Antiresorptives Overlapping Ongoing Teriparatide Treatment Result in Additional Increases in Bone Mineral Density

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ABSTRACT
During teriparatide (TPTD) treatment, high levels of bone formation are accompanied by an increase in bone resorption. The aim of this work was to test if coadministration of raloxifene (RAL) or alendronate (ALN) following 9 months of ongoing TPTD therapy would reopen the anabolic window, thereby exerting additional benefit on bone mineral density (BMD). Postmenopausal women (n = 125) with severe osteoporosis on TPTD treatment for 9 months were randomized into three open-label groups for a further 9 months: ALN (70 mg/week) in addition to TPTD; RAL (60 mg/d) in addition to TPTD; or no medication in addition to TPTD. Amino-terminal propeptide of type I procollagen (P1NP) and cross-linked C-telopeptide (CTX), and areal and volumetric BMD at the lumbar spine and hip were assessed. During the combination period, P1NP concentrations did not change on TPTD monotherapy (693% ± 371%, p < 0.0001) and decreased in the ALN (360% ± 111%, p < 0.0001) and RAL (482% ± 246%, p < 0.0001) combination groups; whereas CTX did not change on TPTD monotherapy (283% ± 215%, p < 0.0001), decreased to the starting level in the ALN combination group (17% ± 34%, p = 0.39), and remained elevated in the RAL combination group (179% ± 341%, p < 0.0001). The increase in lumbar spine BMD was 5% ± 6% in the ALN and 6% ± 5.2% in the RAL combination groups compared with 2.8% ± 9.3% in the TPTD monotherapy group (p = 0.085 and p = 0.033, respectively). The increase of trabecular lumbar spine BMD for both the ALN and RAL combination groups was superior to TPTD monotherapy. Total hip BMD changes were 4% ± 5.3% for the ALN combination group and 1.4% ± 5.1% for the TPTD monotherapy (p = 0.032), and 1.4% ± 3.4% (p = 0.02) for the RAL combination group. With the exception of no differences in the trabecular compartment of femoral neck, volumetric BMD changes in the ALN combination group for all other comparisons were significantly superior to the two other groups. Our data suggest that ALN when added to TPTD 9 months after initiation of TPTD monotherapy results in a more robust increase in BMD, probably due to a reopening of the anabolic window. The clinical relevance of the BMD increase is unknown. © 2013 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BONE DENSITOMETRY; QUANTITATION; BONE QCT; TREATMENTS; TERIPARATIDE

Introduction

Current medications for the treatment of osteoporosis are either antiresorptive or osteoanabolic agents. The primary effect of antiresorptives (anticatabolic drugs, eg, bisphosphonates, raloxifene, calcitonin, and denosumab) is a rapid and sustained reduction in the pathologically elevated bone resorption present in women with postmenopausal osteoporosis. This effect results in a decrease of bone resorption, leading to an increase in secondary mineralization and bone strength. Antiresorptives, especially bisphosphonates, are established as first-line treatment options for postmenopausal osteoporosis. In contrast to this mechanism of action, osteoanabolics, such as teriparatide (recombinant human parathyroid hormone: PTH[1-34] or TPTD), primarily increase bone formation. This is reflected in an elevation of biochemical and histomorphometric markers of bone formation, and therapy results in an increase of bone volume and bone mineral density (BMD). Increased bone formation with a modest elevation of resorption characterizes the initial phase of therapy with subcutaneous daily injections of TPTD. This initial phase is the treatment period with the most marked anabolic changes, including increases in biochemical markers of bone formation, BMD, and histomorphometric indices of bone formation. This
early treatment period, dominated by bone formation, lasts for 6 to 9 months and is also referred to as the anabolic window. During this time, bone resorption activities, while on the increase, are still moderate, with bone formation processes constantly remaining at a high level. Subsequently, increased bone resorption mitigates the overall bone anabolic effect.

Several studies have been performed with different combinations of antiresorptive and anabolic drugs, to evaluate their potential additive, synergistic effects on bone metabolism, bone volume, and BMD. Antiresorptives, depending on their potency, differentially influence the dynamic changes in bone formation and resorption that are induced by TPTD. In one study, raloxifene (RAL), when combined with TPTD, did not impair TPTD-induced stimulation of bone formation. Alendronate (ALN) pretreatment was associated with a 6-month delay in the increase in BMD at the lumbar spine associated with TPTD treatment. In numerous studies, a combination of TPTD with a variety of bisphosphonates, regardless of whether they were administered orally or by intravenous route, did not markedly improve the anabolic effect of TPTD. In all these studies, antiresorptive therapy was started at the same time as TPTD. No data are available on combination therapies when antiresorptive treatment was initiated at a later time point when the anabolic window had closed.

The aim of the current study was to investigate the potential benefit of concomitant administration of TPTD and the antiresorptive agents RAL (with a lower antiresorptive potency) or ALN (with a higher antiresorptive potency), beginning 9 months after initiation of TPTD monotherapy. We studied the effect of TPTD plus RAL, TPTD plus ALN, or TPTD alone on areal and volumetric BMD and on biochemical markers of bone turnover.

**Patients and Methods**

**Study design**

This was a prospective two-center, open-label, randomized, and controlled three-arm study in postmenopausal women with severe osteoporosis receiving TPTD treatment for 9 months. The study was performed by the VINFORCE Study Group at the St. Vincent Hospital, Medical Department II, in Vienna, Austria (Academic Teaching Hospital of the Medical University of Vienna, Austria) and by the Medical University of Graz–Division of Endocrinology and Metabolism (Graz, Austria).

Patients on ongoing TPTD therapy (20 μg/d subcutaneously) for 9 ± 1 months were randomized to receive TPTD 20 μg/d plus 70 mg/week ALN (ALN combination group), TPTD plus 60 mg/d RAL (RAL combination group), or TPTD alone (TPTD monotherapy group) for the subsequent 9 months. A randomization table was generated by an independent statistician and given to clinical nurses not involved in the present study who kept these data confidential. When informed consent had been signed, the investigator assigned a consecutive number to the patient in chronological order. Study medication was assigned according to the randomization table provided by the clinical nurse on the request of the investigator. All participants had daily 1000 mg oral calcium and 800 IU vitamin D supplementation during the entire treatment period. Satisfactory treatment compliance was defined as ≥80% reported consumption of osteoactive drugs. The study was approved and supervised by an independent local ethics committee and conducted according to the ethical principles of the Declaration of Helsinki. All participants signed written informed consent prior to entering the study. The first patient was screened in June 2005; the first patient was randomized in March 2006 and the last participant completed the trial in March 2011. The study has been registered in Clinical Trials: NCT01535027 (Vinforce-003).

Postmenopausal patients on TPTD therapy for 9 ± 1 months were invited to participate in the study. To be eligible for TPTD treatment, patients had to demonstrate a form of “unsatisfactory clinical response to previous antiresorptive therapy” according to the national reimbursement criteria of Austria (either new clinical or radiographic fragility fracture in 2 years and/or accelerated bone loss of ≥3%/year on antiresorptive treatment; discontinuation of oral antiresorptive treatment due to side effects accompanied with substantial risk for osteoporotic fracture defined by a T score ≤ −2.5, or ≥2 clinical risk factors according to the WHO FRAX algorithm). The two investigational centers for osteoporosis adopted a standardized approach for all patients on TPTD therapy. Prior to initiation of TPTD therapy (baseline, visit 0) the patients history was recorded, electrocardiography (ECG) was done, and physical status, vital signs, blood chemistry, and 24-hour urinary calcium excretion were assessed. In addition, digital thoracic and lumbar spine X-ray, and areal BMD, serum type 1 collagen cross-linked C-telopeptide (CTX) marker, and intact amino terminal propeptide of type 1 procollagen (P1NP) marker were measured.

Patients were excluded if they had had any prior use of TPTD or parathyroid hormone (PTH) [1-84], intravenous bisphosphonate, strontium ranelate, hormonal replacement therapy, glucocorticoids, or anabolic steroids. Patients were also excluded if they showed signs of metabolic bone disease other than postmenopausal osteoporosis (eg, Paget’s disease, renal osteodystrophy, osteomalacia, hyperparathyroidism, intestinal malabsorption, vitamin D deficiency, or glucocorticoid induced osteoporosis), or had a malignant neoplasm, nephrolithiasis/ urolithiasis, active liver disease, significantly impaired renal function, or abnormal thyroid function (except patients with chronic hypothyreosis with adequate substitution therapy and normal thyroid-stimulating hormone [TSH] values).

All assessments, with the exception of volumetric BMD determination, were performed when TPTD therapy was initiated (baseline, visit 0), at randomization, 9 months after TPTD initiation (visit 1), 3 months after randomization (visit 2), and at study endpoint, 18 months after TPTD initiation (visit 3). The time frame for each visit was ±30 days. Volumetric BMD was measured at visit 1 and visit 3. Between visit 0 and visit 1 all patients had routine clinical and blood chemistry assessments. Lumbar spine, femoral neck, and total hip areal BMD was measured using dual-energy X-ray absorptiometry (DXA) (GE Lunar iDXA scanner, software version Encore 13, 50,040; GE LUNAR Corporation, Madison, WI, USA). A Philips MX-8000 scanner system was used to assess volumetric BMD in the trabecular compartment of the second lumbar (L2) vertebra and trabecular and cortical compartments of the femoral neck and
total CT slice thickness was 3.2 mm. Prior to the CT scan, cross-calibrations were performed with a standardized CT calibration phantom (serial number 13002). For evaluation of volumetric BMD, quantitative computed tomography (QCT) Pro bone densitometry software (Mindways Software, Inc., Austin TX, USA) was used.

After daily quality protocol procedures, serum levels of the bone turnover markers P1NP and CTX were assessed using IDS-iSYS Specialty Immunoassay System analyzers (Immunodiagnostics Systems Ltd., Boldon, UK). These were determined at each visit after overnight fasting and prior to the administration of study medications. Serum levels of calcium, phosphorus, 25-hydroxy vitamin D, and intact PTH (iPTH) were also evaluated.

Thoracic and lumbar spine X-rays with digitally enhanced delineation of bone structures were performed at visits 0, 1, and 3. X-rays were evaluated by two independent radiologists using a semiquantitative technique. Incident fractures were defined as a new or worsening vertebral fracture, with a threshold of 25% height reduction. Nonvertebral fractures were confirmed by X-ray.

Safety assessments at each study visit included an assessment of vital signs, ECG, body mass index (BMI), serum chemistry and 24-hour urine excretion of calcium/phosphorus, a physical examination, and recording of adverse events (AEs).

Objectives
The primary objective of this study was to investigate any differences between the three patient groups for changes in lumbar spine areal BMD. Secondary objectives included the evaluation of differences between these three groups for changes in areal and volumetric hip BMD, vertebral areal BMD, as well as changes in the biochemical markers of bone turnover (P1NP and CTX).

Statistical analysis
The study was designed to enroll approximately 120 patients. Thirty completers in each group would have at least 80% power to detect a mean within-group difference of 0.0225 g/cm² in areal lumbar spine BMD, assuming an SD of 0.043 g/cm² using a one-sided paired t test with a significance level of 0.05. Patients with valid endpoint values were included in the analysis data set. For each analysis all available and valid values were included. For categorical baseline data, percentages, and for continuous variables, arithmetic means and SD were calculated. Log transformation was used for non-normally distributed data and the Wilcoxon test was implemented if the normalization failed. For BMD and biochemical markers, absolute and percentage changes from baseline to 9, 12, and 18 months and from 9 to 12 and 18 months were summarized by arithmetic means, SD, and SEM. A mixed model repeated measures approach (MMRM) including baseline, treatment, visits, and interaction between treatments and visits was used to calculate changes. For the estimated changes and for pairwise comparisons between the groups, two-sided p values were reported. The level of statistical significance was set to 5%.

Results
A total of 183 patients who had received TPTD treatment for 9 ± 1 months were screened for eligibility and invited to participate. A total of 125 participants entered the study and were randomized to one of three groups: ALN combination (n = 41), RAL combination (n = 37), or TPTD monotherapy (n = 47). Of 117 patients randomized, 93.2% completed the study. Five (10.6%) patients in the TPTD monotherapy, 3 (8.1%) in the RAL combination, and 0 in the ALN combination groups discontinued the study (Fig. 1).

During the initial 9 months of TPTD monotherapy, BMD and bone marker values (mean ± SD) increased significantly (p < 0.001 for all) compared with baseline: 3.7% ± 2.5%, 2.9% ± 0.8%, and 2.8% ± 0.6% in the lumbar spine, total hip, and femoral neck BMD, respectively; 650% ± 296% and 349% ± 324% for P1NP and CTX, respectively (Figs. 2 and 3). At the time of randomization, no significant differences in clinical characteristics were observed between the groups (Table 1).

Areal and volumetric BMD
After 18 months of TPTD treatment, the increase in areal lumbar spine BMD was higher in the ALN (9.2% ± 7.0%) and RAL (10% ± 5.6%) combination groups than in the TPTD monotherapy group (6% ± 8.2%, p = 0.025 and p = 0.07, respectively). The increase in total hip BMD of 7% ± 5.8% in the ALN combination group was significantly greater than that observed in either the TPTD monotherapy (4.4% ± 5.5%, p = 0.047) or the RAL combination group (4.2% ± 3.7%, p = 0.026). For femoral neck BMD, the increase in the ALN combination group (7.4% ± 9.5%) significantly exceeded the increase in the RAL combination group (3.4% ± 4.6%, p = 0.018), but the difference in the TPTD monotherapy group (5.3% ± 7.1%, p = 0.21) was not statistically significant. When the comparison of changes between the groups from randomization to study end (9–18 months) were calculated, the results were similar. The increase in areal lumbar spine BMD was 5% ± 6.3%, in the ALN group and 6% ± 5.2% in the RAL group, compared to 2.8% ± 9.3% in the TPTD monotherapy group (p = 0.085 and p = 0.033, respectively). For total hip areal BMD, the change was 4% ± 5.3% in the ALN group, greater than in the TPTD monotherapy (1.4% ± 5.1%, p = 0.032) or RAL groups (1.4% ± 3.8%, p = 0.02). For femoral neck areal BMD, the change was 4.6% ± 9% in the ALN group, 2.4% ± 6.9% in the TPTD monotherapy group (p = 0.13), and 0.6% ± 4.5% in the RAL group (p = 0.022; Fig. 2).

At the lumbar spine, the increase between 9 and 18 months of treatment in volumetric trabecular BMD, measured in the L2 vertebra, was greater, 12.1% ± 4.5% in the ALN and 14.6% ± 8.9% in the RAL combination groups compared to 7.2% ± 7.0% in the TPTD monotherapy group (p = 0.004 and p = 0.0002, respectively). The highest increase in volumetric BMD at the total hip region was observed in the ALN combination group (integral 9.7% ± 0.9%; trabecular 10.7% ± 4.4%; and cortical 6.6% ± 2.2%; p = 0.0001 for all). The volumetric increase in the ALN combination group at the integral femoral neck was 9.2% ± 1.4% (p < 0.0001), 8.4% ± 4.6% for trabecular (p = 0.0001), and 6.7% ± 4.2% for cortical (p < 0.0001). With
the exception of the trabecular compartment of the femoral neck, the volumetric BMD changes in the ALN combination group for all other comparisons were significantly superior to the other two groups. In addition, increases in the integral volumetric BMDs of the TPTD monotherapy group exceeded those of the RAL combination group both in the femoral neck and the total hip region (Fig. 4).

Biochemical markers of bone turnover

After 3 months of combination therapy there was a significant decrease in both P1NP and CTX in the two antiresorptive combination groups compared with the changes observed in the TPTD monotherapy group (p < 0.001 for both combination treatments and markers when compared with TPTD monotherapy). Whereas the reduction in P1NP was modest and not different between the ALN (−45 ± 26 µg/L) and RAL combination groups (−29 ± 35 µg/L, p = 0.16), CTX was significantly more suppressed in the ALN (−440 ± 200 ng/L) than in the RAL combination group (−250 ± 220 ng/L, p = 0.003). The reduction of both markers in the combination groups was more pronounced after 9 months of antiresorptive combination treatments. P1NP concentrations in both the ALN (−80 ± 25 µg/L) and RAL combination groups (−50 ± 31 µg/L) had decreased significantly versus TPTD monotherapy (+1 ± 50 µg/L, p < 0.0001 for both). In addition, the reduction in the ALN group was more marked than in the RAL combination group (p = 0.0005). Similarly, the CTX reduction was more pronounced in the ALN combination group (−720 ± 190 ng/L) than in the RAL group (−450 ± 230 ng/L, p < 0.0001). Both changes were significantly different to the change observed in the TPTD monotherapy group (+40 ± 260 ng/L, p < 0.0001 for both).

During the combination period, P1NP concentrations did not change on TPTD monotherapy (p = 0.08) and decreased moderately in the ALN and RAL combination groups (p < 0.0001 for both). When compared with values at the initiation of TPTD therapy, P1NP concentrations were increased at study end: change (Δ) +199 ± 41 µg/L, 693% ± 371%, p < 0.0001 in the TPTD monotherapy group; Δ +107 ± 14 µg/L, 360% ± 153%, p < 0.0001 in the ALN combination and
Δ +133 ± 18 μg/L, 482% ± 243%, p < 0.0001 in the RAL combination groups. On the other hand, CTX did not change on TPTD monotherapy, decreased to the starting level in the ALN and remained elevated in the RAL combination group. When compared with values at the initiation of TPTD therapy, CTX concentrations were increased at study end: Δ +700 ± 210 ng/L, 283% ± 215%, p < 0.0001 in the TPTD monotherapy group; did not change Δ - 30 ± 140 ng/L, 17% ± 72%, p = 0.39 in the ALN combination group; and remained elevated Δ +210 ± 180 ng/L, 179% ± 341%, p < 0.0001 in the RAL combination group (Fig. 3).

Safety and tolerability

The treatments were generally well tolerated. Adverse events resulting in study discontinuation occurred in 5 patients in the
TPTD monotherapy group, and 3 in the RAL combination group.
Nausea, stomach pain, and reflux after ingestion of oral study medication were more frequently reported in the ALN combination group, whereas hot flushes occurred more frequently in the RAL combination group. Two incidental nonvertebral fragility fractures in the ALN combination group, one vertebral and one nonvertebral in the RAL combination group and one vertebral in the TPTD monotherapy group were observed during the combination treatment period. There were no deaths and no malignancies were discovered during the study. Mild, asymptomatic transitional hypercalcemia (2.58–2.72 mmol/L) was observed in 20 patients (17.1%) within the initial 9 months on TPTD monotherapy. Similar findings were documented for 4 patients in the RAL combination group (<2.62 mmol/L) and for 3 in the TPTD monotherapy group (<2.65 mmol/L) during the second 9 months of treatment. In all cases, serum calcium values normalized following the reduction of oral calcium supplement from 1000 mg/d to 500 mg/d.

**Discussion**

Our data demonstrate that addition of ALN 9 months after initiation of TPTD treatment resulted in an augmented increase in BMD both in the lumbar spine and hip region. In the ALN combination group, with the exception of areal BMD and the trabecular component of femoral neck BMD, the increase in BMD was significantly greater compared with the TPTD monotherapy group at all other sites investigated. The combination with the less potent antiresorptive RAL had a less positive effect; the higher BMD increase was limited to the lumbar spine, a skeletal site with predominantly trabecular bone.

### Table 1. Patient Characteristics at Time of Randomization, After 9 ± 1 Months of TPTD Monotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPTD monotherapy group (n = 47)</th>
<th>ALN combination group (n = 41)</th>
<th>RAL combination group (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.7 ± 9.3</td>
<td>71.6 ± 8.5</td>
<td>69.7 ± 7.5</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.7 ± 5.3</td>
<td>25.2 ± 3.7</td>
<td>24.9 ± 4.5</td>
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<tr>
<td>Years since menopause</td>
<td>23.3 ± 10.4</td>
<td>23.2 ± 9.9</td>
<td>21.4 ± 9.3</td>
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<td>Previous medication, n (%)</td>
<td>ALN 33 (70.2)</td>
<td>31 (75.6)</td>
<td>26 (70.3)</td>
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<td></td>
<td>Other antiresorptives 12 (25.5)</td>
<td>9 (22.0)</td>
<td>11 (29.7)</td>
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<td></td>
<td>Calcium/vitamin D only 2 (4.3)</td>
<td>1 (2.4)</td>
<td>0</td>
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<td>Prevalent fractures, n (%)</td>
<td>Vertebral fractures 32 (68)</td>
<td>36 (88)</td>
<td>29 (78)</td>
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<td></td>
<td>Nonvertebral fractures 21 (45)</td>
<td>23 (56)</td>
<td>22 (59)</td>
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<td></td>
<td>Hip fractures 7 (5)</td>
<td>5 (12)</td>
<td>5 (14)</td>
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<td>Biochemical markers and serum values, mean ± SD</td>
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<tr>
<td>P1NP (µg/L)</td>
<td>230.9 ± 38.8</td>
<td>220.8 ± 21.1</td>
<td>212.1 ± 29</td>
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<td>CTX (ng/L)</td>
<td>975.9 ± 23.6</td>
<td>996.6 ± 19.2</td>
<td>954.9 ± 19.4</td>
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<td>Calcium (mmol/L)</td>
<td>2.43 ± 0.12</td>
<td>2.39 ± 0.16</td>
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<td>Phosphate (mmol/L)</td>
<td>1.11 ± 0.19</td>
<td>1.22 ± 0.14</td>
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<td>25-OH-vitamin D3 (ng/mL)</td>
<td>33.1 ± 11.8</td>
<td>34.0 ± 11.5</td>
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<td>iPTH (pg/mL)</td>
<td>43.5 ± 15.1</td>
<td>42.5 ± 12.5</td>
<td>45.7 ± 19.3</td>
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<td>Areal BMD (g/cm²)</td>
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<td>L₁–L₄</td>
<td>0.800 ± 0.18</td>
<td>0.833 ± 0.19</td>
<td>0.829 ± 0.18</td>
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<td>Femoral neck</td>
<td>0.702 ± 0.09</td>
<td>0.722 ± 0.10</td>
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<td>Total hip</td>
<td>0.740 ± 0.12</td>
<td>0.738 ± 0.11</td>
<td>0.752 ± 0.09</td>
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<td>Volumetric BMD (mg/cm³)</td>
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<td>Trabecular spine L₂</td>
<td>74.4 ± 19.3</td>
<td>80.2 ± 23.6</td>
<td>76.2 ± 19.4</td>
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<td>Femoral neck</td>
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<tr>
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<td>103.1 ± 19.9</td>
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<td>107.8 ± 19.7</td>
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<tr>
<td>Cortical</td>
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<td>810.6 ± 24.3</td>
<td>805.8 ± 13.8</td>
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<td>Integral</td>
<td>294.2 ± 27.1</td>
<td>291.2 ± 25.2</td>
<td>298.7 ± 25.2</td>
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<tr>
<td>Total hip</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Trabecular</td>
<td>103.5 ± 14.4</td>
<td>101.5 ± 16.7</td>
<td>106.3 ± 14.9</td>
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<tr>
<td>Cortical</td>
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<td>902.5 ± 20.2</td>
<td>900.0 ± 13.6</td>
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<tr>
<td>Integral</td>
<td>303.3 ± 32.9</td>
<td>294 ± 29.3</td>
<td>306.5 ± 31.0</td>
</tr>
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</table>

Values are mean ± SD or n (%). No significant differences were detected between the three groups.

TPTD = teriparatide; ALN = alendronate; RAL = raloxifene; BMI = body mass index; P1NP = intact amino terminal propeptide of type I procollagen; CTX = serum type 1 collagen cross-linked C-telopeptide; iPTH = intact parathyroid hormone; BMD = bone mineral density; L₁–L₄ = 1st through 4th lumbar vertebra.
The effects of ALN and TPTD combination treatment on BMD clearly differ from observations in other studies in which combinations of ALN and TPTD or PTH(1-84) were applied from the initiation of therapy and for the full anabolic treatment period. In contrast to our current findings, the results from the Parathyroid Hormone and Alendronate (PaTH) study indicated that after 1 year, a combination of PTH(1-84) (100 μg/d) and ALN (10 mg/d) might even reduce the anabolic effects of PTH treatment. Based on all this evidence, it would appear that the concomitant treatment of RAL with TPTD does not alter the outcomes for BMD. This is probably due to the relatively low potency of RAL in affecting TPTD-induced changes in bone formation and resorption. Another bisphosphonate, intravenous zoledronic acid, was also studied in combination with TPTD as the initial treatment for bisphosphonate-naive patients over 1 year. When these patients were compared with those receiving TPTD monotherapy, no difference was observed in changes of lumbar spine BMD, but in the hip region the BMD increase was superior in the combination group. However, there were no significant differences in the outcomes of BMD between the combination group and patients receiving zoledronic acid monotherapy. In the current study, TPTD therapy was initiated after long periods of pretreatment with antiresorptives in line with the general clinical practice. This setting reflects the daily clinical situation, which is different from the selective and mostly treatment-naive populations used in clinical studies. In postmenopausal women on long-term hormone replacement therapy, the addition of PTH(1-34) or TPTD resulted in excessive increases in BMD. The BMD increase in osteoporosis treatment-naive patients in the European Study of Forsteo (EUROFORS) trial was only slightly greater during TPTD treatment than in those who had been pretreated with a variety of antiresorptive agents. Nevertheless, irrespective of such differences between groups treated with various antiresorptive agents, TPTD shows a marked anabolic effect in patients pretreated with various antiresorptives.

In the present study, the ALN combination group consistently demonstrated a greater BMD increase than the TPTD monotherapy group at both the spine and hip regions when measured by DXA, as well as at the trabecular and cortical bone sites when assessed by 3D CT. This greater increase in BMD in the ALN combination group is markedly different from those increases observed in studies in which ALN was combined with PTH(1-84).

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**Fig. 4.** Mean percent changes (±SEM) in volumetric BMD of (A) trabecular bone in 2nd lumbar vertebra; (B) cortical, trabecular, and integral bone in femoral neck and (C) total hip between randomization and at study endpoint. Values of *p* indicate differences between groups. *p* < 0.05 within-group changes. TPTD = teriparatide; RAL = raloxifene; ALN = alendronate; L2 = 2nd lumbar vertebra.
or TPTD or PTH from the start of therapy.\textsuperscript{13–15,21,22} These distinct BMD results could at least be partially explained by a different balance between bone formation and resorption during the time course of the anabolic treatment period. The bone turnover status and, consequently, the time point of initiation of ALN treatment, appears to be a crucial factor in the BMD changes. A characteristic of TPTD monotherapy is a pronounced increase in the bone formation marker P1NP but this elevation was severely weakened during the first year of that study when a combination of TPTD and ALN was used.\textsuperscript{14} In the second year of this study, the difference between P1NP values of the two patient groups was reduced due to the partial regression of P1NP in patients on TPTD monotherapy. In comparison, in the present study, both TPTD monotherapy and the ALN combination groups had similar benefits of an increase in bone formation (as characterized by P1NP) in the initial 9 months of treatment. Subsequently, both P1NP and CTX continued to be elevated in the TPTD monotherapy group. In contrast, bone turnover started to decrease in the ALN combination group in a characteristic manner: there was a complete suppression in bone resorption back to the level observed at the initiation of TPTD, accompanied with a partial suppression of bone formation only. Thus, the anabolic window, a characteristic of the first phase of TPTD therapy, where bone formation is greater than resorption, appeared to reopen in the latter period of treatment in the ALN combination group. This favorable shift in bone turnover balance toward higher bone anabolic activity could help explain the larger BMD increase observed in the ALN combination group compared with the RAL combination and TPTD monotherapy groups.\textsuperscript{4,8} Similar changes in bone turnover to the ALN combination group could also be observed in the RAL combination group but to a much lesser extent. Thus, the overall BMD results of the RAL combination did not appear to be more beneficial than TPTD monotherapy and were clearly inferior to those of the ALN combination group. When combined with TPTD, both RAL and ALN preferentially reduced the bone resorption (CTX) compared with the bone formation (P1NP) marker. These observations suggest that both antiresorptives contributed to a reopening of the anabolic window but to differing extents. Whereas the magnitude of reduction was moderate and similar with respect to bone formation, ALN was more effective in reducing bone resorption, resulting in a more effective reopening of the anabolic window.

The total hip BMD increase in the ALN combination group was superior to that observed in either TPTD monotherapy or the RAL combination treatment. More importantly, an increase in cortical BMD at the hip region measured by QCT was only observed in the ALN combination group. The increase in BMD with TPTD monotherapy is usually faster and more extensive in cancellous bone areas such as the spine. TPTD has been shown to improve trabecular microarchitecture both in treatment-naïve patients and in patients after ALN pretreatment.\textsuperscript{34,35} In cortical bone, initiation of TPTD therapy results in the resorption of fully mineralized endocortical and periosteal deposition of fresh, not fully mineralized bone. This process is reflected in a small, transitional decrease of BMD followed by a subsequent increase when secondary mineralization of the new bone occurs.\textsuperscript{5,8} In patients pretreated with potent antiresorptives, as in the present study, the BMD increase in the femoral neck may be even further delayed.\textsuperscript{27} ALN, when combined with TPTD from the start of TPTD treatment, has a negative influence on the increase in BMD at the hip.\textsuperscript{14} This is in contrast with the hip BMD increase observed in the current study. Another possible explanation of BMD changes by the addition of ALN or RAL in the current study could be related more with their genuine antiresorptive features of these substances. BMD increase could also be reached by simply closing down remodeling spaces and promoting secondary mineralization of newly formed bone matrix created during TPTD monotherapy.\textsuperscript{14} Our findings may be analogous with observations from studies in which ALN and/or other bisphosphonates were administered subsequent to PTH or TPTD treatment. Thus, treatment with bisphosphonates was started at a high bone formation stage that resulted in marked hip BMD increases.\textsuperscript{22,23,36–38}

Our study has several limitations. The analysis of the first 9 months of TPTD treatment was retrospective; however, this should not have had a major impact on the validity of the data assessed during this period because all reported data were systematically available at the investigational sites. Similarly, the open label setting is unlikely to affect the evaluation of BMD and biochemical values that were the main outcome measures of the current study. We did not carry out frequent measurements of the biochemical markers during the first 9 months because these data are readily available.\textsuperscript{2,13,21,22} Earlier studies have demonstrated that P1NP and CTX are among the most relevant surrogates in describing bone turnover changes in patients on TPTD and PTH[1-84] therapy and so other biochemical markers were not assessed.\textsuperscript{13,19,20,33,39} We did not evaluate tissue-level changes of bone volume and mineralization, and therefore we cannot discuss the underlying mechanism of the BMD changes observed. The 18-month study duration is shorter than the 24 months of TPTD treatment duration indicated and underestimates the BMD changes of the full-length TPTD monotherapy treatment cycle. Large clinical study data has demonstrated that the BMD increase in the hip region is most pronounced in months 18 to 24 of the TPTD monotherapy.\textsuperscript{12} Finally, our study was not designed to conclude any potential clinical risks or benefits of the investigated combination therapies.

In conclusion, the addition of ALN to TPTD after the first 9 months of TPTD treatment led to a return of bone resorption to levels comparable at the initiation of TPTD therapy, whereas bone formation was less suppressed and remained elevated. The observed incremental BMD increase at the lumbar spine and hip regions may be the result of the favorable influence of ALN on the balance of bone formation and resorption, resulting in the reopening of the anabolic window. If further investigations confirm our preliminary findings, ALN in combination with TPTD therapy, as prescribed in this study, could help to enhance the anabolic effects of TPTD therapy, a treatment option only available for a limited time period of 24 months.

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Authors’ roles: Study design: CM and HR. Study conduct: CM. Data collection: CM, RK, SL, and HR. Data analysis: CM and HR. Data interpretation: CM, AFP, RK, SL, and HR. Drafting manuscript: CM, AFP and HR. Revising manuscript content: CM, HR, and AFP. Approving final version of manuscript and revised/edited manuscript: CM, RK, AFP, SL, and HR. CM takes responsibility for the integrity of the data analysis.

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