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PINP as an aid for monitoring patients treated with teriparatide ☆

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ABSTRACT

Biochemical markers of bone turnover may be useful aids for managing patients with osteoporosis. A 12-month, phase 3, multicenter trial of Japanese patients at high risk of fracture was conducted to assess the effects of teriparatide 20 μg/day on BMD, serum markers of bone turnover, and safety. Two-hundred and seven subjects (93% female; median age 70 years) were randomized in double-blind fashion 2:1 to teriparatide versus placebo. Bone turnover markers including procollagen type I N-terminal propeptide (PINP), bone-specific alkaline phosphatase (bone ALP) and type I collagen cross-linked C-telopeptide (CTX) were collected at baseline, 1, 3, 6, and 12 months. Lumbar spine, femoral neck, and total hip BMD were measured at baseline, 3, 6, and 12 months. Increases in PINP at 1 month correlated best with increases in lumbar spine BMD at 12 months ($r = 0.76$; $P < 0.01$). The proportions of patients with an increase from baseline in PINP >10 μg/L at 1, 3, and 6 months were 3%, 0%, and 2% in the placebo, and 93%, 87%, and 83% in the teriparatide group. The proportions of patients with an increase in PINP >10 μg/L at either 1 or 3 months were 3% in the placebo and 95% in the teriparatide group ($P < 0.001$). The proportions of patients with a significant increase in lumbar spine BMD (increase from baseline ≥3%) at 12 months were 20% in the placebo and 94% in the teriparatide group. The proportions of patients with an increase in PINP >10 μg/L at 1 or 3 months and an increase in lumbar spine BMD ≥3% at 12 months was 0% of placebo group patients and 92% of teriparatide group patients ($P < 0.001$). These data confirm a strong relationship between early change in PINP and later change in lumbar spine BMD during teriparatide therapy. Also, these results suggest that monitoring with PINP and lumbar spine BMD successfully identifies positive responses in most patients taking teriparatide and negative responses in most patients not taking teriparatide. PINP monitoring may be a useful aid in the management of patients with osteoporosis during teriparatide treatment.

Introduction

Patients with osteoporosis span a range from asymptomatic disease to severe skeletal deterioration and symptomatic osteoporotic fractures. In patients with urgent osteoporosis treatment needs, careful monitoring and feedback may be important for optimization of therapy and for encouraging patients to continue treatment. Unfortunately, in osteoporosis, there are few available tools for providing feedback to patients, and changes in bone mineral density (BMD) often require many months to become reliably detectable. As such, osteoporosis is often treated passively and without early feedback. Long-term persistence with therapy is suboptimal in patients with osteoporosis, perhaps at least in part due to a lack of early feedback regarding what is happening in the bones during therapy. Indeed, in a survey of women with osteoporosis, the International Osteoporosis Foundation found that the primary factor motivating women to stay on therapy was “knowing I'm doing something to help” [1].

Markers of bone turnover have the potential to provide early feedback to patients and prescribers, and change the management of osteoporosis from passively to actively monitored treatment. For example, patients treated with an osteoporosis therapy who have a positive marker response can be given a positive message which may increase persistency on their osteoporosis therapy [2]. On the other hand, patients without a significant change in marker during osteoporosis therapy can be assessed for compliance or for conditions which might impair response to therapy, then gotten back on track. However, many markers of bone turnover are affected by a range of issues including food intake, circadian rhythm effects, and a low signal-to-noise ratio, and these issues have limited the acceptability of monitoring in day-to-day patient management. Procollagen type I N-terminal propeptide (PINP) is a marker of bone formation and is cleaved off during the processing of type I procollagen to mature type I collagen. PINP may be

Abbreviations: ANOVA, analysis of variance; BMD, bone mineral density; bone ALP, bone-specific alkaline phosphatase; CTX, type I collagen cross-linked C-telopeptide; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; PINP, procollagen type I N-terminal propeptide.

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particularly clinically useful because this marker is relatively insensitive to the circadian rhythm or the effects of food intake, and has a high signal-to-noise ratio [3].

A range of therapies are available for treating osteoporosis. For patients at high risk for fracture, teriparatide is a skeletal anabolic drug that increases bone formation on cortical and trabecular bone, increases BMD, and increases bone strength. In a clinical trial with a 19-month median treatment duration, teriparatide reduced the risk of vertebral and nonvertebral fractures [4–8]. In patients treated with teriparatide, early changes in PINP are correlated with later changes in BMD [9] and changes in BMD explain a portion of the fracture risk reduction with teriparatide [10].

An algorithm for using PINP in the day-to-day management of patients has been proposed [3] and subsequently tested and revised [11]. A least-significant change approach was used to define a significant increase in PINP as an increase of >10 μg/L during teriparatide therapy.

A clinical trial assessed bone mineral density, markers of bone turnover, and safety in Japanese patients treated with teriparatide versus placebo for 12 months [12]. In this paper, we used data from that trial to study the potential use of PINP as an aid in the day-to-day management of patients treated with teriparatide. Towards that end, we: 1) describe the absolute changes in markers of bone turnover over time; 2) quantify the relationships between early changes in biochemical markers of bone turnover and percent changes in lumbar spine and hip BMD after 12 months of treatment with teriparatide; 3) assess the proportions of patients in the teriparatide and placebo groups with significant increases in PINP and significant increases in lumbar spine BMD; 4) further test the use of PINP as a potential aid in the management of patients with osteoporosis at high risk for fracture treated with teriparatide.

Materials and methods

Study design and participants

The methods for the 12-month, phase 3, randomized, multicenter, double-blind, placebo-controlled trial in Japanese subjects at high risk of fracture to assess the effects of teriparatide 20 μg/day on BMD, serum markers of bone turnover, and safety have been reported [12]. Briefly, Japanese women (≥5 years postmenopause) and men were eligible for enrollment if they were ambulatory, ≥55 years old, able to use the pen injection device correctly, and at high risk of fracture. Two-hundred and seven subjects were randomized 2:1 to teriparatide versus placebo. All subjects received 610 mg calcium and 400 IU vitamin D supplementation to take daily beginning during the screening phase of the study. The study included open-label extensions, but we only included data from the blinded phase of the study in this analysis. Treatment compliance was assessed via the subjects' diary records and cumulative number of treated days was confirmed via measurement of remaining fluid in returned pen cartridges. This study (ClinicalTrials.gov identifier NCT00433160) was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All subjects provided written informed consent before starting any study procedure according to Good Clinical Practice.

Markers of bone turnover

Blood samples for markers of bone turnover were collected in the morning from patients in a fasting state prior to study drug at baseline, 1, 3, 6, and 12 months. Serum measurements of markers of bone formation included PINP, measured using a radioimmunoassay (Orion Diagnostica, Espoo, Finland), and bone-specific alkaline phosphatase (bone ALP), measured using the Ostase assay (Beckman Coulter, Brea, CA, USA). Serum marker of bone resorption type I collagen cross-linked C-telopeptide (CTX) was assessed using an enzyme-linked immunosorbent assay (IDS Nordic, Herlev, Denmark). Samples were frozen at -20 °C or -70 °C prior to shipping on dry ice; samples were batch tested weekly per the normal procedure at the reference laboratory. For bone ALP testing, intra-assay precision (coefficient of variation, CV) was ≤4.4% and inter-assay CV was ≤7.3%. For the PINP assay, the intra-assay CV was 1.7–2.9% and the inter-assay CV was 3–6%; for CTX testing, the intra-assay CV was 4.9–6.4% and the inter-assay CV was 5.0–5.1%. For PINP, a significant change was defined as an increase >10 μg/L from baseline [3].

Bone mineral density

This analysis includes baseline, 3, 6, and 12 month BMD assessed using dual-energy x-ray absorptiometry (DXA) with Hologic QDR4500, Delphi, Explorer or Discovery equipment. BMD in individual subjects was assessed with the same DXA machine throughout the study. Serial measurements of a spine phantom were performed at each center, and a standard phantom was tested at all centers. Data from the phantom measurements was used to correct for minor changes in the performance of the densitometers [13]. The lumbar spine BMD was measured from L-1 through L-4. The BMD measurements were analyzed centrally by Synarc, Inc. (Portland, OR, USA). Only vertebrae that could be evaluated by DXA (i.e., not fractured, clearly identifiable on all scan images, and free of defects) at the last measurement point were included in the BMD assessment. A significant change in lumbar spine BMD was defined as an increase of ≥3% [14]. Subjects were included in the BMD analyses of the hip if the same hip area was imaged throughout the study and that hip had not been fractured.

Statistical analyses

The distribution of the changes in bone turnover markers was skewed; therefore, ranked analysis of variance (ANOVA) was used to compare the changes in bone turnover markers from baseline between groups at each time point. Ranked ANOVA included the terms of treatment and site. The relationship between baseline bone turnover markers and the percent change in BMD were evaluated by Spearman rank correlation analysis. The relationship between changes in bone turnover markers, measured as both absolute and percent values, and the percent change in BMD were also evaluated by Spearman rank correlation analysis. Categorical variables were compared between treatment groups using continuity adjusted chi-square tests. All tests were 2-sided with the nominal significance level set at 0.05 and were performed using SAS statistical software, version 9.1.3 (SAS Institute, Cary, NC).

Results

Baseline characteristics

The baseline patient characteristics were reported previously [12]. There was no significant between-group difference in any baseline parameters. Briefly, over 90% of the patients were women. The mean age was approximately 70 years. Approximately 40% of subjects had previous fractures.

Bone turnover marker response to teriparatide

The median change from baseline and interquartile range at every visit for the 3 bone turnover markers is shown in Fig. 1. PINP increased at 1 month and remained increased at each visit in the teriparatide treatment group. Relative to placebo, bone ALP also increased at all visits, although the changes in this marker were less dynamic than the changes in PINP. CTX did not increase at 1 month, but was increased at 3 months and thereafter remained increased relative to placebo.