Influence on the bone mineral density and bone metabolism marker after the interruption and reinitiation of monthly minodronate therapy in postmenopausal women with osteoporosis

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Abstract

Objectives: The purpose of this study was to investigate the influences of interruption and reinitiation of monthly minodronate therapy on the bone mineral density (BMD) and bone metabolism markers in postmenopausal women with osteoporosis.

Methods: Study patients were included if they had been administered monthly minodronate therapy for ≥6 months, interrupted the therapy, and reinitiated the therapy for ≥12 months. The BMD and bone metabolism markers were assessed at 4 time points: initiation, interruption, reinitiation and 1 year after reinitiation of therapy.

Results: A total of 23 patients were enrolled. The mean monthly minodronate treatment period was 23.8 ± 12.9 months following a mean interruption period of 11.9 ± 5.4 months. Once increased by monthly minodronate treatment for 2 years on average, the BMD of lumbar spine and radius did not significantly decrease even after an interruption for 1 year on average. However, the BMD of the femoral neck did decrease after interruption. The BMD of the lumbar spine and radius increased further after 1 year of monthly minodronate retreatment. The BMD of the femoral neck did not change. Once decreased after the treatment for an average of 2 years followed by an interruption for 1 year, bone metabolism markers increased gradually but did not recover to baseline levels. A potent suppressive effect on bone resorption was noted. The change rate was greater for the bone formation marker procollagen 1 N-terminal propeptide.

Conclusions: Monthly minodronate treatment increases BMD and reduces bone metabolism markers. The effect lessens after treatment interruptions, and can be restored by retreatment.

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more promptly without causing upper gastrointestinal symptoms [9]. These results suggest favorable adherence of minodronate. We also reported that monthly minodronate alleviated low back pain, reduced bone metabolism markers, and increased bone mineral density (BMD) [10]. Furthermore, monthly minodronate induced fewer upper gastrointestinal symptoms after switchover from prior bisphosphonate products, and therefore, it may provide patients with a more convenient treatment option and enhance long-term treatment adherence among patients [10].

However, interruption of bisphosphonate therapy is sometimes required in clinical practices, based on patient request or consultations from a dentist [11]. It has been reported that 1 year after discontinuation of a 3-year treatment with risedronate, BMD decreased at the lumbar spine and femoral neck, and bone metabolism markers returned to control group levels. Despite these changes, the risk of new morphometric vertebral fractures remained lower in patients who had previously taken risedronate than in controls. The timing of interruption of bisphosphonate therapy should be carefully considered taking into account the risk of fracture. Eastell et al. [12] reported that 1 year of discontinuation of risedronate treatment in patients who had received 2 or 7 years of risedronate therapy led to increases in cross-linked N-telopeptide of type 1 collagen/creatinine (NTX/Cr) levels toward baseline and decreases in femoral trochanter and total hip BMD. A report for the alendronate therapy [13] indicated that the risk of fractures following withdrawal correlated only with patient age and BMD at the time of withdrawal, and did not correlate with BMD 1 year after withdrawal or bone metabolism marker values at 2 years. No studies have reported how withdrawal from monthly minodronate (50 mg) influences BMD or bone metabolism. Moreover, there are no studies reporting how monthly minodronate retreatment influences BMD and bone metabolism after withdrawal.

The objective of this study was to clarify, for the first time, the effects of withdrawal from monthly minodronate treatment, and retreatment following withdrawal on BMD and bone metabolism markers in postmenopausal women with osteoporosis.

2. Methods

2.1. Study design

This study was a case series performed in accordance with the Declaration of Helsinki. The purposes and methods of this study were explained to all participants, and they provided informed consent. The study protocol was reviewed and accepted by Institutional Review Board of Okamoto Orthopaedics and Sports Clinic (approval number: 0202).

2.2. Study centers and period

This multicenter, retrospective, observational, case-series study was conducted simultaneously at 4 facilities between October 2011 and March 2017.

2.3. Study subjects

The study population comprised 23 postmenopausal women with primary osteoporosis who met the Japan Osteoporosis Society’s diagnostic criteria for primary osteoporosis, year 2012 revision [14], received monthly minodronate for 6 months or longer, then interrupted the treatment, and subsequently reintegrated the treatment and continued to receive the drug for 12 months or longer. The inclusion criteria were age of ≥55 years and no treatment history with bisphosphonate products. Key exclusion criteria were: patients with esophageal abnormalities such as stricture or achalasia, inability to stand or sit upright for at least 30 minutes, hypocalcaemia, secondary osteoporosis, serious cardiovascular disease, serious renal or hepatic dysfunction, and malignant neoplasm. Patient disposition is shown in Fig. 1.

Patients ranged in age from 56 to 83 years with a mean age of 72.6 ± 7.4 years (mean ± standard deviation). A past history of fractures, such as vertebral fractures and femoral neck fractures, was found in 14 of the 23 patients (60.9%). Seventeen patients received a combination of monthly minodronate and an active vitamin D3 formulation, and the remaining 6 received the minodronate monotherapy. The duration of prewithdrawal minodronate treatment ranged from 6 to 48 months, with a mean duration of 23.8 ± 12.9 months.

As shown in Table 1, the most commonly reported reason for the interruption of minodronate therapy was that the patient or his or her family wanted to withdraw from treatment because of decreases in bone metabolism markers, i.e., bone resorption marker, serum tartrate-resistant acid phosphatase 5b (TRACP-5b) and bone formation marker, serum procollagen 1 N-terminal propeptide (P1NP), compared with respective reference values (11 patients, including overlaps). The treatment was interrupted in 9 patients because of dental treatment (none of them experienced osteonecrosis of the jaw). One patient wanted to discontinue medication because of the disappearance of lumbar back pain. Three patients withdrew for the sake of anxiety about the long-term treatment with the drug.

During the interruption of minodronate treatment, 17 patients were on an active vitamin D3 preparation as a therapeutic or rescue drug for osteoporosis and 6 patients received no such drugs. Commonly reported reasons (including overlaps) for the reinitiation following minodronate withdrawal included recurrent lumbar back pain in 12 patients, anxiety about fractures in 6 patients, dentist permission for reinitiation of oral medication in 5 patients, and restoration of reference values of bone metabolism markers in 5 patients (Table 1).

2.4. Analysis

2.4.1. Measurements of BMD and bone metabolism markers

The BMD was measured at the lumbar spine (L1–4), femoral neck, and distal 1/3 radius using dual energy x-ray absorptiometry. There were a total of 4 time points for evaluation at each institution: start of treatment with minodronate, start of therapy interruption, start of therapy reintegation following the interruption, and 1 year after reintegation of the therapy. The following bone metabolism markers were measured at the same 4 time points at each institution: bone resorption marker, serum TRACP-5b (provided by DS Pharma Biomedical Co., Ltd., Tokyo, Japan), and the bone formation marker, serum P1NP.

| 31 Patients who continued monthly minodronate therapy for ≥6 months, then interrupted the therapy |
| 8 Patients who continued the interruption |
| 23 Patients who reinitiated minodronate therapy |
| 12 Analysis for changes in lumbar spine BMD |
| 13 Analysis for changes in femoral neck BMD |
| 8 Analysis for changes in distal 1/3 radius BMD |
| 20 Analysis for changes in bone metabolism markers |

Fig. 1. Patient disposition. BMD, bone mineral density.
Table 1

Situations of monthly minodronate treatment and the interruption (n = 23).

| Item                                    | Value          |
|-----------------------------------------|----------------|
| Duration of minodronate treatment (prewithdrawal), mo | 23.8 ± 12.9   |
| Duration of minodronate interruption, mo  | 11.9 ± 5.4     |
| Reasons for the interruption (including overlaps) |                |
| Marker                                  | 11 (47.8)     |
| Dentistry                               | 9 (39.1)       |
| Pain mitigation                         | 1 (4.3)        |
| Anxiety about long-term medication      | 3 (13.0)       |
| Reasons for the reinitiation (including overlaps) |            |
| Pain                                    | 12 (52.2)     |
| Anxiety                                 | 6 (26.1)       |
|Permission of the dentist                | 5 (21.7)       |
| Marker                                  | 5 (21.7)       |
| Rescue medicine                         |                |
| Not used                                | 6 (26.1)       |
|Active vitamin D                         | 17 (73.9)      |

Values are presented as mean ± standard deviation or number of patients (%).

2.4.2. Adverse events

New fractures that occurred during the withdrawal period were investigated. Radiographic evaluations were performed in the thoracic and lumbar vertebrae (lateral and anterior-posterior direction), and pelvis (anterior-posterior direction). New morphological fractures and clinical fractures were investigated in this study.

2.5. Statistics

Data were analyzed for statistically significant differences using a 1-way analysis of variance and post hoc analysis using Bonferroni's method for adjusting multiple comparisons, and adjusted P-values were calculated for each comparison (BellCurve for Excel ver. 2.12, Social Survey Research Information Co., Ltd., Tokyo, Japan) with the level of significance set at 0.05.

3. Results

3.1. Changes in lumbar spine BMD

Complete data were collected for 12 of the 23 patients. As shown in Fig. 2A, the BMD values obtained before the start of minodronate treatment, before interruption, at the time of minodronate reinitiation, and at 1 year after reinitiation were 0.784 ± 0.108, 0.707 ± 0.110, 0.716 ± 0.127, and 0.463 ± 0.113, 0.473 ± 0.110, 0.472 ± 0.108, and 0.472 ± 0.108 g/cm², respectively. The BMD values obtained before withdrawal and 1 year after reinitiation were significantly higher than the levels obtained before the start of minodronate treatment. Fig. 4B shows the change rate data.

3.4. Changes in bone resorption marker TRACP-5b

Complete data were collected for 20 of the 23 patients. As shown in Fig. 5A, significant changes were found between most of all time points; before the start of minodronate treatment, before the interruption, at the time of minodronate reinitiation, and 1 year after reinitiation. Change rate data are shown in Fig. 5B.

3.5. Changes in bone formation marker P1NP

Complete data were collected for 20 of the 23 patients. As shown in Fig. 5C, this marker, like TRACP-5b, exhibited significant changes between most of all groups; before the start of minodronate treatment, before interruption, at the time of minodronate reinitiation, and at 1 year after reinitiation. As shown in Fig. 5B and D, TRACP-5b change rates between before the start of minodronate treatment and before interruption, between before interruption and the start of minodronate reinitiation, and between before interruption and 1 year after minodronate reinitiation were 164.3% ± 79.8%, 39.0% ± 27.4%, and 23.7% ± 20.6%, respectively. The P1NP change rates were consistently higher at 228.6 ± 169.8, 89.8 ± 59.7, and 43.0 ± 51.6, respectively.

3.6. Adverse events

No new fractures occurred during the withdrawal period.

4. Discussion

Our analysis of patient background factors showed that the most commonly reported reason for interruption among the 23 patients with a duration of minodronate treatment (prewithdrawal) of 23.8 ± 12.9 months was anxiety about the nonfulfillment of the marker criteria (11 patients). These interruptions came about according to requests from the patient or recommendations of the doctor, and severely suppressed bone turnovers were taken into account. In fact, bone resorption marker TRACP-5b or bone formation marker P1NP was below lower limit (120 mU/L or 26.4 ng/mL, respectively) in these 11 patients before the interruption. Nine patients interrupted the treatment due to the recommendations of the dentist. This seemed to be an effect of the position paper on mandibular osteonecrosis in Japan. One patient reported pain mitigation and 3 patients complained of anxiety about long-term administration. It appeared that severely suppressed bone turnovers were taken into account. Treatment was not interrupted in any patient because of upper gastrointestinal disorders. As stated by Yoshioka et al. [9] and Sakai et al. [10], minodronate treatment may produce lower incidences of upper gastrointestinal disorders. Seventeen patients (73.9%) received a rescue therapy with an active vitamin D₃ formulation in this study. There were no obvious differences in the changes of BMD and bone turnover markers between the patients treated and those not treated with an active vitamin D₃. Therefore, we believe that a rescue therapy with an active vitamin D₃ did not significantly affect the changes of BMD and bone turnover markers. Plain vitamin D and calcium were not provided to the patients in this study.
It is noteworthy that 12 patients experienced pain again after interruption of the treatment, and for this reason, they reinitiated the treatment. This fact demonstrates that minodronate suppresses lumbar back pain, suggesting that this effect was reduced after interruption.

A total of 23 patients were enrolled in this study. Once increased by monthly minodronate treatment for 2 years on average, the BMD of the lumbar spine, femoral neck and radius did not significantly decrease even after a withdrawal for 1 year on average. However, the BMD of the femoral neck decreased more

Fig. 2. Changes in lumbar spine bone mineral density (BMD). The measured data (A) and difference from value at the start of interruption (B) are shown. SD, standard deviation.
prominently after interruption, compared with those of the lumbar spine and radius. In the Fracture intervention trial Long-term E Xtension (FLEX) study previously performed to compare the effects of discontinuing alendronate treatment after 5 years vs. continuing for 10 years [15], the BMD of the femoral neck tended to decrease after alendronate discontinuation, while the BMD of the lumbar spine tended to increase. The finding from the FLEX study supports our result. Furthermore, we speculate that osteoarthritis (OA) progression may be associated with the difference between the femoral neck and lumbar spine in the change of BMD after interruption, because OA frequently occurs in the elderly such as our study patients (mean age, 72.6 years), and higher BMD at the lumbar spine but not at the femoral neck is associated with an increased risk of developing incident radiographic knee OA [16]. The BMD of the lumbar spine and radius tended to increase further with 1 year of monthly minodronate retreatment, although the BMD of the femoral neck did not change. With regard to bone metabolism markers, a study by Eastell et al. [12] showed that 1-year discontinuation of daily risedronate (5 mg) treatment in patients who had received 2–7 years of risedronate therapy led to increases in NTX/Cr levels toward baseline and decreases in femoral trochanter and total hip BMD. After interruption during 1 year following minodronate treatment for 2 years on average, once decreased bone metabolism markers increased gradually but did

Fig. 3. Changes in femoral neck bone mineral density (BMD). The measured data (A) and difference from value at the start of interruption (B) are shown. SD, standard deviation.
not return to baseline values. Although direct comparisons may be difficult because of differences in study design, sample size, patient background, and other factors, the above results suggest that a monthly 50-mg minodronate formulation might more potently suppress bone resorption than a daily 5-mg risedronate formulation.

The bone metabolism marker change rate was greater for the bone formation marker P1NP than for the bone resorption marker TRACP-5b. The potent bone resorption suppression by minodronate and the decrease in bone formation resulting from the associated coupling suggested that bone formation recovers earlier than bone resorption after interruption in treatment. These effects seemed to be reproducible using minodronate retreatment.

This study does not mention the possible effects of minodronate treatment, interruption, and retreatment on BMD and bone metabolism markers, or the duration of its use. Although it seems difficult to compile adequate data on the interruption and reinitiation of the therapy (because of the small sample size, single-arm study without control subjects and short treatment duration), it is hoped that a large-scale, long-term, controlled study will be conducted.

Fortunately, no new fractures occurred in any of the 23 patients. It has been reported that discontinuation of risedronate for 1 year after 3 years of treatment decreased BMD at the lumbar spine and

![Figure 4](image-url)
femoral neck, and bone metabolism markers returned to control group levels. Despite these changes, in our previous study, the risk of new morphometric vertebral fractures remained lower in risedronate patients than in controls [11]. Our present study might reflect those effects reported in that study. However, judging from femoral neck BMD change data, it is unlikely that the risk of femoral neck fractures was reduced.

In a study on patients receiving alendronate [13], we showed that the risk of fractures following withdrawal correlated only with patient age and BMD at the time of withdrawal, and not with BMD at 1 year after withdrawal, or bone metabolism marker values at 2 years. Based on this fact and pain suppression as a possible reason for withdrawal and reinitiation, we consider it to be preferable to continue treatment for long periods without withdrawal. Even if minodronate is unavoidably suspended for various reasons, retreatment will be effective on BMD and bone metabolism markers; therefore, retreatment should be considered to reduce the risk of fractures. Effectiveness or safety has been compared between bisphosphonates agents (minodronate, alendronate, risedronate, ibandronate) in some clinical studies [9,17,18], and we think it is important that these agents may be chosen in the clinical practices, additionally considering the influence on the effectiveness and safety after the interruption and reinitiation of these bisphosphonates agents.

Some study limitations should be noted. In particular, as previously mentioned this was a single-arm observational study with a small sample size. The data were retrospectively analyzed in per protocol populations, and this also causes the decrease in sample size. We also should note that the present study did not standardize the measuring machine for the BMD among participated medical sites. Thus, care should be taken when interpreting the results.

5. Conclusions

In conclusion, monthly minodronate treatment increases BMD and reduces bone metabolism markers. Their effects lessen after treatment withdrawals, but can be restored by retreatment.

Conflicts of interest

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