Opposite Bone Remodeling Effects of Teriparatide and Alendronate in Increasing Bone Mass

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**Background:** Antiresorptive agents for the treatment of osteoporosis suppress bone remodeling and reestablish bone turnover at a lower rate to reduce bone loss. Recombinant teriparatide (human parathyroid hormone 1-34) stimulates bone formation, increases bone mass, and improves bone microarchitecture. We contrasted the effects of once-daily doses of 20 µg of teriparatide and 10 mg of alendronate sodium on bone mineral density (BMD) and markers of bone turnover.

**Methods:** Markers of bone turnover and areal BMD were assessed in 203 postmenopausal women with osteoporosis in an 18-month randomized parallel double-blind study; volumetric BMD was measured in a subset of women.

**Results:** Teriparatide significantly increased markers of bone turnover that peaked at 6 months (serum procollagen type I N-terminal propeptide, 218%; and urinary N-telopeptide corrected for creatinine, 58%; *P*<.001); alendronate significantly decreased the markers at 6 months (–67% and –72%, respectively; *P*<.001). At 18 months, areal and volumetric spine BMDs were significantly higher with teriparatide than with alendronate (10.3% vs 5.5% [*P*<.001] and 19.0% vs 3.8% [*P*<.01], respectively). Areal femoral neck BMD was significantly higher than baseline in the teriparatide and alendronate groups (4.9% and 2.2%, respectively). Cortical volumetric femoral neck BMD was significantly different between the teriparatide and alendronate groups (–1.2% and 7.7%, respectively; *P*=.05).

**Conclusion:** Two distinct options for the management of osteoporosis lead to increases in BMD by opposite mechanisms of action on bone remodeling.

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The target of osteoporosis treatments has been the prevention of fractures by correcting the imbalance in the bone remodeling process that affects mechanical properties related to bone strength, including bone geometry and microarchitecture. Accelerated bone remodeling constitutes an additional risk factor for fracture when bone resorption exceeds bone formation. Osteoporosis therapies can preferentially modulate bone resorption and formation, thus reducing or reversing the negative balance in bone remodeling. Bisphosphonates inhibit bone resorption, thereby improving the bone remodeling balance. This reduction in the rate of bone turnover, with a trend toward positive bone balance, preserves microarchitecture and lowers the incidence of osteoporotic fractures.

Teriparatide (human parathyroid hormone [PTH] 1-34, of recombinant DNA origin), an anabolic agent given once daily that increases bone remodeling, represents a new therapeutic option for osteoporosis. In contrast to antiresorptive agents, teriparatide increases bone formation earlier and to a greater magnitude than resorption, resulting in a positive bone balance, an increase in bone mineral density (BMD), an improvement in bone microarchitecture and strength, and a reduction in fracture incidence. To our knowledge, the present study is the first to compare the effects of the approved daily doses of teriparatide (20 µg) and alendronate sodium (10 mg) on areal (as measured by dual-energy x-ray absorptiometry [DXA]) and volumetric (as measured by quantitative computed tomography [QCT]) BMD and biochemical markers of bone turnover.
STUDY DESIGN AND PARTICIPANTS

This was a randomized, double-blind, active comparator study. The study consisted of a 2-month screening phase and an 18-month treatment phase. Postmenopausal women (n=641) with osteoporosis, 45 to 84 years of age, were screened for the study; 203 women were randomized and followed up at 19 clinical sites globally. Of the 438 women who did not qualify for the study, 385 (87.9%) did not meet inclusion criteria and 45 (10.3%) declined participation before randomization. Subjects were ambulatory, 5 years or more post menopause, had a BMD T score between -2.5 and -4.0 at the lumbar spine or femoral neck, and had normal or clinically insignificant abnormal laboratory values, including serum calcium, PTH 1-84, 25-hydroxyvitamin D, and alkaline phosphatase.

Women were excluded if they had prior treatment with PTH or a PTH analogue; treatment with bisphosphonates within 12 months, anabolic corticosteroids or calcitrol or vitamin D analogues or agonists within 6 months, estrogens or selective estrogen receptor modulators within 3 months, or calcitonin within 2 months; therapeutic doses of fluoride; systemic corticosteroid use within 1 month or for more than 30 days in the prior year; use of anticoagulants within 1 month; history of diseases other than postmenopausal osteoporosis that affect bone metabolism; malignant neoplasms within 5 years; carcinoma in situ of the uterine cervix within 1 year; nephrolithiasis or urolithiasis within 2 years; abnormal corrected thyroid function; liver disease or clinical jaundice; impaired renal function; alcohol or other drug abuse; or poor medical or psychiatric risk for treatment. Patients with an increased risk of osteosarcoma (ie, patients with Paget disease of bone, previous skeletal exposure to external beam radiotherapy, or previous malignant neoplasm involving the skeleton) were also excluded.

The institutional review board at each clinical site approved the study, 385 (87.9%) did not meet inclusion criteria and 45 (10.3%) declined participation before randomization. Subjects were ambulatory, 5 years or more post menopause, had a BMD T score between -2.5 and -4.0 at the lumbar spine or femoral neck, and had normal or clinically insignificant abnormal laboratory values, including serum calcium, PTH 1-84, 25-hydroxyvitamin D, and alkaline phosphatase.

We assessed the severity of back pain, a prespecified end point, was recorded as subjective in all patients at baseline and at 1, 3, 6, and 12 months. Urinary N-telopeptide corrected for creatinine [NTx] was assessed in all patients at baseline and at 1, 3, 6, and 12 months. Urinary N-telopeptide corrected for creatinine was measured by Covance Central Laboratory Services (Indianapolis, Ind) using the Osteomark enzyme-linked immunosorbent assay (OsteX Corporation, Seattle, Wash). Serum procollagen type I N-terminal propeptide was measured by Synarc Laboratory (Lyon, France) using the UniQ radioimmunoassay (iodine 125) kit from Orion Diagnostica (Espoo, Finland). The intraassay and interassay coefficients of variation were 4.5% to 6.6% and 6.7% to 14.8%, respectively, for NTx and 3.6% to 5.0% and 4.1% to 4.8%, respectively, for PINP. We assessed the correlation of early changes in PINP using the area under the curve from the first 6 months of treatment and changes in areal lumbar spine BMD at the study end point. The Spearman rank correlation coefficient was calculated between the 6-month area under the curve values and the last observed lumbar spine DXA BMD measurement.

STUDY TREATMENTS

Women who successfully completed the screening phase were randomly assigned to receive once-daily doses of 20 μg of teriparatide (Eli Lilly and Company) and oral placebo (n=102) or 10 mg of oral alendronate (Fosamax; Merck and Company, Inc) and injectable placebo (n=101). Each woman received daily supplementation of calcium (1000 mg) and vitamin D (400-800 IU) throughout the study.

STUDY OUTCOMES

The study end points were percentage change from baseline in areal and volumetric BMDs measured at the lumbar spine and total hip and biochemical markers of bone turnover. Follow-up visits were conducted at 1, 3, 6, 12, and 18 months of treatment. Serum calcium concentrations were checked at screening, at baseline, and at 1 and 18 months or at an early discontinuation visit. Clinical adverse events were assessed at each study visit and at contacts initiated by the patient. Compliance with study treatments was assessed at each postrandomization visit by direct questioning of the participants and by quantifying the study drugs returned in disposable pens (used and unused) and the remaining tablets.

Areal BMD (in grams per square centimeter) was measured in all patients by DXA using Lunar (GE Lunar Corporation, Madison, Wis) or Hologic (Hologic Inc, Bedford, Mass) densitometers. Lumbar spine (L1-L4) BMD was measured at baseline and at 3, 6, 12, and 18 months; femoral neck BMD was measured at baseline and at 12 and 18 months.

Volumetric BMD (in milligrams per cubic centimeter) of the lumbar spine (L1-L3) and femoral neck was assessed in a subset of patients (teriparatide group, 30 patients, and alendronate group, 26 patients) by QCT at 7 study sites. Measurements were made at baseline and at 6 and 18 months. Trabecular BMD of the lumbar vertebrae (L1-L3) was assessed using 3-mm slices obtained at the midpoint of each vertebra. Femoral neck BMD was determined in the trabecular and cortical envelopes.

Quality assurance and centralized analysis of the BMD scans acquired by DXA and QCT were provided by a central imaging facility (Bio-Imaging Technologies, Inc, Newtown, Pa). Quantitative computed tomography scans were analyzed using commercial software (QCT PRO; Mindways Software, Inc, San Francisco, Calif). A QCT calibration phantom was provided to each site.

Standard clinical laboratory tests were performed at screening and at 1 and 18 months on samples obtained at least 12 hours after the injection of study medication. Biochemical markers of bone formation (serum procollagen type I N-terminal propeptide [PINP]) and of bone resorption (urinary N-telopeptide corrected for creatinine [NTx]) were assessed in all patients at baseline and at 1, 3, 6, and 12 months. Urinary N-telopeptide corrected for creatinine was measured by Covance Central Laboratory Services (Indianapolis, Ind) using the Osteomark enzyme-linked immunosorbent assay (OsteX Corporation, Seattle, Wash). Serum procollagen type I N-terminal propeptide was measured by Synarc Laboratory (Lyon, France) using the UniQ radioimmunoassay (iodine 125) kit from Orion Diagnostica (Espoo, Finland).

We assessed the correlation of early changes in PINP using the area under the curve from the first 6 months of treatment and changes in areal lumbar spine BMD at the study end point. The Spearman rank correlation coefficient was calculated between the 6-month area under the curve values and the last observed lumbar spine DXA BMD measurement.

STATISTICAL ANALYSIS

Statistical analyses were based on a modified intent-to-treat principle using SAS software, version 8.0 (SAS Institute, Cary, NC). The intent-to-treat population included all randomized and treated patients, analyzed according to the treatment assigned. Safety analyses were conducted using all intent-to-treat patients, and efficacy analyses were conducted using all intent-to-treat patients with baseline measurement and at least 1 postbaseline measurement of the factor being analyzed.

Baseline characteristics were compared using t tests for continuous variables and Fisher exact tests for categorical variables. Efficacy analyses were performed using the mixed-model repeated-measures method for changes from baseline. Treatment comparisons were based on contrasts of the treatment—X—visit interaction. Percentage change estimates were derived by dividing the estimates for change from baseline from the model by the mean baseline value for all patients in the analysis.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Fisher exact tests were used to compare the 2 treatments with respect to treatment-emergent incidence rates. Study investigators at the local centers assessed the severity of adverse events. The severity of back pain, a prespecified end point, was recorded as subjective information from the patient.
Table. Baseline Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alendronate Group (n = 101)</th>
<th>Teriparatide Group (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.6 ± 8.5</td>
<td>65.3 ± 8.4</td>
</tr>
<tr>
<td>Years past menopause</td>
<td>19.9 ± 9.6</td>
<td>19.5 ± 10.3</td>
</tr>
<tr>
<td>White race, %</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>25.3 ± 4.5</td>
<td>25.7 ± 4.0</td>
</tr>
<tr>
<td>Preexisting back pain, %</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>PINP, ng/mL</td>
<td>49.6 ± 36.6</td>
<td>47.6 ± 21.0</td>
</tr>
<tr>
<td>NTx/Cr, nmol BCE/mmol Cr</td>
<td>56.6 ± 43.9</td>
<td>52.7 ± 30.6</td>
</tr>
<tr>
<td>DXA T score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>−2.9 ± 0.9</td>
<td>−2.8 ± 0.7</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−2.3 ± 0.8</td>
<td>−2.3 ± 0.6</td>
</tr>
<tr>
<td>Total hip</td>
<td>−2.0 ± 0.8</td>
<td>−1.8 ± 0.7</td>
</tr>
<tr>
<td>QCT bone mineral density, mg/cm²‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine, trabecular</td>
<td>86 ± 22</td>
<td>83 ± 25</td>
</tr>
<tr>
<td>Femoral neck, trabecular</td>
<td>112 ± 21</td>
<td>111 ± 15</td>
</tr>
<tr>
<td>Femoral neck, cortical</td>
<td>1002 ± 330</td>
<td>1157 ± 284</td>
</tr>
</tbody>
</table>

Abbreviations: BCE, bone collagen equivalents; Cr, creatinine; DXA, dual-energy x-ray absorptiometry; NTx, urinary N-telopeptide corrected for creatinine; PINP, serum procollagen type I N-telopeptide; QCT, quantitative computed tomography.

*Data are given as mean ± SE unless otherwise indicated.
†Calculated as weight in kilograms divided by the square of height in meters.
‡The numbers of patients with QCT measurements were 26 in the alendronate group and 30 in the teriparatide group.

RESULTS

BASELINE CHARACTERISTICS AND MARKERS OF BONE TURNOVER

There were no significant differences between the alendronate and teriparatide groups at baseline in patient characteristics, BMD, or biochemical markers of bone turnover (Table). Percentage changes from baseline to 12 months for PINP and NTx are illustrated in Figure 1. Alendronate significantly decreased NTx after 1 month and PINP after 3 months. Conversely, teriparatide significantly increased both markers of bone remodeling: PINP increased 105% above baseline at 1 month and peaked at 6 months (218%). The increases in NTx (58% at peak) reached significance only after 3 months of treatment. The different effects of the 2 drugs on bone remodeling were evident after 1 month of treatment, with significant differences between the groups for each marker at 1, 3, 6, and 12 months (P<.001).

BONE MINERAL DENSITY

Areal BMD of the lumbar spine increased similarly in the alendronate and teriparatide groups after 3 months (2.7% and 3.0%, respectively; Figure 2). From 3 to 18 months, the alendronate group gained an additional 2.8% at the spine, compared with a 7.3% gain in the teriparatide group. The BMD profiles of the 2 treatments were significantly different at each time point, beginning at 6 months (P<.005). The differences between the treatment groups were of greater magnitude when volumetric trabecular lumbar spine BMD by QCT was examined. The gain in trabecular BMD with teriparatide was more than 2-fold higher than with alendronate (12.2% vs 5.1%) at 6 months (P<.02). From 6 to 18 months, there was no further increase in trabecular BMD with alendronate treatment. At 18 months, teriparatide-treated patients exhibited a 5-fold greater increase in volumetric trabecular BMD than did alendronate-treated patients, 19.0% vs 3.8% (P<.01).

Teriparatide therapy and alendronate therapy were associated with similar and significant increases from baseline in areal BMD at the femoral neck after 18 months (3.9% and 3.5%, respectively; Figure 3). Trabecular volumetric BMD of the femoral neck increased significantly from baseline to 18 months with teriparatide (4.9%, P<.01) but not with alendronate treatment (2.2%, P=.22); the between-group difference was not significant (P=.24). In the cortical bone envelope, there was a significant difference in volumetric BMD between the alendronate and teriparatide groups, 7.7% and –1.2%, respectively, after 18 months of treatment (P=.05).

Early changes in PINP were significantly positively correlated with areal BMD of the lumbar spine in the teriparatide-treated group (Figure 4). In the alendronate-treated group, early changes in PINP had significant negative correlations with areal BMD of the lumbar spine.

SAFETY

Both treatments were safe and well tolerated. Except for back pain, there were no clinically meaningful differences between the groups in treatment-emergent adverse events. The number of patients reporting new or worsen-
ing back pain during treatment was lower in the teriparatide group compared with the alendronate group, 26% vs 39% (P = .05). There were significantly fewer teriparatide-treated patients compared with alendronate-treated patients who reported back pain with at least moderate severity, 15% vs 33% (P = .003) for moderate or severe back pain and 4% vs 12% (P = .04) for severe back pain.

The difference in the incidence of hypercalcemia between the teriparatide (2.9%) and alendronate (0.0%) groups was not statistically significant (P = .25). The number of clinical fractures was similar after 18 months of treatment (alendronate group, 8 fractures, and teriparatide group, 9 fractures). Because spine x-rays were not performed, the occurrence of morphometric vertebral fractures could not be assessed.

There were no significant differences between the groups in the number of women who withdrew from the study (alendronate group, 13 patients, and teriparatide group, 18 patients). Compliance with oral and injectable medications averaged 93% and 90%, respectively, for the alendronate group and 94% and 97%, respectively, for the teriparatide group.

**COMMENT**

We compared the effects of alendronate, a potent inhibitor of bone resorption, and teriparatide, a bone formation agent, on BMD and markers of bone metabolism in postmenopausal women with osteoporosis. The improvement in BMD from these approved agents is mediated by distinct and opposite effects on bone cell activity. Both drugs increased BMD in the spine and hip, although the magnitude and nature of these changes differ significantly between drug therapies, consistent with previous findings by Body et al using 40 µg/d of PTH 1-34 and by Black et al using 100 µg/d of PTH 1-84.

Alendronate therapy significantly reduced markers of bone turnover, as reported previously. Bone resorption was suppressed after 1 month of treatment, while inhibition of formation occurred by 3 months. A new steady state of reduced bone turnover was achieved after 6 months and persisted through month 12. As a re-
osteal component of cortical bone but does not adversely affect bone strength. 

Biochemical markers of bone turnover reflect the different mechanisms of action of teriparatide and alendronate. The rapid and early decrease in markers correlates with changes in bone mass and fracture risk reduction associated with antiresorptive treatments. In this study, PINP, a marker of bone formation, exemplified the opposite mechanisms of action, suggesting that PINP may be an appropriate marker to monitor the skeletal response to teriparatide. Early changes in PINP correlate positively with ultimate areal and volumetric BMD responses in teriparatide-treated patients and correlate inversely with areal BMD in alendronate-treated patients.

A clinical characteristic that differs between treatment with teriparatide and alendronate is the effect of therapy on the incidence of back pain. In this study, fewer patients treated with teriparatide reported new or worsening back pain, particularly with respect to moderate and severe back pain, compared with those treated with alendronate. These findings are consistent with those of Body et al, who found that back pain was reported less frequently by patients treated with teriparatide (40 µg/d) than with alendronate.

Our study has important limitations. Spinal radiographs were not obtained, precluding the possibility of assessing preexisting or new vertebral fractures. Therefore, the association of back pain with vertebral fractures could not be evaluated. Although alendronate and teriparatide are known to significantly reduce the incidence of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis, the small numbers of subjects in our study with fractures prevented a comparison of fracture rates. As a consequence, our results demonstrate that teriparatide and alendronate affect BMD, bone turnover, and probably fracture reduction by different mechanisms but do not provide evidence about the comparative fracture protection effectiveness of the 2 therapies.

In summary, this study demonstrates that the 2 treatments, each of which has been previously shown to be effective in the treatment of osteoporosis in men and postmenopausal women, accomplish their salutary effects by different and, in fact, opposite effects on bone metabolism. The significant increases in trabecular BMD observed with teriparatide are accomplished by activating bone formation and increasing trabecular bone volume, while the smaller increases in BMD seen with alendronate are the result of the inhibition of bone turnover, resulting in the filling of remodeling spaces and increased mineralization of bone matrix. Although similar changes in BMD in the proximal femur occur with the 2 treatments, the mechanisms for the changes differ substantially. In no other disease state, to our knowledge, do the options for treatment involve strategies that affect the responsive tissue with opposite consequences (ie, bone turnover increases with teriparatide and decreases with alendronate).
The availability of 2 distinct treatment options for the management of osteoporosis provides the opportunity to select the optimal treatment strategy for a given patient based on different clinical and pathophysiological characteristics.1-3,4,47 The challenge facing clinicians and clinical investigators is to identify those attributes in an individual patient that would determine whether an antiresorptive agent or an anabolic agent would be most appropriate.

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**Correction**

Error in Figure Labels. In the Original Investigation by McClung et al titled “Opposite Bone Remodeling Effects of Teriparatide and Alendronate in Increasing Bone Mass,” published in the August 8, 2005, issue of the *ARCHIVES* (2005;165:1762-1768), the labels in the figure key for Figure 3 on page 1765 should have been switched. The circle indicates the Alendronate Group; the triangle, the Teriparatide Group. Also on the same page in Figures 2 and 3 the labels “Area/DXA” should have been “Integral DXA.”