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Original Research Article

Comparison of efficacy and safety of teriparatide and hyaluronic acid - calcitonin combination treatments in Chinese osteoporotic patients with risk of bone fracture: A preliminary investigation

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Abstract

Purpose: *To evaluate the efficacy and safety of teriparatide and hyaluronic-calcitonin combination treatment in Chinese osteoporotic patients with risk of bone fracture.*
Methods: *Osteoporotic patients aged 30 to 80 years, with at least one vertebral fracture and immediate risk of new vertebral fractures, were recruited from Hangzhou First People's Hospital. They were randomly assigned to two groups (50/group) treated with either teriparatide (20 µg/day) or hyaluronic acid + calcitonin (1:1 ratio, 200 IU daily) for 12 months. The patients were followed up every 3 months. Bone mineral density (BMD) was evaluated using x-ray absorptiometry. The proportion of patients with new fractures was recorded. Changes in serum osteocalcin and serum bone alkaline phosphatase (BSAP) from baseline to endpoint were also measured.*
Results: *Treatment with teriparatide at a dose of 20 µg/day resulted in a significant reduction in the proportion of patients with new fractures ($p < 0.05$), when compared to patients treated with a combination of hyaluronic acid + calcitonin (200 IU daily). Teriparatide treatment for 12 months resulted in significant increase in lumbar BMD. Significant increases in spine BMD were evident after 3 months of treatment. There were significantly greater increases in serum osteocalcin and BSAP levels in teriparatide-treated patients than in those given hyaluronic acid + calcitonin. The most common treatment adverse event reported by both sexes was dizziness.*
Conclusion: *These results demonstrate that teriparatide is efficacious and well tolerated in Chinese men and post-menopausal women with osteoporosis, when compared to the combination of hyaluronic acid and calcitonin. The efficacy of teriparatide is not associated with gender differences.*

Keyword: *Teriparatide, Calcitonin, Hyaluronic acid, Bone-specific alkaline phosphatase, Postmenopausal, Bone mineral density*

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INTRODUCTION

Osteoporosis is one of the key causes of vertebral/non-vertebral fracture, especially in elderly people: every year, more than 1 million fractures in the Unites States are due to osteoporosis [1-3]. The disease is more common in women, especially postmenopausal women

[4,5]. Therefore, several studies have focused mainly on women due to higher prevalence of bone fractures. However, osteoporosis-related mortality is higher in men than in women [6-8]. Thus, it is clinically important to identify safe and efficacious treatments for osteoporosis in the Asian population.

Teriparatide is an anti-resorptive agent usually applied in management of osteoporosis [9-11]. Several reports have shown that patients treated with teriparatide (20 µg) had more than 60 % reduction in the occurrence of bone fractures and reduction in the occurrence of non-traumatic fractures, relative to placebo-treated patients [12-14]. Other studies reported that combination of teriparatide with hormone replacement therapy (HRT) significantly increased BMD in postmenopausal women, when compared to HRT [15-18]. Overall, teriparatide at the dose of 20 µg, is effective and well tolerated in the management of osteoporosis.

Calcitonin has been approved in China for the management of osteoporosis [19,20]. Several lines of clinical evidence have shown that calcitonin administration at a dose of 200 IU/day significantly reduces vertebral fracture risk, and significantly increases lumbar spine BMD [19,20]. Moreover, the efficacy and safety of hyaluronic acid in management of osteoporosis are well established [21]. However, the efficacy and safety of teriparatide, relative to calcitonin-hyaluronic acid combination in Chinese osteoporotic patients with risk of bone fractures, has not been investigated. Thus, the present study was designed to compare efficacy and safety of teriparatide and hyaluronic acid-calcitonin combination in Chinese osteoporosis patients with risk of bone fracture.

METHODS

Patients and study design

Osteoporosis patients aged 30 to 80 years, with at least one vertebral fracture, and high and immediate risk of new vertebral fractures, were recruited from Hangzhou First People's Hospital. They were randomly assigned to two groups treated with either teriparatide (20 µg/day) or 1:1 mixture of hyaluronic acid + calcitonin at a dose of 200 IU daily, for 12 months. Calcium and vitamin D supplements were administered to all enrolled patients. Patients with a history of skeletal radiotherapy, suspected carcinoma or a history of carcinoma or any condition likely to affect the study-related outcome were excluded. Patients who had received treatments that are known to affect bone metabolism were excluded. Moreover, patients with hypersensitivity to teriparatide or calcitonin, diluents or excipients of teriparatide or calcitonin were excluded. The study received approvals from ethics committee of the Institutional Review Board of Hangzhou First People's Hospital (*vide* EC approval no. IRB/2018-EC/HFPH-321), and the standard guidelines for animal care were followed [22].

Efficacy and safety assessment

The primary efficacy endpoint was to determine the proportion of patients with new vertebral fractures in both treatment groups. The secondary endpoint was to evaluate the effect of both treatments on BMD and biochemical markers of bone formation and resorption [serum osteocalcin and serum bone alkaline phosphatase (BSAP)]. Bone mineral density (BMD) was evaluated using x-ray absorptiometry. The proportion of patients with new fractures was recorded. In addition, changes in serum osteocalcin and BSAP from baseline to endpoint were measured. Safety was also evaluated.

Statistical analysis

Comparison of categorical/numerical variable data was done using appropriate statistical methods such as Chi-square/Fisher exact or unpaired *t*-test/Man Whitney. Numerical data with greater variation in response were analyzed using non-parametric test. All analyses were carried out using Statistical Package for the Social Sciences (SPSS) software. Percentage changes in lumbar spine BMD and biomarkers from baseline were analyzed using *t*-test or Wilcoxon signed rank test. Comparison of numerical data with confounding variables was done using analysis of covariance. Statistical significance of difference was assumed at $p > 0.05$.

RESULTS

Patients profile and demography

A total of 100 patients with osteoporosis were recruited (50 per group), and data were included in statistical analysis. Demography and baseline characteristic were similar in both treatment groups (Table 1).

Incidence of fracture

Treatment with teriparatide at a dose of 20 µg/day resulted in statistically significant reduction in the proportion of patients with new fractures, when compared to patients treated

with combination of hyaluronic acid + calcitonin at a dose of 200 IU daily (Table 2). The patients treated with teriparatide had lower risk of vertebral fractures and non- vertebral fractures, when compared to those treated with CAL+ HA.

Bone mineral density

In women, treatment with teriparatide at a dose of 20 µg/day (LS mean: 8.2) for 12 months resulted in statistically significant increases in lumbar BMD, when compared with patients treated with CA +HA (LS mean: 1.2), with LSM diff. (f95% CI) of 7.1 (6.2, 7.7; p <0.01). In men, treatment with teriparatide at a dose of 20 µg/day (LS mean: 6.3) for 12 months resulted in statistically significant increases in lumbar BMD, when compared with those treated with CA +HA (LS mean: 0.57), with LSM diff. (95% CI) of 5.7 (4.7, 6.6; p <0.01). Statistically significant increases in spine BMD were evident after 3 months of treatment.

Effect of treatments on biochemical markers

In men and women, significantly greater increase in level of serum osteocalcin was observed after treatment with teriparatide for 12 months, when compared with treatment with hyaluronic acid + calcitonin. Favorable improvement in serum osteocalcin from baseline was observed in teriparatide-treated patients even after 1 month of treatment (Table 3).

After 12 months of treatment, the percentage change in bone-specific alkaline phosphatase from baseline to endpoint (12 months) in Chinese patients (men and women) with osteoporosis was significantly greater in patients treated with teriparatide than in those who received hyaluronic acid + calcitonin. Favorable improvement in BSAP from baseline was observed in teriparatide-treated patients as early as 1 month of treatment (Table 4).

Table 1: Demography and baseline clinical characteristics of the patients

Variable	Teriparatide (n =50)	CAL+ HA (n =50)	*P*-value
Age (years)	69 (7.5)	68 (7.2)	>0.05*
Sex Female/male (%)	60/40	65/35	>0.05**
Weight (kg)	69.4± 6.4	71.8 ± 5.6	>0.05*
BMI (kg/m^2)	25.2 (3.4)	24.9 (3.5)	>0.05*
Treatment duration (months)	5.2 (1.4)	5.3 (1.2)	>0.05*
Vertebral BMD (%)	0.7	0.8	>0.05**
Non-vertebral BMD (%)	0.8	0.8	>0.05**
Percentage of patients taking osteoporosis medication (%)	15.0	14.3	>0.05**

Data for age, weight, BMI, and treatment duration are presented as mean±SD; CLA + HA= calcitonin + hyaluronic acid

Table 2: Summary of new fracture incidence between the two treatment groups

Variable	Teriparatide (n =50)	CAL+ HA (n=50)	*P*
Vertebral fracture			
Number of patients with ≥1 new fracture (%)	4%	13%	
Relative risk reduction compared to CAL+ HA	65%		<0.001
Relative risk (95% CI)	0.35 (0.21- 0.52)		
Non-vertebral fracture			
Number of patients with ≥1 new fracture (%)	4%	14%	
Relative risk reduction	69%		<0.001
Relative risk (95% CI)	0.31 (0.18-0.50)		

P-value as determined using Fisher exact test. CLA + HA = calcitonin + hyaluronic acid

Table 3: Changes in serum osteocalcin in Chinese patients with osteoporosis

Time point	Patients					
	Women			Men		
	TPT (n=50)	*CAL+HA (n=50)*	*Difference (TPT vs CAL+HA)*	*TPT (n=50)*	*CAL+HA (n=50)*	*Difference (TPT vs CAL+HA)*
Baseline (Median)	20	20	-	18.0	17	-
12 months (Median)	52	18	-	28.0	12.0	-
P-value	0.001		0.001	0.001		0.001

Note: CLA + HA = calcitonin + hyaluronic acid; TPT = teriparatide

Table 4: Change in bone-specific alkaline phosphatase from baseline to endpoint (12 months) in Chinese patients with osteoporosis

Time point	Women			Men		
	TPT (n=50)	*CAL+HA (n=50)*	*Difference (TPT vs CAL+HA)*	*TPT (n=50)*	*CAL+HA (n=50)*	*Difference (TPT vs CAL+HA)*
Baseline (median)	11	12	-	10	12	-
12 months (median)	18	10	-	14	10.4	-
% change (median) *P*-value	52 0.001	-9 0.01	0.001	29 0.001	-16 0.001	0.001

Note: CLA + HA = calcitonin + hyaluronic acid; TPT: teriparatide

Safety profile

More than 30% of patients (33%) experienced at least 1 TEAE in both treatment groups (Table 5). However, only 3 patients experienced TEAEs possibly related to teriparatide. There were no mortalities in any of the groups.

Table 5: Summary of adverse events in Chinese patients treated with teriparatide

Variable	Patients	
	Women	*Men*
	TPT (n=50) n (%)	*TPT (n=50) n (%)*
SAEs (%)	4	4
TEAEs (%)	33	33

The most common TEAE reported in both sexes was dizziness (Table 6).

DISCUSSION

This is the first investigation to evaluate the efficacy and safety profile of teriparatide in the treatment of osteoporosis in China. Treatment with teriparatide at a dose of 20 µg/day for 12 months resulted in statistically significant increases in lumbar BMD, and statistically significant reduction in the proportion of patients with new fractures, when compared to the patients treated with combination of hyaluronic acid + calcitonin at a dose of 200 IU/day. A significant increase in BMD was observed after teriparatide treatment, when compared to the patients treated with combination of hyaluronic acid + calcitonin. Similar results have been reported in other studies: a subset of patients examined in a study in which postmenopausal women were treated with placebo or teriparatide in a dose range of 20-40 ug/day showed significant changes in BMD from baseline [12-19].

Furthermore, teriparatide was found to have superior efficacy profile over calcitonin in terms of enhancement of LS BMD [7]. In this study, teriparatide treatment improved median serum levels of bone biomarkers, while calcitonin decreased median serum osteocalcin levels. Regardless of sex, teriparatide treatment reduced the risk of new vertebral fracture, significantly increased BMD, and also improved

serum levels of the bone biomarker osteocalcin, while calcitonin decreased median serum osteocalcin levels. The efficacies of teriparatide and calcitonin treatments on serum levels of osteocalcin are consistent with their mechanisms of action.

Table 6: Summary of Adverse Events in Chinese patients with osteoporosis

Preferred term	TPT (% of patients)	AE possibly related to TPT (% of patients)
Patients with ≥1 TEAEs/SAEs	33	13
Dizziness	8	4
Alanine aminotransferase increased	4	4
Aspartate aminotransferase increased	4	4
Asthenia	4	4
Blood alkaline phosphatase increased	4	4
Blood creatine phosphokinase increased	4	4
Blood uric acid increased	4	4
Cerebral infarction	4	0
Clavicle fracture	4	0
Diarrhea	4	0
Gamma glutamyl transferase increased	4	4
Multi-organ failure	4	0
Nasopharyngitis	4	0
Pain in extremity	4	0
Plasma cell myeloma	4	0
Pulmonary infarction	4	0
Thirst	4	4

Teriparatide preferentially stimulates osteoblasts while calcitonin acts as an anti-osteoclastic agent. The effect of teriparatide on osteocalcin is consistent with previous findings [19]. In the present study, gradual increases in serum bone-specific alkaline phosphatase were also observed after treatment with teriparatide. This was possibly due to the effect of teriparatide on osteoblast activity and its active involvement in bone formation. Overall, the effect of teriparatide on bone biomarkers (osteocalcin and alkaline phosphatase) was similar in both sub-groups (men and women). This suggests that there are no gender differences in efficacy of teriparatide with respect to its effect on osteocalcin or bone-specific alkaline phosphatase.

The most common adverse event seen was dizziness. Teriparatide was safe and well tolerated among Chinese patients with osteoporosis, and the incidence of TEAEs was similar among Chinese men and women. The results of the present study showed that there were no gender differences in efficacy and safety of teriparatide among patients with osteoporosis.

Since the present trial was conducted at a single hospital in China, the findings cannot to be generalized to the Chinese population. Moreover, the sample size used was small. Thus, a large clinical trial with appropriate sample size is needed to confirm the present findings.

CONCLUSION

The present study has demonstrated that teriparatide (at a dose of 20 µg/day) is efficacious and well tolerated in Chinese men and postmenopausal women with osteoporosis, when compared to combination of hyaluronic acid and calcitonin. Moreover, the results suggest that there are no gender differences in efficacy of teriparatide.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. This manuscript was drafted by Changju Hou. Changju Hou and Jing Li, Xuepeng Wang, Liulong Zhu performed experiments under supervision of Maoqiang Li. Jing Li, Xuepeng Wang performed the statistical analysis for this study.

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