National PBM Drug Monograph
Teriparatide (Forteo™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel
September 2004

Executive Summary:

1. Teriparatide, a recombinant parathyroid hormone, works by inducing bone formation resulting in increased bone mass and strength. All previously approved treatments for osteoporosis work primarily by blocking bone resorption, with minimal effect on bone formation.
2. Teriparatide is approved by the FDA for use in patients with osteoporosis and high risk of fractures, including patients with existing fractures.
3. Daily injection of teriparatide reduced the risk of new vertebral fractures and non-vertebral fractures in osteoporotic postmenopausal women in a large clinical trials[6,7].
4. Teriparatide consistently increased bone mineral density of the lumbar spine and femoral neck in osteoporotic men and women as well as in patients with glucocorticoid-induced osteoporosis[6-11]. The effects on bone mineral density were rapid (after a month of treatment) and dose-dependent.
5. Teriparatide increased biochemical markers of bone turnover in both men and women. The increase in bone formation markers was of greater amplitude and occurred sooner than the increase in bone resorption markers[10,11].
6. The most common side effects with teriparatide are dizziness and leg cramps. Hypercalcemia has been reported in most of the trials, which was usually resolved after the dose of calcium supplement or teriparatide decreased. Osteosarcoma was found in rats in a carcinogenicity study with teriparatide. In that study, rats were exposed to doses of teriparatide 3 to 60 times the recommended human dose. The effect was dependent on dose and treatment duration. No cases of osteosarcoma have been reported in humans[6,9].
7. Long-term safety and efficacy of teriparatide are still unknown. Teriparatide use is recommended for a maximum of two years.
8. Combination treatment with teriparatide and bisphosphonate therapy is not recommended at this time.

Introduction[1,2]

Current treatments for osteoporosis include bisphosphonates, calcitonin, vitamin D and calcitriol, hormone replacement therapy, and selective estrogen-receptor modulators. Selection of the appropriate therapy depends upon patient age, gender, and diagnosis. These treatments primarily reduce bone resorption and moderately increase bone density; some agents were also shown to reduce the risk of fracture (alendronate, risedronate). However, none of these agents routinely restore normal bone mass or strength. Teriparatide (Forteo™), a recombinant human parathyroid hormone, is the first of a new class of osteoporosis treatments that was shown to reduce bone turnover, stimulate the formation of new bone, and thereby increase bone mass and strength following once daily administration in clinical trials. The unique modes of action of teriparatide may make it a useful agent in treating patients who are at high risk of fractures or in need of rapid improvement in bone mineral density.

Pharmacology/Pharmacokinetics[2,3]

Mechanism of action:
Teriparatide is a synthetic polypeptide hormone that is the biologically active N-terminal region of human parathyroid hormone. Teriparatide is produced by recombinant DNA therapy, using a strain of *Escherichia coli.* The actions of teriparatide mimic that of the endogenous parathyroid hormone, including regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The effects of teriparatide on bone metabolism depend upon the mode of administration. Once daily subcutaneous injection of teriparatide stimulates new bone formation by preferentially stimulating osteoblastic activity over osteoclastic activity. Continuous infusion of teriparatide, results in a persistent elevation of parathyroid hormone leading to greater bone resorption than bone formation.

Pharmacokinetics:
Absorption: Teriparatide is extensively absorbed after subcutaneous injection. The absolute bioavailability is approximately 95%. The rate of absorption is rapid, with peak concentrations of about 30 minutes after subcutaneous injection of 20mcg dose.

Distribution: The volume of distribution is approximately 0.12L/kg following intravenous injection.

Metabolism and excretion: No metabolism or excretion studies have been performed with teriparatide. Peripheral metabolism of endogenous PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys. The half-life of teriparatide in serum is 5 minutes after an intravenous infusion and approximately one hour after a subcutaneous injection.

FDA Approved Indication(s) and Off-label Uses[2,6]

FDA approved uses:
- Treatment of postmenopausal women with osteoporosis who are at high risk for fracture, including those with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy.
- To increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture, including those with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant or previous osteoporosis therapy.

Off-label use:
- Diagnostic agent for establishing the diagnosis of hypoparathyroidism and pseudohypoparathyroidism when patients present with hypocalcemia.
- Management of glucocorticoid-induced osteoporosis in postmenopausal women who were receiving hormone replacement therapy[6].

Current VA National Formulary Status

Teriparatide is currently not on VA national formulary and is not to be added to VISN formularies until national review is completed.

Dosage and Administration[2]

Subcutaneous dosage:
Adults: 20 µg SC into the thigh or abdominal wall once daily for up to 2 years.

Forteo™ is supplied as a pen device, which delivers 20mcg of teriparatide per dose each day for up to 28 days. The Forteo™ pen should be stored under refrigeration at 2° to 8°C (36-46°F) at all times. A separate prescription for 31 or 30 gauge pen needles is required at the time of dispensing.

Special populations:
- Patients with renal impairment: Specific guidelines for dosage adjustments in renal impairment are not available.
- Patients with hepatic impairment: Specific guidelines for dosage adjustments in hepatic impairment are not available.

Adverse Effects (Safety Data)[2]

The safety of teriparatide was evaluated in 26 clinical trials that enrolled over 2900 women and men. The maximum duration of treatment was 2 years. Adverse events associated with teriparatide were usually mild and generally did not required discontinuation of therapy. Early discontinuation due to adverse events occurred in 7.1% of teriparatide assigned patients, compared to 5.6% of patients taking placebo in

two Phase 3 placebo control clinical trials[2]. Reported adverse events that appeared to be increased by teriparatide treatment were dizziness and leg cramps.

The following table reports common side effects that occurred at a frequency ≥2% and in more teriparatide-treated patients than in placebo-treated patients in Phase 3 trials. These trials represented both men and postmenopausal women.

	Teriparatide (Forteo™)	Placebo
Event Classification	(%)	(%)
Body as a whole		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck pain	3.0	2.7
Cardiovascular		
Hypertension	7.1	6.8
Angina pectoris	2.5	1.6
Syncope	2.6	1.4
Digestive system		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhea	5.1	4.6
Dyspepsia	5.2	4.1
Vomiting	3.0	2.3
Gastrointestinal disorder	2.3	2.0
Tooth disorder	2.0	1.3
Musculoskeletal		
Arthralgia	10.1	8.4
Leg cramps	2.6	1.3
Nervous system		
Dizziness	8.0	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
Respiratory system		
Rhinitis	9.6	8.8
Cough increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
Skin and Appendages		
Rash	4.9	4.5
Sweating	2.2	1.7

Hypercalcemia has been reported in patients treated with teriparatide. Transient increases in serum calcium, with the maximal effect observed at approximately 4-6 hours post dose, occurred in 11.1% women and 6.0% men treated with teriparatide.
Immunogenicity was detected in 2.8% of women receiving teriparatide. Less than 1% of men in studies had binding activity for teriparatide antibodies in an initial assay, but not on subsequent testing[9]. There was no evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on BMD response in these patients.

Pregnancy: Pregnancy Category C- The effect of teriparatide treatment on human fetal development has not been studied. Teriparatide is not indicated for use in pregnancy.

Nursing Mothers: There have been no studies to determine if teriparatide is secreted into breast milk. Teriparatide should not be administered to women who are nursing their children.

Pediatric Use: The safety and efficacy of teriparatide have not been established in pediatric populations. Teriparatide should not be used in pediatric patients.

Precautions/Contraindications[2]

Contraindications: Teriparatide should not be given to patients with hypersensitivity to teriparatide or to any of its excipients.

Precautions:
- The safety and efficacy of Teriparatide have not been evaluated beyond 2 years of treatment. It is not recommended for use for more than 2 years.
- Symptomatic orthostatic hypotension, especially within the first several doses, was observed in several patients in short-term clinical studies with teriparatide, which was resolved by placing the person in a reclining position.
- Teriparatide may increase serum calcium and urinary calcium. Teriparatide should be used with caution in patients with active or recent urolithiasis. Urinary calcium should be measured if urolithiasis or pre-existing hypercalcemia is suspected.

Warning: In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior radiation therapy involving the skeleton).

Drug Interactions[2]

- Hydrochlorothiazide: Doses of 25mg did not affect the serum calcium response to teriparatide 40mcg. The 24-hour urine excretion of calcium was reduced by a clinically insignificant amount (15%).
- Furosemide: Co-administration of intravenous furosemide (20-100mg) with teriparatide 40mcg resulted in small increases in the serum calcium (2%). 24-hour urine calcium (37%) responses to teriparatide did not appear to be clinically important.

Efficacy Measures

There are three primary measurements used to assess the efficacy of agents used to treat osteoporosis. The first of the primary measures is Bone Mineral Density (BMD), which is a direct measurement of the structural integrity of bone (e.g. bone mass). The second are biochemical markers, which are an indirect measurement of the structural integrity of the bone. The third measurement is an assessment of the incidence of new fractures using bone radiography or similar procedures. Another measurement used in the study by Rehman et al[18] assessed efficacy of parathyroid hormone using vertebral cross-sectional area and vertebral compressive strength.

Bone mineral density (BMD) is the gold standard used in the diagnosis of osteoporosis and in calculating the risk of osteoporotic fractures. Bone mineral density is a direct measurement of the structural integrity of bone. The decrease in bone density sustained in osteoporosis has been linked to an increased risk for fractures in clinical trials[4]. It is estimated that each decrease of one standard deviation in BMD is sites such as the spine or hip is linked to a doubling of the risk for fractures. As a result, increases in bone

mineral density are the primary efficacy measure used in many of the studies. The relationship between increasing bone mineral density and reducing the risk of fractures is not established.
Biochemical markers, such as alkaline phosphatase and deoxypyridinoline, are indirect measurements of the structural integrity of bone. Biochemical markers of bone turnover are generated by bone cells and are byproducts of either bone resorption or bone matrix synthesis. Markers of bone turnover include bone specific alkaline phosphatase and deoxypyridinoline. Alkaline phosphatase is released by osteoblasts during the process of bone formation. Deoxypyridinoline is a byproduct of osteoclast bone resorption. These markers can be measured in either the blood or urine. They are considered important adjunctive measurements to BMD in diagnosing and treating patients.

Since fractures are associated with the most morbidity and mortality among patients with osteoporosis, some studies stress measuring the effects of treatment on fracture prevention as a primary endpoint rather than bone mineral density. The main problem with using fractures as a primary outcome is that the incidence of fractures even in populations at risk is so low that larger sample sizes and longer periods of time are needed to sufficiently detect a difference in this measurement.

The assessment of incidence of new fractures can be accomplished using bone radiography. Anteroposterior and lateral radiography of the thoracic and lumbar spine allow the researcher to detect via visual examination the presence of existing vertebral fractures and the appearance of new fractures. Deformity, which is the most widely used criterion for determining vertebral fracture, is derived from measurements of the vertebral height of a vertebra at its anterior margin, center (or mid-position) and posterior margin on lateral spine radiographs[5].

Vertebral cross-sectional area (VCSA) was calculated as the area within the exterior contour of the mid-vertebral body, excluding the spinal canal and the transverse processes but including the spinous process
Vertebral compressive strength was estimated as a figure of merit (VFSOM) defined as:

$$VFSOM = (TBMD)^2 \times VCSA$$

TBMD is the trabecular bone mineral density measured in the vertebral centrum

Vertebral Cross Sectional Area (VCSA): an index used to measure bone geometry. This measurement is performed with the use of finite elemental models, which are derived from quantitative computed tomography scans. This index may provide better predictions of in vitro measurements of vertebral strength. In fact, one study found that geometry based finite elemental models (r^2 = 0.79) were a better predictor of vertebral strength than CT-derived estimates of density (r^2 = 0.67).

Quantitative Computed Tomography (QCT): an imaging test used to measure bone mineral density of the spine

Vertebral Compressive Strength (VFSOM): an index used to measure vertebral strength, which takes bone geometry and bone mineral density into account

Since these measurements account for both bone geometry and bone mineral density they would only be useful for determining vertebral strength, These efficacy measures are not useful in clinical practice because there have been no clinical trials which have correlated these measurements with risk of fracture

Clinical Trials[6-12]

Citation	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. The New England Journal of Medicine 2001 May 10; 344(19):1434-1441
Study Goals	To determine whether parathyroid hormone provides protection against fractures in postmenopausal women with prior vertebral fractures.
Sponsorship	The study was supported by Eli Lilly
Methods	• **Study Design** ➢ Multi-center, randomized, double-blind, placebo-control parallel-group study. ➢ 1637 women were randomly assigned to 1 of three treatment groups: 544 to placebo, 541 to 20mcg/day of parathyroid hormone, and 552 to 40mcg/day of parathyroid hormone ➢ All enrolled women received daily supplements of 1000mg of calcium and 400-1200 IU of vitamin D. All women gave themselves daily injections of placebo for 2 weeks before randomization. ➢ Outcome measurements: The incidences of new vertebral and nonvertebral fragility fractures, changes in bone mineral density and total-body bone mineral, and adverse events associated with parathyroid hormone therapies. • **Data Analysis** ➢ Pearson's chi-square test was utilized to compare the rates of side effects and the proportions of women with fractures in the three study groups. ➢ Analysis of variance (ANOVA) was used to evaluate all laboratory data and bone mineral measurements. ➢ All statistical tests were two-sided.
Criteria	• **Inclusion criteria** ➢ Ambulatory women ➢ At least 5 years since diagnosis of menopause ➢ At least 1 moderate or 2 mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine ➢ Low BMD of the hip or lumbar spine if < 2 moderate fractures • **Exclusion criteria** ➢ Illnesses that affect bone or calcium metabolism ➢ Urolithiasis within preceding 5 years ➢ Impaired hepatic function ➢ Serum creatinine concentration >2mg/dL (177 μmol/L) ➢ Alcohol or drug abuse ➢ Drugs that alter bone metabolism within the previous 2-24 months
Results	• The study was suspended earlier than planned due to the osteosarcoma incidences found in rat in a long-term teriparatide carcinogenicity study. The average duration of treatment was 19 months. • The baseline characteristics of the women in the three groups were similar. Age of eligible participants ranges from 69±7yr to 71±8yr. • The average rate of compliance with the regimen of injections ranged from 79 to 83% at each visit, which did not differ significantly among the three groups. • Vertebral fractures: ➢ 1326 women (81%) with baseline and follow-up radiographs available for evaluation. 105 of these women had 1 or more new vertebral fractures. ➢ The overall mean loss in height was small and did not differ significantly among the three groups. • Non-vertebral fractures: ➢ New non-vertebral fractures occurred in 119 women and were considered fragility fractures in 58 women. ➢ The protective effects of parathyroid hormone treatment became evident after 9-12 months.

- Bone mineral density (BMD) and total-body bone mineral:
  - The BMD of the shaft of the radius decreased from the baseline values in all three groups. The percent change in the 40mcg PTH group differed significantly from that in the placebo group.
  - The BMD of the distal radius did not differ significantly among the three groups.

Data analysis

Risk	Placebo	20mcg PTH	40mcg PTH
Vertebral fracture			
≥1 Fracture			
Relative risk (95%CI)	-	0.35 (0.22-0.55)	0.31 (0.19-0.50)
Absolute risk reduction (%)	-	9	10
>1 Fracture			
Relative risk (95%CI)	-	0.23 (0.09-0.60)	0.14 (0.04-0.47)
Absolute risk reduction (%)	-	4	4
≥1 Moderate-Severe Fracture			
Relative risk (95%CI)	-	0.10 (0.04-0.27)	0.22 (0.11-0.45)
Absolute risk reduction (%)	-	9	7
Total number of vertebral fractures (per 1000 patient-years)	136	49	30
Absolute risk reduction (per 1000 patient-years)	-	8.7	10.6
# patients needed to treat/yr	-	12	10
Non-vertebral fracture			
>1 Fracture (%)	-	-35	-40
Absolute risk (%)	10	6	6
Absolute risk reduction (%)	-	4	4
# patients needed to treat	-	25	25
≥1 Fragility Fracture (%)		-53	-54
Absolute risk (%)	6	3	3
Absolute risk reduction (%)	-	3	3
Relative risk (95% CI)	-	0.47(0.25-0.88)	0.46(0.25-0.86)
# patients needed to treat	-	33	33

- 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.
  - No cases of osteosarcoma.
  - There were higher incidences of adverse events such as nausea, headache, dizziness, leg cramps, and hypercalcemia among the parathyroid hormone treated groups as compared to placebo group. However, these adverse events appeared to occur more frequent with higher dose of parathyroid hormone.

Events	Placebo	20mcg PTH	40mcg PTH
Withdrew due to adverse events	32 (6%)	35 (6%)	59(11%)
Nausea (P<0.001)	(8%)	(8%)	(18%)
Headache (P=0.01)	(8%)	(8%)	(13%)
Dizziness (P=0.05)	(6%)	(9%)	(6%)
Leg cramps (P=0.02)	(1%)	(3%)	(1%)
>1 Mild hypercalcemia episodes	(2%)	(11%)	(28%)
Halving the dose of study drug due to permanent hypercalcemia	3(<1%)	15(3%)	62(11%)
Treatment withdrawn due to hypercalcemia	1	1	9
Increased serum Uric acid levels		(13-20%)	(20-25%)
Antibodies to PTH	1(<1%)	15(3%)	44(8%)

Conclusions

Treatment of postmenopausal osteoporosis with parathyroid hormone (1-34) decreases the risk of vertebral fractures, femoral fractures, and total-body bone mineral density; and is well tolerated. The 40mcg dose increased bone mineral density more than the 20mcg dose but had similar effects on the risk of fracture and was more likely to have side effects. Daily injections of parathyroid hormone

	reduce the risk of vertebral fractures and the total number of vertebral fractures, as well as the risk of non-vertebral fractures and non-vertebral fragility fractures. Treatment with parathyroid hormone resulted in significant dose-dependent increases in BMD of the spine and hip and in total-body bone mineral.
Critique	• **Strengths:** ➢ Large sample, double-blinded, randomized, and placebo-controlled. ➢ Baseline characteristics were similar in all three study groups. ➢ Allowed 2 weeks of placebo injections before randomization to minimize number of dropouts. ➢ Patient compliance to injection regimen was assessed in this study. • **Limitations:** ➢ Did not specify age group in the inclusion criteria.

Citation	Marcus R, Wang O, Satterwhite J, and 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. Journal of Bone and Mineral Research 2003; 18(1):18-23
Study Goals	To evaluate the relationship between baseline age, bone mineral density and prevalent fractures of the participants in the teriparatide fracture prevention study (Neer et al) and their subsequent BMD and fracture response to teriparatide.
Sponsorship	Eli Lilly and Company funded the study.
Methods	• **Study Design** ➢ 36-month multi-center, randomized, double-blind, placebo-control parallel-group study. ➢ 1637 women were randomly assigned to 1 of three treatment groups: 544 to placebo, 541 to 20mcg/day of teriparatide, and 552 to 40mcg/day of teriparatide. ➢ The studied women were further divided into subgroups based on age (<65yrs, 65to <75yrs, ≥75yrs), vertebral BMD T scores (Low: <-3.3,Medium: -3.3 to –2.1, High: >-2.1), and numbers of vertebral fractures at end points (Zero fracture, 1 fracture, ≥2 fractures) ➢ All enrolled women received daily supplements of 1000mg of calcium and 400-1200 IU of vitamin D and gave themselves daily injections of placebo for 2 weeks before randomization. Calcium and vitamin D were continued throughout the trial. ➢ Outcome measurements: Changes in vertebral bone mineral density and risk of vertebral fractures from baseline to endpoint. • **Data Analysis** ➢ Analysis of variance (ANOVA) was used to evaluate BMD changes and subgroup analyses. Type III sum of squares was used to assess the treatment-by-subgroup interaction. ➢ Logistic regression test was used to evaluate binary response variable of new vertebral fractures and subgroup analyses. The treatment-by-subgroup interaction was examined by using likelihood ratio test. ➢ For the observed vertebral fracture incidences, approximately 80% power was used to detect treatment group differences. For changes in lumbar spine BMD analyses, the power is beyond 99%.
Criteria	• **Inclusion criteria** ➢ Ambulatory women, 42-86 years of age. ➢ At least 5 years since diagnosis of menopause ➢ At least 1 moderate or 2 mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine ➢ Low BMD of the hip or lumbar spine if < 2 moderate fractures

	• **Exclusion criteria** ➢ Illnesses that affect bone or calcium metabolism ➢ Urolithiasis within preceding 5 years ➢ Impaired hepatic function ➢ Serum creatinine concentration >2mg/dL (177 μmol/L) ➢ Alcohol or drug abuse ➢ Drugs that alter bone metabolism within the previous 2-24 months
Results	• The study was suspended earlier than planned due to the osteosarcoma incidences found in rat in a long-term teriparatide carcinogenicity study. The average duration of treatment was 19 months. • The patient's age, vertebral BMD, prevalent vertebral fractures, and other baseline characteristics that could affect the risk of fracture were matched among the three study groups. • Vertebral BMD response: ➢ Teriparatide caused rapid increases in vertebral BMD, with statistically significant increases observed after 3 months of treatment and throughout the trial (P<0.001). ➢ Vertebral BMD at study endpoints (median 19 months) increased by 10% and 14% in the 20mcg and 40mcg teriparatide groups, respectively (P<0.001). • Baseline age, change in vertebral BMD, and risk of vertebral fracture: ➢ Compared with placebo, teriparatide treatment significantly increased vertebral BMD, regardless of age (P<0.001). ➢ The percentage increase of spine BMD was greater in women from older subgroups (P=0.037). ➢ Baseline age has no effect on the relative risk reduction for vertebral fractures (P=0.558) • Baseline vertebral (BMD), change in vertebral BMD, and risk of vertebral fracture: ➢ In women receiving placebo, there was a dose-dependent, inverse relationship between baseline vertebral BMD and the percentage increase in vertebral BMD (P<0.001). However, when compared across the BMD subgroups, the effects of teriparatide on absolute increases in vertebral BMD did not differ significantly (P=0.615) ➢ An inverse relationship between baseline vertebral BMD and the relative risk for developing new vertebral fractures was observed in the placebo group (new fractures occurred in 22.1%, 11.0%, and 7.9% of women in the low, medium, and high vertebral BMD subgroups, respectively, P<0.001). When compared across the BMD subgroups, the effects of teriparatide on the relative risk for developing new vertebral fractures did not differ significantly (P=0.817). • Impact of prevalent vertebral fractures on the incidence of new vertebral fracture: ➢ 10% of patients had zero vertebral fracture at endpoints, 90% had 1 fracture, and 60% had ≥2 fractures. ➢ Placebo treated women with 2 or more prevalent vertebral fractures had a significantly greater risk of developing new vertebral fractures than those with zero or one prevalent vertebral fracture (P<0.001). ➢ When compared within the prevalent vertebral fracture subgroups, the effects of teriparatide on the relative risk for developing new vertebral fractures were similar (P=0.649).
Conclusions	Teriparatide offers clinical benefit to patients across a broad range of age and disease severity.

Critique	• **Strengths:** ➢ The findings were more extensive analyzed than the previous study (Neer et al) ➢ Had assessed the benefits of teriparatide in separate age groups and in women with different levels of risk for fractures. • **Limitations:** ➢ Did not analyze nonvertebral fractures.

Citation	Body JJ, Gaich GA, Wim H, 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. The Journal of Clinical Endocrinology & Metabolism 2002 October; 87(10):4528-4535
Study Goals	To compare the effects of teriparatide and alendronate on bone mineral density, nonvertebral fracture incidence, and bone turnover in postmenopausal women with osteoporosis.
Sponsorship	Eli Lilly and Co granted this study.
Methods	• **Study Design** ➢ 24-month planned treatment phase, multi-center, randomized, double-blind, parallel-group, active-controlled study ➢ 146 women were randomly assigned to either once-daily 40mcg teriparatide sc injection plus oral placebo group (n=73) or once-daily placebo injection plus oral 10mg alendronate sodium group (n=73). ➢ Included a run-in phase of at least 1 month of daily supplements of calcium (1000mg) and vitamin D (400-1200 IU), which were to be continued throughout the trial. During this phase, the participants were instructed to inject themselves at either the lower abdomen or outer thigh, using placebo material. ➢ Primary outcome measurement: Change in lumbar spine (LS)-BMD by dual-energy x-ray absorptiometry (DXA) ➢ Secondary outcome measurements: LS-BMC (bone mineral content) and area, BMD measurements at other skeletal sites, nonvertebral fracture incidence, and biochemical markers of bone formation (bone alkaline phosphatase, ALP) and resorption (N-telopeptides corrected for creatinine, NTX). • **Data Analysis** ➢ The results were analyzed based on an intent-to-treat population. ➢ The measurements of BMD, BMC, and biochemical markers of bone turnover were analyzed by ANOVA ➢ The adverse events and nonvertebral fractures were analyzed using Pearson's chi-square test. ➢ All statistical tests were two-sided, with an alpha level of 0.05.
Criteria	• **Inclusion criteria** ➢ Ambulatory women, age 30-85yr. ➢ At least 5 years past menopause ➢ Free of severe or chronically disabling conditions other than osteoporosis. ➢ Lumbar spine or femoral BMD at least 2.5 SD below the mean for young adult women. • **Exclusion criteria** ➢ Metabolic bone disorders ➢ Diseases that affect bone or mineral metabolism ➢ Carcinomas within the previous 5 years ➢ Nephrolithiasis or urolithiasis within the previous 2 years ➢ Malabsorption ➢ Significantly impaired renal (serum creatinine concentrations >177μmol/L (2.0mg/dL)) or hepatic function ➢ Abnormalities of the LS prohibiting assessment of BMD at L2-L4

	➢ Alcohol abuse ➢ Drugs that alter bone or mineral metabolism within the previous 2-24 months ➢ Allergy or previous exposure to teriparatide, exogenous PTH, or PTH analogs.
Results	• The study was voluntarily brought to an early closure to evaluate the clinical relevance in humans of the observation of osteosarcoma made in rat. Median duration of treatment was 14 months. • There were no significant differences between groups in baseline characteristics. • There were no statistically significant differences between the treatment groups in the reasons for withdrawal from the study. • The median compliance with treatment was similar between the two groups (71% for alendronate and 67% for teriparatide). • <u>BMD and BMC:</u> ➢ Teriparatide increased LS-BMD, LS-BMC, and LS-area significantly more than did alendronate from the baseline to end point (P<0.001). ➢ Teriparatide increased femoral neck and total hip BMD and total bone mineral significantly more than did alendronate (P<0.001), but decreased the one third distal radius more significantly, compared with baseline and the alendronate group (P≤0.001). • <u>Nonvertebral fractures and height:</u> ➢ Nonvertebral fracture frequency was significantly lower in the teriparatide-treated group than in the alendronate group (4.1% vs. 13.7%, P=0.042). ➢ Mean height did not change between baseline and end point in either group. • <u>Bone turnover markers:</u> ➢ Treatment with teriparatide significantly increased biochemical markers of bone formation (bone ALP) and bone resorption (NTX) at 1 month, with maximum increase in bone ALP of 100% at 6 months and maximum increase in NTX of 160% at 12 months. ➢ In contrast, Alendronate reduced ALP and NTX by approximately 50% throughout the duration of therapy. • <u>Adverse Events:</u> ➢ There were no significant differences between treatment groups in the proportion of women reporting any adverse event experiencing a serious adverse event or who withdrew because of an adverse event. ➢ Significantly fewer patients reported new or worsened back pain in the teriparatide group (5.5%) than in the alendronate group (19.2%, P=0.012). ➢ Leg cramps were reported by 6 patients (8.2%) in the teriparatide group and none in the alendronate group (P=0.012). ➢ Transient, asymptomatic hypercalcemia occurred at significantly higher levels and higher frequency in teriparatide-treated group than in the alendronate group (P<0.001). ➢ The proportion of women with at least 1 elevated 24hr urinary calcium in the two groups was not significantly different (30% and 22% for teriparatide and alendronate, respectively). ➢ There was a small increase in serum uric acid in the teriparatide group, but there was no difference between the groups in the number of patients with abnormal uric acid concentrations. ➢ Three women in the teriparatide group had a positive test for anti-teriparatide antibodies without any adverse clinical effects.
Conclusions	Teriparatide, a bone formation agent, increased BMD at most sites and decreased nonvertebral fractures more than alendronate.
Critique	• **Strengths:** ➢ Double-blinded, randomized, parallel group. ➢ Baseline characteristics were similar in the study groups. ➢ Included a run-in phase for self-injection training.

	➢ Being the first study that directly compared the effects of bisphosphonates and teriparatide. • **Limitations:** ➢ Small sample size ➢ Teriparatide dose is doubled of recommended dose, which explained higher incidences of side effects. ➢ Did not explain how compliance to treatment drugs was assessed. ➢ Patient compliance was claimed to be similar between the 2 studied groups without providing p value. ➢ Did not assess the effects of both drugs in high fracture risk populations.

Citation	Orwoll ES, Scheele WH, Paul S, et al. The Effect of Teriparatide [Human Parathyroid Hormone (1-34)] Therapy on Bone Density in Men With Osteoporosis. Journal of Bone and Mineral Research 2003; 18(1): 9-17
Study Goals	To assess the usefulness of teriparatide in a large group of men with osteoporosis and the influence of sex steroid levels, smoking, and other factors on the response to teriparatide.
Methods	• **Study Design** ➢ 24-month multi-center, randomized, double-blind, placebo-control parallel group study. ➢ Patients were stratified based on the initial morning testosterone measurement. ➢ 437 eligible men were randomly assigned to either placebo group (n=147) or teriparatide 20mcg/day group (n=151) or teriparatide 40mcg/day group (n=139). Patients self-administered teriparatide or placebo subcutaneously using a HumaJect injection device. ➢ All patients received daily oral supplements of 1000mg calcium and 400-1200 IU of vitamin D beginning at least 1 month before randomization. ➢ Primary outcome measurement: changes in lumbar spine (LS) BMD over 2 years of treatment using dual energy X-ray absorptiometry (DXA). ➢ Secondary outcome measurements: changes in BMD of the total hip, femoral neck, intertrochanter, trochanter, radial, and whole body, and whole body bone mineral content (BMC); changes in biochemical markers of bone formation [bone alkaline phopsphatase, (ALP), procollagen I carboxy-terminal (PICP)] and bone resorption [urinary N-telopeptide (NTX), urinary free deoxypyridinoline (fDPD), and 1,25 dihydroxyvitamin D (1,25-$(OH)_2D$)]; side effects associated with teriparatide therapy. • **Data Analysis** ➢ The results were analyzed on an intention-to-treat basis. ➢ Continuous measures were analyzed by ANOVA. ➢ Pearson's chi-square test was used for categorical measures. ➢ All tests were 2-tailed with a significance level of 0.05
Criteria	• **Inclusion criteria** ➢ Ambulatory men with age ranges from 30-85 years. ➢ Free of chronic, disabling conditions other than osteoporosis ➢ Lumbar spine or proximal femur (neck or total hip) BMD at least 2 SD below the average for young, healthy men. ➢ Androgen or other anabolic steroid doses had been stable for at least 6 months before randomization and continued such therapy during the study in hypogonadal men. • **Exclusion criteria** ➢ With secondary causes of metabolic bone diseases i.e. glucocorticoid excess, Paget's disease, renal osteodystrophy, osteomalacia. ➢ Using estrogen agonists or antagonists, coumarins and indandione derivatives, anticonvulsants, calcium- or aluminum-containing antacids, or any other drugs that affect bone metabolism.

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Nephrolithiasis or urolithiasis within 2 years
Sprue, inflammatory bowel disease, malabsorption syndrome, or any indication of poor calcium absorption.
Impaired hepatic or renal function
Alcohol or drug abuse within 1 year
Had received treatment for osteoporosis with androgen or other anabolic steroid therapy, calcitonins, progestins, fluorides, oral bisphosphonates, vitamin D >50,000 IU/week, or calcitriol analogs within 6 months.
With growth hormone deficiency from any cause
Had suspected carcinoma or a history of carcinoma except skin cancer within 5 years
Abnormal lumbar spine severe enough to prohibit assessment of BMD

</td></tr>
<tr><td>Results</td><td>

Treatment was stopped early because of the finding of osteosarcoma in rat. The median treatment exposure was 11 months.
The baseline characteristics of the men in the three study groups were similar.
The average percentage of study medication taken in each treatment group was 79%.
81 withdrawals: 17 in placebo group (12%), 28 in the 20mcg group (19%), and 36 in the 40mcg group (26%) (p=0.052).
<u>BMD and whole body BMC:</u>

Daily treatment with 20mcg and 40mcg teriparatide increased lumbar spine and femoral neck BMD dose-dependently, which began to occur at 3 months.
Whole body BMC also increased in both teriparatide groups.
At study end point, the percent changes in total hip, intertrochanteric, and whole body BMD were greater than that in the placebo group.
BMD changes at the distal and ultradistal radius were not different between the teriparatide and placebo group.

<table>
<tr><th></th><th>Placebo</th><th>Teriparatide 20mcg/day</th><th>Teriparatide 40mcg/day</th></tr>
<tr><td># Patients with LS BMD increased at endpoint (%)</td><td>-</td><td>55</td><td>71</td></tr>
<tr><td>Changes in BMD at endpoint (%)
Lumbar spine
Femoral neck

Intertrochanter
Total hip</td><td>
0.52±3.9
0.31±4.1

0.61±2.87
0.54±2.70</td><td>
5.87±4.5 (P<0.001)
1.53±3.95 (P=0.029)

1.18±3.09 (NS)
1.17±2.94 (NS)</td><td>
9.03±6.46 (P<0.001)
2.93±6.34 (P<0.001)

2.34±4.41 (P<0.001)
2.33±4.41 (P<0.001)</td></tr>
<tr><td>Changes in whole body BMC (%)</td><td>-0.45±2.75</td><td>0.64±3.65 (P=0.021)</td><td>0.87±3.65 (P=0.005)</td></tr>
</table>

<u>Biochemical markers:</u>

Treatment with teriparatide was associated with dose-dependent increases in biochemical indices of bone formation (bone ALP, PICP) and resorption (NTX,fDPD).
Bone ALP concentrations were above baseline in both teriparatide groups after 12 months (29% in 20mcg group and 59% in 40mcg group, P<0.001).

<u>Subgroup analyses:</u>

Responses to teriparatide treatment (LS BMD, changes in BMD at other sites, changes in biochemical markers) were independent of baseline free testosterone or estradiol levels and unaffected by age, body mass index, baseline LS BMD, smoking, and alcohol intake.

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</table>

	• Adverse events: ➢ The overall incidence of adverse events was similar in the three groups. ➢ The percentages of withdrawals due to adverse events were higher in the teriparatide groups (9.3% and 12.9% in 20mcg and 40mcg group, respectively, versus 4.8% in the placebo group) ➢ The most common adverse events associated with teriparatide therapy were nausea and headache, which also occurred more frequent in the higher treatment group. ➢ Mean serum calcium concentrations measured at 4-6h after injection were higher in teriparatide groups throughout the study period. Three patients (2%) in the 20mcg group and six patients (4%) in the 40mcg group were withdrawn from the study due to elevated post-injection serum calcium levels. ➢ There were no differences among the treatment groups in the frequency of abnormal urine calcium excretion or urinary calcium to creatinine ratio. ➢ The incidence of urolithiasis was not different in placebo and teriparatide groups (0.7% in placebo vs. 1.3% and 1.4% in the 20mcg and 40mcg groups, respectively, P=0.81).
Conclusions	Teriparatide treatment results in an increase in bone mineral density and is a potentially useful therapy for osteoporosis in men
Critique	• **Strengths:** ➢ Randomized, double-blind, placebo-controlled trial ➢ Stratification based on testosterone and estrogen levels whose low levels are common in men with osteoporosis; age and alcohol consumption, which have been associated with reduction in bone formation. ➢ Detailed inclusion and exclusion criteria ➢ Intention-to-treat trial • **Limitations:** ➢ Relatively short duration of therapy. ➢ Study subjects are mostly white. ➢ Did not assess risks of fracture. ➢ No power analysis was noted. ➢ Use of androgen and other anabolic steroids in inclusion /exclusion may confound the results. ➢ The authors' conclusion did not account for the high drop out rates across the study groups.

Citation	Lane NE, Sanchez S, et al. Parathyroid Hormone Treatment Can Reverse Corticosteroid-Induced Osteoporosis: Results of a Randomized Controlled Clinical Trial. Journal of Clinical Investigation 1998 October 15; 102(8):1627-1633
Study Goals	To determine if treatment with human parathyroid hormone [hPTH (1-34)] could increase bone mass in osteoporotic postmenopausal women taking hormone replacement therapy and low doses of corticosteroids.
Sponsorship	
Methods	• **Study Design** ➢ 12-month randomized, active-control study. ➢ 51 women were randomly assigned to either 400U (25mcg)/day of hPTH (1-34) plus estrogen group (n=28) or estrogen only group (n=23). ➢ All enrolled women received daily supplements of 1500mg of calcium and 800 IU of vitamin D at randomization and to be continued throughout the study. ➢ Patients were taught subcutaneous self-injection at the start of the study. Placebo injections or tablets were not used.

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Outcome measurements: Changes in bone mineral density (BMD) of the lumbar spine by QCT; changes in BMD of the lumbar spine, hip, and forearm by DXA; and changes in biochemical markers of bone turnover (osteocalcin, bone-specific alkaline phosphatase (ALP), and deoxypyridinoline crosslinks (DPD).

• Data Analysis

Student's t test was used for normally distributed variables of baseline differences between the groups.
Analysis of variance (ANOVA) was used to evaluate the differences between the two study groups.
Tukey's method was used for post-hoc analysis.

</td></tr>
<tr><td>Criteria</td><td>
• Inclusion criteria

Postmenopausal women, 50-82 years of age.
Had been menopausal for ≥ 3 years.
With a variety of chronic noninfectious inflammatory diseases.
Low BMD of the lumbar spine or femoral neck (>2.5 SD below mean young normal values).
Had been taking hormone replacement therapy (Premarin 0.625mg/d or an equivalent dose of another estrogen) for ≥1 year.
Had been treated with prednisone or its equivalent at a mean dose of 5-20mg/d for the previous 12 months and to be continued for at least another year.

• Exclusion criteria

Had secondary osteoporosis other than from rheumatic diseases and corticosteroids.
Renal or hepatic dysfunction.
Abnormalities on spinal radiographs that precluded accurate measurements of the lumbar spine by QCT or DXA.

</td></tr>
<tr><td>Results</td><td>

There were no significant differences between the groups in patient's baseline characteristics.
None of the study subjects was a current smoker.
63% of all patients taking methotrexate (n=20), hydroxychloroquine (n=9), azathioprine (n=5), and cyclophosphamide (n=1). The numbers of patients on these agents are similar in both groups.
Three patients from the estrogen-only group withdrew from the study.
BMD response:

The BMD of the lumbar spine measured by QCT and DXA increased significantly in the PTH plus estrogen group and remained the same in the estrogen-only group (P<0.001).
There were no significant differences between the groups with respect to BMD of the total hip, femoral neck, trochanter, or 1/3 distal radius at 6 and 12 months.

<table>
<tr><th>Changes in BMD at 12 month (%)</th><th>P value</th><th>PTH + Estrogen (n=28)</th><th>Estrogen only (n=23)</th><th>Differences (%)</th></tr>
<tr><td>Lumbar spine
• by QCT
• by DXA</td><td>P<0.001</td><td>
35.2±5.5
11.1±1.4</td><td>
1.7±1.7
1.3±0.8</td><td>
33.5
9.8</td></tr>
<tr><td>Femoral neck</td><td>NS</td><td>2.9±1.1</td><td>1.2±1.5</td><td>1.7</td></tr>
<tr><td>Trochanter</td><td>NS</td><td>1.3±0.7</td><td>0.9±0.9</td><td>0.4</td></tr>
<tr><td>Total hip</td><td>NS</td><td>1.9±0.8</td><td>0.4±0.8</td><td>1.5</td></tr>
<tr><td>1/3 Distal radius</td><td>NS</td><td>-0.9±0.6</td><td>-0.6±0.5</td><td>0.3</td></tr>
</table>
</td></tr>
</table>

	• Biochemical markers: ➢ Bone formation markers (osteocalcin and bone ALP) increased significantly after 1 month of PTH treatment and remained increase until the end of the study (P<0.01). ➢ Bone resorption marker (DPD) also increased significantly after 1 month and continued to increase until at 6 months when it remained at this level until the end of the study (P<0.01). • Other biochemical tests: ➢ Among patients in the hPTH-treated group, serum calcium and 1,25 $(OH)_2D_3$ increased slightly and intact PTH decreased slightly from baseline but remained within normal range at 6 months (P<0.05). ➢ No significant changes in serum phosphorus, $25(OH)D_3$, and 24-h urinary calcium noticed during the study in both groups. ➢ Hypercalciuria occurred in 2 women (1 in each group), which returned to normal after calcium intake was reduced, and in 3 women (in hPTH-treated group) which also returned to normal after hPTH and calcium doses reduced. ➢ No evidence of specific antibody to hPTH (1-34) in the blood of hPTH-treated patients.
Conclusions	Daily administration of human parathyroid hormone for 1 year significantly increased spinal bone mass in osteoporotic postmenopausal women taking chronic corticosteroids and estrogen.
Critique	• **Strengths:** ➢ Randomized, controlled trial ➢ Baseline characteristics of patients in the two study groups were similar. ➢ Did compare results with those from previous studies. • **Limitations:** • Small sample size. • The numbers of women in the two study groups are not equal. • Subjects and investigators are not blinded. • Did not assess if increases in bone mass would be associated with reduction in fracture risk. • Did not assess the effects of parathyroid hormone in patients taking high dose of corticosteroids.

Citation	Lane NE, Sanchez S, et al. Short-term Increases in Bone Turnover Markers Predict Parathyroid Hormone-Induced Spinal Bone Mineral Density Gains in Postmenopausal Women with Glucocorticoid-Induced Osteoporosis. Osteoporosis International 2000; 11:434-442
Study Goals	To test the ability of early changes in markers of bone turnover to predict subsequent changes in bone mineral density (BMD) induced by parathyroid hormone fragment, PTH (1-34), in postmenopausal osteoporotic women treated with estrogen and glucocorticoids.
Sponsorship	
Methods	• **Study Design** ➢ 12-month randomized, active-control study. ➢ Subjects were followed for an additional year at the end of treatment period. ➢ 51 women were randomly assigned to either 400U (25mcg)/day of hPTH (1-34) plus estrogen group (n=28) or control group (estrogen only) (n=23). ➢ All enrolled women received daily supplements of 1500mg of calcium and 800 IU of vitamin D at randomization and to be continued throughout the study. ➢ Placebo injections or tablets were not used. ➢ Outcome measurements: Changes in bone mineral density (BMD) of the lumbar spine by QCT; changes in BMD of the lumbar spine and total hip by DXA; and changes in biochemical markers of bone turnover (osteocalcin

	(OC), bone-specific alkaline phosphatase (BAP), and deoxypyridinoline crosslinks (DPD). • **Data Analysis** ➢ Mean/median, standard deviation (SD)/standard error (SE)/interquartile range, paired or unpaired two-tailed t test with p value <0.05 were used to analyze continuous variables. ➢ Uncoupling Index (UI) was calculated to assess the relative balance of the formation and resorption processes of bone remodeling. [$UI=Z_{BAP}+Z_{OC}/2-Z_{DPD}$), Z=subject value-$Mean_{baseline}/SD_{baseline}$] ➢ The proportions of women who could be identified as biochemical or BMD responders to PTH were determined by comparing to the least significant change (LSC). [LSC= t x square root of 2 x median long-term CV (coefficients of variation) for each measure]. One-sided value of t with 90% confidence interval was selected. ➢ Spearman rank correlation was used to determine the associations between markers and BMD. ➢ Receiver operating characteristic (ROC) curves constructed to compare subjects whose change in marker or BMD values exceeded the LSC with those whose marker or BMD changes did not. Areas under the ROC curves (AUC) were compared to determine diagnostic accuracy for predicting BMD changes between markers and BMD.
Criteria	• **Inclusion criteria** ➢ Postmenopausal women, 50-82 years of age. ➢ Had been menopausal for ≥ 3 years. ➢ With a variety of chronic noninfectious inflammatory diseases. ➢ Low BMD of the lumbar spine or femoral neck (>2.5 SD below mean young normal values). ➢ Had been taking hormone replacement therapy (Premarin 0.625mg/d or an equivalent dose of another estrogen) for ≥1 year. ➢ Had been treated with prednisone or its equivalent at a mean dose of 5-20mg/d for the previous 12 months and to be continued for at least another year. • **Exclusion criteria** ➢ Had secondary osteoporosis other than from rheumatic diseases and corticosteroids. ➢ Renal or hepatic dysfunction. ➢ Abnormalities on spinal radiographs that precluded accurate measurements of the lumbar spine by QCT or DXA.
Conclusions	Serial bone marker measurements may be useful in identifying skeletal responders to an anabolic therapy, such as PTH, in estrogen-replete postmenopausal women with glucocorticoid-induced osteoporosis.
Critique	• **Strengths:** ➢ This is an extended analysis of previous trial (Lane et al, 1998) ➢ The subjects were followed for longer period than the previous trials. • **Limitations:** • Small sample size. • The numbers of women in the two study groups are not equal. • Subjects and investigators are not blinded. • Did not assess the effects of parathyroid hormone in patients taking high dose of corticosteroids.

Citation	Black DM, Thompson DE, Bauer DC, et al. Fracture Risk Reduction with Alendronate in Women with Osteoporosis: The Fracture Intervention Trial. The Journal of Clinical Endocrinology & Metabolism 2000;85(11):4118-4124
Study Goals	To compare the effect of alendronate treatment on fracture risk reduction in women with existing vertebral fracture with that in women without existing vertebral fracture but with BMD T score <-2.5, to assess the effect of alendronate in these two groups of women combined, and to examine the time course of the effect of alendronate on clinical fracture risk in these women.
Sponsorship	Merck Research Laboratories
Methods	• **Study Design** ➢ 3-4year multi-centers, randomized, double blind, placebo-control study. ➢ Two study arms: Vertebral Fracture Arm included women who had vertebral fractures identified on radiographs at baseline (n=2027, 1005 placebo and 1022 alendronate), Clinical Fracture Arm included women without vertebral fracture, but with femoral neck T score –1.6 or less at baseline (n=1631, 812 placebo and 819 alendronate). ➢ The alendronate treated patients were placed on alendronate 5mg/day for 2 years, which then increased to 10mg/day. The women with existing vertebral fracture received alendronate for total of 3 years; those without vertebral fracture received alendronate for 4 years. ➢ 82% of women of each group had dietary calcium intake at baseline of less than 1000mg/d; they were given a daily supplement with 500mg elemental calcium and 250IU Vitamin D. ➢ Outcome measurements: clinical fractures (diagnosed by a physician and confirmed by a copy of radiograph) which included clinical vertebral fractures, nonvertebral fractures, hip fractures and wrist fractures; radiographic vertebral fractures which were determined by lateral spine radiographs obtained according to published guidelines at baseline and at 2-3 yr (Vertebral Fracture Arm) and 4 yr (Clinical Fracture Arm). A new radiographic vertebral fractures was defined as a decrease of 20% and at least 4mm in the height of any vertebral body from baseline to end of study. Annual BMD at the hip and posterior-anterior spine using Hologic QDR-2000 densitometers was also examined. • **Data Analysis** ➢ Intention-to-treat analysis in which all events after randomization were analyzed. All P values were 2-sided. ➢ Survival analysis techniques with the log rank test (CIs) for clinical fractures, and the Mantel-Haenszel estimate for the odds ratio for radiographic vertebral fractures. Both outcomes were presented as relative risk (RR). ➢ Breslow-Day test for homogeneity of odds ratios was performed to test the statistical appropriateness of combining patients with and without baseline vertebral fractures for the analysis of fracture endpoints. ➢ Parallel analyses were conducted using definitions of osteoporosis based on BMD at the total hip and at the lumbar spine to confirm the general findings with respect to femoral neck BMD. ➢ Kalbfleisch and Prentice test to determine whether there was an interaction between study time and treatment effect. First time points (using 6-month intervals) were reported for significant reduction in RR ($P<0.05$). ➢ Number needed to treat (NNT) with alendronate for 5 yr to prevent one fracture was estimated by taking reciprocal of the difference between the 5yr incidence of fracture in placebo group and the 5yr incidence of fracture in alendronate group. ($NNT=1/(I_{p5}-I_{a5})$
Results	• The two groups of subjects (with and without fracture) were similar in baseline characteristics, except that the women without vertebral fractures were about 2yr younger and were less likely to have a history of clinical fracture since age 45. Mean baseline BMD at both the hip and the femoral neck was lower in patients without existing vertebral fractures.

- The magnitudes of reduction of fracture incidence with alendronate were similar in both groups of patients (with and without existing vertebral fractures).
- There was no significant heterogeneity in the reduction in risk between the two osteoporotic groups for any of the types of fractures. Rate of vertebral fracture were much higher, and rates of nonvertebral fracture were somewhat higher in those patients with existing vertebral fractures.
- Reductions in risk of clinical fracture of the two groups combined were statistically significant for clinical vertebral fracture by month 12 (59%, p<0.001), for any clinical fracture by month 18 (27%, p=0.017), for nonvertebral fracture by month 24 (26%, p=0.011), for hip fracture by month 18 (63%, p=0.014), and for wrist fracture by month 30 (34%, p=0.046).
- The 5yr-NNT to prevent clinical and hip fracture was similar in the two groups. The lower NNT to prevent vertebral fracture among patients with existing vertebral fracture (8 vs. 29 in the other group) reflects an incidence of new vertebral fracture that was 4-5 times higher in patients with existing vertebral fractures than in those without.
- In women with BMD T scores <-2.5 at either the total hip or the lumbar spine, alendronate was associated with significant reductions in clinical and vertebral fractures in these groups. On the basis of total hip BMD, there were 45% reduction in hip fracture risk (p=0.028) and 23% (p=0.005) reduction in nonvertebral fracture risk in the combined osteoporotic groups. On the basis of BMD at the spine, the risk reductions were 47% (p=0.026) for hip fracture and 25% (p=0.002) for nonvertebral fracture

	Combined osteoporotic group	**Women with existing vertebral fracture** (n=2027)		**Women without existing vertebral fracture** (n=1631)	
Annual incidence (per 100 person-yrs)		PCB	ALN	PLB	ALN
Radiologic vertebral		5.01	2.61	1.41	0.72
Multiple vertebral (radiologic)		1.62	0.17	0.51	0.22
Clinical vertebral		1.77	0.82	0.41	0.35
Any clinical		6.15	5.14	5.12	3.30
Nonvertebral		5.50	4.45	4.81	3.11
Nonvertebral (osteoporotic)		3.44	2.32	2.88	1.73
Hip		0.77	0.37	0.53	0.23
Wrist		1.44	0.75	1.13	1.00
Relative Risk (95%CI)					
Radiologic vertebral	0.52 (0.42, 0.66)	0.53 (0.41, 0.68)		0.51 (0.31, 0.84)	
Multiple vertebral (radiologic)	0.13 (0.07, 0.25)	0.10 (0.05, 0.22)		0.40 (0.08, 1.95)	
Clinical vertebral	0.55 (0.36, 0.82)	0.46 (0.28, 0.75)		0.84 (0.38,1.83)	
Any clinical	0.70 (0.59, 0.82)	0.74 (0.59, 0.92)		0.64 (0.50, 0.82)	
Nonvertebral	0.73 (0.61, 0.87)	0.81 (0.64, 1.03)		0.65 (0.50, 0.83)	
Nonvertebral (osteoporotic)	0.64 (0.51, 0.80)	0.68 (0.49, 0.92)		0.60 (0.43, 0.83)	
Hip	0.47 (0.26, 0.79)	0.49 (0.23, 0.99)		0.44 (0.18, 0.97)	
Wrist	0.70 (0.49, 0.98)	0.52 (0.31, 0.87)		0.88 (0.55, 1.40)	

*Clinical vertebral: defined as fractures reported by participants to have been diagnosed by a physician.

- Nonvertebral osteoporotic fractures: including fractures of the clavicle, humerus, wrist, pelvis, hip, and leg

Conclusions

The reductions in fracture risk during treatment with alendronate are consistent in women with existing vertebral fractures and those without such fractures but with bone mineral density in the osteoporotic range. The reduction in risk is evident early in the course of treatment.

Critique	• **Strengths:** ➢ Large sample size ➢ Randomized, double blind, placebo-controlled trial ➢ Intention-to-treat analysis • **Limitations:** ➢ The alendronate doses are not consistent throughout the study. ➢ The alendronate dose was half of recommended dose for treatment of osteoporosis, thus the observed risk reductions may be underestimated.

Citation	Finklestein JS, et al. The Effects of Parathyroid Hormone, Alendronate or Both in Men with Osteoporosis. The New England Journal of Medicine 2003 Sept 25; 349(13): 1216-1226
Study Goals	To determine whether combining parathyroid hormone with an antiresorptive agent will enhance bone mineral density
Sponsorship	The study was supported by Lilly
Methods	• **Study Design** ➢ Randomized control trial of alendronate, parathyroid hormone or alendronate plus parathyroid hormone ➢ 83 men were assigned to one of three treatment groups: 28 to alendronate 10mg daily; 27 men to parathyroid hormone 37mcg SQ daily; 28 men to both alendronate 10mg daily and parathyroid hormone 37mcg SQ daily ➢ Men were stratified on the basis of age (<65 years age or ≥65 years of age) and according to the bone mineral density of the spine (higher or lower than 2 SD below the mean for the men's age) ➢ Calcium intake was estimated by a research dietitian and was maintained at 1000 to 1200mg daily through diet or supplementation ➢ All men received 400 U of vitamin D daily ➢ Alendronate therapy began at the baseline visit and continued for 30 months ➢ Parathyroid hormone therapy began at the 6-month visit and continued for 24 months ➢ Outcome measurements: bone mineral density of the lumbar spine in the posteroanterior and lateral projections, the proximal femur, the distal one third of the radial shaft, and the total body was measured with the use of dual-energy x-ray absorptiometry and densitometer. Trabecular bone mineral density of the lumbar spine was measured using quantitative CT; serum alkaline phosphatase levels measured every 6 months. • **Data Analysis** ➢ Mixed model analysis of variance was used to assess the effect of treatment on each variable ➢ Rates of adverse events were compared using the Fischer's exact test
Criteria	• **Inclusion Criteria** ➢ Males 46-85 years of age with a bone mineral density of the lumbar spine in the posteroanterior or lateral projection or on the femoral neck that was at least 2 SD below the mean value for young normal men. ➢ Serum calcium level of less than 10.6mg/dL ➢ Serum creatinine level of less than 2mg/dL ➢ Serum alkaline phosphates level of <150U/LSerum 25-hyrdoxyvitamin D level of at least 15ng/mL ➢ Serum aspartate aminotransferase and alanine aminotransferase levels that were less than twice the upper limit of the normal range ➢ Normal serum levels of parathyroid hormone, thyrotropin, and testosterone

	• **Exclusion Criteria** ➢ Men who had disorders or who were taking medications that are known to affect bone metabolism ➢ Men with nephrolithiasis, active peptic ulcer disease, severe reflux esophagitis, clinically significant cardiac, renal, or hepatic disease, or cancer
Results	• The baseline characteristics were similar among all 83 men who underwent randomization ➢ None of the men had received previous drug therapy for osteoporosis • A total of 20 men (3 in the alendronate group, 10 in the parathyroid hormone group, and 7 in the combination therapy group) discontinued treatment. ➢ Most of them discontinued parathyroid hormone therapy because of discomfort or inconvenience related to injections ➢ Ten males discontinued treatment before any follow-up measurements of bone density could be obtained during treatment with their assigned study medication (data for these patients are were not included in the longitudinal analysis) • Of the remaining subjects all but three took at least 95% of their doses of alendronate, and all but nine took at least 95% of their doses of parathyroid hormone • <u>Bone Mineral Density: Posteroanterior Spine</u> ➢ The bone mineral density at the posteroanterior spine increased more in men treated with parathyroid hormone alone than in those treated with alendronate alone or with combination of the two ($p<0.001$, for both comparisons) ➢ The bone mineral density of the posteroanterior spine increased more with combination therapy than with alendronate alone ($P<0.001$). • <u>Bone Mineral Density: Lateral Spine</u> ➢ The bone mineral density at the lateral spine also increased more in the parathyroid hormone group than in the alendronate group or the combination therapy group ($P<0.001$ for both comparisons) and increased more in the combination therapy group than in the alendronate group ($P=0.02$) • <u>Bone Mineral Density: Femoral Neck</u> ➢ The bone mineral density at the femoral neck increased more in the parathyroid hormone group than in the alendronate group ($P<0.001$) or with combination therapy group ($P=0.01$) ➢ There were no significant differences in bone mineral density at the femoral neck between the alendronate group and the combination therapy group ($P=0.18$) • <u>Bone Mineral Density: Total Hip</u> ➢ The bone mineral density at the total hip increased more in the parathyroid hormone group than in the alendronate group ($P=0.005$) ➢ There were no significant differences in the changes between the alendronate group and the combination therapy group ($P=0.20$) ➢ There were no significant differences in the changes between the parathyroid hormone group and the combination-therapy group ($P=0.08$) • <u>Total Bone Density</u> ➢ There were no significant differences among groups in the changes in total-body bone mineral density ($P=0.360$ for the three-way comparison) • **<u>Trabecular Bone Density</u>** • The trabecular bone mineral density at the spine increased more in the parathyroid hormone group than in the other two groups ($P<0.001$ for both comparisons) and also increased more in the combination therapy group

than in the alendronate group (P=0.0**05**Alkaline Phosphatase

- The peak serum alkaline phosphatase levels at month 12 were significantly higher in the parathyroid hormone group than in the other two groups (P<0.001 for both comparisons) but did not differ significantly between the alendronate group and the combination therapy group (P=0.14)

- Adverse Events
- There were several differences among treatment groups, but these differences were generally small
- No cases of hypercalcemia
- There was clearly a higher incidence of adverse effects (headache, joint pain, back pain, muscle aches) in the combination therapy group

Percentage of Visits at Which Men Reported Side Effects

Side Effect	Alendronate Group (N=28)	Parathyroid Hormone Group (N=20)	Combination Therapy Group (N=25)	Three Way Comparison (P Value)
		% of visits		
Headache	11	16	21	0.002
Dizziness	4	7	8	0.03
Mood Swings	4	6	7	0.43
Joint Pain	33	54	43	<0.001
Bone Pain	4	7	9	0.06
Back Pain	26	38	29	0.008
Muscle aches	24	26	29	0.44
Chest Pain	8	3	6	0.04
Shortness of Breath	6	5	11	0.01
Nausea	3	5	7	0.05
Constipation	8	12	8	0.27
Bloating	6	7	10	0.15
Heartburn	18	20	25	0.10
Diarrhea	9	7	10	0.58
Gas	17	16	20	0.45
Frequent Urination	25	22	22	0.67
Discomfort at Injection Site	NA	18	17	NA

*P values were calculated with the use of Fischer's exact test. NA denotes not applicable

Conclusions

Alendronate, a potent inhibitor of bone resorption, impairs the ability of parathyroid hormone to increase bone mineral density both at the spine and femoral neck. Additionally, alendronate also reduced the parathyroid hormone associated increase in the serum total alkaline phosphatase levels, which reflects the stimulation of osteoblast activity by parathyroid hormone. This suggests that alendronate impairs the ability of parathyroid hormone to stimulate new bone formation in men. Combination of alendronate and parathyroid hormone prevented parathyroid hormone induced decrease in bone density of non-weight bearing cortical bone. The results of this study do not correlate with risk of fracture. Therefore, additional studies are required before combinations of antiresorptive agents and parathyroid hormone can be recommended for treatment of men with osteoporosis

Critique	• **Strengths:** ➢ Baseline characteristics among patients were similar ➢ Three way comparison among treatment arms on all outcome measures and adverse effects ➢ Assessment of compliance among remaining subjects in study Equal randomization of subjects in the three treatment arms • **Limitations:** ➢ Small sample size (83 patients) ➢ Large drop out rate (31% of patients on parathyroid treatment dropped out) No conclusive data on the risk of fracture ➢ Dose of teriparatide in the study (37mcg daily) higher than the currently approved FDA dose of 20mcg daily ➢ Power analysis is questionable due to small sample size

Citation	Rehman Q, Lang TF, et al. Daily Treatment with Parathyroid Hormone is Associated with an Increase in Vertebral Cross-Sectional Area in Postmenopausal Women with Glucorticoid-induced Osteoporosis. Osteoporosis Int 2003 14: 77-81.
Study Goals	To determine whether treatment with human parathyroid hormone (1-34) was associated with an increase in vertebral size by measuring vertebral cross sectional area in postmenopausal women with osteoporosis on chronic HRT and glucocorticoids
Sponsorship	Public Health Services Grants and the Rosalind Russell Arthritis Research Center
Methods	• **Study Design:** ➢ Prospective randomized controlled trial ➢ 51 postmenopausal women on chronic stable doses of HRT and glucocorticoids who had osteoporosis were randomized to one of two treatment groups: 28 women received human parathyroid hormone (1-34) 40mcg/day SQ for 12 months with 12 months of follow-up while continuing HRT; 23 women were continued on estrogen alone for 24 months ➢ All the enrolled women received 1500mg calcium and 800IU vitamin D daily ➢ Outcome measurements: Vertebral cross-sectional area measurement (VCSA) of L1 and L2 measured at baseline, 1 year and 2 years Vertebral compressive strength measurement (VFSOM) Bone Mineral Density (BMD) • **Data Analysis:** ➢ Student's t-test was used to assess demographic variables in each treatment group ➢ Analysis of variance (ANOVA) was used to determine changes in vertebral strength in both groups
Criteria	• **Inclusion Criteria** ➢ Women who has been postmenopausal for ≥3 years ➢ On Premarin® 0.625mg daily for at least one year prior to enrollment ➢ On prednisone (5-20mg/day) for at least one year prior to enrollment ➢ Osteoporosis (defined asT-score ≤-2.5 at the lumbar spine and/or hip)

<table>
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Exclusion Criteria
Patients with secondary osteoporosis other than from glucocorticoids
Patients with underlying rheumatic disease or abnormalties on spine radiograph that precluded accurate measurement of vertebral bone mass on quantitative computed tomography (QCT) or DEXA scan

</td></tr>
<tr><td>Results</td><td>

There were no statistically significant differences between the two groups in age, glucocorticoid dose, duration of glucocorticoid or estrogen therapy, or years since menopause or body mass index

Table 1: Baseline Characteristics of the Study Subjects
<table>
<tr><th>Characteristics</th><th>PTH + HRT (n=28)</th><th>HRT only (n=23)</th><th>P value</th></tr>
<tr><td>Age (years)</td><td>65.1 (±9.6)</td><td>59.9 (±10.2)</td><td>NS</td></tr>
<tr><td>BMI (kg/m^2)</td><td>26.1 (±1)</td><td>25.6 (±0.8)</td><td>NS</td></tr>
<tr><td>Years since menopause</td><td>19.3 (±8.9)</td><td>16.3 (±11.2)</td><td>NS</td></tr>
<tr><td>Years on HRT</td><td>16.6 (±11.1)</td><td>11.4 (±10.3)</td><td>NS</td></tr>
<tr><td>Mean dose of prednisone or equivalent (mg/day)</td><td>8.0 (±3.8)</td><td>9.4 (±4.5)</td><td>NS</td></tr>
</table>
Values are the mean ±SD

<u>Vertebral Cross Sectional Area (VCSA)</u>
No significant differences in VCSA were observed between the treatment groups at either 12 or 24 months
<u>Vertebral Compressive Strength Measurement (VFSOM)</u>
A significant difference was observed between both groups at 12 and 24 months
<u>Vertebral Bone Mineral Density (BMD)</u>
A significant difference was observed between both groups at 12 and 24 months

<table>
<tr><th>VCSA L1 and L2</th><th>% change from baseline at 12 months</th><th>P value</th><th>% change from baseline at 24 months</th><th>P value</th></tr>
<tr><td>PTH+HRT</td><td>+4.8%</td><td>0.0003</td><td>+2.6%</td><td>0.036</td></tr>
<tr><td>HRT only</td><td>-0.4%</td><td>NS</td><td>-0.8%</td><td>NS</td></tr>
<tr><td colspan="5"></td></tr>
<tr><th>BMD by QCT (L1-L4)</th><th>% change from baseline at 12 months</th><th>P value</th><th>% change from baseline at 24 months</th><th>P value</th></tr>
<tr><td>PTH+HRT</td><td>+34.9%</td><td><0.001</td><td>44.1%</td><td><0.001</td></tr>
<tr><td>HRT only</td><td>+1%</td><td>NS</td><td>1%</td><td>NS</td></tr>
<tr><td colspan="5"></td></tr>
<tr><th>VFSOM (estimated vertebral strength)</th><th>% change from baseline at 12 months</th><th>P value</th><th>% change from baseline at 24 months</th><th>P value</th></tr>
<tr><td>PTH+HRT</td><td>+200%</td><td><0.01</td><td>+206%</td><td><0.01</td></tr>
<tr><td>HRT only</td><td>+1.1%</td><td>NS</td><td>-16%</td><td>NS</td></tr>
</table>
</td></tr>
<tr><td>Conclusions</td><td>The outcomes of the study clearly demonstrate that treatment with human parathyroid hormone(1-34) along with HRT and calcium-vitamin D supplementation had a significant impact on increasing vertebral cross</td></tr>
</table>

	sectional area, bone mineral density and vertebral strength compared with HRT and calcium-vitamin D supplementation alone.
Critique	• **Strengths** ➢ Baseline characteristics were similar in both treatment groups ➢ All subjects participated in the study throughout treatment and follow-up (i.e. no drop outs) ➢ All subjects were given standard doses of calcium and vitamin D supplementation • **Limitations** ➢ Small sample size ➢ No measurement of compliance ➢ No measurement of adverse effects ➢ VCSA measurements not done on the entire length of spinal column (only L1 and L2) usually performed on L1-L4 ➢ Measurement indices (VFSOM AND VCSA) are only applicable to strength of vertebral bone ➢ Questionable reliability of these measurements due lack of use of efficacy measures in clinical practice ➢ Power analysis is questionable due to small sample size ➢ Measurements do not correspond to incidence of fractures

Citation	Ettinger, B, et al. Differential Effects of Teriparatide on BMD After Treatment With Raloxifene or Alendronate
Study Goals	To investigate the skeletal effects (BMD) with 18 months of treatment with teriparatide in women whose osteoporosis was previously treated with either alendronate or raloxifene in a prospective, open label, nonrandomized single-armed 12 month trial, with a 6 month extension phase.
Sponsorship	Eli Lilly and Company
Methods	• Study Design ➢ Prospective, open label, nonrandomized, single-armed 12 month trial with a 6-month extension phase, examining effects of rhPTH(1-34) treatment in patients previously treated with either alendronate or raloxifene ➢ 59 postmenopausal women age 60-87 years of age previously treated with alendronate 10mg daily or raloxifene 60mg daily all received teriparatide 20mcg daily ➢ All women received calcium 1000mg and vitamin D 400IU daily ➢ Baseline information on demographics, health history, and medication use as well as laboratory tests was obtained prior to initiating treatment ➢ BMD was measured using DXA of the L2 – L4 lumbar spine and total hip ➢ Follow-up visits occurred at 1, 3, 6, 12 and 18 months after the start of teriparatide therapy ➢ Bone turnover markers (bone specific alkaline phosphatase (bone ALP), osteocalcin, N-propeptide of type 1 procollagen (PINP), and N-telopeptide of collagen (NTX)) were obtained at all but the one month visit ➢ Outcome measurements**:** Primary study outcome was change from baseline in lumbar spine BMD after 12 months of follow-up. Secondary outcomes included 12 month change from baseline in total hip BMD in each of the four serum markers of bone turnover; and during the 6 month extension phase • Data Analysis ➢ Baseline characteristics of the two treatment groups were compared using Pearson's X^2 tests for categorical variables and Student's t-test for continuous variables (p=NS)

	➢ Differences in BMD response were calculated using analysis of covariance (ANCOVA), with pretreatment drug as the factor and the corresponding baseline BMD measurement as the covariate ➢ Primary comparison in study was the mean difference in lumbar spine BMD from baseline to 12 months, calculated separately for each antiresorptive pre-treatment group ➢ One sided paired *t* test with a significance level of 0.05, at least 80% power to detect a mean within group difference of 0.025g/cm^{2,} assuming an SD of 0.043g/ cm^{2,} and a 20% drop out rate
Criteria	• Inclusion Criteria ➢ Women 60-87 years of age with a prior lumbar spine or total hip BMD measurement of ≤-2.5 T-score, who regularly (using >70% of pills prescribed) had used either alendronate 10mg/day or raloxifene 60mg/day for 18-36 months before study entry ➢ All participants were required to have a lumbar spine or total hip BMD T-score ≤-2.0 on entry • Exclusion Criteria ➢ History of metabolic bone disease, cancer (except non-melanoma skin cancer), coronary disease, stroke or transient ischemic attack, venous thromboembolism, uncontrolled hypertension, uncontrolled thyroid disease, liver disease, fasting triglycerides >300mg/dl, fasting glucose >180mg/dl, or had taken estrogen or progestin within 3 months of randomization
Results	• Baseline characteristics were similar among all women enrolled in the study (p=NS) • Of the 59 enrolled subjects, 58(98.3%) completed 12 months of treatment, and 50 continued in the 6 month extension phase • Of the 50 subjects who elected to continue past 12 months, 48(96%) completed the additional 6 months of teriparatide treatment • Among women who enrolled in the study, pen measurements revealed that 93% of the women used at least 75% of their expected amount of teriparatide • Bone Turnover Markers ➢ After 1 month of teriparatide treatment, both prior alendronate and raloxifene groups showed significant increases in bone turnover markers ➢ Changes in bone turnover markers were similar at 3, 6, 12 and 18 months; and reached a plateau at 6-12 months for both the prior alendronate and raloxifene treated groups • Lumbar Spine Bone Mineral Density (BMD) ➢ Raloxifene group: increased 2.1% and 5.2% relative to baseline at 3 and 6 months, respectively ➢ Alendronate group: remained close to baseline values at 3 and 6 months ➢ From 6 to 18 months, increases in BMD were similar between groups ➢ At 18 months, significant increase in lumbar spine BMD 10.2% for prior raloxifene group versus 4.2% for prior alendronate group (p<0.0001) • Total hip Bone Mineral Density (BMD) ➢ At 6 months mean change (0.5%) in raloxifene group versus (-1.8%) in the alendronate group p<0.002
Conclusion	Teriparatide treatment in postmenopausal women with osteoporosis previously treated with alendronate produces less than expected increases in bone turnover markers and BMD. In contrast, women previously treated with raloxifene showed increases in bone turnover markers and BMD similar to teriparatide naïve patients in previous trials. Also, future should have longer treatment periods (24 months) to assess benefits of teriparatide on BMD between 12 and 24 months of therapy.

Critique	• **Strengths** ➢ Prospective study design ➢ All subjects received calcium and vitamin D supplementation • **Limitations** ➢ Small study population ➢ Did not investigate adverse effects experienced by the subjects ➢ Study period only 12 months versus 24 months ➢ Outcomes do not correlate with risk of fracture

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Teriparatide injection	20mcg QD	11.90 9.11	4358 3325.15
Alendronate tablet	10mg QD 70mg weekly	1.18 0.81 1.29 0.81	431 295.65 474 295.65
Risedronate tablet	5mg QD 35mg weekly	1.08 1.33 1.081.33	395 488.05 395 488.05
Calcitonin nasal spray	200IU QD	1.31 1.62	479 591.30
Raloxifene tablet	60mg QD	1.28 1.47	467 536.55

Cost Analysis[6,8]

	Teriparatide 20mcg injection	Alendronate 10mg tablet
Acquisition costs per dose	$11.90 $9.11	$1.18 $0.81
Acquisition costs per day	$11.90 $9.11	$1.18 $0.81
Cost per year	$4358 $3325.15	$431 $295.65
Relative Risk: -Vertebral fracture -Non-vertebral fracture	 0.35 (0.22-0.55) * 0.47 (0.25-0.88) *	 0.52 (0.42-0.66) ** 0.64 (0.51-0.80) **
Relative Risk Reduction -Vertebral fracture -Non-vertebral fracture	 65%* 53%*	 48%** 23%**
Absolute Risk Reduction Compared to Placebo (per 100 pts-yrs) -Vertebral fracture -Non-vertebral fracture	 8.7* 2.9*	 2.4** 1.05**
Cost per 1 % Absolute Risk Reduction of new fracture (per 100 pts-yrs) -Vertebral fracture -Non-vertebral fracture	 $38218 $114655	 $12319 $28190
NNT(Cost of treatment to prevent 1 fracture per 100 pts-yrs) -Vertebral fracture -Non-vertebral fracture	 12 patient years ($39900 34 patient years $113050	 42 patient years $12432 95 patient years $28120

NNT: number of patient needed to treat
* based on 19-month study period, Neer et al, 2001
** based on 3-year study period, Black et al, 2000

Comparison of Active Control Parallel Group			
	Absolute Risk Reduction per year (% of patients)	**NNT to prevent one event**	**Incremental Cost Effectiveness Ratio per year†**
Nonvertebral Fractures	9.6%	10	$39,270

*Data pulled from Body et al, October 2002.
†Cost of drug based on teriparatide 20mcg daily. 40mcg daily was the dose used in this trial; however this is not a recommended dose for treatment. Neer et al trial has shown that the fracture rate is similar with the 20mcg and 40mcg daily doses[6].

Limitations of cost analysis:

This cost analysis has several limitations. A majority of the studies included women, with the exception of two studies which included men. Although the major randomized controlled clinical trials conducted to measure BMD and fracture outcomes in osteoporosis have focused enrollment to female patients and this data has commonly been extrapolated to treatment in men.. Secondly, patient compliance was not factored into the analysis as an outcome to impact cost-effectiveness for women. Teriparatide trials reported moderate to high compliance (ranging from about 67% in Body et al to 95% compliance with Finkelstein et al trial), which may contribute significantly to issues on how this will translate into clinical care. Although Finkelstein et al[17] reported good compliance among the participating subjects, it is difficult to determine overall compliance due to large drop out rate, especially among subjects receiving teriparatide. Body[8] and Finkelstein[17] compared alendronate to teriparatide head to head, which showed similar compliance rates between the two treatments despite the difference in dosage form.. Thirdly, dosing of alendronate in Black et al trial was not consistent throughout the trial. Patients were given 5 mg/day of alendronate for 2 years and 10mg/day thereafter due to the unveiling of new data demonstrating better therapeutic outcomes at dose of 10mg versus 5mg. The dosing of teriparatide in the studies by Finkelstein[17] and Rehman[18] used higher doses (37mcg/day, and 40mcg/day, respectively) than the manufacturer's recommended daily dose (20mcg/day). Fracture rates could have been significantly increased due to the under-dosing at 5mg/day. Fourth, the length of study with teriparatide was much shorter (19 months vs. 3 years with alendronate), thus may not reflect the full effects of teriparatide on bone fractures. Fifth, in the direct comparative trial (Body et al), nonvertebral fractures were not a primary end point of study, although there was a statistical difference demonstrated between event rates for teriparatide and alendronate despite a small sample size (p=0.042). The nonvertebral fracture incidence was significantly lower in the teriparatide group than in the alendronate group is technically true, but does not reveal the details of the study data. Sixth, none of the studies thus far have considered once weekly doses of alendronate. This will have an impact on overall compliance for two reasons: 1) oral dosage form versus injectable dosage form; 2) once weekly dosing versus once daily dosing. Fractures were recorded without regard to trauma, and information on the how this impacts the outcome measured was not defined. A larger study is more than likely required to confirm this conclusion. Finally, baseline fracture rates of patients from these data were different. Patients in Neer et al study with reported number of vertebral fractures of 2.3±1.8 at baseline (90% had at least 1 baseline fracture, 60% had at least 2 or more), while only 58% of patients in Black et al study reported a clinical fracture since age 45. This data was not reported in Body et al, and thus it cannot be determined if same types of patients are compared when reviewing all 3 trials for cost analysis.

Conclusions

The efficacy and safety of once daily subcutaneous injection of teriparatide in treating osteoporosis compared to placebo have been demonstrated previously in clinical trials. Teriparatide injections increase BMD and decrease relative risk of vertebral and nonvertebral fracture as well as absolute incidences of fractures. Teriparatide has demonstrated to be equally efficacious to alendronate with improved outcomes over alendronate in increasing BMD and decreasing nonvertebral fractures Teriparatide significantly increased bone mineral density of the spine and femoral neck in comparison with alendronate. On the contrary, there were no significant differences among the groups in the changes in total body bone mineral density.

The acquisition cost of teriparatide is 11 times more than that of alendronate per year. The cost is triple or quadruple to prevent 1 incidence of fracture (depends upon whether it is vertebral or nonvertebral fracture) when treating with teriparatide instead of alendronate. The incremental cost/effective ratio (extra cost) for choosing teriparatide over alendronate to prevent nonvertebral fractures is almost $40,000 per year. However, considering the high costs of fracture itself and its complications (i.e. cost of hospital stay, reduction in productivity, pain treatment, etc.), reduced quality of life and increased mortality associated with fractures, the use of teriparatide may be justified, especially in high-risk patients. The expense of caring for fractures is significant. With ever increasing costs of health care it can be anticipated that treatment costs of fractures will also likewise inflate over time. In 1995, the total direct medical expenditures for osteoporotic fractures care in the U.S. were estimated at $13.8 billion and 17.1 billion in 2000. The estimated 1-year cost of a vertebral fracture was approximately $1000. Whereas the total cost of a hip fracture, the most common type of nonvertebral fracture, ranged from $26,400 to 36,800[16]. Thus, after adjusted to today dollars, the cost of one hip fracture may exceed the cost of one-year teriparatide therapy. Furthermore, first fractures were also known to be an indicative of risk for further fractures. For instance, vertebral fracture showed to increase the risk of another vertebral fracture by fivefold, with 1-year risk of almost 20%[13]. Since teriparatide associated with better fracture risk reductions than alendronate, it appears that in high risk for fracture osteoporosis patients it may be even more cost effective to treat patients with teriparatide and target preventing further fractures.

A concern with teriparatide therapy is patient long-term safety. Osteoporosis is a chronic debilitating disease. Safety with teriparatide has not been established past 25 months of treatment in clinical trial data. Based on the results of osteosarcoma in rats, all clinical trials with teriparatide were stopped before 2 years, which raise the concerns of safety with treatment longer than 2 years and whether to switch patients to other osteoporotic agents when 2 years is reached. In Rittmaster et al trial[15], subsequent use of bisphosphonate (alendronate) after 1-year treatment with parathyroid hormone showed to enhance the increase in vertebral bone density, compared to the use of alendronate or estrogen alone, suggests that the effect of teriparatide can be optimized when a bisphosphonate is used followed teriparatide treatment. However, Finkelstein[17] suggests that when alendronate is used in combination with parathyroid hormone there is a reduction in parathyroid hormone associated increase in serum total alkaline phosphatase levels, which reflects the stimulation of osteoblast activity by the parathyroid hormone. Thus, alendronate impairs the ability of parathyroid hormone to stimulate new bone formation in men. However, whether subsequent use of bisphosphonate after teriparatide preserves its effects on fracture risk reductions are still not known.

One final concern of teriparatide therapy is patient compliance. Previous trials showed moderate to high compliance (67-95%) with teriparatide injections. In fact, head to head clinical trials of alendronate and teriparatide[17] compliance rates among subjects participating in the study were the same for both alendronate and teriparatide. When comparing the undesirable daily injection of teriparatide with weekly oral dosing of bisphosphonates, patient compliance is expected to be even lower in real clinical settings, especially in patients who have not yet experienced the impacts of fracture. It would be difficult to place this therapy in as a preferred agent prior to bisphosphonates in patients with a less morbid condition secondary to fractures.

Recommendations

Based on the available efficacy, safety and cost data, teriparatide 20mcg/day should be recommended as non-formulary for treating patients with osteoporotic fracture while compliant on bisphosphonate after minimum of 6 months of treatment or are intolerant to bisphosphonates defined as moderate to severe chronological event related to the drug. For patients who are noncompliant or intolerant to oral bisphosphonates may be candidates for an IV bisphosphonate such as zolendronic acid. Combination therapy or add-on therapy of teriparatide and bisphosphonate is not recommended at this time in both men and women.

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