Bone 66 (2014) 26–30

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Determinants associated with bone mineral density increase in response to daily teriparatide treatment in patients with osteoporosis

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ARTICLE INFO

Article history:
Received 24 March 2014
Revised 14 May 2014
Accepted 29 May 2014
Available online 5 June 2014

Edited by Robert Recker

Keywords:
Osteoporosis
Teriparatide
BMD
Determinant
PINP

ABSTRACT

Introduction: Several factors associated with bone mineral density (BMD) increase are reported with daily teriparatide treatment, but there has been no systematic analysis to summarize these associations. The purpose of this study was to investigate the clinical determinants associated with BMD increase to daily teriparatide treatment.
Methods: This was a retrospective study. We performed an analysis of 306 patients diagnosed with osteoporosis. Teriparatide was administered at 20 μg/day for 12 months. The primary efficacy measure was a change in lumbar spine (LS) BMD from baseline at 12 months. To determine the response variables of BMD changes, we investigated the clinical determinants using univariate and multivariate analyses.
Results: There was a 9.8 ± 8.2% increase in LS BMD after 12 months. Prior bisphosphonate treatment and baseline procollagen type I N-terminal propeptide (PINP) concentration were significantly associated with LS BMD absolute response by univariate analyses. In the multiple regression model, patients with higher baseline PINP concentration had a significantly greater LS BMD absolute increase. Prior bisphosphonate use lost its correlation in the multiple regression models.
Conclusion: Our results showed that baseline PINP concentration was a useful predictor of LS BMD absolute increase regardless of prior treatment.

Introduction

Osteoporosis is a major public health problem characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in an increased risk of fracture [1]. Recombinant human parathyroid hormone (PTH) (1–34), teriparatide, is a bone anabolic agent indicated for the treatment of postmenopausal women and men with osteoporosis. Teriparatide administered on a daily basis is the only bone formation agent approved by the Food and Drug Administration and increases bone mineral density (BMD) through the formation of new bone [2–4]. Although the daily use of teriparatide in patients with osteoporosis has resulted in improved outcome, not all patients benefit equally. Studies have found associations between early treatment-related changes in bone formation markers, especially procollagen type I N-terminal propeptide (PINP), and subsequent changes in BMD [2,3,5–7]. However, a clinical problem still persists in that clinicians have little guidance for predicting improvements in BMD before initiation of teriparatide treatment.

Several determinants were reported to be associated with higher BMD increases, such as higher baseline PINP concentration [8], age (older [8–10]/younger [11]), and lower BMD [8,9]. In contrast, pretreatment with antiresorptives such as bisphosphonates, especially alendronate [9,12,13], reduced the efficacy of teriparatide treatment on BMD increase [9]. Furthermore, Orwoll et al. found that responses to teriparatide treatment were similar, regardless of age, gonadal status, smoking, or alcohol intake [14].

Although several factors have been associated with BMD increase in response to daily teriparatide treatment, there is no study which evaluated the consistency of these associations. Therefore, the objective of this study was to investigate the clinical determinants associated with BMD response to daily teriparatide treatment.

Materials and methods

Study subjects

We performed a retrospective analysis of 306 of 448 patients (68%) beginning with teriparatide treatment and completed 12-month

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http://dx.doi.org/10.1016/j.bone.2014.05.017
8756-3282/

teriparatide treatment. The reasons for the discontinued teriparatide treatment were as follows: lost to follow-up, 45 patients; loss of motivation for teriparatide treatment, 25 patients; discontinuation for illness unrelated to teriparatide treatment, 22 patients; relocation, 12 patients; dizziness, 7 patients; death of unrelated cause of teriparatide treatment, 7 patients; nausea, 5 patients; fatigue, 2 patients; hypercalcemia, 2 patients; expensive medical expenses, 2 patients; nettle rash, 2 patients; palpitation, 2 patients; dry mouth, 1 patient; diarrhea, 1 patient; itch, 1 patient; headache, 1 patient; loss of hair, 1 patient; bruising at the injection site, 1 patient; high level of serum alkaline phosphatase with unknown cause after one month (315 U/L at baseline → 2319 U/L at one month), 1 patient; and instruction by other doctor with incomprehensible reason, 1 patient. The inclusion criteria were postmenopausal females and males diagnosed with osteoporosis and at high risk of fracture. A high risk of fracture was defined when patients met at least one of the following criteria [15]: (1) BMD at lumbar spine (LS) L1–4 < 80% of the young adult mean (YAM; for all subjects reported in the Japanese Normative Female Database [16]) (approximate T-score - 1.9), with a minimum of one prevalent fragility fracture; (2) BMD at L1–4 < 70% of YAM (approximate T-score - 2.8) and age ≥ 65 years; (3) BMD at L1–4 < 65% of YAM (approximate T-score - 3.2) and age ≥ 55 years; or (4) more than three previous osteoporotic fractures. The exclusion criteria were patients with illnesses affecting bone and calcium metabolism or other bone disorders other than osteoporosis, as well as patients with serious cardiovascular, renal, or hepatic dysfunction. Patients with a high concentration of serum calcium (>11 mg/dl) at baseline were also excluded.

Measurements

We measured the BMD of the LS and femoral neck (FN) using dual-energy X-ray absorptiometry (DXA) on the DPX-BRAVO instrument (GE Healthcare, Madison, WI) at baseline and 12 months after treatment. Intra-observer coefficient of variation (% CV) for the DXA were 0.5% in LS and 1.0% in FN, respectively. Inter-observer % CV were 0.6% in LS and 0.9% in FN, respectively. The concentration of PINP at baseline was also measured by a radioimmunoassay (Orion Diagnostica, Espoo, Finland). Normal range are 21.9–71.9 μg/l in female patients and 19.0–83.5 μg/l in male patients. Intra-assay and inter-assay % CV for PINP were 3.5% and 4.2%, respectively. urinary N-telopeptide (uNTX) was measured by an enzyme-linked immunosorbent assay (ELISA; Alere Medical Co., Ltd., Tokyo, Japan). Normal range are 14.3–89.0 μg/l in female patients and 13.0–66.2 nmolBCE/mmol Cr in male patients. Intra-assay and inter-assay % CV for uNTX were 6.6% and 6.5%, respectively.

Determinants

The following possible determinants of response to teriparatide treatment were considered: age, gender, height, body weight, body mass index (BMI), body surface area (BSA) [17], prior bisphosphonate treatment, prior osteoporotic fractures, baseline LS BMD, baseline serum calcium concentration, baseline serum PINP, and uNTX concentration.

Statistical analysis

To determine the response variables of BMD changes, univariate analyses were performed by Spearman correlation coefficients and Mann–Whitney *U* test. Data were further analyzed by multiple regression analysis. The multiple regression model included gender and all determinants mentioned in the previous reports. As serum PINP and uNTX are bone turnover markers with strong relation between PINP and uNTX ($r = 0.79$, $p < 0.01$; Spearman rank correlation), multivariate analyses were performed using one bone turnover marker which was stronger relation to BMD change by Spearman rank correlation. In addition, to exclude the effect of confounding factors between baseline PINP concentration and prior bisphosphonate treatment, multivariate statistics were performed after stratification by prior bisphosphonate treatment.

The analyses were performed using the SAS software program, version 9.1 (SAS Institute, Inc., Cary, NC, USA). All data are expressed as means ± standard deviation (SD), unless otherwise indicated. p-Values <0.05 were considered statistically significant.

Compliance

The medication compliance was assessed at each visit. Participants were queried regarding the number of missed doses of medication and were considered compliant if they consumed ≥85% of the study drug.

The protocol was in compliance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ethics Committee of Tomidahama Hospital. Written informed consent was obtained from the patients.

Results

Baseline characteristics

The age, gender, height, body weight, BMI, BSA, prior bisphosphonate treatment, prior osteoporotic fractures, baseline LS and FN BMD, serum calcium, serum PINP and uNTX concentrations are reported in Table 1. One hundred and thirty-four patients (44%) had been previously treated with antiresorptive agents for at least three months before switching to the teriparatide treatment. The antiresorptive agents

Table 1
Baseline clinical characteristics (n = 306).

Variable	Mean (SD), n (%)
Age (years)	78.1 ± 7.8
Gender, n (%)	
Females	271 (89%)
Males	35 (11%)
Height (cm)	150.5 ± 7.8
Body weight (kg)	47.9 ± 9.1
BMI (kg/m^2)	21.1 ± 3.6
BSA (m^2)	1.41 ± 0.14
Prior treatment, n (%), period (months)	Total 134 (44%)
Alendronate	86 (28%), 41 months (3–84 months)
Risedronate	23 (8%), 19 months (4–73 months)
Minodronate	5 (2%), 15 months (4–34 months)
SERM	20 (7%), 31 months (4–76 months)
Previous osteoporotic fractures, no of patients (%)	Total 221 (72%)
No of patients with multiple fractures	132 (43%)
Vertebral body	202 (66%)
Proximal femur	63 (21%)
Distal radius	18 (6%)
Proximal humerus	7 (2%)
BMD	
Lumbar spine (g/cm^2), T-score	0.822 ± 0.167 (g/cm^2), −2.5 ± 1.4
Femoral neck (g/cm^2), T-score	0.610 ± 0.120 (g/cm^2), −2.5 ± 1.0
Serum calcium (mg/dl), normal range 8.5–10.2 mg/dl	9.4 ± 0.6
Bone turnover marker	
serum PINP μg/l	54.0 ± 36.9
uNTX (nmolBCE/mmol Cr)	51.0 ± 37.0

SD: standard deviation; BMI: body mass index; BSA: body surface area; SERM: selective estrogen receptor modulator; BMD: bone mineral density; PINP: procollagen type I N-terminal propeptide; uNTX: urinary N-telopeptide.