Assessing adherence to teriparatide therapy, causes of nonadherence and effect of adherence on bone mineral density measurements in osteoporotic patients at high risk for fracture

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Abstract:

Objectives: To determine (a) adherence rates at 6, 9 and 18 months amongst patients receiving teriparatide treatment for severe osteoporosis and (b) causes of therapy discontinuation and the effect of teriparatide on bone mineral density (BMD) in adherent and nonadherent patients at different time intervals.

Methods: A retrospective chart review of 111 patients receiving teriparatide from September 2004 to June 2007 was performed. Patients' self-reports were used to record adherence and causes of nonadherence at 6, 9 and 18 months. BMDs for all patients were measured using the same DXA scanner at baseline and follow up.

Results: Of 111 participants, 17 were male (mean age 60 years) and 94 were female (mean age 69 years). Of these, 12 did not initiate therapy and 4 were lost to follow up. Reported adherence was 89.6% at 6 months, 87.6% at 9 months and 74.7% at 18 months. Causes of nonadherence included cost ($n=4$), no benefit ($n=1$) and adverse events ($n=8$). Common adverse events were leg cramps ($n=9$), headache ($n=5$) and myalgia ($n=4$). Mean spine and femur BMD changes were 3.30% and 0.67% at 4–9 months respectively, and 5.39% and 0.77% at 10–18 months respectively.

Conclusion: Adherence to teriparatide was almost 90% at 9 months and decreased to 75% at 18 months. Adverse events led to nonadherence in 20% of patients. Those who were nonadherent had lower baseline BMD values than those who were adherent. Changes in BMD at the lumbar spine were greater than changes observed at the femoral neck.

Keywords: teriparatide, compliance, adverse events, osteoporosis, adherence

Introduction

Teriparatide (parathyroid hormone [1–34]) is the only anabolic agent currently available for the treatment of osteoporosis in Canada. It stimulates new bone formation on the trabecular and cortical bone surfaces by preferential stimulation of osteoblastic over osteoclastic activity [Dempster *et al.* 2001; Rosen and Bilezikian, 2001; Dempster *et al.* 1993;]. It has been found to significantly reduce vertebral fractures by 65% and nonvertebral fragility fractures by 53% in a randomized controlled trial of treatment-naïve

postmenopausal women who have previously suffered a vertebral fracture [Neer *et al.* 2001]. However, therapeutic benefits such as these are highly dependent upon medication adherence, a term which combines compliance (following the prescribed medication dose regimen) with persistence (continuing medical administration). In most clinical trials, adherence is monitored closely in order to ascertain that study findings are truly a result of the medication efficacy and not whether or not a particular medication was taken. Unfortunately, in clinical practice, many

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patients exhibit poor adherence to the recommended regimen for osteoporosis [Cortet and Benichou, 2006; Siris *et al.* 2006; Caro *et al.* 2004; Yood *et al.* 2003]. Studies have shown that poor adherence has direct clinical implications including lower increases in bone mineral density (BMD) and higher risk of new fractures. In the treatment of osteoporosis, good adherence has generally been defined as the use of 80% or more of prescribed medication [Gold *et al.* 2006]. Adherence is influenced by several factors including age, fracture history, frequency of administration, type of medication prescribed, perception of benefits, comorbidity, fear of adverse events (AEs) and cost [Gold *et al.* 2006; Rossini *et al.* 2006; Weycker *et al.* 2006].

Adherence rates for asymptomatic disease treatments including osteoporosis are typically low; approximately 50% at 1 year outside of clinical trials [Turbi *et al.* 2004]. In osteoporosis therapy, adherence to prescribed regimens declines sharply in the first 3 months following initial diagnosis and continues to decline over subsequent years [Downey *et al.* 2006]. An analysis that included all osteoporosis medications revealed that only 30% of patients were adherent at 1 year and 16% at 3 years [Weycker *et al.* 2006]. Another study that tracked bisphosphonate use found that 43% of patients were adherent at 2 years [Siris *et al.* 2006].

A higher level of disease activity is generally associated with better adherence, and for patients with a previous fracture history, there is evidence that adherence may be greater [Cortet and Benichou, 2006; Rossini *et al.* 2006; Weycker *et al.* 2006]. Given that the risks of new fractures are 3–5 fold greater in patients with a prevalent fracture compared to those without, adherence is an important consideration, particularly for those with severe symptomatic osteoporosis [Gold *et al.* 2006; Gaudio and Morabito, 2005; Reginster *et al.* 2000].

The method of administration of teriparatide, a daily subcutaneous (SC) injection, may have a negative effect on patient acceptance and adherence as opposed to some bisphosphonates that are taken orally once a week. This study sought to examine adherence and causes of nonadherence of daily teriparatide 20 µg SC for 18 months in patients with osteoporosis who had an inadequate response or were intolerant to available treatment.

Methods

Approval from the local research ethics board committee was obtained prior to study commencement. A retrospective chart-review was conducted on all patients from a single rheumatology clinic who were started on teriparatide therapy between September 2004 and November 2007. These patients had been started on teriparatide because they had been diagnosed with osteoporosis, were at high risk for fracture despite available treatments and had experienced an inadequate response or were intolerant to previous treatment. Patients were on concomitant osteoporosis treatments other than bisphosphonates (continued or new) at the discretion of the clinician and most patients were also receiving supplemental calcium and vitamin D. Training and assistance was provided for the use of the teriparatide pen by a contract health-care organization (FCC-Forteo Customer Care program).

Self-reported adherence, defined by administration of the drug 80% or more of the time, was recorded during their follow up at 6, 9 and 18 months. Conversations with the nurse regarding compliance as well as adverse events (AEs) were noted during clinic visits. AEs were also noted through patient self-reports during follow up. Baseline BMD measurements were obtained either at teriparatide initiation or within 1 year prior to initiation of therapy. Additional BMD results were obtained during the course of therapy, or at least at cessation of treatment. Only those BMD measurements acquired on the same DXA unit for each individual patient were included in the analyses. Changes in BMD were calculated by taking the difference from the baseline BMD scan to each follow-up BMD. A multivariate analysis of variance was carried out to determine if age, sex, presence of fragility fracture at baseline (excluding fingers, toes, face and skull), location of fracture at baseline (hip, vertebral or other fragility fracture) or baseline BMD at the lumbar spine or femoral neck were associated with nonadherence.

Results

Charts were reviewed for a total of 111 patients prescribed teriparatide treatment. Of these, 17 were male (15.3%) and 94 were female (84.6%). Study population demographics are presented in Table 1.

Twelve patients who entered the study did not start teriparatide treatment due to cost issues (primarily the lack of drug formulary coverage) or patient preference. Four were lost to follow up at 18 months. Four additional patients stopped teriparatide due to cost issues during the course of the treatment. The average length of time that the nonadherent patients (unrelated to cost) were on teriparatide was 10 months. The number of adherent and nonadherent patients at each time-point in the study is shown in Table 2.

Reasons for nonadherence were related to cost ($n=4$), no benefit ($n=1$) and the occurrence of AEs ($n=8$). Other events that did not lead to nonadherence but were noted included difficulty with injections ($n=2$) and minor AEs such as headaches and leg cramps. A total of 40 AEs were reported by eight patients. A detailed list of the frequency of various AEs is shown in Table 3. Multivariate analyses revealed that, of all variables considered, only the lowest baseline BMD of the femoral neck or lumbar spine was significantly associated with nonadherence. Specifically, when comparing the baseline characteristics of adherent *versus* nonadherent patients, those who

were nonadherent had significantly lower BMD values than those who were adherent ($p=0.041$).

BMD data were not analyzed in 15 patients due to a change in the machine used, lack of follow-up data or loss to follow up. Therefore, BMD data were assessed from 96 cases, some of whom had more than one BMD report for comparison at different times during therapy. Longitudinal changes in BMD are numerically represented in Table 4. Figures 1 and 2 represent changes in spine BMD and proximal femoral BMD, respectively. Changes in BMD per patient year are shown in Figure 3. Although changes in BMD at the femoral neck appear larger in the discontinued group than those that occurred in the teriparatide-treated group over 10–18 months, an ANOVA revealed that these differences were not statistically significant ($F=0.07$, $p=0.93$). Percentage changes in BMD from baseline were, in general, greater at the L-spine compared to the total hip (Table 4) and persisted after adjusting for duration of treatment (Figure 1).

Discussion

Reported adherence with 80% or more of daily teriparatide injections was 89.6% at 6 months,

Table 1. Demographic statistics of study population.

	Female	Male
Number of patients (%)	95 (86%)	16 (14%)
Mean age (SD) years	69.4 (10.3)	59.7 (11.8)
Mean baseline lumbar-spine T-score (SD) ($n=105$) (g/cm ²)	-2.4 (1.5)	-2.3 (1.5)
Mean baseline femoral neck T-score (SD) ($n=105$) (g/cm ²)	-2.2 (1.0)	-2.0 (1.0)
Prior vertebral fracture	47	10
Prior hip fracture	7	0
Prior 'other' fractures	36	8

Table 2. The number and proportion of adherent and nonadherent patients at 3 timepoints.

		Females, n (%)	Males, n (%)
6 months ($n=111$)	Adherent*	73 (65.8%)	14 (12.6%)
	Nonadherent	8 (7.2%)	2 (1.8%)
	Not started	12 (10.8%)	0
	Not followed	2 (1.8%)	0
9 months	Adherent*	71 (63.9%)	14 (12.6%)
	Nonadherent	10 (9.0%)	2 (1.8%)
	Not started	12 (10.8%)	0
	Not followed	2 (1.8%)	0
18 months	Adherent*	60 (54.1%)	11 (9.9%)
	Nonadherent	19 (17.1%)**	5 (4.5%)
	Not started	12 (10.8%)	0
	Not followed	4 (3.6%)	0

*, calculated from only those patients who started therapy and were followed.

**, 4 of 19 patients lost provincial coverage and therefore were not on therapy.

87.6% at 9 months and 74.7% at 18 months in this clinical setting. Adherence in those with severe osteoporosis is reportedly higher than those with asymptomatic disease, likely because patients are well informed about fracture risks associated with the disease and are therefore motivated to prevent the pain of a new fracture [Gold *et al.* 2006]. This could explain the high rates of adherence in our study cohort as 51.3% ($n=57$) had vertebral fractures at baseline.

Our results are similar to those reported in a multicenter, open-label, prospective study that used the same dose of teriparatide and showed adherence rates of about 80% at 18 months [Adachi *et al.* 2007]. Without including the four patients who terminated teriparatide therapy due to cost issues, our adherence results are close to those achieved in this clinical trial scenario of 78% at 18 months. The higher rates of adherence in our study may be explained by the fact that these injections were given for a predefined 18-month period as opposed to a lifelong commitment, repeated interaction and training from the Forteo Customer Care program and ease of use of the pen. Another possibility is that patients may have exaggerated or over-reported their adherence. The only factor which was revealed

to be associated with nonadherence was lower BMD at baseline. It is unknown why those with a lower baseline BMD would be more likely to be nonadherent than those with a higher baseline BMD. While BMD reports are informative for the rheumatologist, its meaning to patients may be limited. Hence, a lower BMD may not necessarily be a factor that promotes increased patient drug adherence. On the other hand, those with lower BMD may have been on more aggressive therapy historically, not only for osteoporosis treatment, but possibly for other comorbidities. The requirement for more rigorous treatment regimens may be overwhelming and consequently reduce adherence. Although we do not have information regarding comorbidities in these patients, it has been suggested that those on other chronic treatments for asymptomatic conditions (i.e. antihyperlipidemics, antidepressants, glaucoma medications and oral diabetes agents) predict nonadherence to bisphosphonates [Curtis *et al.* 2009]. In nursing home patients, low BMD has been associated with older age, greater dependency and increased comorbidities, the latter of which is found to correlate with use of glucocorticoids and antiepileptic drugs [Itkin *et al.* 1999]. Hence, future analyses of adherence in a clinical population may consider assessing whether nonadherence in those with low BMD is independently predicted by concomitant use of these medications.

Table 3. Frequency and type of adverse events reported by study patients.

	Number of patients [% of total]
Leg cramps	9 (9.2%)
Headache	5 (5.2%)
Myalgia	4 (4.1%)
Nausea	3 (3.1%)
Lightheadedness	3 (3.1%)
Hypercalcemia	2 (2.1%)
Other events*	14 (12.6%)
*, other events included mood changes, rectal bleeding, diarrhea, bruising, itchy arms, arthralgia, nephrolithiasis, and abnormal liver function tests.	

The most common side effects in our study were leg cramps (9.2%), headache (5.1%) and myalgia (4.1%). Routine measurements of calcium levels were not performed in our study population. Significant AEs occurred in eight patients that led to discontinuation of treatment (8.2%). Specific events in this subgroup of patients included rectal bleeding, allergic reaction, kidney stone, radiation therapy for lung cancer, transient ischemic attack, diarrhea, weight loss with personality changes and a new diagnosis of prostate cancer. The most commonly reported

Table 4. Changes in bone mineral density over time in patients receiving teriparatide.

	4–9 months ($n=16$)	10–18 months ($n=48$)	Discontinued teriparatide* ($n=7$)
Lumbar spine [% change from baseline, SD]	3.30 [6.65]	5.39 [6.20]	3.16 [6.02]
Femur neck [% change from baseline, SD]	0.67 [9.60]	0.77 [4.56]	1.72 [7.44]
*, these are patients who were adherent but stopped taking teriparatide after an average of 10 months of therapy because of loss of coverage or the presence of side effects.			

AEs associated with teriparatide include injection-site pain and swelling (<3.3% of patients), nausea (8.5%), headaches (7.5%), leg cramps (2.6%), and dizziness (8%). These events resulted in discontinuation rates of 6–19% in clinical trials [Stroup *et al.* 2008; Hodsman *et al.* 2005; Body, 2002]. Our study had similar discontinuation rates. However leg cramps were more frequent in our patient population as opposed to headache, nausea and dizziness seen in other trials.

There has been a concern of development of osteosarcomas in rodents that are given long-term parathyroid hormone in toxicity studies which led to the black box warning in teriparatide labeling in the United States [Vahle *et al.* 2004]. A case of osteosarcoma has been reported in a woman who received teriparatide for one year [Harper *et al.* 2007]. However, this was reported after 300,000 exposures to teriparatide and this has been interpreted as consistent with epidemiological expectations with respect to cases of

Figure 1. Changes in lumbar spine bone mineral density (BMD) after various ranges of treatment periods with teriparatide. Discontinued PTH (parathyroid hormone) refers to seven patients who discontinued PTH due to side effects or loss of coverage after an average duration of 10 months of therapy. Error bars represent standard error of the mean.

Figure 2. Changes in femoral neck bone mineral density (BMD) after various ranges of treatment periods with teriparatide. Discontinued PTH (parathyroid hormone) refers to seven patients who discontinued PTH due to side effects or loss of coverage after an average duration of 10 months of therapy. Error bars represent standard error of the mean.

Figure 3. Changes in lumbar spine and femoral neck bone mineral density (BMD) expressed per patient year (PPY). Error bars represent standard error of the mean.

osteosarcoma in the general population. At the time of data collection, there was no incidence of osteosarcoma in our study population.

In this study, BMD measurements in patients on teriparatide showed an average increase of 5.39% at the lumbar spine and 0.77% at the femoral neck after 10–18 months of therapy. An earlier study by Neer and colleagues reported BMD increases of 9.7% and 2.6% at the lumbar spine and total femur, respectively, after a median of 21 months of therapy in the 20 µg/day group compared with placebo ($p < 0.001$ for both sites) [Neer *et al.* 2001]. In another 18-month study, 203 postmenopausal women with a history of osteoporosis were treated with teriparatide 20 µg/day ($n = 102$) or alendronate 10 mg/day ($n = 101$) [McClung *et al.* 2005]. Areal and volumetric BMD increased from baseline by 10.3% and 3.9% at the spine and femoral neck, respectively, in the teriparatide group. It is likely that patients in this study had less severe disease and fewer baseline vertebral fractures than our patients.

Study limitations

Adherence was measured by patients' self reports collected at 6, 9 and 18 months. It is recognized that self reports depend on memory and honesty, both factors which have potential to affect rate of adherence. This may have been overcome through the Forteo Customer Care program which would notify us when patients came off therapy. The limitations of our study included

the fact that BMD measurements were not done at prespecified intervals nor were they done for all patients at baseline (i.e. initiation of teriparatide treatment). In some patients, baseline BMD values were acquired up to 1 year prior to starting teriparatide. Changes in BMD did not account for the fact that patients were on different therapies prior to starting teriparatide. This may have played a role in the response to therapy. Most studies were performed exclusively in women while this study included men [Miller *et al.* 2008]. These factors may explain the difference in our results from previously published studies.

Conclusion

Adherence to therapy with teriparatide is high with close to 90% remaining on therapy at 9 months and close to 75% completed the full 18 months of therapy. Those who were nonadherent had lower baseline BMD values than those who were adherent. Consistent with previously reported results, changes in BMD at the lumbar spine were generally greater than those observed at the femoral neck.

Conflict of interest statement

None declared.

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