Effects of Intravenous Zoledronic Acid Plus Subcutaneous Teriparatide [rhPTH(1–34)] in Postmenopausal Osteoporosis


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ABSTRACT
Clinical data suggest concomitant therapy with bisphosphonates and parathyroid hormone (PTH) may blunt the anabolic effect of PTH; rodent models suggest that infrequently administered bisphosphonates may interact differently. To evaluate the effects of combination therapy with an intravenous infusion of zoledronic acid 5 mg and daily subcutaneous recombinant human (rh)PTH(1–34) (teriparatide) 20 μg versus either agent alone on bone mineral density (BMD) and bone turnover markers, we conducted a 1-year multicenter, multinational, randomized, partial double-blinded, controlled trial. 412 postmenopausal women with osteoporosis (mean age 65 ± 9 years) were randomized to a single infusion of zoledronic acid 5 mg plus daily subcutaneous teriparatide 20 μg (n = 137), zoledronic acid alone (n = 137), or teriparatide alone (n = 138). The primary endpoint was percentage increase in lumbar spine BMD (assessed by dual-energy X-ray absorptiometry [DXA]) at 52 weeks versus baseline. Secondary endpoints included change in BMD at the spine at earlier time points and at the total hip, trochanter, and femoral neck at all time points. At week 52, lumbar spine BMD had increased 7.5%, 7.0%, and 4.4% in the combination, teriparatide, and zoledronic acid groups, respectively (p < .001 for combination and teriparatide versus zoledronic acid). In the combination group, spine BMD increased more rapidly than with either agent alone (p < .001 versus both teriparatide and zoledronic acid at 13 and 26 weeks). Combination therapy increased total-hip BMD more than teriparatide alone at all times (all p < .01) and more than zoledronic acid at 13 weeks (p < .05), with final 52-week increments of 2.3%, 1.1%, and 2.2% in the combination, teriparatide, and zoledronic acid groups, respectively. With combination therapy, bone formation (assessed by serum N-terminal propeptide of type I collagen [PINP]) increased from 0 to 4 weeks, declined minimally from 4 to 8 weeks, and then rose throughout the trial, with levels above baseline from 6 to 12 months. Bone resorption (assessed by serum β-C-telopeptide of type I collagen [β-CTX]) was markedly reduced with combination therapy from 0 to 8 weeks (a reduction of similar magnitude to that seen with zoledronic acid alone), followed by a gradual increase after week 8, with levels remaining above baseline for the latter half of the year. Levels for both markers were significantly lower with combination therapy versus teriparatide alone (p < .002). Limitations of the study included its short duration, lack of endpoints beyond DXA-based BMD (e.g., quantitative computed tomography and finite-element modeling for bone strength), lack of teriparatide placebo, and insufficient power for fracture outcomes. We conclude that while teriparatide increases spine BMD more than zoledronic acid and zoledronic acid increases hip BMD more than teriparatide, combination therapy provides the largest, most rapid increments when both spine and hip sites are considered. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: BISPHOSPHONATE; OSTEOPOROSIS; INFUSION; ZOLEDRONIC ACID; TERIPARATIDE

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Introduction

In women with postmenopausal osteoporosis, the antifracture benefits of bisphosphonates and the amino-terminal parathyroid hormone peptide teriparatide [PTH(1–34)] are well established. Unlike the bisphosphonates, which reduce bone remodeling, teriparatide is an anabolic agent that stimulates bone formation and increases bone remodeling. While both classes of agents improve bone mineral density (BMD) and reduce fracture risk, teriparatide also improves the microarchitecture of cancellous and cortical bone in the iliac crest providing even greater improvements in bone strength (as measured by finite-element analysis) than those observed with antiresorptive agents alone. In one head-to-head comparison of alendronate and teriparatide in patients with glucocorticoid-induced osteoporosis, vertebral fracture (but not nonvertebral fracture) incidence was lower with teriparatide than with alendronate. At the hip, teriparatide increases areal BMD as assessed by dual-energy X-ray absorptiometry (DXA), volumetric BMD as assessed by quantitative computed tomography (QCT), cortical cross-sectional area (but not diameter) of the femoral neck, and hip strength as assessed by finite-element modeling and by hip structural analysis. However, the pivotal teriparatide trial was not powered adequately for hip fracture outcome (there were only 9 hip fractures), and the areal BMD effects of teriparatide at the hip as assessed by DXA are smaller than those seen in the spine and not consistently greater than those of alendronate. In contrast, the antifracture effects of once-yearly zoledronic acid at the hip over 3 years are well documented (41% reduced hip fracture risk in postmenopausal women with osteoporosis). In the absence of any comparative data on hip fracture incidence, it is unclear which agent might be preferable for patients at high risk of hip fracture or whether combining anabolic and antiresorptive agents might produce an additive effect.

Prior studies evaluating combinations of PTH or teriparatide with antiresorptive agents have yielded inconsistent results, with differences related to which antiresorptive agent is used, whether patients are treatment-naive or have been on antiresorptive therapy when combination treatment is started, and, for patients on prior antiresorptives, whether the antiresorptive agent is continued or stopped when teriparatide is added. In one study, treatment-naive patients were randomized to alendronate or intact PTH(1–84) monotherapy versus combination therapy. DXA results indicated no additive effects of the combination on spine BMD, although BMD at the total hip (as assessed by DXA) did increase more with combination therapy than with PTH alone. However, changes in volumetric BMD of trabecular bone, assessed by QCT, and bone turnover levels suggested that the concurrent use of alendronate might reduce the anabolic effect of PTH.

In rodents, chronic exposure to bisphosphonates reduces the anabolic activity of PTH. This inhibitory effect appears to differ substantially when bisphosphonates are administered less frequently, perhaps because only small quantities are taken up at each administration. Therefore, a single administration of intravenous zoledronic acid in humans could provide a different response to coadministration with PTH compared with more frequently administered bisphosphonates.

The objective of this study was to determine whether a single intravenous administration of zoledronic acid coadministered with teriparatide would provide an additive or at least noninferior effect on BMD of either the spine or hip compared with zoledronic acid or teriparatide monotherapy in postmenopausal women with osteoporosis. Bone turnover markers also were assessed.

Methods

Study design

This was a 1-year partial double-blinded, randomized, multicenter, multinational study in postmenopausal women with osteoporosis. At randomization, treatment-naive participants received a single intravenous infusion of zoledronic acid 5 mg plus daily teriparatide 20 μg via subcutaneous injection (Forteo, Eli Lilly, Indianapolis, IN, USA), zoledronic acid alone, or placebo infusion plus daily teriparatide 20 μg. Participants receiving teriparatide were blinded to zoledronic acid versus placebo infusion, but teriparatide was administered on an open-label basis because no placebo injector was available. Likewise, in the zoledronic acid–alone arm, placebo teriparatide injections were not available. All participants received oral daily calcium (1000 to 1200 mg) and vitamin D (400 to 800 IU).

The study was reviewed by the independent ethics committee or institutional review board of each center and conducted according to the ethical principles of the Declaration of Helsinki. All participants provided written informed consent. The first participant was screened in December 2006, and the last participant completed the trial in February 2009.

Participants

Eligible participants were postmenopausal women aged 45 to 89 years with BMD T-scores of −2.5 or less at the femoral neck, total hip, or lumbar spine or a BMD T-score of −2.0 or less at any site plus one or more documented vertebral or nonvertebral fractures (not due to excessive trauma, as determined by individual investigators). Women were excluded for any prior use of PTH or bisphosphonates for more than 3 consecutive months; shorter-term use was acceptable if followed by a 1-year washout. Other ineligibility criteria included prior strontium treatment; chronic use of systemic corticosteroids within the prior year; raloxifene, calcitonin, or hormone therapy within the prior 6 months; creatinine clearance <30 mL/min (assessed by estimated glomerular filtration rate [Cockcroft-Gault equation]); serum calcium ≥2.75 mmol/L or <2.0 mmol/L; or 25-hydroxyvitamin D levels <15 ng/mL.

Randomization was performed via sponsor-produced treatment-allocation cards using a validated system that automates random assignment of treatment arms to randomization numbers in the specified ratio (1:1:1). An unblinded pharmacist/other designated person at each site stored and distributed study drug according to the randomization scheme on the treatment-allocation card.
Study assessments

BMD measurements of the lumbar spine (L₁ – L₄) and total hip by DXA (Hologic, Waltham, MA, USA, or GE Lunar, Madison, WI, USA) were performed on all participants at screening and at weeks 13, 26, and 52. Scans were acquired locally and sent to a central imaging facility (BioClinica, Inc., Newtown, PA, USA) for evaluation with standard quality control. Lumbar spine X-rays were performed on all participants at screening and at week 52 and sent to a central imaging facility (BioClinica, Inc.) for evaluation. Fracture evaluation was not an efficacy endpoint of this trial but was used in the patient-inclusion process and for determining exclusion of vertebrae from the lumbar spine DXA evaluations.

Measurements of serum markers of bone resorption (β-C-telopeptide of type I collagen [β-CTX]) and bone formation (N-terminal propeptide of type I collagen [PINP]) were performed at baseline and at weeks 4, 8, 26, 39, and 52 (electrochemiluminescence immunoassay; Modular E 170 Automated Analyzer, Roche Diagnostics, Mannheim, Germany). Serum samples were obtained after an overnight fast, and study medication, calcium, and vitamin D were not to be taken on the morning prior to sample collection. Bone marker measurements were performed at Synarc SAS (Lyon, France). All safety laboratory samples were analyzed at a central laboratory (Covance Laboratory Services, Indianapolis, IN, USA, and Geneva, Switzerland). Lateral lumbar spine and thoracic spine X-rays were obtained for assessment of preexisting vertebral fractures (for subject inclusion). Lateral lumbar spine (but not thoracic) X-rays were repeated at the end of the 1-year treatment period to identify incident vertebral fractures or degenerative disease that may have artifactually affected the BMD analyses.

Safety assessments included monitoring and recording of all adverse events (AEs); monitoring of serum chemistry and urine, vital signs, and body weight; and physical examination. AEs were categorized according to codes in the Medical Dictionary for Regulatory Activities. Analysis plans were submitted and approved prior to conduct of all analyses.

Endpoints

The primary objective was to demonstrate the noninferiority of combined zoledronic acid plus teriparatide to teriparatide alone on the basis of percentage increase in lumbar spine BMD at 52 weeks relative to baseline. Secondary efficacy endpoints were percentage change in lumbar spine BMD at earlier time points; percentage change in total hip, trochanter, and femoral neck BMD at all time points; and changes in serum β-CTX and serum PINP at all time points. Clinical fractures were assessed only as AEs.

Statistical analysis

The primary efficacy analysis was based on a two-sided 95% confidence interval (CI) for between-treatment differences in percentage change in lumbar spine BMD at week 52 relative to baseline for the combination group minus teriparatide alone, with the CI calculated using the least-squares-mean (LSM) difference from an analysis-of-variance (ANOVA) model with country and treatment (all three treatments) in the model (country was included because of the small number of participants enrolled at some centers).

Noninferiority was established if the lower bound of the CI was greater than the predefined noninferiority margin of −2.0% in both the intent-to-treat and per-protocol populations. Selection of the noninferiority margin was based on clinical relevancy of antifracture benefit. Previous studies of antiresorptive therapies described by Hasselblad and Kong demonstrated that lumbar spine BMD increases of 3% or more are associated with an antifracture benefit. In addition, the −2.0% noninferiority margin ensured that the combination therapy would be statistically superior to a putative placebo based on the data from the pivotal placebo-controlled teriparatide study by Neer and colleagues using the method described by Hasseblad and Kong.

If noninferiority was demonstrated, superiority was tested using a two-way ANOVA in the intent-to-treat population. All secondary analyses were performed in the intent-to-treat population, with missing values excluded. For secondary BMD analyses, between-treatment differences were estimated using LSM differences from the two-way ANOVA. For secondary serum biomarker analyses, the log(e) ratio of treatment versus baseline value at each time point was transformed to normalize distribution of marker parameters. A two-way analysis of covariance with treatment and country as factors and log(e) baseline value as a covariate was performed, with relative treatment effect defined as the exponential of the difference in log(e) ratio between two treatment groups. The two-sided 95% CI for the between-treatment difference of the log(e)-transformed data was constructed using the linear contrast approach. All between-treatment differences were evaluated at a significance level of .05. AE data are summarized descriptively.

The intent-to-treat population comprised all randomized participants, the safety population comprised all participants receiving a dose of study medication, and the per-protocol population excluded all participants with major protocol deviations. A sample size of approximately 108 participants per treatment group was estimated to provide 90% power to ensure that the lower bound of the two-sided 95% CI for the percentage change in lumbar spine BMD at week 52 for the combination group versus the teriparatide group was greater than −2.0%, assuming a standard deviation of 4.5%. To account for a possible 10% dropout rate, the total sample size required was approximately 360 participants.

Role of the funding source

The study was sponsored by Novartis Pharmaceuticals Corporation of East Hanover, NJ, USA, and the sponsor was involved in the study design; the collection, analysis, and interpretation of data; and the decision to approve publication of the finished article.

Results

Baseline and follow-up

A total of 412 participants were randomized to zoledronic acid alone (n = 137), zoledronic acid plus teriparatide (n = 137), or
### Table 1. Baseline Characteristics of Participants Randomized to Zoledronic Acid (ZOL) Plus Teriparatide (TPTD), TPTD Plus Placebo, or ZOL Alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>ZOL 5 mg IV + TPTD 20 µg/day (n = 137)</th>
<th>Placebo IV + TPTD 20 µg/day (n = 138)</th>
<th>ZOL 5 mg IV (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, n (%)</td>
<td>132 (96.4)</td>
<td>135 (97.8)</td>
<td>135 (98.5)</td>
</tr>
<tr>
<td>White</td>
<td>132 (96.4)</td>
<td>135 (97.8)</td>
<td>135 (98.5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.6)</td>
<td>3 (2.2)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.0 (8.8)</td>
<td>63.8 (9.1)</td>
<td>66.1 (9.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 (4.14)</td>
<td>25.3 (4.15)</td>
<td>25.3 (4.42)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, n (%)</td>
<td>21 (15.3)</td>
<td>22 (15.9)</td>
<td>30 (21.9)</td>
</tr>
<tr>
<td>History of clinical fracture, n (%)</td>
<td>85 (62.0)</td>
<td>76 (55.1)</td>
<td>90 (65.7)</td>
</tr>
<tr>
<td>Standardized lumbar spine BMD (g/cm²)</td>
<td>0.74 (0.096)</td>
<td>0.73 (0.087)</td>
<td>0.72 (0.095)</td>
</tr>
<tr>
<td>Lumbar spine T-score, mean (SD)</td>
<td>-2.79 (0.892)</td>
<td>-2.87 (0.807)</td>
<td>-2.88 (0.883)</td>
</tr>
<tr>
<td>Standardized total hip BMD (g/cm²)</td>
<td>0.71 (0.104)</td>
<td>0.71 (0.087)</td>
<td>0.68 (0.087)</td>
</tr>
<tr>
<td>Total hip T-score, mean (SD)</td>
<td>-1.79 (0.851)</td>
<td>-1.79 (0.684)</td>
<td>-2.03 (0.726)</td>
</tr>
<tr>
<td>Serum β-CTX (ng/mL)</td>
<td>0.45 (0.191)</td>
<td>0.46 (0.222)</td>
<td>0.44 (0.218)</td>
</tr>
<tr>
<td>Serum PINP (ng/mL)</td>
<td>52.72 (24.815)</td>
<td>55.69 (28.631)</td>
<td>53.64 (29.233)</td>
</tr>
</tbody>
</table>

β-CTX = serum C-telopeptide of type I collagen; IV = intravenous; PINP = serum N-terminal propeptide of type I collagen.

aPremenopausal reference range for serum β-CTX (95% CI): 0.114–0.628 ng/mL. (33)

bPremenopausal reference range for serum PINP (95% CI): 16.3–78.2 ng/mL. (33)

teriparatide plus intravenous placebo (n = 138). Groups had similar baseline characteristics, including similar spine and hip BMD values and serum β-CTX and PINP levels. There were numerical but not statistically significant differences among groups with respect to clinical fracture history and prevalent vertebral fractures (Table 1). Overall, 94.2% of participants completed the study, with AEs being the most common reason for discontinuation. Participant disposition for the study is summarized in Fig. 1. Teriparatide was self-administered beginning at visit 2 and continuing throughout the study. Compliance was defined as administration of 80% or more of the 52-week supply of teriparatide. Twenty participants in each of the combination and teriparatide treatment groups (14.6% and 14.5%, respectively) self-administered less than 80%, largely owing to premature discontinuation (31 of these 40 participants).

Bone mineral density

At 52 weeks, increases in spine BMD were 7.5% with combination therapy, 7.0% with teriparatide, and 4.4% with zoledronic acid (Fig. 2A). The lower bound of the two-sided 95% CI (−0.6%) for the treatment difference (0.5%) between the combination group and the teriparatide group was greater than the prespecified noninferiority margin of −2.0%, indicating noninferiority of combination versus teriparatide therapy in increasing BMD. Results of between-treatment comparisons at 52 weeks in the per-protocol population were similar to those in the intent-to-treat population: increases of 7.3% with combination therapy, 7.3% with teriparatide, and 4.3% with zoledronic acid (data not shown), also indicating noninferiority of combination versus teriparatide therapy. There was no significant difference between the combination and teriparatide groups at week 52; however, spine BMD increments were higher with combination versus teriparatide at weeks 13 and 26, for combination versus zoledronic acid at all time points, and for teriparatide versus zoledronic acid at week 52 (all p < .001).

Increases in total-hip BMD at 52 weeks (Fig. 2B) were 2.3% with the combination, 1.1% with teriparatide, and 2.2% with zoledronic acid. BMD increments were higher (p < .02) for combination versus teriparatide at all times, for combination versus zoledronic acid at week 13, and for zoledronic acid versus teriparatide at all times. Increments in femoral neck and trochanteric BMD (Fig. 2C, D) with combination therapy also exceeded those with teriparatide alone throughout the study (at 52 weeks, for femoral neck, 2.2% versus 0.1%, p < .001; for trochanter, 4.4% versus 2.4%, p < .01). Combination therapy also produced numerically but not significantly greater increases than zoledronic acid at all time points.

Fractures

Clinical fractures (recorded as AEs only) occurred in 13, 4, and 8 participants in the zoledronic acid, combination, and teriparatide groups, respectively (Table 2). Clinical fracture incidence was significantly lower in the combination group than in the zoledronic acid–alone group (p = .04; risk ratio [95% CI]: 0.31 [0.10, 0.92]) but was not significantly different for combination versus teriparatide alone. Because of the slight difference in baseline fracture history between the groups, fracture rates during the trial were compared between the combination and
Zoledronic acid groups using logistic regression adjusted for baseline prevalent vertebral fracture and history of clinical fracture. The difference remained significant ($p = .04$).

Biochemical markers of bone turnover

Serum $\beta$-CTX was reduced to its nadir by week 4 with zoledronic acid, with small increases thereafter (Fig. 3A). In the teriparatide group, mean levels were unchanged through week 4, then increased to a peak at week 26, and decreased slightly thereafter. An initial prominent reduction with combination therapy, of similar magnitude to the reduction seen with zoledronic acid alone, was followed by a gradual increase after week 8, with levels remaining above baseline for the latter half of the year. Between-treatment differences were significant for combination therapy versus the teriparatide and zoledronic acid groups at all time points and for zoledronic acid versus teriparatide at all time points (all $p < .001$).

In the zoledronic acid group, PINP declined through week 8 with little subsequent change (Fig. 3B). In the teriparatide group, in contrast to what was seen with $\beta$-CTX, PINP was elevated by week 4 ($p < .001$ versus baseline). With combination therapy, PINP also increased through week 4, declined slightly between weeks 4 and 8, and then increased progressively, with levels above baseline from 6 to 12 months. The decline in PINP in the combination group was much less prominent than the decline seen with zoledronic acid alone, however, and all between-treatment differences were significant ($p < .001$) for all comparisons of combination treatment versus teriparatide and versus zoledronic acid, and for zoledronic acid versus teriparatide.

Adverse events

AE rates were 91.2% in the combination and zoledronic acid groups and 85.4% with teriparatide alone. AEs occurring with greater frequency with combination versus teriparatide alone were short-term postinfusion symptoms (eg, nausea, influenza-like illness, chills, fatigue, pyrexia, arthralgia, myalgia, and headache) observed after zoledronic acid infusion. Rates of AEs within the first 3 days after infusion were 68.6% with combination, 58.4% with zoledronic acid, and 27.0% with teriparatide, whereas those after 3 days were comparable across the three groups (84.7%, 87.6%, and 84.7%, respectively). There was one death during the study (in the zoledronic acid group) owing to pancreatic carcinoma, deemed not to be related to study treatment by the study investigator at that site. There were
no significant differences in serious AEs among groups. AEs causing study discontinuation were reported for 11 participants (8.0%) receiving combination therapy, 7 participants (5.1%) receiving teriparatide alone, and 6 participants (4.4%) receiving zoledronic acid alone.

There were no incidents of hypocalcemia in any group. Notable hypercalcemia (predefined as serum calcium > 2.89 mmol/L) occurred in one participant (0.7%) in the combination group and two participants (1.5%) in the teriparatide group and resulted in study discontinuation for one participant in each group. The percentages of participants with calcium values that were normal at baseline but above the normal range during the study were 13.4% for the combination group, 15.0% for the teriparatide group, and 4.4% for the zoledronic acid group. There were no reports of long-term effects on renal function (comparing creatinine clearance values at baseline versus 12 months) for any group.

**Discussion**

Our data show that concomitant administration of a single infusion of zoledronic acid with daily teriparatide increased lumbar spine BMD more than teriparatide alone during the first 13 weeks. At 52 weeks, increments in bone mass at the spine were similar to those seen with teriparatide alone, but spine BMD increments were greater than with zoledronic acid alone throughout the study. Furthermore, concomitant therapy led to rapid, pronounced, and persistent gains in total-hip, trochanter, and femoral neck BMD versus teriparatide alone and increased total-hip BMD more than zoledronic acid alone at 13 weeks. Treatment with all three regimens generally was safe and well tolerated; the overall percentage of AEs was comparable for the three treatment groups.

Concomitant therapy resulted in a prominent and immediate reduction of bone resorption that was sustained for the first 2 months, with gradual resolution of this reduction and increased bone resorption over the latter 6 months of treatment. Thus the duration of zoledronic acid–induced reduction of bone resorption was shorter in the presence of teriparatide than when zoledronic acid was administered alone (based on zoledronic acid monotherapy data from this and prior studies), possibly owing to more rapid removal of zoledronic acid from the bone surface in the presence of teriparatide. Furthermore, BMD increments were largest at both spine and hip during the first 3 to 6 months of combination therapy, possibly owing to expansion of the anabolic window (the magnitude of stimulation of bone formation versus bone resorption). There was a prominent and rapid decline in bone resorption during this period compared with an initial increase, followed by a minimal and very brief decline in bone formation. These results suggest that zoledronic acid does not interfere with the osteoblastic response to teriparatide and that the early anabolic effect of teriparatide in combination with zoledronic acid is independent of new bone remodeling. During the second half of the study, the anabolic effect in the combination group occurred with increased bone remodeling, with formation and resorption marker levels above baseline. One of the potential limitations of PTH treatment is that its stimulatory effect on intracortical bone remodeling can increase cortical porosity. This may not translate into decreased mechanical strength, however, because the porosity is concentrated at the endocortical surface (close to the neutral axis of bone) and may be offset by increased cortical thickening.

Fig. 2. LSM percentage change in BMD from baseline at lumbar spine (A), total hip (B), femoral neck (C), and femoral trochanter (D) according to treatment. *p < .001 versus teriparatide (TPTD) alone and versus zoledronic acid (ZOL) alone; †p < .001 versus ZOL alone; ‡p < .05 versus TPTD alone; ‡p < .05 versus ZOL alone. Data are from intent-to-treat population excluding missing values. Bars show standard error.
periosteal apposition and increased cortical thickness.\(^{(36–38)}\) Nevertheless, cotreatment with zoledronic acid may prevent the teriparatide-induced increase in cortical porosity, thus potentially strengthening the cortex and, as observed in this study, increasing hip BMD beyond values achieved with teriparatide alone.\(^{(39)}\) The lack of continued increase in BMD at the hip during the latter 6 months in the combination group of our study may be due to increased cortical remodeling and resulting increases in cortical porosity as the effect of zoledronic acid wanes.

We performed an English-language MEDLINE search through November 2009 to identify relevant trials of combination therapy with bisphosphonates and PTH/teriparatide. One other clinical trial has evaluated combination therapy with PTH(1–84) and a bisphosphonate in previously untreated patients with osteoporosis.\(^{(14)}\) In that study, PTH(1–84) alone and the combination of PTH with 10 mg of daily alendronate increased integral spine BMD (by DXA) similarly, but there were no time points before 1 year, so the rapidity of the BMD effect could not be ascertained. In that trial, combination treatment increased areal BMD at the total hip significantly more than PTH alone, but interpretation of the DXA results was overshadowed by quantitative computed tomographic (QCT) results indicating that trabecular bone mass levels at the spine and hip were increased more by PTH alone than by combination treatment. The significance of the difference between the QCT and DXA findings in that study is unclear. It is possible that PTH might affect marrow fat content\(^{(40)}\) and artificially exaggerate BMD increases assessed by QCT.\(^{(41,42)}\) In the current trial, we did not investigate QCT outcomes.

Any differences between the current study and that of Black and colleagues\(^{(14)}\) may be attributable to several factors. First, this study used a different form of PTH (N-terminal PTH peptide versus intact PTH[1–84]), with possible pharmacokinetic and pharmacodynamic differences.\(^{(43)}\) Alendronate was given daily in the study by Black and colleagues, and a high frequency of bisphosphonate administration might impair the osteoblastic response to PTH,\(^{(25,26)}\) an effect avoided by annual administration of an intravenous bisphosphonate. There also may be additional factors inherent to the specific bisphosphonates.\(^{(44)}\)

### Table 2. All Clinical Fractures by Fracture Type and Treatment

<table>
<thead>
<tr>
<th>Clinical fracture type</th>
<th>ZOL 5 mg IV + TPTD 20 µg/day (n = 137), n (%)</th>
<th>Placebo + TPTD 20 µg/day (n = 137), n (%)</th>
<th>ZOL 5 mg IV (n = 137), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4 (2.9)</td>
<td>8 (5.8)(^{a})</td>
<td>13 (9.5)(^{b})</td>
</tr>
<tr>
<td>Thoracic vertebral</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Lumbar vertebral</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Rib</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Wrist</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Humerus</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Spinal compression</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Ankle</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Clavicle</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Facial bone</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fibula</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Foot</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Note: Fracture types are sorted in descending frequency of occurrence, as reported in the ZOL 5 mg group. A participant with multiple occurrences of an event under one treatment is counted only once in the event category for that treatment. IV = intravenous; TPTD = teriparatide; ZOL = zoledronic acid.

\(^{a}\)p = not significant versus combination therapy (with or without inclusion of facial bone fractures).

\(^{b}\)p = .04 versus combination therapy.

Fig. 3. Mean serum β-C-telopeptide of type I collagen (β-CTX) (A) and N-terminal propeptide of type I collagen (PINP) (B) according to treatment. Data are from intent-to-treat population with missing values excluded. Bars show standard error. Premenopausal reference ranges (indicated by horizontal lines above the x axis) are based on data from Glover and colleagues.\(^{(33)}\) TPTD = teriparatide; ZOL = zoledronic acid.
Other studies evaluating combination therapy with teriparatide and bisphosphonates enrolled patients in whom bisphosphonates were given prior to the introduction of teriparatide treatment. In one trial,[23] alendronate was given for only 6 months prior to the introduction of teriparatide. In that study, after 1 year of teriparatide treatment, results for the combination group and the teriparatide-alone group were quite similar to those seen in this study. In all other trials, the duration of bisphosphonate use prior to the initiation of teriparatide was much longer. Differences in parathyroid dynamics and magnitude of active bone surface, which may be substantial in established bisphosphonate users compared with those new to therapy, may account for variable results in trials involving long-term bisphosphonate users versus those who are treatment-naïve.

Limitations of this study include its short duration; different conclusions might be drawn after a second year of therapy, particularly for femoral neck BMD, which has increased more during the second year of therapy in several clinical trials.[3,13,23] Also, this study did not include other endpoints beyond DXA (e.g., QCT and finite-element modeling for bone strength or assessments of bone structure, such as bone biopsy or high-resolution computed tomography). The zoledronic acid arm was not blinded, owing to the lack of teriparatide placebo; however, those who assessed endpoints in this study were blinded to the treatment assignment, and these were objective parameters. As a result, there should have been no bias with respect to reporting of efficacy data. The only potential for bias was in investigator reporting of AEs for the zoledronic acid-alone group. Finally, this study was not powered for fracture outcomes and did not comprehensively assess morphometric vertebral fractures. Further studies are warranted to assess the implications of the BMD findings in this study for fracture risk reduction and to determine the underlying mechanisms for observed differences in BMD gains between combination therapy and monotherapy.

Thus, when considering the endpoints of both spine and hip BMD, concomitant administration of a single infusion of intravenous zoledronic acid (5 mg) with daily subcutaneous teriparatide (20 μg) yielded larger, more rapid increments than either agent alone. At 1 year, compared with combination treatment, teriparatide alone produced similar effects at the spine and zoledronic acid produced similar effects at the hip; however, combination therapy was able to achieve the greatest impact on both spine and hip BMD endpoints. These observations in the combination group likely result from teriparatide-induced increases in osteoblastic activity, together with zoledronic acid–induced reductions in bone remodeling and cortical porosity. Combination therapy therefore may be appropriate treatment for patients at high risk for hip or other fractures.

Disclosures

ClinicalTrials.gov number, NCT00439244; study registration date, February 22, 2007. FC consults for Amgen, Eli Lilly, Merck, and Novartis. EFE has been an employee of and owns stock in Novartis. CR receives research grants from Procter & Gamble; consults for Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, NPS, Roche, Procter & Gamble, and Zelos; and speaks for Aventis, Eli Lilly, GlaxoSmithKline, Merck, Procter & Gamble, and Roche. PDM receives research grants from and/or consults for Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, NPS, Procter & Gamble, Roche, and Sanofi-Aventis. NG has served on advisory boards for Amgen, Wyeth, and MSD. CK has received research grants from and consulted for Amgen, Novartis, and Servier. PP is an employee of and owns stock in Novartis. AR and HR are employees of Novartis. JAG is an employee of the Novartis Institute for BioMedical Research. CBR is an employee of and owns stock in Novartis. SB is senior clinical investigator of the Fund for Scientific Research, Flanders, Belgium (FWO-Vlaanderen) and receives research grants from Amgen, Eli Lilly, Novartis, Pfizer, Procter & Gamble, Sanofi-Aventis, and Roche-GlaxoSmithKline and consults or speaks for Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, Sanofi-Aventis, and Servier.

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