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ORIGINAL ARTICLE

The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone(1–34)]

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Abstract Teriparatide, the active fragment of human parathyroid hormone (hPTH 1–34), is an anabolic agent for the treatment of osteoporosis. Important questions remain regarding management strategy beyond the recommended 18- to 24-month course of teriparatide treatment. We followed 21 men for up to 2 years after discontinuing teriparatide. Twelve men (57%) chose treatment with bisphosphonate immediately after teriparatide withdrawal, while 9 (43%) opted for no pharmacologic agent. At the end of 1 year lumbar spine bone density increased an additional $5.1 \pm 1.0\%$ in the bisphosphonate group, while it declined by $3.7 \pm 1.7\%$ in those on no medication ($P < 0.002$). In six men who delayed initiation of bisphosphonate until 1 year after teriparatide withdrawal, their subsequent gains in the second year, $2.6 \pm 1.7\%$, still placed them below the peak gains they achieved on teriparatide. In contrast, the 12 men who began bisphosphonates immediately and continued treatment for the entire 2-year post-PTH period had continued gains at the lumbar spine, $8.9 \pm 1.5\%$ above their post-PTH values ($P = 0.002$). For the 4-year period, including 2 years of teriparatide and 2 years of bisphosphonate, the total gains at the lumbar spine were $23.6 \pm 2.9\%$. Men, who received bisphosphonate in only the 2nd year post-teriparatide, had cumulative gains of $11.1 \pm 3.4\%$. Three men who did not receive any bisphosphonate at any time during the post-PTH period had cumulative gains of only $5.5 \pm 3.7\%$. These findings suggest that the use of bisphosphonates following teriparatide is an important component of any strategy utilizing this anabolic drug for osteoporosis in men. The immediate use of bisphosphonates after teriparatide withdrawal may help to optimize gains in bone density at the lumbar spine.

Keywords Bisphosphonates · Osteoporosis in men · Osteoporosis treatment · Parathyroid hormone · PTH (1–34) · Teriparatide

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Introduction

With the approval of teriparatide (the generic name for all human parathyroid hormone 1–34, whether synthesized chemically [hPTH 1–34] or by recombinant DNA technology [rhPTH 1–34]), an anabolic drug has been added to currently available therapies for osteoporosis. Because use of this medication is recommended for only 18–24 months, it is important to consider whether antiresorptive therapy is necessary to maintain the gains achieved with teriparatide. We have previously reported that men treated with hPTH (1–34) for 18 months experienced a 13.5% increase in bone mass at the lumbar spine, and a 2.9% increase at the femoral neck [1]. These data are similar to the experience in postmenopausal women [2]. After the period of teriparatide treatment in women, either endogenous or exogenous estrogen helps to improve or maintain gains in bone density [3, 4, 5]. For postmenopausal women not on estrogen, the addition of alendronate for 1 year after discontinuing PTH (1–84) results in a further 6% increase in lumbar spine density [6]. Without additional data, however, no guidelines can be established as to whether or not it is

necessary to use antiresorptive therapy after a therapeutic course of teriparatide. The purpose of this study was to evaluate the course of men who had been treated with teriparatide and then either given a bisphosphonate or followed without specific therapy.

Materials and methods

Subjects and study design

Twenty-one men from an original cohort of 24 who had participated in a randomized, double-blind placebo controlled trial of hPTH (1–34) as a treatment for idiopathic osteoporosis in men [1], were monitored approximately every 6 months for up to 2 years after discontinuing PTH (hPTH 1–34 obtained from Bachem, Inc., San Diego, Calif., USA). The hPTH (1–34) component of this study had two phases: an initial 18-month randomized, double-blind phase, and a second 18-month segment in which 22 of the 24 patients continued to participate in a study that was open label and cross-over in design. Men originally randomized to the placebo arm received hPTH (1–34) for 18 months ($n = 11$) and men initially randomized to hPTH (1–34) ($n = 11$) received an additional year of treatment (total PTH exposure 30 months). After completing their course of hPTH (1–34), the 21 patients who continued to be followed were offered a bisphosphonate in addition to calcium and vitamin D. Twelve men (57%) chose to take a bisphosphonate, while nine (43%) declined. Of the 12 men who received bisphosphonate (BisP), ten were treated with alendronate 10 mg daily, one with risedronate 35 mg weekly, and one with cyclic etidronate. Since this sample was too small to allow us to distinguish among the various bisphosphonate drugs, the data were pooled. Of the nine men who initially declined bisphosphonate, six (67%) ultimately took bisphosphonate as follows: two men began treatment within 6 months of discontinuing PTH (alendronate 10 mg daily), four men began treatment after 1 year (one man alendronate 10 mg daily; three men risedronate 35 mg weekly), and three men did not take bisphosphonate at all. Thus, for at least 1 year of monitoring, seven men did not receive any osteoporosis medication after hPTH (1–34) besides calcium and vitamin D. These two groups, bisphosphonate versus non-bisphosphonate therapy, were not determined by random selection, but were well matched in terms of age, body mass index, months of hPTH (1–34) therapy, *T*- and *Z*-score, and percentage gain at LS after completing PTH (Table 1).

Bone mineral density

During the blinded, randomized and open label phases of the PTH trial, bone mineral density (BMD) of the lumbar spine (LS), right hip, and non-dominant radius was measured by dual energy X-ray absorptiometry (DXA) using a QDR-1000 bone densitometer (Hologic, Waltham Mass., USA) at one study site, and a QDR-1500 bone densitometer at a second center. The QDR-1000 was replaced with a QDR-4500 when all patients completed their course of hPTH (1–34). An in vivo cross-calibration between the two densitometers (1000 and 4500) was performed with 91 patients (including the male osteoporotic cohort) measured on the same day at the AP spine, and 79 patients measured on the same day at the total hip and femoral neck. Results for the AP spine include an R of 0.99 and a slope (intercept of 0) of 0.995, with no significant difference detected in the bone mineral density (BMD) obtained on both machines. In contrast, differences were detected for total hip and femoral neck BMD results between machines, and cross calibration for the forearm was not available. Consequently, only densitometric data for the AP spine are presented. To improve comparability between the two machines at the two study sites, results are expressed as percentage changes from baseline.

Statistical analysis

Data, presented as mean ± SEM, were analyzed by mixed model analysis of variance with repeated measures using SAS/STAT 9.0 software (SAS Institute, Cary, N.C., USA).

Table 1 Characteristics of men with idiopathic osteoporosis upon completion of PTH treatment: bisphosphonates versus non-pharmacologic therapy[a]

Characteristic/index	Bisphosphonates ($n = 12$) Mean ± SEM	No medication ($n = 7$) Mean ± SEM	p-value
Age (years)	53.3 ± 2.6	49.4 ± 4.6	NS
Body mass index kg/m^2	24.3 ± 1.1	24.2 ± 1.8	NS
Duration of treatment with hPTH (1–34) in months	22.2 ± 1.7	23.6 ± 2.4	NS
Mean % change at LS after PTH therapy	13.7 ± 2.9	8.9 ± 2.7	NS
Lumbar spine *T*-score	−2.4 ± 0.4	−2.9 ± 0.5	NS
Lumbar spine *Z*-score	−1.9 ± 0.4	−2.5 ± 0.6	NS

[a]Groups were determined by patient self-selection, are non-randomized and open label. These data are for the first year of monitoring post-PTH therapy. Only men who took no bisphosphonates during the first year have been included in the "No medication" column. Two men who began bisphosphonates within the first year of completing PTH were not included in the analyses

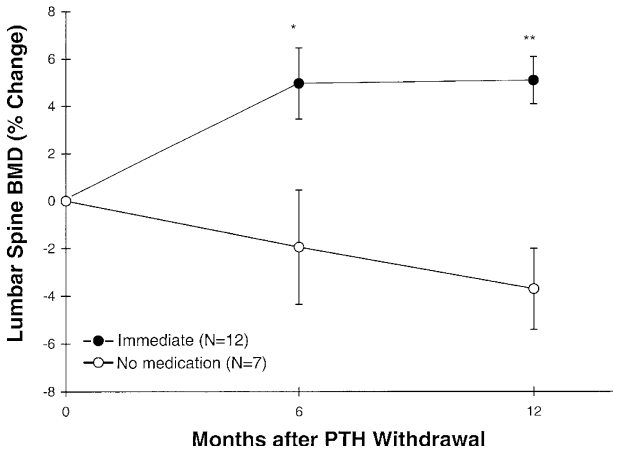

Fig. 1 Changes in bone density 1 year after cessation of hPTH (1–34) treatment: Bisphosphonates versus non-pharmacologic therapy. Lumbar spine % change ± SEM, 1 year after discontinuing hPTH (1–34). Comparison is between 12 men who took bisphosphonates immediately (*closed circles*) and seven men who took no medication (*open circles*) (data are available for only ten of the 12 men at 6 months). $*P = 0.005$, $**P \leq 0.002$

Results

The men who took BisP immediately following hPTH (1–34) therapy experienced a 5.0 ± 1.5% increase in lumbar spine (LS) BMD after 6 months, while men not receiving BisP declined by 1.9 ± 2.3% ($P = 0.005$, Fig. 1). After 1 year, LS BMD in the BisP group had increased by a total of 5.1 ± 1.0% (95% CI 2.43–7.83), while men on no medication had declined further by 3.7 ± 1.7% below their post-PTH baseline value (95% CI –7.21 to –0.14, $P < 0.002$, Fig. 1). The overall impact of sequential osteoporosis therapy, i.e. treatment with PTH followed by BisP, can be appreciated better by comparing the cumulative increase in bone density achieved by either group, that is the increase encompassing both the hPTH (1–34) and post-hPTH (1–34) periods. LS BMD increased by a total of 19.3 ± 3.1% in those on 34 months of sequential treatment (22.2 ± 1.7 months PTH, followed by 12 months BisP) compared with a net gain of only 4.7 ± 3.1% in those who took only 23.6 ± 2.4 months PTH and no BisP therapy for the ensuing 12 months ($P < 0.001$, Fig. 2).

Within 1 year of completing hPTH (1–34), six of the nine men who had initially chosen no follow-up treatment (12.7 ± 3.1 months with no osteoporosis medication) decided to begin bisphosphonates. At 2 years post-hPTH (1–34) follow-up, corresponding to 12.0 ± 3.8 months of bisphosphonate treatment for this "delayed" group of patients, LS bone density improved by 2.6 ± 1.7% but this represented a LS BMD 0.82 ± 3.7% below the post-PTH values. In the 12 men who started bisphosphonate therapy immediately and continued for a second year, the cumulative 2-year improvement was 8.9 ± 1.5% above the post-PTH value (Fig. 3). Thus, at the final point of monitoring, the 12 men who had been treated for almost 4 years [22.2 ± 1.7 months on hPTH (1–34) + 24 months of BisP] had a mean total increase in LS bone density of 23.6 ± 2.9% ($P = 0.006$ for within-group comparison, 12–24 months), while the men who delayed initiation of BisP had recouped most of the bone density lost in the first year after PTH, and returned to their post-hPTH (1–34) gains of 11.1 ± 3.4% (NS for within group comparison, 12–24 months). Three men who took no bisphosphonates for the 2 years after completing hPTH (1–34) had cumulative gains of only 5.5 ± 3.7%.

One final question that was addressed was whether the duration of pre-treatment with hPTH (1–34) had any impact on the magnitude of response to bisphosphonates. Because of the original study design (see Materials and methods), the 12 men who took BisP immediately upon completing hPTH (1–34) comprised two subsets of patients: four men who had been treated with hPTH (1–34) for 30.3 ± 0.7 months ("long duration"), and eight men who had received only 18.1 ± 0.2 months of hPTH (1–34) treatment ("short duration"). After 1 year on BisP, the four men with longer duration of PTH treatment had a further increase in LS bone density of 3.1 ± 1.7%, while the eight men with shorter duration PTH treatment had a further increase in LS bone density of 6.2 ± 1.2% (NS). After 2 years on BisP, the four men whose PTH exposure was of "long duration" had an increase of 5.1 ± 1.7% at the LS. In contrast, the eight men

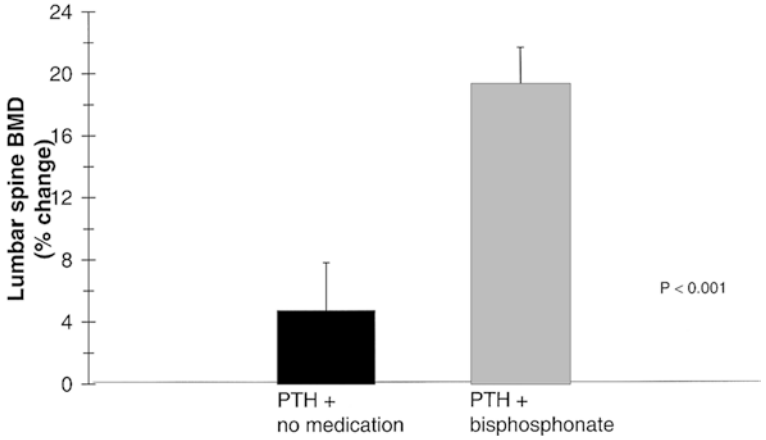

Fig. 2 Cumulative lumbar spine bone density change: baseline through 1 year after hPTH (1–34) withdrawal. Cumulative % change ± SEM in lumbar spine density for men who took bisphosphonates immediately after completing hPTH (1–34) ($n = 12$, *gray bar*) and men who took no medication for 1 year after hPTH (1–34) withdrawal ($n = 7$, *black bar*). Comparison is from baseline, prior to beginning hPTH (1–34) treatment, until 1 year after discontinuing hPTH (1–34). $P < 0.001$

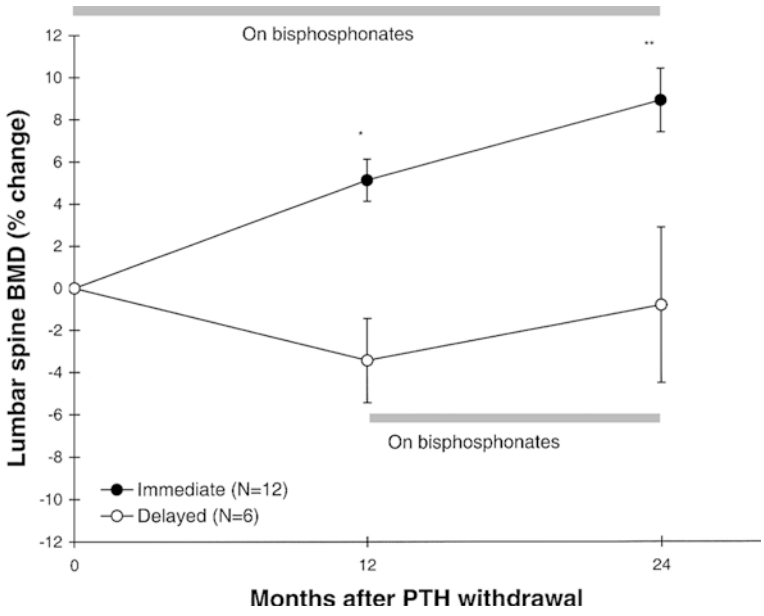

Fig. 3 Changes in bone density 2 years after cessation of hPTH (1–34) treatment: Immediate treatment with bisphosphonates versus delayed bisphosphonate therapy. Lumbar spine % change ± SEM, 2 years after discontinuing hPTH (1–34). Comparison is between 12 men who took bisphosphonates immediately (*closed circles*) and six men who delayed initiation of bisphosphonates until 1 year after hPTH (1–34) withdrawal (*open circles*). $*P = 0.005$, $**P \leq 0.002$

whose PTH exposure was of "short duration" had a greater increase of 10.8 ± 1.8% at the LS ($P = 0.02$). However, the ultimate gain in LS BMD after 2 years of BisP, among those whose exposure to PTH was short or long, was the same: 21.5 ± 3.0% versus 27.5 ± 5.0% ($P = 0.33$).

Discussion

The results of this study demonstrate that in order to maintain BMD gains achieved when teriparatide is used in men with idiopathic osteoporosis, subsequent antiresorptive therapy is beneficial. When a bisphosphonate was not used after teriparatide, bone density was rapidly lost, results consistent with recent observations of Zanchetta et al. [7]. In contrast, those who began bisphosphonate therapy immediately, showed further lumbar spine gains. One year after teriparatide was discontinued, these men showed a cumulative increase in bone mineral density of the lumbar spine (for the teriparatide and bisphosphonate periods considered together) that was 4-fold greater than for those who did not take bisphosphonate in that first year (19.3% versus 4.7% above the pre-teriparatide baseline values).

This study has provided additional insights. Men who delayed the start of bisphosphonate therapy until 1 year after they had discontinued teriparatide did experience gains in lumbar spine bone density over the next year. However, these gains merely matched the losses they had experienced in the preceding year when they had not taken bisphosphonates after completing teriparatide. It would seem necessary, therefore, to institute bisphosphonate therapy immediately after teriparatide is discontinued, in order to maintain the bone density gains achieved with teriparatide and to enhance them.

It is intriguing to postulate why the robust bone formation that results from PTH stimulation would dissipate so rapidly upon its withdrawal. Aged male rats show the same rapid loss in bone density after PTH withdrawal, but maintenance of gains when bisphosphonate is used [8]. Studies by Misof et al. [9] and Roschger et al. [10] utilizing the technique of quantitative backscattered electron imaging (qBEI) [11] may help to explain both the animal and human observations. This technique, which assesses the actual degree of bone mineralization, reveals that hPTH (1–34) increases bone formation but results in deposition of bone that has a lower mineral content than bone formed prior to PTH treatment [9]. With bisphosphonate therapy, in contrast, qBEI has shown that the increased bone density appears to be a function of increased mineralization of existing bone, and not the formation of new bone tissue [10]. Thus, a particular synergy between the two treatment modalities, teriparatide and bisphosphonates, could be occurring when bisphosphonates follow teriparatide. Teriparatide stimulates formation of bone, albeit with less mineral, enabling increased secondary mineralization and maturation of this new bone to occur when bisphosphonate is used subsequently. In the absence of anti-resorptive therapy, bone induced by PTH is likely to be rapidly resorbed, particularly if bone turnover is still increased as a function of PTH therapy [1].

It follows, therefore, that the use of teriparatide does not appear to diminish the ability of bone to respond subsequently to an antiresorptive agent. In fact, the further 8.9% increase in LS bone mineral density after 2 years of bisphosphonate therapy, following 2 years of a robust response to teriparatide, is equivalent to the increases in bone mineral density after use of bisphosphonates alone in clinical trials [12, 13, 14]. Moreover, the cumulative increase in lumbar spine bone density of 23.6% observed with 4 years of sequential therapy, approximately 2 years of hPTH (1–34) and 2 years of bisphosphonate, exceeds the published experience for any of these drugs alone [1, 2, 12, 13, 14, 15, 16],

and is clearly superior to the concomitant administration of PTH and bisphosphonate [17, 18]. While increases in bone density are not the only endpoint for demonstrating efficacy of an osteoporotic medication or regimen, there are clearly significant correlations between bisphosphonate-induced increases in bone density and reductions in fracture risk [19]. It is possible, therefore, that the sequential regimen of teriparatide followed by bisphosphonate may confer fracture reduction beyond that achieved by either drug alone. Such expectations would need to be documented by a prospective clinical trial.

One final observation worthy of attention is the apparent difference in densitometric response of the lumbar spine between the men who had a ''shorter duration'' (18 months) or ''longer duration'' (30 months) of exposure to teriparatide prior to beginning bisphosphonate therapy. Although our results are limited by small sample size, there is biological plausibility to the finding that a shorter duration of pre-treatment with PTH results in a significantly greater increase in lumbar spine bone mass with subsequent bisphosphonate therapy. After 18 months of treatment with hPTH (1–34) bone turnover markers that reach their peak values between 9 and 12 months of therapy [1, 15] are still significantly elevated above baseline [1], while these markers have essentially returned to pre-treatment values after 30 months of therapy [20]. Thus, the primary actions of bisphosphonates to reduce bone turnover [21], in turn, reducing the remodeling space, increasing bone volume, as well as increasing the mineral content of the matrix [22], are enhanced in the setting of both the higher bone turnover and larger remodeling space of 18 versus 30 months of PTH therapy. This observation leads to the possibility that repeated, shorter cycles of hPTH (1–34) followed by the administration of bisphosphonates, in the interim, while bone markers are still elevated, may be a particularly effective approach to the optimal use of these drugs [23]. Future larger studies of longer duration are necessary to confirm this point.

This study demonstrates the importance of utilizing bisphosphonates immediately following treatment with teriparatide. Patients who did not take bisphosphonate treatment lost bone mass after teriparatide withdrawal, while bisphosphonates were effective at preventing this loss. In addition, the lumbar spine appears capable of responding well to bisphosphonates even after sustaining a brisk anabolic response to teriparatide. Finally, the timing of bisphosphonate initiation after hPTH (1–34) appears to have an impact on the ultimate densitometric response to bisphosphonates at the lumbar spine. The sequential use of teriparatide followed by bisphosphonate may represent a powerful pharmacologic treatment strategy for osteoporosis in men.

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