The Effects of Low-Dose Bisphosphonate Treatment on Bone Mineral Density and Bone Turnover Markers in Elderly Patients With Osteoporosis

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Received: June 25, 2016 Revised: August 16, 2016 Accepted: August 26, 2016

Key Words: Frail elderly, Bone mineral density, Bisphosphonates

INTRODUCTION

Osteoporosis is a condition characterized by impaired bone strength and an increased risk of fractures, and osteoporotic fractures can result in morbidity and mortality. Therefore, appropriate treatment is crucial for patients who are at a high risk of fractures. Bisphosphonates, among other drugs with different action mechanisms, are the most widely used for osteoporosis treatment, especially in postmenopausal women.

Bisphosphonates directly promote osteoclast apoptosis and have strong antiresorptive efficacy in treating osteoporosis. Several clinical trials have shown that this class of drugs significantly increases bone mineral density (BMD) and has strong antifracture effects. However, there are also potential alarming side effects, including flu-like symptoms and gastrointestinal symptoms, associated with bisphosphonate use, and this can be one of the major reasons for discontinuing the medication. In addition, a recent report raised concerns about the oversuppression of bone remodeling due to long-term bisphosphonate use, which can impair microfracture repair. Taking into consideration these potential accumulating effects, the concept of a drug holiday has recently been proposed for patients who are prescribed bisphosphonates. According to this recommendation, the risks and benefits associated with long-term use of bisphosphonates for treating osteoporosis should be carefully considered. Furthermore, it is recommended that bisphosphonate therapy be continued in patients who still have lower BMD and are at a high risk of fractures despite of long-term bisphosphonate use.

There are only a limited numbers of studies that have reported comparable effects between the administration of low-dose and conventional dose of bisphosphonates.
One study reported that low-dose alendronate (20 mg weekly) suppressed bone turnover markers levels in a group of postmenopausal women with moderate bone loss\(^{17}\). Another study also showed that a half dose of alendronate (70 mg every 2 weeks) improved the percent change in BMD, and there was no significant difference from the effect induced by the standard dose (70 mg weekly)\(^{20}\).

Here, we report our experience with the use of low-dose bisphosphonates, which is the conventional weekly bisphosphonate dose but is administered every other week, in 7 elderly women with osteoporosis to investigate whether the lower dose was effective in improving BMD and suppressing bone turnover markers.

**MATERIALS AND METHODS**

1. **Patients**

All patients were from a Seoul National University Bundang Hospital, Endocrinology after January 2010. The study subjects were all postmenopausal women who did not have a history of taking antiosteoporosis drugs, such as selective estrogen receptor modulators, bisphosphonates, and teriparatide. Age, sex, body mass index (BMI), and comorbidities were collected retrospectively. Laboratory data, such as blood urea nitrogen (BUN), creatinine, and C-terminal telopeptide (CTX) levels; BMD; and radiologic findings of fracture were also collected.

2. **Methods**

BMD was measured by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Medical Systems, Madison, WI, USA) at the anterior-posterior lumbar spine, femoral neck, and total hip. The coefficient of variation (CV) value for BMD measurement in our hospital is 1.0%–1.5% at the lumbar spine, femur neck, and total hip. Therefore, the least significant change is 2.8%–4.2% as calculated by multiplying CV with 2.77, according to the guidelines of the International Society of Clinical Densitometry. A follow-up DXA evaluation was carried out at a 12-month interval after the first administration of low-dose bisphosphonates. Serum CTX, the bone turnover marker, was measured by using the Electrochemiluminescence Immunoassay (Roche, Basel, Switzerland). CTX was assessed at the baseline and at 3, 6, and 12 months after the first administration.

3. **Outcome**

We calculated the percent change in BMD and CTX (mean± standard error [SE]) from the baseline at the lumbar spine, femur neck, and total hip. The mean percent change and SE were calculated using the IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA).

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital, Seongnam, Korea (approval number: B-607/354-701).

**RESULTS**

1. **Baseline Characteristics**

Table 1 shows the baseline clinical parameters and characteristics.

1) **Case 1**

A 79-year-old woman visited the Emergency Department after she had a fall, and a simple lateral spine radiograph revealed a compression fracture at the 12th thoracic spine and 13th lumbar spine. She was undergoing treatment for dyslipidemia and hypertension. Her BMI was 28.2 kg/m\(^2\) and estimated glomerular filtration rate (GFR) was 43.4 mL/min/1.73 m\(^2\). DXA revealed that her lowest BMD T-score was -3.0 (0.581 g/cm\(^2\)) at the femur neck. For treating osteoporosis, alendronate (70 mg) and cholecalciferol (5,600 IU) were administered every other week.

2) **Case 2**

An 84-year-old diabetic woman with a BMI of 27.9 kg/m\(^2\) underwent DXA, which revealed the lowest BMD T-score to be -2.1 (0.692 g/cm\(^2\)) at the femur neck. A simple radiograph showed multiple compression fractures along the whole lumbar spine. The calculated GFR was 107 mL/min/1.73 m\(^2\). The antosteoporotic drugs alendronate (70 mg) and cholecalciferol (5,600 IU) were administered every other week for treating the vertebral fractures.

3) **Case 3**

A 79-year-old woman was diagnosed with type 2 diabetes mellitus (T2DM). She was a carrier of the hepatitis B virus and had dementia. She had no history of fracture, and her BMI was 22.4 kg/m\(^2\) and estimated GFR was 54.1 mL/min/1.73 m\(^2\). The lowest BMD T-score was -2.6 (0.849 g/cm\(^2\)) at the lumbar spine, and therefore, osteoporosis was diagnosed. For the treatment of osteoporosis, alendronate (70 mg) and cholecalciferol (5,600 IU) every other week were prescribed.

4) **Case 4**

A 70-year-old woman who had been treated for dyslipidemia underwent DXA. Her lowest BMD T-score was -2.8 (0.817 g/cm\(^2\)) at the femur neck. She had no history of fracture.
Her BMI was 23.6 kg/m². Her renal function was mildly decreased (BUN, 32 mg/dL; serum creatinine, 1.56 mg/dL) and calculated GFR was 35 mL/min/1.73 m². For the treatment of osteoporosis, alendronate (70 mg) and cholecalciferol (5,600 IU) were administered every other week.

5) Case 5

An 87-year-old woman with T2DM underwent DXA. Her lowest BMD T-score was -2.8 (0.611 g/cm²) at the femur neck. She had no history of fracture. Her BMI was 24.2 kg/m², and

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Comorbidity</th>
<th>Baseline BMD</th>
<th>BUN/Cr (mg/dL)</th>
<th>CTX</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>F</td>
<td>150.0</td>
<td>63.4</td>
<td>28.2</td>
<td>Dyslipidemia, hypertension</td>
<td>LS: -2.3 (0.870)¹ FN: -3.0 (0.581) TH: -2.6 (0.616)</td>
<td>23/1.1</td>
<td>0.751</td>
<td>Alendronate (70 mg every other week)</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>F</td>
<td>156.4</td>
<td>68.3</td>
<td>27.9</td>
<td>Diabetes</td>
<td>LS: -0.3 (1.091)¹ FN: -2.1 (0.692) TH: -1.6 (0.741)</td>
<td>9/0.57</td>
<td>0.259</td>
<td>Alendronate (70 mg every other week)</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>F</td>
<td>146.5</td>
<td>48</td>
<td>22.4</td>
<td>Diabetes, hepatitis B virus, dementia</td>
<td>LS 2-3: -2.6 (0.849) FN: -1.9 (0.717) TH: -1.2 (0.784)</td>
<td>24/1.00</td>
<td>0.473</td>
<td>Alendronate (70 mg every other week)</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>150.8</td>
<td>53.7</td>
<td>23.6</td>
<td>Dyslipidemia</td>
<td>LS 1-4: -2.8 (0.817) FN: -1.5 (0.762) TH: -1.1 (0.806)</td>
<td>32/1.56</td>
<td>0.634</td>
<td>Alendronate (70 mg every other week)</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>F</td>
<td>149.9</td>
<td>54.35</td>
<td>24.2</td>
<td>Diabetes</td>
<td>LS: -1.9 (0.927) FN: -2.8 (0.611) TH: -2.8 (0.594)</td>
<td>36/1.41</td>
<td>0.513</td>
<td>Alendronate (70 mg every other week)</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>F</td>
<td>153.0</td>
<td>56.6</td>
<td>24.2</td>
<td>Diabetes, hypothyroidism, hypertension, dementia, unstable angina</td>
<td>LS 1-4: -2.6 (0.842) FN: -3.4 (0.536) TH: -2.8 (0.599)</td>
<td>20/1.22</td>
<td>0.706</td>
<td>Alendronate (70 mg every other week)</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>F</td>
<td>150.0</td>
<td>51.8</td>
<td>23.0</td>
<td>Diabetes, dyslipidemia, hypertension</td>
<td>LS 1-3: -2.5 (0.831) FN: 0.1 (0.957) TH: 0.7 (1.017)</td>
<td>23/0.75</td>
<td>0.197</td>
<td>Risedronate (35 mg every other week)</td>
</tr>
</tbody>
</table>

BMI, body mass index; BMD, bone mineral density; BUN/Cr, blood urea nitrogen to creatinine; CTX, C-terminal telopeptide; LS, lumbar spine; FN, femur neck; TH, total hip.

BMD: T-score (absolute value [g/cm²]).

¹Degenerative changes were noticed on radiographs.

Fig. 1. Mean percentage change in bone mineral density at the lumbar spine, femur neck, and total hip. Values are presented as the mean ± standard error. LS, lumbar spine; FN, femur neck; TH, total hip; BMD, bone mineral density.

Fig. 2. Mean percentage change in CTX from the baseline. Values are presented as the mean ± standard error. CTX, C-terminal telopeptide.
her renal function was mildly decreased (at the baseline: BUN, 36 mg/dL; creatinine, 1.41 mg/dL) and estimated GFR was 34.0 mL/min/1.73 m². For osteoporosis treatment, alendronate (70 mg) and cholecalciferol (5,600 IU) were administered every other week.

**6) Case 6**

An 84-year-old woman had a history of unstable angina, dementia, T2DM, and hypothyroidism. She had no history of fracture, and BMI was 24.2 kg/m². Her renal function was mildly decreased (BUN, 20 mg/dL; creatinine, 1.22 mg/dL), and the estimated GFR was 41.4 mL/min/1.73 m². When DXA was performed, the lowest BMD T-score was found to be -3.4 (0.536 g/cm²) at the femur neck. For the treatment of osteoporosis, alendronate (35 mg) and cholecalciferol (5,600 IU) were prescribed every other week.

**7) Case 7**

A 78-year-old woman had T2DM, dyslipidemia, and hypertension. She had no history of fracture, and BMI was 23.0 kg/m². Her estimated GFR was 77.7 mL/min/1.7 m². She underwent DXA, and the lowest BMD T-score was found to be -2.5 (0.831 g/cm²) at the lumbar spine. Therefore, risedronate (35 mg) and cholecalciferol (5,600 IU) were prescribed every other week.

### 2. BMD Changes

Fig. 1 shows the mean percentage change in BMD at 12 months after the first administration of a lower dose of bisphosphonates. At the 12-month follow-up, the values (mean ± SE) were 4.0%±0.7% at the lumbar spine, 3.2%±1.1% at the femur neck, and 1.5%±0.6% at the total hip.

### 3. Bone Turnover Marker Changes

Fig. 2 shows the changes in the bone turnover marker CTX over 12 months. The CTX levels decreased in all the 7 cases, and the values (mean±SE) were as follows: -34.0%±6.4% at 3 months, -42.1%±9.6% at 6 months, and -44.7%±9.9% at 12 months.

## DISCUSSION

We observed the therapeutic efficacy of administering bisphosphonates every other week, which is lower than the conventional weekly dose, for osteoporosis in 7 elderly postmenopausal women in Korea. With this regimen, we observed improvements in the BMD at the lumbar spine, femur neck, and total hip, as well as suppressed CTX levels at 12 months from treatment initiation. Furthermore, there was no specific adverse effect or discontinuation of treatment during the 12-month follow-up period. With regard to renal function, the average GFR declined only slightly by 5.7 mL/min/yr after 1 year of follow-up. However, 1 patient showed decreased BMD after 12 months of bisphosphonate administration, and the administration frequency was changed from every 2 weeks to weekly. Despite increasing the frequency of bisphosphonate administration, CTX levels did not improve further, and this was indicated by the increase in CTX levels 6 months later from 0.398 to 0.512. Therefore, it is possible these negative effects were caused by this patient’s compliance to the drug and were not related to the dosing frequency.

The efficacy and safety of bisphosphonate therapy for osteoporosis in postmenopausal women have been proven by many previous randomized, placebo-controlled studies. However, long-term bisphosphonate use is associated with an increased risk of adverse events, such as osteonecrosis of the jaw and atypical femur fractures. Therefore, the balance between benefits and potential risks should be carefully considered when prescribing bisphosphonates.

Recently, some studies reported that a low dose of bisphosphonates can be as effective as higher doses, particularly in Asians when compared with Caucasians. Gertz et al. reported that the cumulative urinary clearance rate of a 10-mg dose of alendronate was 0.4% in Caucasian women, which was similar to the values in Korean (0.48%) and Japanese (0.43%) women who were administered half the dose (5 mg) of alendronate. Furthermore, a subsequent study was performed to confirm the efficacy of administering half the dose of bisphosphonates in Asians. One study on early postmenopausal Korean women reported that when once-weekly, low-dose alendronate (20 mg weekly) was administered to women with moderate bone loss, the bone resorption marker improved considerably as compared to the effect observed with the placebo. Another study from China reported similar efficacy for low-dose alendronate (70 mg every 2 weeks) as compared to the standard dose (70 mg every week) with respect to the percentage change in BMD at the lumbar spine, femoral neck, and total hip; however, the bone turnover marker level decreased moderately in the standard-dose group as compared to the low-dose group.

However, data showing the efficacy of low-dose alendronate (70 mg every 2 weeks) in the Korean population are lacking. We observed an improvement in BMD and bone turnover marker after administering alendronate or risedronate every other week in all the 7 elderly postmenopausal women in this case series, including the patient who had marginal renal function. One patient had multiple compression fractures, one showed poor compliance to bisphosphonate medication, and two had decreased renal function. Moreover, the patients ranged in age from 70 to 87 years.
Usually, bisphosphonates are contraindicated when the glomerular filtration rate is less than 35 mL/min/1.73 m². Additionally, it is known that sufficient water intake can prevent renal toxicity when bisphosphonates are administered in patients who show a moderate decline of renal function. However, theoretically, as renal function declines, drug accumulation in the bones increases, and the protective effect of fracture prevention persists for 5 years after discontinuing the medication\textsuperscript{10}. Therefore, when prescribing bisphosphate treatment for patients with marginal renal function, a lower dose might help preserve renal function and provide therapeutic efficacy.

Several unexpected side effects, such as gastrointestinal intolerance and musculoskeletal pain, are associated with bisphosphonates. These side effects can decrease medication compliance, especially in older patients. Therefore, administering low-dose bisphosphonates rather than the standard dose might increase compliance by decreasing the adverse side effects and improving BMD. Moreover, there are some concerns around the potential risk of the oversuppression of bone turnover after long-term bisphosphate use. Several animal experiments have shown that prolonged use of alendronate inhibits the normal repair of bone microdamage, resulting in microdamage accumulation\textsuperscript{29-31}. For these reasons, a low-dose therapy could be considered for elderly women, especially those who are at a higher risk of developing over-suppression of bone turnover.

Previous studies usually included postmenopausal women with an average age of 60 years\textsuperscript{17,18,20}; however, all our patients were over 70 years of age and had many comorbidities. As we are in the midst of an aging society, this report provides useful clinical information to guide the prescription of bisphosphonates for elderly Korean women.

In conclusion, although this study included a very limited number of study subjects, we observed the potential therapeutic efficacy of a lower dose of bisphosphonates, indicating that the administration of oral bisphosphonates every other week rather than the conventional weekly regimen can improve BMD and suppress bone turnover markers in elderly Korean women. However, further clinical studies are required to address the efficacy of prescribing a lower dose or less frequent dose of bisphosphonates.

**Conflict of Interest Disclosures:** The researchers claim no conflicts of interest.

**Supplementary Materials**

Supplementary Table can be found via http://dx.doi.org/10.4235/src/sm/agmr-20-131-s001.pdf.

**REFERENCES**


