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Effects of 1 Year of Daily Teriparatide Treatment on Iliacal Bone Mineralization Density Distribution (BMDD) in Postmenopausal Osteoporotic Women Previously Treated With Alendronate or Risedronate

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ABSTRACT

Anabolic treatment with teriparatide of postmenopausal osteoporotic patients previously treated with bisphosphonates is a new therapeutic approach. However, its effects on the bone mineralization density distribution (BMDD) are unknown. We studied paired transiliac bone biopsy samples taken before and after 1 year of treatment with recombinant human parathyroid hormone peptide 1-34 (teriparatide) from 16 osteoporotic women treated with either alendronate (priorALN) or risedronate (priorRIS) for at least 2 years and subsequently treated for 12 months with teriparatide. Cancellous (Cn.) and cortical (Ct.) BMDD values were measured using quantitative backscattered electron imaging. At baseline, BMDD values of priorALN and priorRIS women were similar and within the normal range. One year of teriparatide treatment caused significant effects on the BMDD. Analyzing changes from baseline for each bisphosphonate group separately, priorALN patients revealed increases in the portion of low mineralized bone areas ($Cn.Ca_{Low}$ +25.9%, $Ct.Ca_{Low}$ +62.0%, both $p < .05$) and Ct. heterogeneity of mineralization ($Ct.Ca_{Width}$ +22.8%, $p < .001$). PriorRIS patients showed increased mineralization heterogeneity ($Cn.Ca_{Width}$ +14.8%, $p < .05$, and $Ct.Ca_{Width}$ +15.8%, $p < .001$). Analysis of the influence of the prior bisphosphonate treatment showed that the BMDD response to 1 year of teriparatide treatment did not depend on the type of prior bisphosphonate. In consequence, priorALN and priorRIS groups were combined. The pooled groups revealed increased $Cn.Ca_{Width}$ and $Ct.Ca_{Width}$ (+10.7%, $p < .01$, and +19.6%, $p < .001$, respectively) as well as increased $Cn.Ca_{Low}$ and $Ct.Ca_{Low}$ (+18.2%, $p < .05$, and +36.6%, $p < .01$, respectively). In summary, our findings indicate a significant effect of teriparatide on BMDD when administered subsequent to a bisphosphonate in agreement with teriparatide's anabolic action. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: TERIPARATIDE; BISPHOSPHONATES; BONE MINERALIZATION DENSITY; QUANTITATIVE BACKSCATTERED ELECTRON IMAGING (QBEI); POSTMENOPAUSAL OSTEOPOROSIS

Introduction

The bone anabolic agent teriparatide [human parathyroid hormone (1-34)] is known to reduce fracture risk and increase bone mineral density (BMD) and markers of bone formation.[1–6] However, the use of teriparatide is recommended as a second-line treatment for severe osteoporosis.[6] Since bisphosphonates are used commonly as first-line therapy in osteoporosis, the majority of teriparatide-treated patients will have been treated previously with a bisphosphonate. Ettinger and colleagues reported that the effects of parathyroid hormone (PTH) treatment on BMD were delayed for patients previously treated with alendronate compared with non-bisphosphonate-treated patients.[7] Smaller increases in BMD owing to teriparatide for patients treated previously with antiresorptives compared with treatment-naive patients also have been reported in the European Study of Forsteo (EUROFORS).[8] In contrast, a recent study revealed similar changes in bone turnover markers and BMD induced by teriparatide in patients with previous long-term bisphosphonate therapy compared with treatment-naive patients.[9] Apart from the question of whether the effects of teriparatide might be delayed and/or blunted, osteoporotic patients treated long term with bisphosphonates did have increases in bone-formation and -resorption markers when switching from the antiresorptive to teriparatide treatment.[10] Moreover, the EUROFORS study and the Open-Label Study to

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Determine How Prior Therapy with Alendronate or Risedronate in Postmenopausal Women with Osteoporosis Influences the Clinical Effectiveness of Teriparatide (OPTAMISE study) have both shown that, generally, teriparatide treatment had positive effects on bone mass and bone-formation markers even in bisphosphonate-treated patients.[11,12] Based on finite-element simulation, the patients from both the EUROFORS and OPTAMISE studies had significantly improved predicted mechanical bone properties after teriparatide, with the prior risedronate group having a greater increase in stiffness and vertebral failure load[13,14] than the group of patients previously treated with alendronate. Recently, teriparatide also was shown to reduce the accumulation of microdamage in patients who were treated previously with alendronate.[15]

In light of this possible delay in response to teriparatide, it is of clinical importance to determine how the prior bisphosphonate treatment influences the action of teriparatide on the bone mineralization density distribution (BMDD). The separate effects of bisphosphonates or teriparatide treatment on bone mineralization are well characterized. The antiresorptive action of the bisphosphonates with up to 3 years of treatment was shown to increase the homogeneity of mineralization and to increase slightly the mean calcium concentration compared with normal individuals or individuals treated with placebo.[16–19] However, longer treatment led to the normalization of BMDD.[19–21] This dependency of BMDD outcome on the duration of bisphosphonate therapy also was shown using a mathematical model for computed modeling of BMDD.[22] The anabolic agent PTH, on the other hand, is known to decrease bone mineralization homogeneity and mineralization densities consistent with the increase in bone turnover.[23–25] In this study, we analyzed BMDD in transiliac biopsies from participants of the OPTAMISE study. The objective of our study was to evaluate the effects of sequential antiresorptive and anabolic treatment on BMDD, as well as any differences in the BMDD response to teriparatide owing to the previous bisphosphonate therapy.

Materials and Methods

Patients and biopsies

Details of patients have been published previously.[12] Postmenopausal women with osteoporosis who received alendronate (ALN; either 10 mg/day or 70 mg/week) or risedronate (RIS; 5 mg/day or 30 to 35 mg/week) for at least 24 months (mean duration of bisphosphonate therapy was 37.2 months for ALN and 38.0 months for RIS) stopped their bisphosphonate therapy and then were treated with teriparatide (20 μg/day subcutaneously) for 12 months. The time between stopping bisphosphonate and beginning teriparatide treatment was not longer than 14 days for 98% of the patients. Paired transiliac biopsies were obtained from 16 women at the end of the bisphosphonate treatment (priorALN, $n = 8$; priorRIS, $n = 8$) and after 12 months of teriparatide treatment.

Quantitative backscattered electron imaging (qBEI)

BMDD was determined by qBEI in trabecular and cortical bone of transiliac biopsies. Full details, including the validation and precision of this technique, have been published previously.[26,27] Block samples of undecalcified bone embedded in polymethyl methacrylate were prepared by grinding and polishing in order to obtain parallel surfaces. The sample surface then was coated with carbon. qBEI analysis was done in a digital scanning electron microscope (DSM 962, Zeiss, Oberkochen, Germany) using the following microscope settings: an accelerating voltage of 20 kV, a probe current of 110 pA, and a working distance of 15 mm. Backscattered electrons were collected by a four-quadrant semiconductor backscattered electron detector. The entire trabecular and cortical bone tissue areas were recorded by images of the same size (2×2.5 mm) at $\times 50$ nominal magnification (corresponding to a resolution of 4 μm per pixel) using a scan speed of 100 seconds per frame. The intensity of the signal of the backscattered electrons depends on the local calcium concentration of the sample; the denser the mineralization, the brighter in the image (Fig. 1). These images were used for evaluation of the gray-level histograms for spongiosa and cortex. The gray levels of the histograms were further transformed to weight percent calcium, as described previously,[26] resulting in weight percent calcium histograms (BMDD) with a bin width of 0.17 weight percent Ca (for typical BMDDs, see Fig. 1). Five variables were obtained for statistical comparison of the BMDD curves[28,29]: Ca_{Mean}, the weighted mean calcium concentration of the bone area; Ca_{Peak}, the mode calcium concentration (the peak position of the histogram), which indicates the most frequently occurring calcium concentration of the studied bone area; Ca_{Width}, the full width at half maximum of the distribution, describing the variation in mineralization density; Ca_{Low}, the percentage of mineralized bone with a calcium concentration less than the 5th percentile of the reference BMDD (less than 17.68 weight percent calcium), which approximates the amount of bone area undergoing primary mineralization; and Ca_{High}, the portion of bone areas with a calcium concentration higher than the 95th percentile of the reference BMDD (higher than 25.30 weight percent calcium), which is predominantly interstitial bone.[28,29] The reference BMDD data were obtained from trabecular bone of a cohort of healthy individuals ($n = 52$) from different skeletal sites (ie, transiliac bone, vertebrae, femoral neck and head, and patella). This cohort comprised adult individuals (aged 25 to 90 years) of different ethnicity (African Americans and white Americans) and gender. Since none of these biologic factors was associated with significant differences in the BMDD, such a general reference trabecular BMDD for adults including all the biologic factors could be established.[29]

Statistical analysis

Statistical analysis was performed using SigmaStat for Windows, Version 2.03 (SPSS, Inc., Chicago, IL, USA). Only biopsies with intact spongiosa or intact cortical plates were included for data evaluation (in one sample, the trabecular compartment was not intact, and in three samples, only one cortex was available for measurement, and these samples were excluded from the respective analyses). The study data were found normally distributed (via the Kolmogorov-Smirnov test) and are presented as means ± SD in text and table.

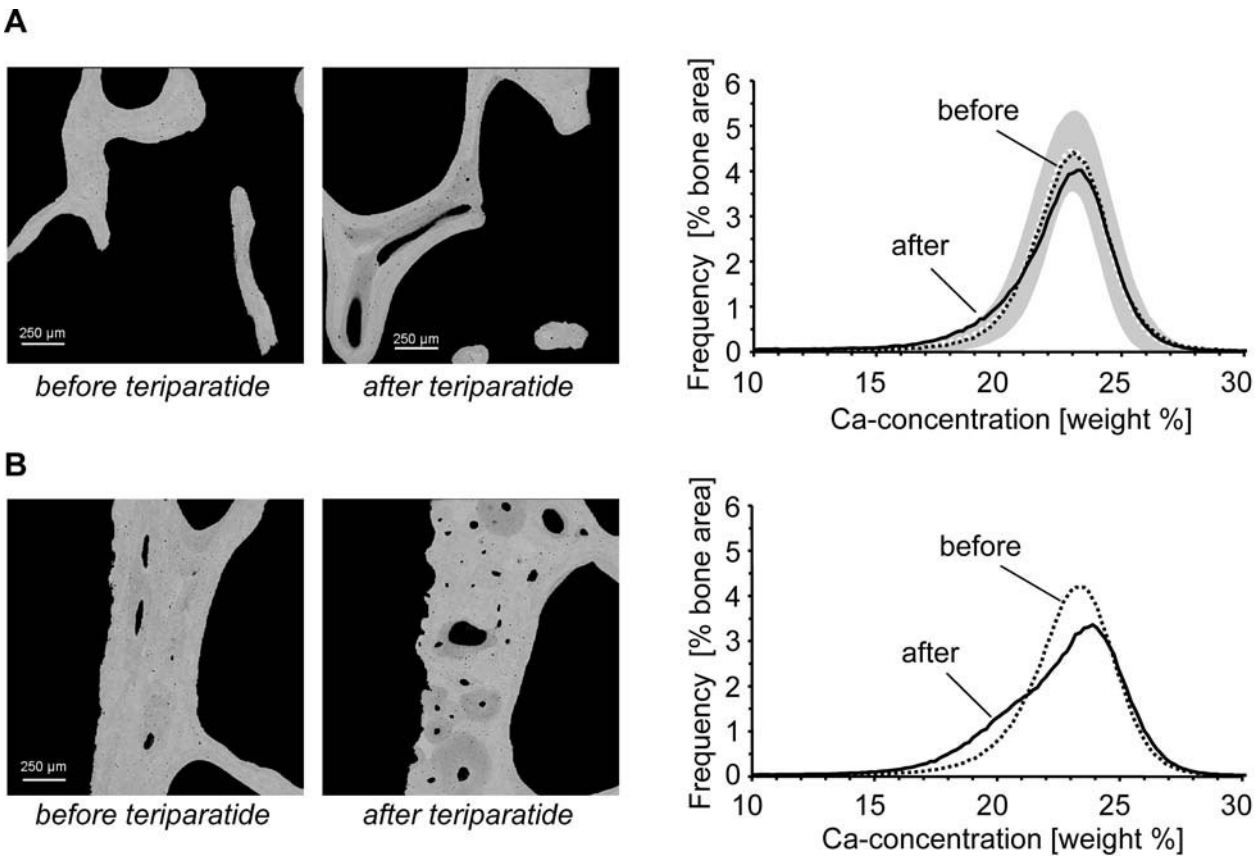

Fig. 1. Backscattered electron images of paired transiliac bone biopsy samples (the brighter the gray level, the higher is the local Ca concentration) and corresponding BMDD values before and after PTH treatment. Dotted black lines represent BMDD curves before and solid black lines represent BMDD curves after PTH. White dotted line and gray areas indicate mean and 95% confidence interval of normal reference values.[29] (*A*) Cancellous bone of a priorRIS patient and (*B*) cortical bone of a priorALN patient before and after teriparatide treatment.

The BMDD outcomes were analyzed statistically addressing four different questions: (1) Unpaired *t* tests were used to analyze the differences between the study groups priorALN and priorRIS at baseline and after 12 months of teriparatide treatment; (2) unpaired *t* tests or Mann-Whitney rank-sum tests were used for comparison of Cn. BMDD variables of the study groups (priorALN or priorRIS) versus normal reference BMDD data[29] (cortical BMDD reference data were not available for comparison); (3) paired *t* tests were used for analysis of the changes from baseline within each study group separately (priorALN or priorRIS; for information on the teriparatide effects in one study group independent of the other); and (4) two-way repeated measures ANOVA was used for analyzing whether teriparatide had differential effects in the two study groups (priorALN versus priorRIS). Two-way repeated measures ANOVA tests three hypotheses: (1) There is no significant effect owing to the factor prior bisphosphonate treatment, (2) there is no significant effect owing to the factor 1 year of teriparatide treatment, and (3) there is no interaction between the factor prior bisphosphonate and the factor 1 year of teriparatide, indicating that the changes from baseline in one prior bisphosphonate group are not significantly different from those in the other prior bisphosphonate group.

Table 1 presents all BMDD data for the priorALN and priorRIS groups separately along with the complete results from the two-way repeated measures ANOVA test. Two-sided $p < .05$ was considered statistically significant.

Results

BMDD at baseline and after 1 year of teriparatide (comparison of priorALN versus priorRIS and comparison versus normal)

Baseline Cn. and Ct. BMDD values were not significantly different between the priorALN and priorRIS groups, whereas after 1 year of teriparatide, the priorRIS group had a significantly higher $Cn.Ca_{Width}$ ($p = .018$), and the priorALN group had a significantly higher $Ct.Ca_{Low}$ ($p = .040$; Table 1).

None of the baseline Cn. BMDD values in either bisphosphonate group was significantly different from normal reference values.[29] After teriparatide treatment, all Cn. BMDD values remained at normal levels except Ca_{Width} and Ca_{High} in the priorRIS group, which were both significantly increased compared with normal (comparison of the median values of priorRIS versus normal: +18%, $p = .001$, for $Cn.Ca_{Width}$ and +103%, $p = .005$, for $Cn.Ca_{High}$).

Teriparatide effects on BMDD (comparison to baseline)

Paired comparison within each bisphosphonate group separately revealed that 1 year of teriparatide treatment had no

Table 1. BMDD Outcomes of priorALN and priorRIS Patients at Baseline and After 1 Year of Teriparatide

	Cancellous bone						
	Baseline		1 Year of TPD		Two-way rm ANOVA[a]		
	priorALN ($n=7$)	priorRIS ($n=8$)	priorALN ($n=7$)	priorRIS ($n=8$)	Interaction term	Factor 1 year of TPD	Factor priorBP
Ca_{Mean} (wt%)	22.30 (0.68)	22.29 (0.40)	22.20 (0.68)	22.54 (0.77)	ns	ns	ns
Ca_{Peak} (wt%)	22.85 (0.68)	22.90 (0.41)	23.00 (0.61)	23.27 (0.79)	ns	ns	ns
Ca_{Width} (Δwt%)	3.27 (0.23)	3.38 (0.28)	3.47 (0.32)	3.88 (0.32)	ns	+10.7% $p<.01$	−7.2% $p=.037$
Ca_{Low} (%)	4.17 (1.20)	4.27 (1.10)	5.25 (1.21)	4.77 (0.89)	ns	+18.2% $p<.05$	ns
Ca_{High} (%)	7.08 (4.04)	6.98 (3.28)	7.37 (4.76)	12.41 (8.38)	ns	ns	ns
	Cortical bone						
	Baseline		1 Year of TPD		Two-way rm ANOVA[a]		
	priorALN ($n=7$)	priorRIS ($n=6$)	priorALN ($n=7$)	priorRIS ($n=6$)	Interaction term	Factor 1 year of TPD	Factor priorBP
Ca_{Mean} (wt%)	22.37 (0.88)	22.17 (0.47)	21.82 (0.44)	22.26 (0.57)	ns	ns	ns
Ca_{Peak} (wt%)	22.94 (0.94)	22.72 (0.52)	22.81 (0.59)	22.99 (0.61)	ns	ns	ns
Ca_{Width} (Δwt%)	3.64 (0.28)	3.73 (0.31)	4.47 (0.29)	4.32 (0.30)	ns	+19.6% $p<.001$	ns
Ca_{Low} (%)	4.05 (1.35)	4.73 (0.74)	6.56 (0.82)	5.25 (1.13)	ns	+36.6% $p<.01$	ns
Ca_{High} (%)	8.77 (5.30)	8.51 (3.09)	7.33 (3.14)	10.17 (4.43)	ns	ns	ns

Note: Data shown are mean (SD). TPD = teriparatide. *n* indicates number of samples (which differs for cancellous and cortical bone because only intact cancellous or cortical compartments were used for data analysis).

[a]Results from the two-way repeated measures ANOVA comparison for interaction term, factor TPD treatment (percentage indicates the changes after 1 year of TPD versus baseline for priorALN and priorRIS combined), factor prior bisphosphonate treatment (percentage indicates priorALN versus priorRIS, baseline and 1 year of TPD combined). Combined data are not shown.

significant effects on cancellous or cortical Ca_{Mean}, Ca_{Peak}, or Ca_{High} in either bisphosphonate group, but Ca_{Width} and Ca_{Low} were partly affected (Fig. 1 and Table 1). In the priorALN group, $Cn.Ca_{Low}$ (+25.9%, $p=.045$), $Ct.Ca_{Width}$ (+22.8%, $p<.001$), and $Ct.Ca_{Low}$ (+62.0%, $p=.011$) were increased; in the priorRIS group, $Cn.Ca_{Width}$ (+14.8%, $p=.016$) and $Ct.Ca_{Width}$ (+15.8%, $p<.001$) were elevated (Table 1).

In order to analyze whether the teriparatide action was influenced by the type of prior bisphosphonate treatment, two-way repeated measures ANOVA was performed. The latter revealed that the interaction term was not significant for all measured Cn. and Ct. BMDD variables, indicating that teriparatide treatment–induced changes from baseline were not significantly different for priorALN versus priorRIS. Comparison for the factor teriparatide treatment (both prior bisphosphonate groups combined) showed that 12 months of teriparatide treatment significantly increased Ca_{Width} and Ca_{Low} of both cancellous and cortical bone ($Cn.Ca_{Width}$ +10.7%, $p<.01$; $Cn.Ca_{Low}$ +18.2%, $p<.05$; $Ct.Ca_{Width}$ +19.6%, $p<.001$; and $Ct.Ca_{Low}$ +36.6%, $p<.01$). Teriparatide had no significant effect on the other Cn. and Ct. BMDD variables (Table 1). Comparison for the factor prior bisphosphonate treatment revealed no significant difference between the priorALN and priorRIS groups with the exception of $Cn.Ca_{Width}$, which was lower (−7.2%, $p=.037$) in the priorALN patients (baseline and 1 year of teriparatide data combined; Table 1).

Discussion

In paired bone biopsy samples from subjects previously treated with ALN or RIS,[12] 1 year of teriparatide treatment produced significant changes in trabecular and cortical BMDD. The most distinct effect, however, was the large broadening of the cortical BMDD observed in both priorALN and priorRIS patients, which is indicative of the anabolic effect of teriparatide.

Normal baseline BMDD of priorALN and priorRIS

At baseline, none of the BMDD variables was significantly different between the two bisphosphonate groups, and none differed significantly from the normal BMDD of a healthy adult reference group.[29] The distinct bisphosphonate effects on BMDD described in several previous studies[16–20] were not apparent at baseline in this cohort of patients. Generally, 2 to 3 years of treatment with ALN[16,17] or RIS[19] produced a transient decrease in heterogeneity and a small increase in Ca_{Mean} and/or Ca_{Peak} owing to the decrease in bone turnover. This decrease in bone turnover transiently causes fewer amounts of newly formed bone and a prolonged time for secondary mineralization. However, after longer administration of bisphosphonate, when bone turnover has been at a new steady state for a prolonged period, these effects diminish, and the BMDD returns to normal.[19,21,22] Hence the reason why baseline BMDD was not different from normal in this study might have resulted from the

duration of the previous bisphosphonate therapies, the mean of which was more than 3 years, with a range of 2 to 6.5 years, and/or from low compliance or adherence to the bisphosphonate therapy. The latter is consistent with the observation that the OPTAMISE study population had a broad range of bone turnover values with a high percentage of patients within the normal range.[12]

Effects of teriparatide on cancellous and cortical BMDD

Considering the effect of factor 1 year of teriparatide treatment (priorALN and priorRIS combined), a significant increase in Ca_{Width} and Ca_{Low} in both cancellous and cortical bone compartments was found (two-way repeated measures ANOVA analysis). When the paired biopsies of the priorRIS and priorALN groups were analyzed separately (paired *t* test), $Cn.Ca_{Width}$ but not $Cn.Ca_{Low}$ was increased in the priorRIS group, whereas $Ct.Ca_{Width}$ was increased in both groups. $Cn.Ca_{Low}$ and $Ct.Ca_{Low}$ were increased only in the priorALN group. The observed peak broadening of BMDD (increase of Ca_{Width}) after teriparatide treatment can be explained by the enhanced deposition of new bone. Thus, within 1 year of stimulation of new bone formation, bone packets with lower mineral content were integrated into the preexisting bone features of higher mineral content, leading in total to a higher heterogeneity in mineralization densities (Ca_{Width}). Consistently, this was accompanied by an increase in Ca_{Low}, indicating the corresponding increase in sites in the stage of primary mineralization on the bone surface. In line with this, computer simulation studies have shown that a transition to higher bone turnover will increase Ca_{Width}, whereas a transition to lower bone turnover will reduce Ca_{Width} transiently.[22]

After 1 year of teriparatide treatment, $Cn.Ca_{Width}$ and $Cn.Ca_{High}$ of the priorRIS group were significantly greater than than normal (normal reference data from a previous work[27]). The teriparatide-induced increase in Ca_{Width} even above normal in cancellous bone and the increase in cortical bone in this study are comparable with that reported previously in one study on patients who were naive to bisphosphonate treatment.[24] In this previous work,[24] as well as in a second study in bisphosphonate-naive patients,[25] teriparatide also decreased the average mineral content of the bone material, which was not seen in this study cohort. It is not clear whether this difference was due to the prior bisphosphonate treatment or to the shorter period of teriparatide treatment (12 months in this study versus 18 to 36 months in the previous study). Further, larger effects on cortical BMDD have been described for osteoporotic women who continued hormone-replacement therapy during PTH treatment.[24]

No differential effects of teriparatide treatment on BMDD between priorRIS versus priorALN

The teriparatide effects on BMDD were not significantly influenced by the type of prior bisphosphonate (interaction term was not significant by two-way repeated measures ANOVA). This seems to be inconsistent with the results of the separate paired *t* tests (significant increases in $Cn.Ca_{Width}$ only for the priorRIS group and increases in $Cn.Ca_{Low}$ and $Ct.Ca_{Low}$ only for the priorALN group, as mentioned earlier). However, it has to be emphasized that these paired *t* tests analyzed the treatment-induced changes within the two prior bisphosphonate groups separately and independent of each other. Since one of the aims of this study also was to compare the teriparatide treatment effects between the two prior bisphosphonate groups, we used two-way repeated measures ANOVA analysis. Part of latter is analysis of the interaction of the studied factors, which was found not to be significant for all measured BMDD variables, giving evidence that there is no differential effect of the type of previous bisphosphonate in the BMDD response to 1 year of teriparatide treatment. The reason why separate *t* tests show some differences while the interaction term is not significant is most likely the relatively low sample size of each prior bisphosphonate group together with the relatively high biologic variation in Ca_{Width} and Ca_{Low}.

In the EUROFORS and OPTAMISE studies, the increase in bone-formation markers after initiation of teriparatide treatment was delayed in the first few months in subjects previously treated with alendronate compared with those previously treated with risedronate.[11,12] Thus it could have been expected that the faster increase in bone turnover in the priorRIS group would induce larger changes in BMDD compared with the priorALN group. However, this was not observed, and there were minor differences only in some BMDD variables between the two bisphosphonate groups after 1 year of teriparatide treatment. One reason for this apparent inconsistency may be the small size of the biopsy subgroup, whose bone turnover marker response may not reflect the response of the total study population. Moreover, it is possible that changes in bone turnover over a prolonged period (in the range of years) are needed to alter the fraction of newly formed bone significantly[28] and that the transient difference in turnover of less than 6 months was insufficient to produce different effects on BMDD at 12 months.

Limitations of our study

A limitation of our study is that there was no placebo group available for comparison of the teriparatide effects without previous bisphosphonate treatment. Therefore, we cannot determine the effect of teriparatide alone, and we cannot distinguish the effects of stopping bisphosphonate from those of teriparatide treatment. However, we reported previously that in patients who stopped alendronate after 5 years and were subsequently treated for 5 years with placebo, there were no changes in the BMDD.[21] In addition, the increase in Ca_{Width} after teriparatide in the present patients is consistent with the observed increase in bone turnover markers[12] and is indicative of an increase in bone turnover, as seen in other patients.[24] Another limitation is the relatively small sample number within each bisphosphonate group. While the paired biopsy study design was successful in the detection of teriparatide effects with respect to baseline, the sample numbers likely were too small to detect any differences between pretreatment with ALN or RIS on the BMDD response. In particular, the small sample size also is likely responsible for the odd finding of $Cn.Ca_{High}$ after teriparatide treatment exceeding normal levels in the priorRIS patients. It has to be mentioned that $Cn.Ca_{High}$ generally shows a larger biologic variability than the other Cn. BMDD parameters.

Additionally, the priorRIS group included two patients who may not have had much new bone formation in the cancellous compartment with teriparatide treatment.

Conclusion

In conclusion, teriparatide treatment altered the BMDD in patients treated previously with ALN or RIS in accordance with the anabolic action of PTH. No differential effect of the type of prior bisphosphonate (ALN or RIS) in the response of Cn. or Ct. BMDD to teriparatide could be detected.

Disclosures

All the authors state that they have no conflicts of interest.

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