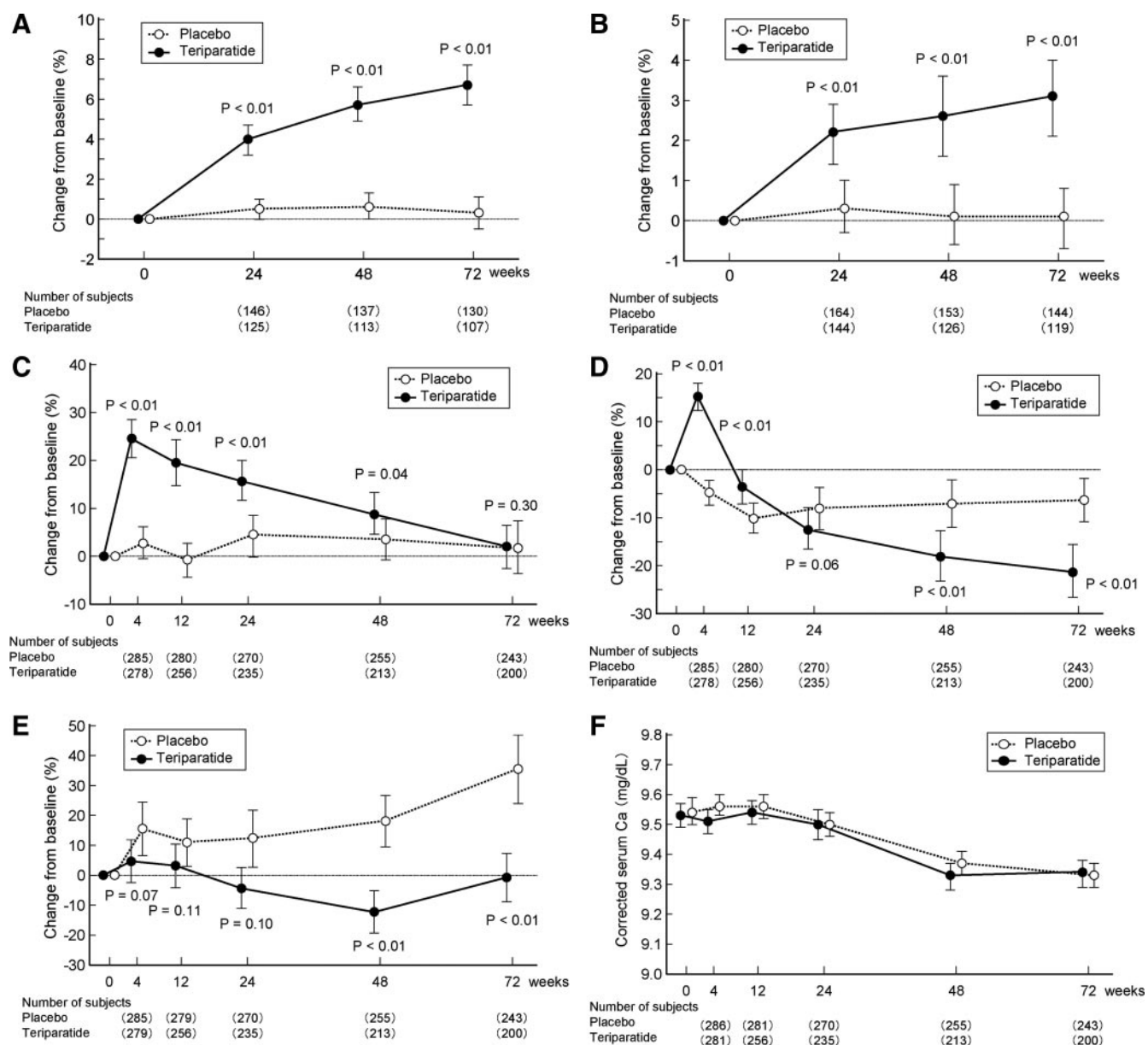


FIG. 3. Changes over time in BMD and biochemical markers. For the BMD analysis, the difference in percentage changes from baseline was compared between the teriparatide and placebo groups for the bone turnover markers. A, Lumbar spine BMD; B, total hip BMD; C, serum osteocalcin; D, serum P1NP; E, u-NTX; and F, corrected serum calcium. A comparison was performed using a paired *t* test with the Wilcoxon test; bars indicate 95% CI.

TABLE 3. Adverse events

Treatment group	Placebo, n (%)	Teriparatide, n (%)	P value ^a
n	288	290	
General			
Any AE	266 (92.4)	271 (93.4)	0.63
Death	4 (1.4)	3 (1.0)	0.72
Any SAE	44 (15.3)	34 (11.7)	0.23
AE			
Nasopharyngitis	111 (38.5)	102 (35.2)	0.44
Nausea	13 (4.5)	59 (20.3)	<0.01
Contusion	48 (16.7)	43 (14.8)	0.57
Headache	22 (7.6)	39 (13.4)	0.03
Vomiting	16 (5.6)	33 (11.4)	0.02
Eczema	30 (10.4)	25 (8.6)	0.48
Abdominal discomfort	9 (3.1)	22 (7.6)	0.03
Constipation	29 (10.1)	21 (7.2)	0.24
Malaise	10 (3.5)	21 (7.2)	0.06
Dermatitis contact	20 (6.9)	19 (6.6)	0.87
Upper respiratory tract inflammation	19 (6.6)	18 (6.2)	0.87
Diarrhea	16 (5.6)	17 (5.9)	1.00
Back pain	18 (6.3)	17 (5.9)	0.86
Dizziness	20 (6.9)	16 (5.5)	0.50
Gastritis	9 (3.1)	16 (5.5)	0.22
Osteoarthritis	21 (7.3)	15 (5.2)	0.31
Calculus ureteric	0 (0.0)	1 (0.3)	
Hypercalcemia	0 (0.0)	0 (0.0)	
SAE			
Cardiac disorders	3 (1.0)	2 (0.7)	0.69
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	9 (3.1)	3 (1.0)	0.09
Discontinuation of follow-up due to AE	19 (6.6)	56 (19.3)	<0.01

^a Statistical analyses were performed by applying Fisher's exact test in the incidences of AE between the teriparatide and placebo groups.

ratide administration may be associated with increased material properties of bone, as was observed in ovariectomized monkeys (27). The apparent increase in u-NTX in the placebo group in the present study may suggest that a daily oral supplement including calcium 610 mg and vitamin D 400 IU may not be enough to down-regulate bone resorption in the older subjects recruited for the study (28–31). However, because BMD values were maintained at each measured skeletal site in the placebo group, the amounts of calcium and vitamin D supplements may not have affected the efficacy of the therapeutic agent on bone relative to the placebo.

There were no differences in deaths, SAE, or AE between the 56.5 $\mu\text{g}/\text{wk}$ teriparatide and placebo groups. Neoplasms including benign and malignant tumors developed in 3.1% of subjects in the placebo group and 1.0% of subjects in the teriparatide group. Although the total number of subjects with AE did not differ between the groups, the frequencies of nausea, headache, and vomiting were higher in the teriparatide group than placebo in the

present study. Frequencies of nausea and headache were reportedly 18 and 13%, respectively, in the 40 $\mu\text{g}/\text{d}$ teriparatide treatment in women with postmenopausal osteoporosis and 5 and 16%, respectively, in the 20 $\mu\text{g}/\text{d}$ teriparatide treatment in men with osteoporosis (21). Dizziness and leg cramps were also frequently observed with daily teriparatide injections and weekly injections as well. These AE commonly observed with daily and weekly teriparatide injections were amenable to treatment and seem to be related to acute reactions to teriparatide injections (32). The dropout rate by AE in the teriparatide group was 19.3% in this study. Reportedly, the rates in the study using 20 and 40 $\mu\text{g}/\text{d}$ teriparatide dosing were 6 and 11%, respectively (3). Thus, the dropout rate for subjects given weekly 56.5 μg teriparatide injection may be higher than those receiving 20 $\mu\text{g}/\text{d}$ teriparatide injection.

This trial has certain limitations. The trial included subjects at least 65 yr of age who were at high risk of fracture; the effect of treatment on the risk of fractures might differ in younger patients with osteoporosis. The trial was not powered to detect the efficacy on the risk of nonvertebral fracture in terms of the numbers of subjects. Significant difference between the two groups in the numbers of the subjects who discontinued the study could be another limitation. However, in the analysis excluding patients who discontinued the study, there was no difference between the teriparatide and placebo groups in terms of patient characteristics associated with fracture risk at the start of the study such as prevalent fracture, BMD, age, and body mass index. Similarly, no difference was found in the baseline characteristics of the patients who completed the study between the two groups. Thus, the numbers of dropouts did not seem to affect the results in this study. We measured serum calcium levels before teriparatide injection at weekly visits, and we did not frequently measure the serum calcium levels after the injection. Thus, we are not able to eliminate the concern of the transient increase in serum calcium levels after teriparatide injection.

In conclusion, weekly teriparatide injection at a dose of 56.5 μg reduced the incidence of vertebral fracture in patients with primary osteoporosis, including older men and postmenopausal women. It may provide another option of anabolic treatment for osteoporosis.

Acknowledgments

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