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ORIGINAL ARTICLE

Teriparatide vs. calcitonin in the treatment of Asian postmenopausal women with established osteoporosis

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Abstract This study compared the clinical efficacy, safety, and tolerability of daily subcutaneous injections of teriparatide and salmon calcitonin in the treatment of postmenopausal women with established osteoporosis in Taiwan. This 6-month, multicenter, randomized, controlled study enrolled 63 women with established osteoporosis. They were randomized to receive either teriparatide 20 μg or calcitonin 100 IU daily in an open-label fashion. Lumber spine, femoral neck, total hip bone mineral density (BMD), and biochemical markers of bone turnover were measured, and adverse events and tolerability were recorded. The results at 6 months showed that patients using teriparatide had larger mean increases in spinal BMD than those who used calcitonin (4.5% vs. 0.1%), but the BMD changes in these two groups at the femoral neck and the total hip were not significant. There were also larger mean increases in bone markers in the teriparatide group than in the calcitonin group (bone specific alkaline phosphatase 142% vs. 37%; osteocalcin 154% vs. 23%). We conclude that teriparatide has more positive effects on bone formation than salmon calcitonin, as shown by the larger increments of lumbar spine BMD and bone formation markers, and caused only mild adverse events and no significant change in liver, kidney or hematological parameters. Compared with the published global results, teriparatide seems to be equally effective and safe to use in this Asian population.

Keywords Teriparatide · Calcitonin · Osteoporosis · Bone mineral density

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Introduction

Osteoporosis is a major public health problem in many countries, including in Taiwan [1, 2, 3]. The fractures associated with osteoporosis have been shown to cause considerable disability, loss of quality of life, and mortality [4]. Several therapeutic options are available for the treatment or prevention of osteoporosis. Antiresorptive agents have been useful in the treatment of osteoporosis [5], leading to small increments of bone mineral density (BMD) and substantial decreases in fracture incidence [6, 7, 8, 9]. Recently the effects of a bone formation-stimulating agent-teriparatide, biosynthetic human parathyroid hormone (PTH) were demonstrated in women with

osteoporosis and in men [10]. While larger increments in BMD were seen, they were also accompanied by increases in the biochemical markers of bone formation and a reduction in the incidence of both vertebral and nonvertebral fractures [11, 12, 13]. Teriparatide was reported to be particularly well tolerated at the dose of 20 μg/day. A significant increase in minor leg cramps and rarely some transient dizziness were seen after the first few injections [11]. However, the effect of PTH in an Asian osteoporotic population has not been clarified.

Calcitonin is an approved drug for the treatment of osteoporosis and has been used for more than 20 years in many countries. Clinical experience has shown that the most effective form of calcitonin for treatment of osteoporosis is salmon calcitonin, available for subcutaneous injection or in a nasal spray [8, 14]. Some early studies have supported the use of salmon calcitonin in the prevention and treatment of involutional osteoporosis, using a 100-IU dose injected subcutaneously [15, 16, 17]. A recent report using salmon calcitonin showed that the incidence of vertebral fracture was significantly reduced by one third with a dose of 200 IU transnasally [8].

Thus far there has not been a clinical study comparing teriparatide and salmon calcitonin directly in postmenopausal osteoporotic patients. This study was designed to compare the effects of teriparatide and calcitonin injections on the BMD of the lumbar spine, femoral neck, and total hip and the biochemical markers of bone turnover in Asian postmenopausal women with established osteoporosis.

Materials and methods

Study design

This multicenter, randomized, open-label, controlled study was conducted at five urban medical centers in Taiwan. The study protocol was approved by the institutional review board of each institution prior to initiation of the study, and all 63 enrolled patients gave written informed consent before any study procedure was performed. The study was conducted in compliance with the current revision of the Helsinki Declaration and in accordance with the Good Clinical Practice guidelines.

The study included a 6-month treatment phase after a screening period of up to 2 months; the patients were randomized to receive either teriparatide ($n = 34$) or calcitonin ($n = 29$). Spine and hip BMD were measured at baseline and at the end of the study. Biochemical markers of bone metabolism were assessed at baseline, 3 months and 6 months, at approximately the same time in the morning. Physical examinations were performed during each visit. Adverse events were assessed and laboratory tests performed to evaluate safety. The subjects were excluded if there was evidence of a previous treatment with estrogen, selective estrogen receptor modulator in 3 months, or bisphosphonate in the 12 months prior to the study. Throughout the study period any other drug known to affect bone metabolism was prohibited. Compliance was assessed by asking the patients directly and by quantifying the study materials returned. Any patient who missed more than 50% of the study medication in any of the 2-month visit intervals was considered noncompliant. The compliance criteria were satisfied by 79.4% of those in the teriparatide group and 72.4% of those in the calcitonin group (n.s.).

Subjects

The centers recruited postmenopausal (at least 3 years after menopause) women with established osteoporosis. Patients were required to have a BMD value as measured by dual energy X-ray absorptiometry (DXA; Hologic, Waltham, Mass., USA) 2 standard deviations below the mean of young women or lower, based on the manufacturer's reference values (spine < 0.827 g/cm^2, femoral neck < 0.695 g/cm^2) and a radiographically documented, prevalent osteoporotic vertebral or nonvertebral fragility fracture. Patients were excluded who had any secondary osteoporosis or other diseases which could affect bone metabolism, who had the risk of

Table 1 Demographic and baseline characteristics

	Teriparatide ($n = 34$)	Calcitonin ($n = 29$)
Age (years)	68.06 ± 1.07	66.90 ± 1.39
Height (cm)	150.87 ± 0.81	151.57 ± 0.93
Weight (kg)	55.32 ± 1.41	54.31 ± 1.31
Body mass index	24.34 ± 0.62	23.62 ± 0.50
Years since menopause (years)	20.06 ± 1.38	19.72 ± 1.38
Previous osteoporosis drug user	18	15
BMD (g/cm^2)		
Lumber spine	0.751 ± 0.018	0.748 ± 0.021
Femoral neck	0.585 ± 0.014	0.594 ± 0.014
Total hip	0.697 ± 0.013	0.672 ± 0.019
Bone markers		
Serum BSAP (μg/l)	9.25 ± 1.02	10.86 ± 1.64
Osteocalcin (ng/ml)	17.69 ± 1.63	16.76 ± 1.85

osteosarcoma, active nephrolithiasis or urolithiasis, significant hepatic or renal diseases, malignant neoplasm, and recent use of drugs known to affect bone metabolism. Patients with a BMD more than 4 standard deviations below the young normal mean were also excluded. A total of 118 subjects were evaluated for inclusion, and 63 subjects met all of the eligibility criteria. As a result of the randomization program the number of patients in was not equal in the two treatment groups. Among them, 30 subjects had used drugs for osteoporosis previously. They were 16 of 34 in the teriparatide group; 3 with alendronate, 1 with calcitonin, and 12 with estrogens, and 14 of 29 in the calcitonin group; 2 with alendronate, 3 with raloxifene, 1 with calcitonin and 8 with estrogens.

The overall mean age of the subjects was 67.5 years (range 55–85), and the mean body mass index (BMI) was 24.0 (15.9–32.9). The mean years since menopause were 19.7 (range 6–40). Among the 63 subjects there were eight who had undergone hysterectomy, two of whom had also had bilateral ovaries removed. For the 63 subjects, the mean baseline spine, femoral neck, and total hip BMD were 0.750, 0.589, and 0.686 g/cm^2, respectively. The demographic and baseline characteristics of the patients were similar in the two groups (Table 1).

Treatments

The patients were randomized to receive open-label use of 20 μg teriparatide (Forteo, Eli Lilly) or 100 IU calcitonin (Miacalcic, Novartis) subcutaneously per day, and all patients were supplemented daily with 500 mg elemental calcium and 400 IU vitamin D_3 throughout the 6-month period. The patients subcutaneously injected teriparatide into their lower abdomen or outer thigh on a daily basis during the study period; similar instructions were given for the calcitonin injections. Teriparide was delivered via a prefilled cartridge placed in a Gemini injection device. Calcitonin was provided via prefilled disposable insulin syringes containing 100 IU salmon calcitonin.

BMD, radiography, and bone markers

BMD was measured using either a Delphi A, 4500A, or 4500C model of the Hologic DXA instrument. Each patient was evaluated by the same technician using the same instrument. The long-term coefficient of variation of each instrument was less than 1% using phantom blocks in each center (as well as a phantom block used by all the five centers). The BMD assessment and the determination of the patient's eligibility for entry into the screening phase were made by a centralized quality assurance setup and required at least three vertebrae from L1–L4 were without fractures, osteophytes, or other abnormalities that would interfere with the analysis of the posteroanterior lumbar spine BMD measurement. Vertebral deformities were evaluated on lateral radiography of the thoracic and lumbar spine.

The radiographs were performed according to a standardized protocol. A visual semiquantitative grading of vertebral fractures was performed, based on the criteria of Genant et al. [18]. They were interpreted by a qualified radiologist specialized in skeletal radiology in one of the participating centers. This radiologist was blinded to the treatment, the BMD reading and the eligibility for entry.

The bone markers checked were two osteoblastic products, i.e., bone-specific alkaline phosphatase (BSAP) and osteocalcin (OC). BSAP was measured using a chemoluminescence immunoradiometric (CLIA) assay (Access Ostase; Beckman-Coulter, Brea, Calif., USA) on an automatic analyzer; OC was also measured by a CLIA assay (ELSA Osteo; CIS bio, Bedford, Mass., USA) on an automatic analyzer. The day-to-day variation in these two assays was less than 5%.

Efficacy and safety measures

The primary end-point of the study was lumbar spine BMD. A positive efficacy result was defined as a statistically significant change in lumbar spine BMD from baseline to endpoint. The secondary objectives were the femoral neck or total hip BMD and two biochemical markers, BSAP and OC. Adverse events were recorded and assessed. Physical examinations and laboratory tests, including blood chemistry profiles and complete blood cell counts, were measured to evaluate the safety at baseline, 3 months, and 6 months.

Statistical methods

All statistical tests for the efficacy and safety parameters were two-sided and evaluated at a 5% level of significance. The analyses for the efficacy endpoints were both based on the intention-to-treat principle. Baseline demographic data and clinical characteristics were compared between treatment groups using analysis of variance for continuous variables and Pearson's χ^2 test for categorical variables. The changes in BMD and biochemical markers from baseline to endpoint were compared between the two treatment groups using a two-sample t test. The paired t test was used to test the changes from baseline to each visit within each treatment group. Compliance conditions and the frequencies of adverse effects between the two groups were compared using Pearson's χ^2 and Fisher's exact test.

Results

The mean percentage of change in BMD at the lumber spine, femoral neck, and total hip are shown in Fig. 1. The increase in BMD at the lumber spine in the

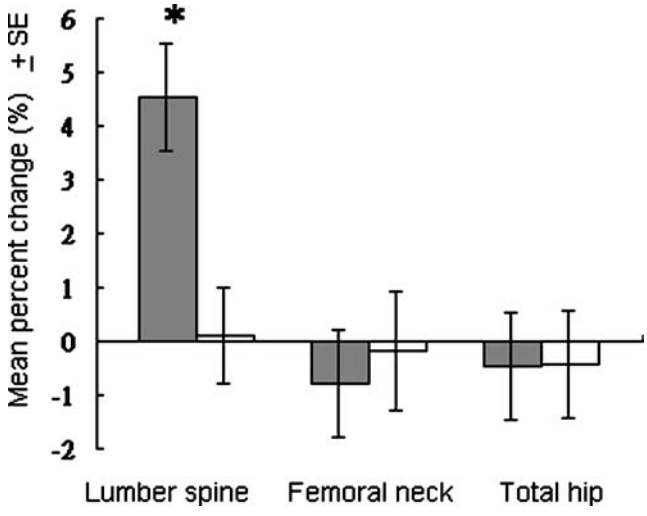

Fig. 1 Mean proportional change (±SEM) in BMD of the lumbar spine, femoral neck, and total hip from baseline. *Gray bars* Subjects given 20 μg PTH; *white bars* subjects given 100 IU calcitonin. *$p = 0.003$ between-group comparison of teriparatide vs. calcitonin

teriparatide group was 4.5 ± 1.0% at 6 months, significantly larger than the 0.1 ± 1.0% increment in the calcitonin group ($p = 0.003$). With teriparatide 60.6% of subjects had a BMD increase of more than 2%, while only 25.9% of the calcitonin group reached this level ($p = 0.007$). The BMD at the femoral neck and total hip showed no significant change throughout the study period in either group. The changes in bone formation markers are shown in Fig. 2. In the teriparatide group BSAP had increased by 67 ± 17% at 3 months ($p < 0.05$) and 142 ± 25% at 6 months ($p < 0.001$; Fig. 2a), and OC had increased by 149 ± 28% ($p < 0.001$) at 3 months and 154 ± 28% at 6 months ($p < 0.001$; Fig. 2b). The increases in BSAP and OC levels of the teriparatide group were significantly greater than those of the calcitonin group at both 3 and 6 months.

No study drug-related serious adverse events were reported during treatment, but two non-drug-related serious adverse events were reported in this study, one in each group. The clinical adverse events are shown in Table 2. There were more hypercalcemia and elevations in alkaline phosphatase observed in the teriparatide group. In the calcitonin group dizziness, vasodilation, and vomiting were more commonly reported. Otherwise, there was no significant difference between the groups in terms of cardiovascular, digestive, musculoskeletal, nervous system, or general systemic adverse effects

Discussion

This study is the first clinical trials comparing the effects of subcutaneous PTH and salmon calcitonin among Asian patients in a head-to-head fashion. The results of this study demonstrate that teriparatide 20 μg subcutaneous daily injections significantly increase lumbar spine BMD and bone turnover markers over 6 months in women with established osteoporosis, with a much more pronounced effect than therapy with calcitonin.

In this trial the effects on spinal BMD were consistent with previous reports which have shown that PTH markedly increases BMD at the lumbar spine, a section composed mainly of trabecular bones [19]. The magnitude of the increments at the 6-month time point in our study was similar to those of other studies in white populations [11, 20]. The changes in BMD in the calcitonin group in this study were also similar to those of previous reports [17, 21, 22] which showed increases of 1–2% at various sites after 2 years of treatment and little change at 6 months. While most of the recent reports of calcitonin treatment used salmon calcitonin nasal spray of 100, 200, or 400 IU daily [8], the bioavailability of the nasal route is about one-half of that of the subcutaneous injection [23, 24]. Thus the comparison between this study and those using nasal calcitonin is apparently valid.

The changes in femoral BMD observed in our study are in agreement with those of other reports looking at a 6 months only short duration, in that a slight reduction or no change was seen at the femoral neck, which is composed primarily of cortical bones [20, 25]. The explanation for these results may be multifactorial. Firstly, in calculating the BMD the increased neck width due to endocortical resorption and periosteal mineral apposition [26] could have compensated partly for the increased bone mass. Secondly, the newly formed bone tissue was less mineralized in the periosteum region, and therefore the response of a cortical bone was not as predominant as that of a trabecular bone. In addition, PTH may require a longer treatment at this site to achieve its effects [10, 11]. Also, the daily dietary calcium intake of our population was only about 450 mg per day. Insufficient total calcium intake may also have contributed to the smaller increase in hip bone density in our patients, as compared to previous studies [11].

The ability of intermittent teriparatide injections to stimulate bone formation was confirmed by the elevation in serum BSAP and OC after 6 months. The increments were consistent with those of previous reports [11, 20]. On the other hand, the salmon calcitonin group showed only slight and nonsignificant increases in BSAP and OC. Calcitonin is an antiresorptive agent which was not expected to show greater effects on bone formation. There may have been a significant decrease in bone resorption markers, but, unfortunately, we did not assess bone resorption markers in this study.

Regarding safety, most of the adverse events in this study were graded as mild in severity. Similar incidence rates were observed in the two groups. No study drug or procedure-related serious adverse events were reported during the treatment period. Comparable laboratory safety profiles were also observed in these two groups. Increase in alkaline phosphatase and hypercalcemia were observed occasionally in the teriparatide group, but the difference in frequency was not statistically significant to that in the calcitonin group. The increase

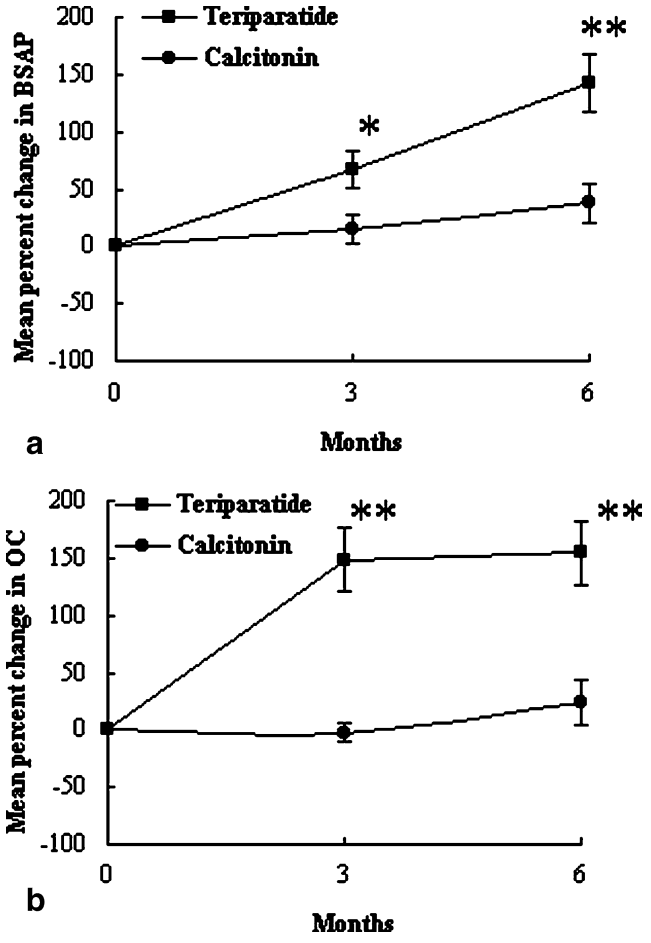

Fig. 2 Mean proportional change (± SEM) in biochemical markers of bone turnover: (**a**) serum BSAP and (**b**) OC at 1, 3, and 6 months from baseline. *Filled squares* Subjects given 20 μg PTH; *filled circles* subjects given 100 IU calcitonin. $*p < 0.05$, $**p < 0.001$ between-group comparison of teriparatide vs. calcitonin

in alkaline phosphatase was probably related to the increases in serum BSAP levels caused by teriparatide injections.

Some limitations of the study need to be mentioned. The sample size was relatively small, and the observational period of 6 months too short for an evaluation of fracture risk reduction (no fractures observed in the study), and probably the changes in hip BMD. We evaluated bone formation markers only and not resorption markers. Therefore some actual effects of calcitonin could not be seen. Nevertheless, there is evidence that an increase in BMD is associated with a reduction in vertebral fracture incidence after PTH treatment [11].

Teriparatide caused significantly greater increase in BMD than salmon calcitonin. However, the association between the magnitude of increases in BMD and the magnitude of reduction in fracture rate remains controversial [27]; whether such an increase in BMD translates into a significantly greater effect on fracture rate reduction in the bone formation-stimulating agent

Table 2 Clinical adverse experiences (*AE*)

	Teriparatide ($n = 34$)		Calcitonin ($n = 29$)	
	n	%	*n*	%
Any clinical AE	31	91.2	29	100.0
Any serious AE	1	2.9	1	3.4
Any drug-related AE[a]	9	26.5	9	31.0
Dizziness	2	5.9	3	10.3
Vasodilatation	0	–	3	10.3
Vomiting	1	2.9	3	10.3
Nausea	1	2.9	1	3.4
Palpitation	0	–	1	3.4
Dyspnea	0	–	1	3.4
Rashes	0	–	1	3.4
Constipation	0	–	1	3.4
Gastrointestinal disorder	0	–	1	3.4
Alkaline phosphatase increased	4	11.8	1	3.4
Hypercalcemia	2	5.9	0	–
Hyperuricemia	0	–	1	3.4
Blood urea nitrogen increased	0	–	1	3.4
Liver function abnormal	0	–	1	3.4

[a]Any AE judged by the investigator as possibly, probably, or definitely drug related

teriparatide than an anti-resorptive agent such as calcitonin remains to be examined.

In conclusion, teriparatide treatment induced significant increases in spine BMD and bone formation markers within 6 months, much more than calcitonin injections, in postmenopausal women with established osteoporosis in this Asian population, and was proved to be safe and well tolerated.

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