

Treatment responses with once-weekly teriparatide therapy for osteoporosis

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Abstract

Summary Monitoring bone mineral density is useful to assess treatment response for osteoporosis, but it does not always reflect fracture prevention. Two types of bone mineral density thresholds were used to analyze data from a once-weekly teriparatide trial, and they appear to be useful indicators of treatment success for osteoporosis.

Introduction This study aimed to clarify whether the criteria of treatment response could be used to evaluate treatment success with once-weekly teriparatide.

Methods The data of subjects whose lumbar or femoral neck bone mineral density (BMD) was measured in the TOWER study were included. The least significant change (LSC) and the absolute change were used as the criteria for judgment of treatment success. The correlation between the incidence of fractures and the treatment response was also assessed.

Results There was no significant difference in baseline characteristics between the placebo and teriparatide groups. Once-weekly teriparatide therapy for 72 weeks showed treatment success in 79.2 % of the subjects for lumbar BMD and 44.1 % for femoral neck BMD by LSC and in 50.5 and

39.6 % by absolute change, respectively. A lower incidence of vertebral fracture was observed in patients who achieved treatment success for lumbar BMD. With the LSC, some treatment success was observed in the early phase of treatment, and it increased with treatment duration.

Conclusions It appears that the LSC could be used as a surrogate efficacy indicator at an earlier stage of treatment, and the absolute criterion of $-2.5SD$ was confirmed as a useful marker of long-term treatment success.

Keywords Bone mineral density · Incident fracture · Teriparatide · Treatment success

Introduction

Osteoporosis is a well-characterized disease with increasing risk of a fragility fracture due to decreased bone strength in elderly men and postmenopausal women [1]. The aim of the treatment of osteoporosis is the prevention of fragility fractures. Progress in osteoporosis treatment has reduced fracture risk. However, although there are many effective ways to prevent osteoporotic fractures, the treatment gap has been reported to still be high [2]. This may be due to a lack of treatment strategy; thus, efforts to determine treatment targets and goals have been proposed [3]. Fragility fracture risk increases with increasing age, decreasing bone mineral density (BMD), and the presence of prevalent fractures [4]. Although the aim of osteoporosis treatment is to reduce fracture risk, BMD is the only modifiable marker. Therefore, the measurement of BMD after treatment is the most useful tool for the assessment of treatment effect [5].

Osteoporosis is diagnosed by the presence of a fragility fracture or measurement of BMD, because if the BMD is below $-2.5SD$ of the young adult mean (YAM), a higher

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fracture risk is observed. In other words, when the absolute BMD value is increased to $-2.5SD$ by treatment, it could be said that the fracture risk will decrease significantly. However, this concept of treatment goal has not been adequately studied [3]. Fracture risk reduction judged by achievement of BMD after treatment has been reported to be poor for alendronate, risedronate, and raloxifene, but more attractive for denosumab and zoledronic acid [3]. Furthermore, the site of BMD measurement should be defined. Although many clinical trials have used lumbar BMD measurement as an indicator, the fracture risk model has used femoral neck BMD because of fewer confounding factors. The BMD change after weekly teriparatide treatment is more prominent for lumbar BMD, but small for femoral neck BMD [6]. Another issue related to BMD for determining the treatment effect is whether the BMD effect should be represented as percent changes of BMD or the absolute value of BMD. We have reported that the percent change in BMD after treatment was less sensitive for assessing fracture risk reduction than the achievement of $-2.5SD$ of the YAM [7]. Although limitations exist, the change in BMD has been considered a useful marker to evaluate the treatment response, not only in clinical studies but also at an individual patient level.

In 2012, judgment of treatment failure using measurements of BMD or bone turnover markers (BTMs) was proposed by the Scientific Task Force Group of the International Osteoporosis Foundation (IOF) [8], which was based on the concept of least significant change (LSC) in each measure of BMD. According to the authors, since the LSC is calculated by the coefficient of variation (CV) of BMD measurement, a value that exceeds the LSC can be recognized as a significant change in BMD during short-term observation. The assessment of treatment effect shortly after initiation is quite important to establish the therapeutic dynamism of osteoporosis, because the achievement of the treatment goal is judged after long-term treatment by the presence or absence of incident fracture occurrence, until which time one cannot judge whether the treatment given for the patient was appropriate. However, few studies have used the IOF criteria for treatment failure to judge treatment success at the patient level.

The current study aimed to evaluate whether the criteria of IOF and absolute value of $-2.5SD$ of the YAM can be used to evaluate treatment failure or success in a subset of patients who participated in the Teriparatide Once-Weekly Efficacy Research (TOWER) trial.

Material and methods

Subjects

Treatment responses were analyzed using the data from the original TOWER trial [6]. The TOWER trial was a

randomized, multicenter, placebo-controlled trial performed in Japan. Subjects with osteoporosis were randomly divided into two groups: those who received once-weekly subcutaneous injections of 56.5 μg of teriparatide (teriparatide group) or placebo (placebo group) for 72 weeks. All subjects received daily oral supplements of calcium 610 mg, vitamin D 400 IU, and magnesium 30 mg. Subjects who had taken bisphosphonates within the past 52 weeks or the other drugs for osteoporosis within the past 8 weeks were excluded. The protocol was conducted according to the Declaration of Helsinki and in compliance with Good Clinical Practice. Written, informed consent was obtained from all subjects before undergoing any examinations.

For this analysis from the TOWER trial, postmenopausal women who underwent measurements of lumbar or femoral neck BMD at baseline and two times after the initiation of the treatment regimens were included.

Measurement

From the original TOWER trial, baseline age, weight, and height were analyzed. The lumbar and femoral neck BMD values were measured at baseline and 24, 48, and 72 weeks after the initiation of treatment using dual-energy X-ray absorptiometry, either QDR (Hologic, Bedford, MA) or DPX (GE Healthcare, Fairfield, CT). Incident vertebral fracture was identified by a semi-quantitative (SQ) method using lateral spine X-ray films [9]. The SQ grade was evaluated at baseline and 24, 48, and 72 weeks after treatment initiation by an independent physician.

Criteria for treatment response

Treatment response was defined using the criteria described in the IOF report [8]. The CVs were 2.0 % for lumbar BMD and 1.6 % for femoral neck BMD; the LSC with a one-tailed test would be 1.19 times for evaluation of individual cases, with 80 % confidence. Therefore, the patients' percent change of BMD after treatment was classified as failure ($<-2.4\%$), success ($\geq+2.4\%$), or borderline (-2.4 to $+2.4\%$) for lumbar BMD and as failure ($<-1.9\%$), success ($\geq+1.9\%$), or borderline (-1.9 to $+1.9\%$) for femoral neck BMD.

Another criterion for treatment response, "absolute change," was also used to classify the patients based on the achievement of BMD at the last observation exceeding $-2.5SD$ of the YAM value, i.e., the mean \pm SD of the YAM measured by QDR was 0.790 ± 0.090 g/cm^2 at the femoral neck and 1.011 ± 0.119 g/cm^2 at the lumbar spine, and the value measured by DPX was 0.939 ± 0.114 g/cm^2 at the femoral neck and 1.192 ± 0.146 g/cm^2 at the lumbar spine.

In order to evaluate the treatment effectiveness of weekly teriparatide for osteoporosis, the number needed to treat (NNT) in this dataset [$1/(\text{absolute risk reduction})$] [10] was calculated.

Statistical analysis

Baseline characteristics are reported as means and SD or percentages. Significant differences between groups were tested by ANOVA or Chi-square test. Correlations were analyzed by Pearson's correlation coefficient. The proportion of treatment response (failure or success) was calculated at 24, 48, and 72 weeks from the start of treatment, and the relationships between BMD response criteria and the incident vertebral fracture number were assessed.

Results

A total of 317 subjects from the original TOWER trial were included in this analysis. The baseline characteristics of the teriparatide group ($n=145$) and the placebo group ($n=172$) are shown in Table 1. The baseline age, BMI, and BMD were not significantly different between the teriparatide and placebo groups. Incident vertebral fractures occurred in 20 subjects (11.6 %) in the placebo group and 4 subjects (2.8 %) in the teriparatide group ($P=0.003$). The NNT was calculated as 11.4.

The percent changes of BMD using the LSC criteria in the teriparatide and placebo groups are shown in Fig. 1. The number of patients defined as treatment success ($\geq+2.4$ %) in lumbar BMD increased significantly as the treatment period lengthened, with 79.2 % (80/101 subjects) at 72 weeks (Fig. 1a). On the other hand, treatment success ($\geq+1.9$ %) in femoral neck BMD did not change for 72 weeks, and the value was 44.1 % (49/111 subjects) (Fig. 1b). The treatment success rate judged by both measurement sites was 35.1 % (33/94 subjects). The correlation in percent change between lumbar and femoral neck BMD at 72 weeks in the teriparatide group was significant, but R^2 was very low ($R^2=0.06$, $P=0.015$), suggesting that the teriparatide effect on BMD was observed mainly in the lumbar area.

The treatment responses judged by “absolute change” in both measurement sites in the teriparatide-treated group are shown in Fig. 2. Treatment success (≥-2.5 SD) in lumbar BMD was significantly increased with a longer treatment period, and the proportion at the final observation (72 weeks) was 50.5 % (51/101 subjects). For femoral neck BMD, treatment success (≥-2.5 SD) was observed in 39.6 % (44/111 subjects) at 72 weeks. The proportion of subjects who reached success (≥-2.5 SD) at both measurement sites was 27.7 % (26/94 subjects). After subtracting the subjects who had baseline BMD above -2.5 SD, the numbers of subjects who reached a BMD over -2.5 SD were 14 of 64 subjects (21.9 %) for lumbar BMD, 11 of 76 (14.5 %) for femoral BMD, and 1 of 58 (1.7 %) for both. Thus, a total of 24 of 58 subjects (41.3 %) showed recovery of BMD from osteoporotic levels at either measurement site.

Incident vertebral fractures were observed in three subjects in the teriparatide group with the measurement of lumbar BMD and four subjects in the teriparatide group with the measurement of femoral neck BMD. Table 2 shows the contribution of treatment response to the incidence of fracture. The incidence of vertebral fracture was lower in subjects with $BMD \geq -2.5$ SD at final observation. While the incidence was significantly lower in the subjects with $BMD \geq -2.5$ SD when measured at the femoral neck ($P=0.049$), no significant difference was observed when BMD was measured in the lumbar area because of the lack of statistical power.

The correlation between LSC criteria of lumbar BMD at 24 weeks of treatment and lumbar $BMD \geq -2.5$ SD at final observation was calculated. The judgment of treatment success and failure in the early phase tended to be carried over to lumbar $BMD \geq -2.5$ SD at final observation ($P=0.06$) (data not shown).

Discussion

The “treatment goal” or “treat to target” of osteoporosis has been discussed in previous reports [2, 3, 11]. Other diseases, which need longer management periods, such as hypertension and hypercholesterolemia, have established treatment goals (prevention of vascular events) and targets (blood pressure and LDL cholesterol, respectively). When a drug cannot achieve target levels, changes in treatment are considered, because a variety of options are available for other chronic diseases.

Osteoporosis treatment must be long term, and the prevention of fractures would be an acceptable treatment goal, but the targets for the treatment of osteoporosis have not yet been established. The percent change of BMD was used as a typical surrogate marker of treatment for osteoporosis. The surrogate relationship of the change of BMD to incident fracture risk reduction was evaluated by the proportion of treatment effect explained (PTE) analysis. The PTEs were different among evaluated drugs, sites of BMD measurement, and fracture evaluation. The estimated PTEs of lumbar BMD for incident vertebral fracture differed among previous reports for bisphosphonates such as alendronate (16 %) or risedronate (18 %) [12, 13]. PTEs of total hip BMD to non-vertebral fracture with other anti-resorptive agents were estimated with zoledronate (61 %) and denosumab (87 %) [14, 15]. Regarding bone-forming agents, daily teriparatide showed an estimated PTE of 30–41 % [16], while weekly teriparatide showed an estimate as high as 83 % [17], indicating that the percent change of BMD would be a significant surrogate for fracture risk. In addition, we have reported that the absolute value of BMD up to >-2.5 SD with anti-resorptive agents reduces the risk of further fracture [7].

Table 1 Patients' baseline characteristics

Characteristic	Teriparatide group	Placebo group	P
Age, years	74.4 ± 5.6 (145)	74.9 ± 5.8 (172)	0.368
BMI, kg/m ²	23.2 ± 3.3 (145)	23.0 ± 3.1 (172)	0.475
Femoral neck BMD, T-score	-2.91 ± 0.91 (140)	-2.94 ± 0.91 (166)	0.795
Lumbar BMD, T-score	-2.74 ± 0.91 (120)	-2.63 ± 0.93 (146)	0.336
BMD category			
Lumbar <-3.5SD	24 (20.0 %)	28 (19.2 %)	0.146
-3.5 to <-3.0SD	24 (20.0 %)	24 (16.4 %)	
-3.0 to -2.5SD	29 (24.2 %)	23 (15.8 %)	
≥-2.5SD	43 (35.8 %)	71 (48.6 %)	
Femoral neck <-3.5SD	32 (22.9 %)	44 (26.5 %)	0.517
-3.5 to <-3.0SD	35 (25.0 %)	30 (18.1 %)	
-3.0 to -2.5SD	30 (21.4 %)	38 (22.9 %)	
≥-2.5SD	43 (30.7 %)	54 (32.5 %)	

Values are means ± SD or number (%)

In this analysis, the treatment response with weekly teriparatide was evaluated using the percent change categorized by the IOF criteria and the absolute change by the -2.5SD threshold, and their contribution to anti-fracture efficacy was evaluated. The treatment success rate by the LSC criterion for lumbar BMD (≥+2.4 %) increased with longer treatment duration and reached 79.2 % at the end of observation (72 weeks). Moreover, 50 % of the subjects achieved treatment success judged by the absolute change in lumbar BMD (≥-2.5SD). On the other hand, changes in femoral neck BMD were smaller than those in lumbar BMD. Therefore, measurement of lumbar BMD showed a clearer treatment response.

Other factors contributing to treatment response were investigated in this dataset (data not shown). First, the changes of bone turnover markers did not show a significant contribution to vertebral fracture incidence. This was thought to be because the changes of bone turnover markers occur in a very short time and to a small extent after the injection of weekly teriparatide. Second, the correlation with clinical fragility fractures was investigated, but the incidence was too small (one case in the teriparatide group, five cases in the placebo group) to show a significant distribution along with the treatment response. Regarding the treatment response to weekly teriparatide, the changes in BMD would be the dominant

Fig. 1 Treatment responses by LSC criteria. Proportions of patients in the LSC categories of percent change from baseline in lumbar (a) and femoral neck (b) BMD are shown in the placebo and teriparatide groups at the time of measurement. Numbers in square brackets show the number of subjects

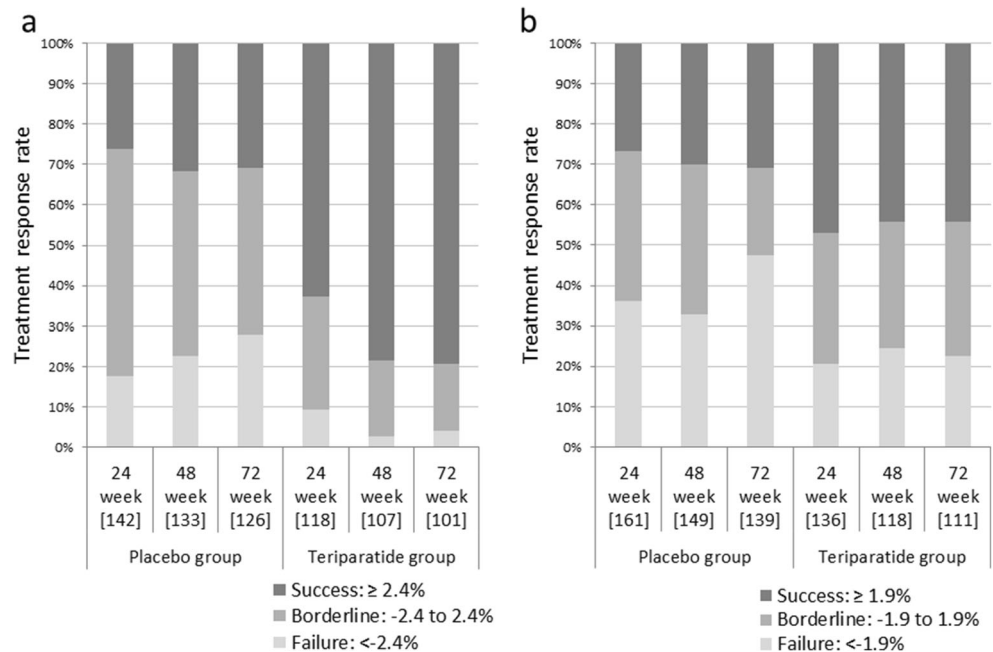
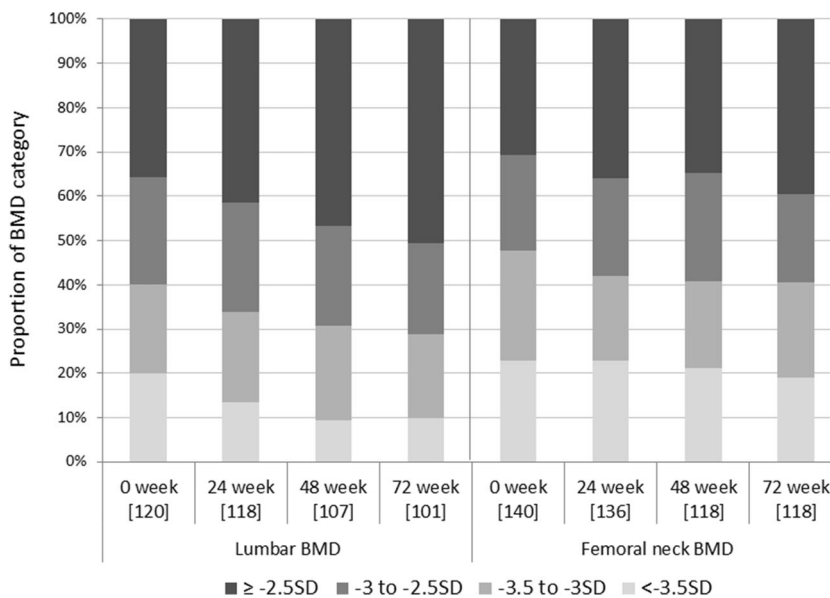


Fig. 2 Treatment responses by absolute change criteria in the teriparatide group. The proportions of patients in the absolute change categories defined by the BMD of the young adult mean value are shown in the lumbar and femoral neck regions at the time of measurement. Numbers in square brackets show the number of subjects



contributor to fracture prevention, but we believe there should be other factors.

Recently, changes in radial BMDs at the distal one tenth (trabecular bone-rich site) and one third (cortical bone-rich site) with once-weekly teriparatide were reported to be different [18], namely a larger increase of BMD was observed at one tenth compared to one third. This difference was explained by the difference in the bone compartment by measurement site. This report indicated that teriparatide was more effective at trabecular bone-rich sites than at cortical bone-rich sites. In contrast to the daily teriparatide preparation, weekly teriparatide reduced bone resorption with a small increase in bone formation [19, 20]. The metabolic effect of weekly teriparatide may be beneficial on trabecular bone sites, where bone remodeling occurs more prominently.

In the present study, treatment success or failure judged by the LSC criterion for lumbar BMD indicated a time-dependent increase in the rate of treatment success, indicating that the LSC criterion for lumbar BMD may be an early phase indicator for the treatment response. On the other hand, the absolute BMD value category ($\geq -2.5SD$) at 72 weeks of treatment, which reflected a significantly lower incidence of fractures, may be

useful to evaluate vertebral fracture risk reduction. The rate of patients achieving over the $-2.5SD$ criterion was around 30 %, suggesting that 30 % of patients recovered their BMD from the osteoporosis level with weekly teriparatide treatment. Considering that the absolute criterion of $\geq -2.5SD$ of the YAM has been established as the diagnostic criterion at an individual level, and that the fracture incidence is correlated with this BMD threshold, this criterion could be also useful for the assessment of treatment success, though some caution is needed.

The NNT of weekly teriparatide was also calculated and found to be 11.4. In the previous reports, NNT values of osteoporosis medications ranged from 9 to 21 to prevent a new vertebral fracture over 3 years [21]. Comparing the reports, it could be considered that the NNT value of weekly teriparatide is comparatively low, despite the fact that the TOWER trial was a 72-week study, which indicates that weekly teriparatide is effective treatment for osteoporosis.

Injections of weekly teriparatide are given to patients at medical institutions, so that compliance with drug administration is guaranteed to be 100 % as long as the patients visit such institutions to receive the injections. Thus, one of the characteristics of weekly teriparatide could be considered to be that treatment failure is extremely rare in the earlier phase.

There were some limitations in this analysis. First, the number of subjects in this analysis was limited to 317 of the subjects of the original TOWER trial ($n = 542$). This is because not all study subjects had BMD measured using DXA. There was no selection bias, because there were no significant differences in baseline characteristics such as age and BMI between the subjects included in this analysis and all subjects in the TOWER trial. This small sample size might be a reason why the difference was not significant between the teriparatide and placebo groups. Second, the incidence of vertebral

Table 2 Fracture incidence by treatment response at final observation

BMD measurement site	Treatment response		Incident fracture rate (%)	P
	Absolute change category	Number of fractures/total		
Lumbar	$\geq -2.5SD$	1/60	1.7 %	0.555
	$< -2.5SD$	2/60	3.3 %	
Femoral neck	$\geq -2.5SD$	0/53	0.0 %	0.049
	$< -2.5SD$	4/87	4.6 %	

fracture was low. Incident vertebral fracture was observed in 20 subjects in the placebo group and 4 subjects in the teriparatide group in this analyzed dataset. However, there was a significantly lower incidence in the teriparatide group, and the incidence was relatively higher in the treatment failure group.

In conclusion, the LSC criterion for lumbar BMD appears to be a useful surrogate marker at an earlier time during treatment for the assessment of treatment success at an individual level, based on the finding of a time-dependent change in the patient proportion with once-weekly teriparatide treatment. Simultaneously, the criterion of $-2.5SD$ was also confirmed to be useful to evaluate treatment efficacy, reflecting the fracture incidence at the final observation. It might be more efficient to use both criteria for treatment assessment to select the most appropriate medications for osteoporosis.

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Compliance with ethical standards

Conflicts of interest MS has received consulting fees from Teijin Pharma, MSD, and Asahi Kasei Pharma and received lecture fees from Chugai Pharmaceutical, Ono Pharmaceutical, Astellas, Pfizer, Daiichi-Sankyo, Eisai, and Eli Lilly Japan. TS has received consulting fees from Asahi Kasei Pharma and research grants from Eli Lilly Japan, Taisho-Toyama Pharmaceutical, Chugai Pharmaceutical, Daiichi-Sankyo, and Ono Pharmaceutical. TN has received research grants and/or consulting fees from Asahi Kasei Pharma, Merck Sharp & Dohme, Daiichi-Sankyo, Eli Lilly Japan, Pfizer, Chugai Pharmaceutical, Amgen, and Taisho-Toyama Pharmaceutical. SU and TK are employees of Asahi Kasei Pharma.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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