Osteoporosis and Sarcopenia 4 (2018) 61–68

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: http://www.elsevier.com/locate/afos

Original article

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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ARTICLE INFO

Article history:
Received 13 March 2018
Received in revised form
19 April 2018
Accepted 8 May 2018

Keywords:
Minodronate
Therapy interruption
Therapy reinitiation

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.

1. Introduction

Osteoporosis is a metabolic bone disorder characterized by skeletal fragility and deterioration of bone structure that occurs most commonly in elderly people [1,2]. Currently, several types of antiosteoporotic drugs are available for the treatment of osteoporosis [1]. In Japan, bisphosphonates remain the most frequently prescribed drugs in clinical settings. Oral tablet formulation of daily bisphosphonate was first launched in the 1990s. Since then, weekly and monthly oral tablets and injection formulations have been sequentially developed to increase therapeutic options for patients, decrease adverse drug reactions, and improve patient adherence [3–8].

We previously reported that, compared with weekly alendronate, daily minodronate improved bone turnover and back pain

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Peer review under responsibility of The Korean Society of Osteoporosis.

https://doi.org/10.1016/j.afos.2018.05.001

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 reinitiated 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 D_3 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 D_3 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 reinitiation following the interruption, and 1 year after reinitiation 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.

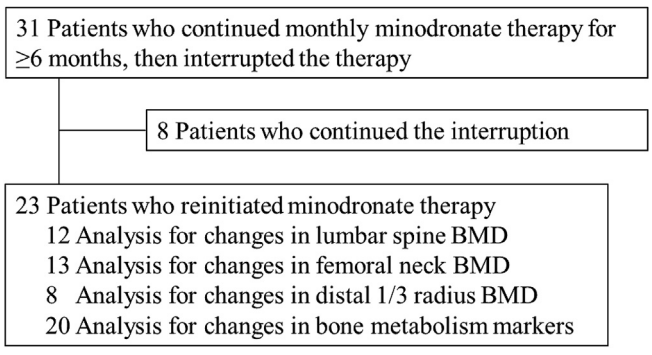

Fig. 1. Patient disposition. BMD, bone mineral density.