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Reduction in vertebral fracture risk in teriparatide-treated postmenopausal women as assessed by spinal deformity index ☆

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Abstract

Teriparatide is the first bone-building drug available for the treatment of osteoporosis. We investigated the efficacy of this compound as assessed by spinal deformity index (SDI) using data from the Fracture Prevention Trial (FPT). The FPT was a randomized, double blind trial of placebo versus teriparatide 20 μg (TPTD20) versus teriparatide 40 μg (TPTD40) administered by daily self-injection. Patients included in the current analyses were those patients from the placebo (n = 398) and TPTD20 (the approved dose, n = 403) groups with baseline and follow-up radiographs and at least one vertebral fracture at baseline. For each vertebra, a visual semiquantitative grade of 0, 1, 2, or 3 was assigned for no fracture or mild, moderate, or severe fracture, respectively; the SDI was calculated by summing the fracture grades of all T4 to L4 vertebrae. The mean SDI increased in the placebo and TPTD20 groups by 0.485 and 0.134, respectively ($P < 0.001$). The proportions of patients with SDI increases >1, >2, and >3 were reduced by 85%, 80%, and 80%, respectively. In the placebo group, increasing baseline SDI was correlated with the mean increase in SDI during the trial (r = 0.080, P = 0.01), consistent with the progressive natural history of osteoporosis. However, in the TPTD20 group, increasing baseline SDI was not correlated with the mean increase in SDI during the trial (P = 0.297) indicating that teriparatide mitigated or eliminated the increased risk associated with increasing fracture burden. Increases in SDI during the trial were associated with increasing proportions of patients with new or worsening back pain and greater mean height loss ($P <$ 0.0001), demonstrating an association with important clinical consequences. The results indicate that teriparatide greatly reduced the increase in fracture burden in the FPT and mitigated or eliminated the risk for future fractures imparted by increasing baseline fracture burden.

Keywords: Spinal deformity index; Teriparatide; Postmenopausal women; Osteoporosis; Fracture risk; Height loss; Back pain

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength and increased fracture risk [1]. It is a major public health problem, affecting nearly 200 million people worldwide and an estimated 20 million people over the age of 45 years in the United States alone [2,3]. Vertebral fractures are the most common type of fractures occurring in patients with osteoporosis, and may have consequences including back pain, height loss, and diminished quality of life [4,5].

Teriparatide, [rh PTH (1–34)], is the first bone-forming drug approved for the treatment of osteoporosis. In a large multinational study of postmenopausal women with osteoporosis, treatment with teriparatide at 20 μg/day for a median duration of 19 months was shown to reduce the risk of vertebral and nonvertebral fractures by 65% and 53%, respectively, and to increase the spinal and femoral neck bone mineral density and total body bone mineral content [6].

Because vertebral fractures are of substantial clinical importance, several methods of fracture ascertainment have been described including morphometric and visual inspec-

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tion methodologies [7]. One of the most widely used methods in clinical trials is the visual semiquantitative method of fracture ascertainment described by Genant et al. [8]. This method consists of a visual inspection of lateral spine images and grading each vertebra from T4 to L4 as normal (grade 0), or as mild (~20–25% compression), moderate (~25–40% compression), or severe (>~40% compression).

Many studies have shown that prior vertebral fracture increases the risk of future vertebral fracture. Using data from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, Delmas and colleagues demonstrated that both the number of prior vertebral fractures and the maximum severity of prior vertebral fractures are important predictors of future fracture risk [9]. Because both the number and the severity of prior vertebral fractures are important predictor variables, Genant et al. combined the information into one measure, the so-called spinal deformity index (SDI) [8]. This index is calculated by summing the semiquantitative grades of all vertebrae from T4 to L4. Thus, if a patient has one mild and one moderate vertebral fracture, the SDI would be 1 + 2 = 3. We have recently validated this index using data from the MORE trial, demonstrating that the baseline SDI was highly correlated with vertebral fracture risk during the trial, and the risk determined using this index was highly correlated with the risk determined by a logistic regression model incorporating the number of mild, number of moderate, and number of severe fractures and their interactions [10].

In the current work, we use SDI as both a predictor variable and an outcome variable to illustrate the importance of baseline SDI as an important determinant of fracture risk in placebo-treated patients and the mitigation of this risk in teriparatide-treated patients. Additionally, to investigate the clinical significance of increased SDI, we evaluated the impact of increases in SDI in the placebo group on back pain and height loss.

Methods

Study subjects

A description of the Fracture Prevention Trial was previously published [6]. Briefly, the study was a multicenter, randomized, double blind, placebo-controlled trial. A total of 1637 postmenopausal women who met protocol criteria was randomized to placebo (n = 544), teriparatide (recombinant human parathyroid hormone, 1–34) 20 μg per day (TPTD20, n = 541), or teriparatide 40 μg per day (TPTD40, n = 552). Patients administered the study drug daily by self-injection. All patients received daily supplements of 1000 mg of calcium and 400 to 1200 IU of vitamin D. The trial was halted after a median study drug exposure of 19 months. In this report, we include the findings for the placebo and TPTD20 groups, because TPTD20 is the approved dose. Findings for the TPTD40 group were similar to those reported for the TPTD20 group. Patients were required by protocol to have one or more prevalent vertebral fractures as assessed by investigative site. However, some placebo (n = 50) and TPTD20 (n = 41) patients were subsequently judged by the central reader to not have prevalent vertebral fractures. Because the vertebral fracture status of these patients is ambiguous, and some of the analyses herein depend on this variable, their data were not included. Some placebo (n = 96) and TPTD20 (n = 97) patients lacked a baseline and/or postbaseline radiograph. There were no significant differences in baseline characteristics between placebo and TPTD20 groups of patients with missing radiographs (data not shown), suggesting that the missing data did not impact the efficacy results.

Vertebral fracture assessment

Lateral thoracic and lumbar spine radiographs were taken at baseline and study endpoint and evaluated by central readers (Osteoporosis and Arthritis Research Center, University of California San Francisco, San Francisco, CA, USA). Radiologists were blinded to group assignment but not to temporal sequence of the radiographs. Fracture severity was assessed using semiquantitative (SQ) visual assessment [8], and SQ scores were assigned to each individual vertebra from T4 to L4. An SQ score of '0' was assigned to normal, nonfractured vertebrae; '1' for mild deformities (~20–25% *reduction in anterior, middle, or posterior vertebral height*); '2' for moderate deformities (~25–40% *reduction*); '3' for severe deformities (>~40% *reduction*). Vertebrae that were not radiographically evaluable due to kyphosis, fusion, or other anomalies were not graded. The SDI score was calculated by summing the SQ grade for each of the 13 vertebrae from T4 to L4:

$$\mathrm{SDI} = \mathrm{SQ_{L1}} + \ldots + \mathrm{SQ_{L4}} + \mathrm{SQ_{T4}} + \ldots + \mathrm{SQ_{T12}}$$

An increase in SDI could occur either due to a new vertebral fracture or due to worsening of mild or moderate prevalent vertebral fractures.

Assessment of back pain

Back pain data were collected during adverse event monitoring at each visit. Women were considered to have new or worsening back pain if they reported new back pain or back pain with greater severity than that experienced prior to randomization.

Assessment of height loss

Height was measured with a stadiometer at randomization and study endpoint. Height measurements were taken 3 times at approximately the same time of day throughout the study, and the average height measurement was recorded.