Effects of Previous Antiresorptive Therapy on the Bone Mineral Density Response to Two Years of Teriparatide Treatment in Postmenopausal Women with Osteoporosis

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Introduction: EUROFORS was a 2-yr prospective, randomized trial of postmenopausal women with established osteoporosis, designed to investigate various sequential treatments after teriparatide 20 μg/d for 1 yr. The present secondary analysis examined the effects of 2 yr of open-label teriparatide in women previously treated with antiresorptive drugs for at least 1 yr.

Methods: A subgroup of 245 women with osteoporosis who had 2 yr of teriparatide treatment were stratified by previous predominant antiresorptive treatment into four groups: alendronate (n = 107), risedronate (n = 59), etidronate (n = 30), and non-bisphosphonate (n = 49). Bone mineral density (BMD) at the lumbar spine and hip was determined after 6, 12, 18, and 24 months, and bone formation markers were measured after 1 and 6 months.

Results: Significant increases in bone formation markers occurred in all groups after 1 month of teriparatide treatment. Lumbar spine BMD increased at all visits, whereas a transient decrease in hip BMD, which was subsequently reversed, was observed in all groups. BMD responses were similar in all previous antiresorptive groups. Previous etidronate users showed a higher increase at the spine but not at the hip BMD. Duration of previous antiresorptive therapy and lag time between stopping previous therapy and starting teriparatide did not affect the BMD response at any skeletal site. Treatment-emergent adverse events were similar to those reported in treatment-naive postmenopausal women with osteoporosis treated with teriparatide.

Conclusions: Teriparatide induces positive effects on BMD and markers of bone formation in postmenopausal women with established osteoporosis, regardless of previous long-term exposure to antiresorptive therapies. (J Clin Endocrinol Metab 93: 852–860, 2008)
Several osteoporosis treatment guidelines, mainly in Europe, recommend the use of teriparatide for the treatment of severe established osteoporosis as a second-line treatment (10). Thus, many patients initiating teriparatide therapy have often been previously treated with antiresorptives for long periods of time (11). An important clinical question is whether the response to teriparatide in these patients is similar to the response in patients who have never received treatment. Preclinical studies in ovariectomized rats indicate that teriparatide significantly enhances bone mass and bone strength regardless of previous therapies (12). Clinical studies have shown that the sequential use of teriparatide (20 μg/d) after long-term daily alendronate or raloxifene therapy stimulated bone turnover; however, previous treatment with alendronate prevented early bone mineral density (BMD) responses to teriparatide (3). Other studies suggest that concomitant use of alendronate with PTH therapy reduces the ability of PTH to stimulate new bone formation (13–15).

Using data from the European Study of Forsteo (EUROFORS) (16), the effects of 2 yr of open-label teriparatide treatment on BMD and biochemical markers of bone formation was determined in women with established osteoporosis who were previously treated with antiresorptive therapy for at least 1 yr.

Subjects and Methods

Study design and participants

EUROFORS was a prospective, open-label, randomized trial of 865 postmenopausal women with established osteoporosis designed to investigate various sequential treatments of teriparatide over 2 yr. The study was conducted at 95 centers in 10 European countries. The present analyses were conducted using data from 245 patients treated with open-label teriparatide therapy for more than 12 months and up to 24 months and who had previously been treated with one predominant antiresorptive drug for a minimum of 12 months. These patients were stratified by type of previous antiresorptive therapy. Participants were women age 55 yr and above that were at least 2 yr postmenopausal at the time of study entry. Patients were required to be ambulatory and free of severe chronically disabling conditions other than osteoporosis and to have normal laboratory values for serum calcium, alkaline phosphatase, and PTH, with a lumbar spine (L1–L4), femoral neck, or total hip BMD T-score below −2.5 SD. At least two lumbar vertebrae were required to be without artifacts, fractures, and/or other abnormalities. Patients were required to have at least one documented preexisting clinical vertebral or nonvertebral fragility fracture within the last 3 yr before enrollment. Additional inclusion criteria for the present prespecified subgroup analysis included patient self-reported use of alendronate, risedronate, or etidronate for more than 12 months with less than 3 months of any other bisphosphonate, or the use of any non-bisphosphonate (including calcitonin, raloxifene, estrogen therapy/estrogen progestagens therapy (ET/EPT) and vitamin D metabolites) for more than 12 months with less than 3 months bisphosphonate use. Women were excluded if they had other diseases affecting bone metabolism; past radiation therapy involving the skeleton, skeletal tumors, or metastases; nephrolithiasis within the past 2 yr; carcinoma of the breast or estrogen-dependent neoplasia ever or other malignancies in the past 5 yr; and abnormal thyroid, liver, or renal function. Each patient provided written informed consent, and institutional review board approval was obtained at each study center. All study methods and procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Treatments and blinding

All 245 patients received open-label teriparatide 20 μg/d and daily supplements of 500 mg elemental calcium and 400–800 IU vitamin D for up to 24 months. A screening visit was completed within 1 month of obtaining written informed consent, and eligible women began teriparatide treatment at a baseline enrollment visit. Additional visits were conducted at 1, 6, 12, 18, and 24 months of treatment. Patient compliance was assessed by direct questioning of the patients and by quantifying the amount of study drug returned. The study protocol predefined non-compliance as missing more than 30% of study medication over two consecutive visits.

Baseline and follow-up assessments

Patient demographics, health history, and previous medication use were obtained at baseline. Lumbar spine and hip BMD was assessed by dual x-ray absorptiometry at baseline and 6, 12, 18, and 24 months. Anteroposterior and lateral spine radiographs were obtained at baseline to determine whether at least two evaluable vertebrae in the lumbar region (L2–L4) were present in each patient fulfilling BMD entry criteria. All scans were sent to a reading center for analysis of areal BMD and quality assurance (Bioimaging Technologies, Leiden, The Netherlands). BMD results of the total hip obtained on Hologic, GE-Lunar, and Norland scanners were converted to standardized values, and BMD results of the lumbar spine and femoral neck obtained on Lunar and Norland scanners were converted to Hologic values using published and validated formulae (17, 18). Quality control procedures for densitometric equipment were performed at each laboratory by validating scanners with a standard anthropomorphic spine phantom.

Biochemical markers of bone formation, including N-terminal propeptide of type 1 collagen (PINP) (two-site immunoassay; Roche Diagnostics, Indianapolis, IN), bone-specific alkaline phosphatase (BSAP) (enzyme-linked immunoassay, Alkphase-B; Metra Biosystems, Mountain View, CA), and total alkaline phosphatase (TAP) (dry slide; Ortho-Clinical Diagnostics, Bucks, UK) were measured in serum collected after an overnight fast at baseline and after 1 and 6 months of teriparatide treatment. All samples were analyzed at the University of Sheffield (Sheffield, UK). Detailed assay methodology has been previously reported (19). Assay coefficients of variation were PINP, 9.9%; BSAP, 6.8%; and TAP, 7.0% (19).

Serum calcium, albumin, and alkaline phosphatase levels were measured before the injection of teriparatide during clinic visits at month 6, 12, 18, and 24. Serum calcium was corrected for serum albumin according to the following formula: corrected calcium = total calcium, + [ (40 – albumin,) × 0.02] (20). Fasting clinical chemistry, hematology, and urinalysis laboratory tests were performed at baseline and 24 months at the local investigative site laboratory. Hypercalcemia was defined as an albumin-corrected serum calcium level above the upper limit of normal serum calcium using the assay employed by the local investigative site. Study site personnel were instructed to note the occurrence and nature of each patient’s medical condition before study entry and monitor any changes in these conditions and the occurrence and nature of any adverse events throughout the study.

Statistical analysis

The primary objective of the EUROFORS study was to compare change in lumbar spine BMD after 24 months of teriparatide treatment with change in lumbar spine BMD after 12 months of teriparatide treatment followed by 12 months of no active treatment. The aim of the secondary analysis presented in this manuscript was to examine the change in BMD after 24 months of teriparatide treatment stratified by long-term previous antiresorptive treatment.

Mixed-model repeated measures (MMRM) was used to analyze changes from BMD at baseline using changes in BMD as the response variable and previous antiresorptive therapy, visit, and their interaction as fixed effects using SAS Proc Mixed. Models were fitted with adjustment for baseline BMD, duration of previous therapy, lag time between stopping previous therapy and starting teriparatide, age, time since...
...menopause, body mass index (BMI), and baseline P1NP. A sensitivity analyses was completed looking at absolute differences in changes in BMD without adjustment for baseline data. Pairwise differences between least-square means gave estimates for between-group differences in changes from baseline. The least-square means of change from baseline were divided by the mean baseline BMD, which gave a crude estimate of percent change for a patient with average baseline BMD.

Biochemical markers were not normally distributed and were log transformed before modeling and analyzed using MMRM. The logged actual endpoint was the explanatory variable in the model. Fixed effects for previous treatment, visit, and their interaction were used. Other explanatory variables were age, BMI, lag time between the end of previous antiresorptive treatment and the start of teriparatide, and duration of previous treatment. Pairwise differences were exponentiated to give within-group percent changes from baseline. The raw data were summarized and medians and interquartile ranges plotted.

All models allowed for the correlations between repeated measurements on subjects, and these correlations were estimated by the data. The models were fit using the restricted maximum likelihood method, with Kenward Roger degrees of freedom (21). Assumptions of normality were checked. The MMRM methodology assumes data are missing at random. All nonmissing data contribute to the model, and no missing data are imputed. All efficacy and safety analyses were conducted on a modified intent-to-treat basis and included all data from patients starting a second year of teriparatide treatment.

Differences in baseline characteristics were tested using ANOVA for parametric data and the Kruskal-Wallis test for nonparametric data.

All adverse events were categorized as treatment-emergent if first occurrence of the event was observed after initiating teriparatide therapy or the event worsened in severity on teriparatide treatment compared with the baseline period. No formal comparisons between groups were made.

Analyses were performed using SAS software (SAS Institute, Cary, NC).

**Results**

**Patient disposition**

Of the 865 women enrolled to EUROFORS and initiating teriparatide treatment, 659 had been previously treated with antiresorptive therapy (Fig. 1). Three hundred seventy-seven of these pretreated patients had been treated with one antiresorptive drug for at least 12 months. Of these, 315 (83.6%) completed the first year of teriparatide treatment, and 245 women were randomized to continue into a second year of teriparatide therapy and constituted the population for analysis in this study (Fig. 1). For the purpose of the analysis, the women were classified into subgroups according to previous predominant antiresorptive treatment as follows: alendronate (n = 107), risedronate (n = 59), etidronate (n = 30), and non-bisphosphonate antiresorptive (n = 49). In total, 228 (93.1%) women completed a second year of teriparatide treatment (Fig. 1). Among these women, measurements of returned pens used for the sc administration of teriparatide revealed that 96.5% of them used at least 70% of the expected amount of teriparatide.

**Baseline demographics**

The baseline characteristics are shown in Table 1. There were no significant differences for age, BMI, or spine or hip BMD.

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**FIG. 1.** Patient disposition.
Lag time was defined as the time between stopping antiresorptive therapy and starting teriparatide.

Time since menopause was lower in the non-bisphosphonate group, probably reflecting postmenopausal ET/EPT use. Biochemical markers of bone formation were significantly different between study groups at baseline (Table 1). This result was expected given the differences in the degree of bone turnover suppression induced by antiresorptive therapies with the lowest values being observed in alendronate or risedronate users and the highest values in the etidronate group. Lag time between stopping antiresorptive treatment and initiating teriparatide therapy and duration of previous predominant antiresorptive treatment were both significantly different between subgroups (Table 1). The majority of previous alendronate-, risedronate-, and non-bisphosphonate-treated women initiated teriparatide therapy within 1 month of stopping antiresorptive treatment, whereas the majority of previous etidronate-treated women initiated teriparatide treatment after 1 month of stopping etidronate therapy due to the cyclic dosing scheme of this drug (Table 1).

**BMD**

Lumbar spine BMD significantly increased relative to baseline at all time points in each subgroup (Fig. 2A). Significant increases compared with baseline were observed in all subgroups at 24 months, ranging between 0.062 ± 0.004 gm/cm² (mean ± SE) (9.3%) in the previous alendronate to 0.089 ± 0.009 gm/cm² (13.3%) in the previous etidronate subgroup (Fig. 2A). Changes in lumbar spine BMD from baseline were similar at each time point among previous alendronate, risedronate, and non-bisphosphonate subgroups. However, women previously treated with etidronate experienced significantly greater lumbar spine BMD increases at all time points compared with women previously treated with alendronate and risedronate, and at 18 and 24 months compared with women previously treated with non-bisphosphonates (Table 2).

Although the pattern of early changes in total hip BMD appeared to differ between the subgroups, the differences were not significantly different at any time point in the study (Fig. 2B). Total hip BMD decreased at 6 months but was not significantly different from baseline in the previous etidronate (−0.006 ± 0.006 gm/cm², −0.9%, P = 0.32) and non-bisphosphonate (−0.002 ± 0.005 gm/cm², −3.3%, P = 0.71) subgroups, whereas total hip BMD decreased significantly in the previous alendronate (−0.008 ± 0.003 gm/cm², −1.2%, P = 0.004) and risedronate (−0.011 ± 0.004 gm/cm², −1.6%, P = 0.003) subgroups. At 24 months, total hip BMD was significantly increased compared with baseline in all subgroups, and changes were not significantly different among subgroups (Table 2).

Femoral neck BMD decreased in all subgroups at 6 months, although this decrease was significant only in the previous alendronate subgroup (−0.011 ± 0.003 gm/cm², −2.0%, P < 0.001). No statistically significant differences between subgroups at any time point in the study were found, except for the difference at 18 months between the etidronate and alendronate subgroups (Fig. 2C). At 18 and 24 months of treatment, BMD at the femoral neck was statistically increased compared with baseline in all subgroups, except the previous alendronate subgroup, where the change at 18 months (0.006 ± 0.003 gm/cm², 1.1%) was not significant (P = 0.06). Pairwise BMD differences between previous predominant groups at 24 months are detailed in Table 2. The small symmetric confidence intervals around zero indicate similar results among the four previous treatment groups. Our conclusions regarding the differences between previous treatment and changes from baseline were consistent whether the analysis is adjusted for baseline values or unadjusted.

The MMRM models showed that baseline BMD and P1NP levels and either age or time since menopause were associated with the BMD changes at the three sites. Lower baseline BMD values, higher baseline P1NP values, and older age were associ-
Biochemical markers of bone formation

After 1 month of teriparatide treatment, all subgroups showed statistically significant increases from baseline for P1NP and BSAP (Fig. 3, A and B). Comparisons of P1NP levels between treatment groups at baseline and month 1 showed P1NP levels in the previous alendronate group were significantly lower compared with all other previous treatment groups. TAP significantly increased after 1 month of teriparatide treatment in all subgroups except in the previous etidronate group (data not shown).

At month 6, P1NP levels in the previous risedronate group were significantly greater compared with the previous alendronate and non-bisphosphonate groups. A similar trend was observed for changes in BSAP levels, which were significantly lower at all time points in the previous alendronate treatment group compared with previous etidronate and risedronate groups and at baseline and month 1 compared with the previous non-bisphosphonate group.

Type of previous predominant antiresorptive medication, time since stopping previous antiresorptive therapy and starting teriparatide treatment, visit were associated with bone turnover marker levels after initiating teriparatide treatment in the MMRM models. Previous risedronate treatment was associated with a higher increase in P1NP and BSAP at 6 months. Each additional week of lag time between stopping antiresorptives and starting teriparatide was associated with a 0.9% increase in P1NP and 0.4% in BSAP. The duration of previous antiresorptive therapy, age, and BMI did not influence the bone marker values.

A sensitivity analysis of the biochemical markers of bone formation was performed to exclude 29 women who sustained an incident fracture during the first 6 months of teriparatide. The absolute changes and the conclusions from the MMRM did not show any substantial variation to the results of the overall cohort (data not shown).

Safety

Treatment-emergent adverse events occurring in more than seven patients (≥3%) during the 2-yr continuous teriparatide treatment are presented in Table 3. Hypercalcemia, defined as greater than the upper limit of normal at the local laboratory level, developed in 15 women (6.1%) in the study: seven (6.5%) in previous alendronate, five (8.5%) in previous risedronate, and three (6.1%) in previous non-bisphosphonate study groups. The incidence of hypercalcemia was not significantly different (P = 0.38) among study groups. No adverse treatment effects were observed in the other hematology or chemistry tests with the exception of hypercholesterolemia, which occurred in five patients (2.0%).
The results of the BMD changes and biochemical markers of bone formation in the EUROFORS trial support the concept that treatment with teriparatide induces positive effects on bone mass and osteoblast function regardless of previous long-term exposure to antiresorptive therapies in postmenopausal women with established osteoporosis. Duration of antiresorptive therapy and lag time between stopping previous therapy and starting teriparatide did not affect the BMD response at any skeletal site. The skeletal responses at the lumbar spine were similar among previous antiresorptive therapy groups at each time point during the study, although previous users of etidronate showed a higher increase, probably reflecting its weaker anti-remodeling activity. At month 6, total hip and femoral neck BMD significantly decreased in the previous alendronate subgroup, and total hip BMD significantly decreased in the previous risedronate subgroup. Total hip and femoral neck BMD was numerically decreased from baseline in all other subgroups at 6 months. However, this transitory decrease was reversed with longer teriparatide treatment, with all subgroups showing a statistically significant increase compared with baseline after 18 and 24 months of treatment, and without differences between the groups at any time point in the study.

Previous studies have reported the effect of teriparatide administered cyclically or sequentially with antiresorptive therapy on BMD. Cosman et al. (22) showed that giving teriparatide in 3-month cycles (daily for 3 months, switch to alendronate for 3 months) for 15 months gave a similar increase in spine BMD as daily teriparatide for 15 months in patients previously treated with long-term alendronate therapy. These results indicate that teriparatide stimulates bone formation and increases BMD in the presence of long-term and continued alendronate and are consistent with the findings in alendronate-pretreated men who were treated sequentially with teriparatide (14). In the Anabolic After Antiresorptive trial (3), pretreatment with alendronate mitigated the early BMD and formation marker responses to teriparatide compared with more robust changes in patients previously treated with raloxifene.

BMD data in osteoporosis treatment-naive patients from the EUROFORS trial have shown a more robust response to teriparatide (19, 23). In 84 treatment-naive patients treated for 24 months, BMD increases were 13.5, 3.9, and 4.6% at the lumbar spine, total hip, and femoral neck, respectively (23). Overall, the BMD increase was higher in this group than in patients previously treated with potent antiresorptive therapies, and similar to etidronate-pretreated patients. Although percent increase in PINP seems lower in treatment-naive patients (252% vs. baseline) compared with antiresorptive-pretreated patients (approximately 600%) (23), this is the result of the much lower baseline bone turnover values of the pretreated patients. The increase in the absolute values of bone markers was similar regardless of previous treatment (23).

The early decrease in hip BMD after therapy with oral nitrogen-containing bisphosphonates and subsequent reversal with longer teriparatide treatment deserves further discussion. Previous studies have reported that teriparatide-induced BMD changes at skeletal sites with a high proportion of cortical bone are less than at sites with predominantly trabecular bone (3, 9, 13, 24). This phenomenon has been postulated to be the result of the mechanism of action of teriparatide in cortical bone (3). At cortical sites, teriparatide induces the simultaneous periosteal apposition of young bone matrix and endosteal resorption of old

| Drug/comparator | Estimate | se  | 95% confidence interval | P value |
|-----------------|----------|-----|------------------------|---------|
| ALN/ETI         | -0.032   | 0.0111 | -0.0542, -0.0106      | 0.004   |
| Lumbar spine    | -0.012   | 0.0083 | -0.0283, 0.0044       | 0.152   |
| Total hip       | -0.002   | 0.0103 | -0.0227, 0.0180       | 0.819   |
| Femoral neck    | 0.004    | 0.0085 | -0.0127, 0.0210       | 0.627   |
| ALN/Non-BP      | -0.002   | 0.0092 | -0.0206, 0.0157       | 0.789   |
| Lumbar spine    | 0.000    | 0.0069 | -0.0132, 0.0141       | 0.946   |
| Total hip       | 0.004    | 0.0085 | -0.0127, 0.0210       | 0.627   |
| Femoral neck    | 0.004    | 0.0085 | -0.0127, 0.0210       | 0.627   |
| ALN/RIS         | -0.002   | 0.0077 | -0.0167, 0.0135       | 0.831   |
| Lumbar spine    | -0.003   | 0.0059 | -0.0143, 0.0088       | 0.641   |
| Total hip       | -0.004   | 0.0073 | -0.0189, 0.0100       | 0.544   |
| Femoral neck    | 0.030    | 0.0127 | -0.0063, 0.0298       | 0.193   |
| ETI/Non-BP      | 0.012    | 0.0095 | -0.0006, 0.0232       | 0.193   |
| Lumbar spine    | 0.007    | 0.0118 | -0.0167, 0.0298       | 0.58    |
| Total hip       | 0.031    | 0.0117 | 0.0077, 0.0538        | 0.009   |
| Femoral neck    | 0.009    | 0.0088 | -0.0082, 0.0266       | 0.298   |
| Non-BP/RIS      | -0.002   | 0.0110 | -0.0237, 0.0195       | 0.85    |
| Lumbar spine    | 0.001    | 0.0103 | -0.0194, 0.0210       | 0.936   |
| Total hip       | -0.003   | 0.0078 | -0.0185, 0.0121       | 0.679   |
| Femoral neck    | -0.009   | 0.0095 | -0.0273, 0.0101       | 0.366   |
bone matrix. Patients who have received more potent nitrogen-containing bisphosphonates experienced more pronounced early decreases in hip BMD after starting teriparatide. This finding supports the hypothesis that in patients whose bone turnover was more inhibited, the resorption of highly mineralized bone results in a transitory BMD decrease during the first few months of teriparatide therapy, which is then transformed into an increase during the further course of treatment as the new bone fully mineralizes. These findings may have practical consequences in the interval assessment and interpretation of dual x-ray absorptiometry results in patients receiving teriparatide treatment, where it may be advisable to measure BMD at the end of the approved treatment duration, i.e. after 18 or 24 months depending on the country of use.

The results of the biochemical markers of bone formation and TAP after short-term teriparatide treatment were similar to previous findings by Ettinger et al. (3) in a smaller cohort of pretreated patients and in a study of men with osteoporosis (15). Statistically significant increases from baseline for P1NP and BSAP were observed in all groups after 1 month of teriparatide treatment, which provides additional evidence that teriparatide activates osteoblast function in women with severe osteoporosis after previous antiresorptive treatment use. Levels of bone formation markers varied according to the type of previous treatment and according to the time since stopping previous antiresorptive therapy. Previous treatment with alendronate was associated with a consistent trend among all biochemical markers of bone formation for lower values at 1 month compared with all other previous treatment groups. Interestingly, previous risedronate treatment was associated with a higher P1NP and BSAP at 6 months than the other groups, although the clinical significance of this is unclear. Additionally, time since stopping previous antiresorptive therapy and starting teriparatide treatment was associated with 6-month changes in these two markers. These findings suggest that early treatment response to teriparatide is attenuated by previous use of potent nitrogen-containing bisphosphonates but that these effects are overcome with longer treatment. These biochemical differences, although reflecting a possible inhibitory effect on osteoblast function, are not paralleled by differences in BMD response and thus may not have clinical implications.

Treatment-emergent adverse events were similar to those reported in osteoporosis treatment-naive women in the Fracture Prevention Trial (1, 25) and in men (26). Hypercalcemia developed in 6.1% of women in the study and was not statistically significant between study groups. The incidence of hypercalcemia observed in this study was comparable to the proportion reported by Cosman et al. (22) (3%) and Orwell et al. (26) (6.2%) and was lower than the proportion reported by Ettinger et al. (3) in women previously treated with alendronate (12.1%) or raloxifene (9.1%). Importantly, no patient discontinued the study due to hypercalcemia.

Limitations of our analyses should be noted. First, the EU-ROFORS study was an open-label design, and during the first year, there was no control group. However, the main outcomes (BMD and biochemical markers of bone turnover) are unlikely to be influenced by a lack of blinding. Second, the use of antiresorptive therapies before the study was not randomized, and previous treatment duration was not uniform among the different groups, because each individual therapy has been available for the treatment of osteoporosis for different lengths of time. However, the protocol contained stringent requirements for a standardized and detailed documentation of previous antiresorptive treatment, which allowed statistical modeling to account for any imbalances. Furthermore, these heterogeneous cohorts reflect real-life clinical practice, enhancing the clinical validity of these results. Bone resorption markers were not measured in the study, which prevented a complete understanding of

FIG. 3. Median values of serum bone turnover markers over time stratified by previous predominant treatment. A, P1NP; B, BSAP. Error bars indicate 25–75% interquartile range. A, $P < 0.001$ within-group change from baseline at each time point for all subgroups; between-group comparisons at baseline: $P < 0.001$ alendronate (ALN) vs. etidronate (ETI) and ALN vs. non-bisphosphonate (NONBP), $P < 0.01$ risedronate (RIS) vs. ETI and RIS vs. NONBP, $P < 0.05$ ALN vs. RIS. At month 1, $P < 0.001$ ALN vs. NONBP, $P < 0.01$ ALN vs. RIS, and $P < 0.05$ ALN vs. ETI. At month 6, $P < 0.01$ ALN vs. RIS, and $P < 0.05$ NONBP vs. RIS. Unless noted above, all other comparisons were not statistically significant. B, $P < 0.001$ within-group change from baseline at each time point for all subgroups, except $P < 0.05$ ETI at month 1; between-group comparisons at baseline: $P < 0.001$ ALN vs. ETI, $P < 0.01$ ALN vs. NONBP, $P < 0.05$ ALN vs. RIS. At month 1, $P < 0.05$ ALN vs. ETI, ALN vs. NONBP, and ALN vs. RIS. At month 6, $P < 0.01$ ALN vs. RIS, $P < 0.05$ ALN vs. ETI, and $P < 0.05$ NONBP vs. RIS. Unless noted above, all other comparisons were not statistically significant.
the effects of previous antiresorptive treatment on bone turnover, although this was done previously in a smaller study (3) with a design that was similar to the EUROFORS study. Finally, the study lacked statistical power to assess the association of fracture with changes in BMD and bone marker data. However, recent data from the Fracture Prevention Trial shows that relative fracture risk reduction seen with teriparatide was independent of pretreatment bone turnover (27).

In conclusion, although teriparatide was effective in increasing bone formation markers and BMD after previous antiresorptive treatment use regardless of type or duration of therapy, the BMD increase was less robust for patients previously treated with alendronate and risedronate than in the treatment-naïve group. Adverse events and hypercalcemia rates were very similar to those reported in treatment-naïve patients. These findings support the use of teriparatide as an effective treatment option in women with severe osteoporosis after previous antiresorptive treatment use, including long-term previous alendronate and risedronate treatment.

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References

1. Nener RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Register JY, Hodman AB, Eriksson EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH 2001 Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441

2. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, Donley DW, Dalsky GP, Eriksson EF 2005 Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med (Eratrum) (2005) 165:2120 165:1762–1768

3. Ettinger B, San Martin J, Crans G, Pavo I 2004 Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 19:745–751

4. Ma YL, Zeng Q, Donley DW, Ste-Marie LG, Gallagher JC, Dalsky GP, Marcus R, Eriksson EF 2006 Teriparatide increases bone formation in modeling and remodeling osteons and enhances IGf-II immunoreactivity in postmenopausal women with osteoporosis. J Bone Miner Res 21:855–864

5. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksson EF 2003 Reconstituent human parathyroid hormone (1–34) [teriparatide] improves both cortical and cancellous bone structure. J Bone Miner Res 18:1932–1941

6. Paschalis EP, Glass EV, Donley DW, Eriksson EF 2005 Bone mineral and collagen I levels in iliac crest biopsies of patients given teriparatide: new results from the Fracture Prevention Trial. J Clin Endocrinol Metab 90:4644–4649

7. Misof BM, Roscher P, Cosman F, Kurland ES, Tesch W, Messmer P, Dempster DW, Nieves J, Shane J, Fratzl P, Klausbohler K, Bilezikian J, Lindsay R 2003 Effects of intermittent parathyroid hormone administration on bone mineralization density in iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. J Clin Endocrinol Metab 88:1150–1156

8. Lindsay R, Cosman F, Zhou H, Bosstrom MP, Shen VW, Cruz JD, Nieves JW, Dempster DW 2006 A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. J Bone Miner Res 21:366–373

9. Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA 2007 The effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. J Bone Miner Res 22:149–157

10. NICE Guideline TA087 The clinical effectiveness and cost effectiveness of technologies for the secondary prevention of osteoporotic fractures in postmenopausal women. http://www.nice.org.uk/page.aspx?o=115560 (accessed December 12, 2007)

11. Marin F, Tynan AJ, Mullarney T 2006 Study description and baseline characteristics of the population in the European Fracture Observational Study (EFOS). Ann Rheum Dis 65(Suppl II):429

12. Ma YL, Bryant HU, Zeng Q, Schmidt A, Hoover J, Cole HW, Yao W, Jee WS, Sato M 2003 New bone formation with teriparatide [human parathyroid hormone (1–34)] is not retarded by long-term pretreatment with alendronate, estrogen, or raloxifene in ovariectomized rats. Endocrinology 144:2008–2013

13. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Boussemie EL, Bilezikian JP, Rosen CJ 2003 The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 349:1207–1215

14. Finkelstein JS, Hayes A, Hunzelman JL, Wyland J, He L, Neri RM 2003 The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 349:1216–1226

15. Finkelstein JS, Leder BZ, Burnett SA, Wyland J, Lee H, de la Paz AV, Gibson K, Neri RM 2006 Effects of teriparatide, alendronate, or both on bone turnover in postmenopausal women. J Clin Endocrinol Metab 91:2882–2887

16. Eastell R, Hadi P, Farrerons P, Audran M, Boonen S, Brixen K, Melo-Gomes J, Obermayer-Pietsch B, Avramids A, Sigurdsson G, Gluer CC, Clegg S, Marín F, Nickelsen T 2006 Comparison of three sequential treatment regimens of teriparatide: final results from the EUROFORS Study. J Bone Miner Res 21(Suppl 1):S70

17. Geenat HK, Grampp S, Gluer CC, Faulkner KG, Jergas M, Engelke K, Hagiwara S, Van KC 1994 Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res 9:1503–1514

18. Hanson J 1997 Standardization of femur bone mineral density. J Bone Miner Res 12:1316–1317

19. Blumsohn A, Brixen K, Sigurdsson G, Marin F, Ochs P, Liu-Leage S, Graebc A, Eastell R 2005 Early change in bone turnover following teriparatide (rPHT 1–34) in the EUROFORS Study: influence of prior therapy and association with BMD change at one year. J Bone Miner Res 20(Suppl 1):S411

20. Payne RB, Little AJ, Williams RB, Milner JR 1973 Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J 463–464

21. Kenward MG, Roger JH 1997 Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 53:983–997

22. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R 2003 Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 353:566–575

23. Obermayer-Pietsch BM, Nickelsen T, Marin F, Barner C, Hadi P, Farrerons J, Audran M, Boonen S, Anastasilakis A, McCloskey E 2006 Response of BMD to 24 months of teriparatide (rPHT 1–34) in patients with and without prior antiresorptive treatment: final results from the EUROFORS Study. J Bone Miner Res 21(Suppl 1):S543

24. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hui T, Lang TF, McGowan JA, Rosen CJ 2006 Study description and baseline characteristics of the population in the European Fracture Observational Study (EFOS). Ann Rheum Dis 65(Suppl II):429

25. Orwoll ES, Schelke WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA, Reginster JY, Eriksen EF 2006 The effects of parathyroid hormone and alendronate alone or in combination in older women. N Engl J Med 353:555–565

26. Boonen S, Marin F, Mellström D, Xie L, Desai D, Krage JH, Rosen CJ 2006 Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. J Am Geriatr Soc 54:782–789

27. Delmas PD, Licata AA, Register JY, Crans GG, Chen P, Misurski DA, Wagman RB, Mitlak BH 2006 Fracture risk reduction during treatment with teriparatide is independent of pretreatment bone turnover. Bone 39:237–243