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Original Article

Effect of Alendronate and Teriparatide on Bone Mineral Density in Postmenopausal Women

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Background: Alendronate and teriparatide have been proved to benefit osteoporosis patients in some prospective studies. However, no data have been described about the clinical practice of these medications and their efficacy in Taiwanese people.

Method: We reviewed the medical records of an outpatient clinic at National Taiwan University Hospital from 2008 to 2010, and collected data on the postmenopausal women diagnosed with osteoporosis or spinal compression fracture. Lumbar spinal bone mineral density (BMD) was recorded at baseline and at 6, 12, 18, 30, and 42 months after initiating therapy. We compared the patients' BMD before and after the treatment by paired *t* test. Mixed model for repeated BMD measurement was used to determine the effect of age, baseline BMD, and different medications on BMD.

Results: Thirty-seven patients received alendronate and 25 received teriparatide. Mean T scores of BMD before treatment were -3.18 ± 0.57 and -3.30 ± 0.74 in the alendronate and teriparatide groups, respectively. After treatment, BMD increased significantly (alendronate group, p = 0.003; teriparatide group, p<0.001). The effects on BMD were comparable between the alendronate and teriparatide groups (p=0.74). Patients with higher baseline BMD responded to the medications significantly better than patients with lower baseline BMD. Adverse events were mild and few for both medications.

Conclusions: Alendronate and teriparatide could increase lumbar spinal BMD in postmenopausal Taiwanese, with comparable efficacy between the two drugs. Patients with higher baseline BMD responded better to the medications. (Tw J Phys Med Rehabil 2012; 40(3): 135 - 140)

Key Words: alendronate, teriparatide, bone mineral density, osteoporosis

INTRODUCTION

Osteoporosis is an important issue in the geriatric population worldwide. The prevalence of osteoporosis in individuals over the age of 50 years in Taiwan between 1999 and 2001 was 1.63% in men and 11.35% in women.[1] Many women who sustain a fragility fracture are not appropriately diagnosed with and treated for probable osteoporosis.[2,3] Osteoporosis can take a huge personal and economic toll. In Europe, the disability due to osteoporosis is greater than that caused by cancers

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(with the exception of lung cancer).[4]

Current strategies for treating osteoporosis include suppressing bone resorption, promoting bone formation, or both.[5] Bisphosphonates are antiresorptive agents, with efficacy supported by many clinical trials showing an increase in bone mineral density (BMD) and a reduction in fracture.[6] Alendronate was the first bisphosphonate approved in the United States as a 5- or 10-mg tablet for daily administration. The formulation was changed to 35-mg or 70-mg tablets supplemented with cholecalciferol 2,800 IU or 5,600 IU, for weekly administration.[7] Teriparatide is a recombinant formulation of the N-terminal chain 34 amino acid fragment of parathyroid hormone. A single daily 20-μg subcutaneous injection provides a transient increase in serum concentrations of teriparatide and stimulates osteoblast over osteoclast activity, resulting in a net positive bone balance.[7]

The guidelines developed by the European Foundation for Osteoporosis and Bone Disease,[5] the National Osteoporosis Foundation,[6] and the World Health Organization,[8] define osteoporosis based on BMD: AT score lower than -2.5 correlates with a higher risk of fracture.[9]

The course of osteoporosis may have racial difference. Asian individuals have many differences from westerners, including diet, lifestyle, and the intention to receive treatment. However, no data have been described about the clinical practice of these two medications and their efficacy in Taiwanese people. We hypothesized that alendronate and teriparatide could equally increase BMD in postmenopausal female Taiwanese, and that individuals with younger age and/or higher baseline BMD may respond better to the medications.

MATERIALS AND METHODS

This retrospective cohort study was conducted after the approval of National Taiwan University Hospital's Institutional Review Board. We reviewed the medical records of outpatients visiting the authors' clinic at this hospital between 2008 and 2010, and collected data on postmenopausal women who were diagnosed with osteoporosis or spinal compression fracture. These subjects received health education about fall prevention and usual physical activities in their daily life at the outpatient clinic. Inclusion criteria included the treatment with either alendronate or teriparatide for more than 6 months, and the availability of lumbar spinal BMD at least 1 record before and 1 after the treatment. All BMD data were measured by dual-energy x-ray absorptiometry (Lunar Prodigy; GE Healthcare, Pittsburgh, PA, USA). We excluded patients with secondary osteoporosis, such as chronic steroid users, and patients who received other medications for osteoporosis within 3 months prior to the study medication.

Patient data, including general information, previous osteoporotic fracture, and history of medication use for osteoporosis, were collected. We also collected patients' serum calcium and creatinine levels before therapy. BMD was determined at baseline and at 6, 12, 18, 30, and 42 months after initiating therapy. We defined the post-treatment BMD as the last time BMD recorded. Alendronate (Fosamax Plus, alendronate 70 mg with cholecalciferol 2,800 IU, Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA) was used as oral medication of 1 tablet weekly. Teriparatide (Forteo, Eli Lilly and Company, Indianapolis, IN, USA) was used as a 20-μg subcutaneous injection daily.

In the alendronate group, 2 patients had been prescribed alendronate previously, and the others had never received any medication for osteoporosis. In the teriparatide group, four patients had been treated previously: one with spinal fracture received calcitonin nasal spray, two with spinal fracture received alendronate, and one with low BMD (T score -3.03) but no fracture also received alendronate.

Statistical analysis was done with Microsoft Windows-based SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Results were described as mean ± SD, and significance was defined as $p < 0.05$. All tests were two-tailed. The normality was assessed by Kolmogorov-Smirnov test and Shapiro-Wilk test. The pre-treatment and post-treatment BMD in either group was compared by paired *t* test. Mixed model for repeated BMD measurement was used to determine the effect of age, baseline BMD, and different medications on each patient's BMD. Fixed effect of age, baseline BMD, and treatment was applied in this model. Time was put in the repeated factor.

RESULTS

We recruited a cohort of 209 patients, 172 among them

received alendronate or teriparatide treatment. Eighty-three of these 172 patients met the inclusion criteria. We further excluded 16 patients whose BMD was not recorded during continuous treatment course, and 5 patients who received prior treatment and did not have enough washout time of minimally 3 months. Data from a final of 62 patients constituted to the analysis; among them, 37 patients received alendronate and 25 received teriparatide. For the alendronate group and teriparatide group, respectively, the mean age of patients was 72.8 ± 10 and 76.9 ± 10.1 years, the mean T scores of lumbar spinal BMD before treatment were -3.18 ± 0.57 and -3.30 ± 0.74, the post-treatment mean follow-up time were 15 and 9 months (Table 1). In the alendronate group, 8 patients had previous spinal compression fracture and 1 patient had distal radius fracture. In the teriparatide group, 15 patients had spinal compression fracture and among these 15 patients, two patients also had hip fractures. The serum calcium and creatinine levels in all patients were within normal limits before treatment.

Adverse effects of alendronate occurred on one patient with gastrointestinal upset when taking the drug, but she tolerated it for more than 3 years. Adverse effects of teriparatide included gastrointestinal upset on one patient and skin rash on another.

In both groups, mean post-treatment T scores increased significantly when compared with the baseline values (paired *t* test, $p=0.003$ and $p<0.001$ for alendronate and teriparatide group, respectively) (Table 2). In mixed model analysis, the effect on BMD did not show significant difference between the two groups ($p=0.74$). Age did not affect drug effect ($p=0.20$), either. However, patients with higher baseline BMD responded to the medications significantly better than patients with lower baseline BMD ($p<0.001$) (Table 3).

Table 1. Patients' profiles before treatment

Group	Alendronate	Teriparatide	*P*
Number of patient	37	25	
Age	72.8±10	76.9±10.1	0.88
Number of previous fracture			0.25
None	28	10	
Spine	8	15	
Wrist	1	0	
Hip	0	2	
T score of lumbar spinal BMD	-3.18±0.57	-3.30±0.74	0.50
Previous medication for osteoporosis			0.002
None	35	21	
Alendronate	2	3	
Others	0	1	
Serum calcium (mmol/l)	2.31±0.18	2.38±0.15	0.82
Serum creatinine (mg/dl)	0.87±0.22	0.95±0.35	0.30
Number of adverse effects			0.02
None	36	23	
Gastrointestinal discomfort	1	1	
Skin rash	0	1	

Mean values are shown in mean ± SD.

Table 2. Comparison of baseline BMD and post-treatment BMD by paired *t* test

	Alendronate	Teriparatide
Baseline BMD	-3.18±0.57	-3.30±0.74
Post-treatment BMD	-2.60±0.66	-2.73±0.93
P	0.003	< 0.001

BMD: bone mineral density; data are shown as mean±SD.

Table 3. Mixed model for repeated BMD measurements

Fixed factor	Estimate	*P*
Intercept	0.54	0.38
Alendronate vs. teriparatide	-0.05	0.74
Age	-0.01	0.20
Baseline BMD	0.78	< 0.001

Repeated factor: time (0, 6, 12, 18, 30, 42 months); dependent variable: BMD.

DISCUSSION

To our knowledge, this is the first study about the effect of alendronate and teriparatide on BMD in postmenopausal Taiwanese. Despite limitations in using small case numbers and short follow up time, this study had comparable result with previous studies, which showed that alendronate and teriparatide can increase spinal BMD.[10-13] In a previous report, spinal BMD increased to a greater extent in women treated with teriparatide alone than in those treated with alendronate alone.[10] However, in our study, there was no significant difference in the BMD increment between the alendronate and teriparatide groups.

In our series, the percentage of previous spinal fractures in the teriparatide group was higher than that in the alendronate group (60% vs. 22%). This difference may be due to the criteria for the payment of teriparatide is stricter than for the payment of bisphosphonates by the National Health Insurance system. Before January 2011, the insurance system paid for bisphosphonates for postmenopausal women or men with (1) osteoporotic spinal compression fractures or hip fractures, and (2) serum creatinine less than 1.6mg/dl. The system paid the teriparatide for patients with at least 2 spinal compression fractures or at least 1 hip fracture caused by severe osteoporosis. However, after January 2011, the insurance system only pays for bisphosphonates for postmenopausal women with (1) T score ≤ -2.5 and with at least 1 osteoporotic spinal compression fracture or hip fracture, or (2) T score between -2.5 and -1.0 and with at least 2 osteoporotic spinal compression fractures or hip fractures; the teriparatide became the second line therapy for postmenopausal women older than 55 years old or hypogonadic men with (1) at least 2 osteoporotic spinal compression fractures or hip fractures if new osteoporotic fracture occurred after antiresorptive agent treatment for one year or the side effects of antiresorptive agents was intolerable, and (2) T score ≤-3.0. In Taiwan, alendronate costs USD $ 8.94 per week, or USD $ 1.28 per day, whereas teriparatide injection costs USD $ 18.1 per day. The different cost may cause the larger number of patients receiving alendronate than teriparatide. In addition, the average age of these patients was above 70 years; the elderly often favor taking oral medication than administering injections by themselves.

As for compliance, more than two-thirds of the patients were lost to follow-up when reviewing the charts, which may be due to poor drug adherence or the possibility that patients purchased medications by themselves. In female Chinese, once-weekly alendronate 70 mg is an effective and well-tolerated agent for the treatment of postmenopausal osteoporosis.[14] A previous study analyzed the factors affecting long-term compliance with oral bisphosphonate on osteoporotic patients, and found that noncompliance occurred mainly due to the adverse effects, the inconvenience of visiting a medical facility, the unusual methods of ingestion, and the poor understanding of the disease.[15] Poor compliance by patients with drug therapies for osteoporosis over a year leaves them at risk for fractures and higher health care costs.[16,17]

Future prospective or large scale studies will be needed to see if these two medications have the similar effect on BMD in Asian people. Although alendronate and teriparatide can increase BMD, we should keep in mind that not only BMD, but also bone quality, is responsible for skeletal fragility. Determining how to emphasize the importance of osteoporosis treatment, how to increase patients' compliance with the treatment, and how to prevent falling are important issues to examine in the future.

This study revealed that alendronate and teriparatide had benefit on spinal BMD in postmenopausal Taiwanese, and that patients with higher baseline BMD responded significantly better than patients with lower baseline BMD. In addition, the adverse effects of these two medications rarely occurred and were minor in our study. Therefore, the treatment for osteoporosis should be started as early as possible.

CONCLUSION

Alendronate and teriparatide increased spinal BMD in postmenopausal Taiwanese with comparable efficacy, disregarded of the patient's age. For either drug, patients with higher baseline BMD responded significantly better than patients with lower baseline BMD. Like patients who have diabetes mellitus or hypertension needed to be followed up for a long time, patients with osteoporosis

also needed to follow up osteoporosis at outpatient clinic regularly. However, how to increase patients' compliance and the will of follow up become an important issue in the future.

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阿崙膦酸鈉及特立帕肽對停經後婦女骨密度的影響

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背景：雖然阿崙膦酸鈉及特立帕肽已被證實可以增加骨質密度，但目前在台灣，仍缺少相關的臨床研究報告。

方法：本研究回溯從 2008 年至 2010 年，停經後婦女於台灣大學醫學院附設醫院有就診並且有骨質疏鬆或脊椎骨折診斷的門診病歷，納入使用阿崙膦酸鈉或特立帕肽連續六個月以上，而且在使用前後至少有一次腰椎骨質密度報告的病人。排除條件包含有次發性骨質疏鬆症(例如:長期服用類固醇者)、合併使用其他骨質疏鬆藥物者。分別紀錄用藥前，用藥 6、12、18、30 及 42 個月後的骨質密度(T score)。接著用配對 t 檢定比較兩組用藥前後骨密度的變化，並以混合模式分析年齡、用藥前骨密度和兩種藥物對骨密度增加的影響。

結果：有 37 位病人接受阿崙膦酸鈉治療，25 位病人接受特立帕肽治療，治療前的骨密度分別爲爲 -3.18 ± 0.57 和 -3.30 ± 0.74。兩組病人在治療後骨密度皆有顯著增加(p=0.003 及 p<0.001)。此外，混合模式分析發現兩組藥物對骨密度增加無顯著差異(p=0.74)，年齡也不會影響藥物治療效果(p=0.20)。然而，用藥前骨密度較高的病人，對藥物治療的反應較好(p<0.001)。治療期間除零星腸胃和皮膚副作用，並無其他嚴重副作用產生。

結論：阿崙膦酸鈉及特立帕肽皆可增加台灣停經後婦女的骨密度，兩者藥物效果不分軒輊。(台灣復健醫誌 2012；40(3)：135 - 140)

關鍵詞：阿崙膦酸鈉(alendronate)，特立帕肽(teriparatide)，骨密度(bone mineral density)，骨質疏鬆症(osteoporosis)

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