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Original Article

Effect of minodronate on the speed of sound of the calcaneus in postmenopausal women with an increased risk of fractures: A clinical practice-based observational study

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Abstract

Background: We previously reported that alendronate and risedronate reduce the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) by 44.9% and 34.7%, respectively, at 3 months after the start of treatment, and increase the speed of sound (SOS) of the calcaneus by 0.6% and 0.65%, respectively, at 12 months after the start of treatment in postmenopausal women with osteoporosis. The aim of the present clinical practice-based observational study was to examine the effect of treatment with minodronate for 12 months on the SOS of the calcaneus and on bone turnover markers in postmenopausal women with an increased risk of fractures.
Methods: Forty-two postmenopausal women with osteoporosis or osteopenia with a clinical risk factor for fractures who had been treated with minodronate for > 12 months were enrolled in the study. The SOS and bone turnover markers were monitored during treatment with minodronate for 12 months.
Results: Compared to their baseline values, the urinary levels of NTX at 3 months and the serum levels of alkaline phosphatase at 12 months were significantly decreased at 47.5% and 25.8%, respectively. At 12 months, the SOS increased modestly, but significantly, by 0.47%, compared to the baseline value.
Conclusion: The present study confirmed that minodronate suppressed bone turnover and modestly increased the SOS of the calcaneus in postmenopausal women with an increased risk of fractures.

Keywords: bone turnover; minodronate; postmenopausal women; quantitative ultrasound; speed of sound

1. Introduction

Osteoporosis mostly affects postmenopausal women and substantially increases the risk of bone fracture. Oral bisphosphonates such as alendronate and risedronate are widely used as first-line drugs for the treatment of postmenopausal osteoporosis. Oral minodronate, a nitrogen-containing bisphosphonate, was developed in Japan. A randomized, placebo-controlled, double-blind study demonstrated that 1 mg of minodronate daily for 2 years reduced the risk of vertebral fractures by 59% in postmenopausal women with established osteoporosis.[1] A recent randomized controlled trial (RCT) showed that 50 mg of monthly minodronate had a similar efficacy as 1 mg daily dose of minodronate in terms of the bone mineral density (BMD) of the lumbar spine and bone turnover markers with a similar tolerability in patients with involutional osteoporosis.[2] In Japan, monthly minodronate is the first-line drug for treating postmenopausal osteoporosis

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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because of the preference of patients and the convenience of a monthly dosing regimen, compared to a weekly dosing regimen.[3]

Minodronate increases the BMD of the lumbar spine and total hip in patients with involutional osteoporosis[2]; therefore, using dual-energy X-ray absorptiometry (DXA) to measure the BMD remains the optimal method for monitoring the response to minodronate treatment. Quantitative ultrasound (QUS) is a more recently developed noninvasive method to determine bone density and structure *in vivo*. Quantitative ultrasound parameters such as speed of sound (SOS), broadband ultrasound attenuation, and stiffness index can predict the risk of hip, wrist, and total nonvertebral fractures up to 10 years later.[4] Quantitative ultrasound may also provide a better assessment of the structural changes of bone, compared to DXA.[5]

The SOS of the calcaneus can be measured using a QUS device (CM-200; Elk Corp., Osaka, Japan). We recently reported the effects of 12 months of treatment with alendronate and risedronate on the SOS and on bone turnover markers in Japanese postmenopausal women with osteoporosis.[6,7] Alendronate and risedronate reduced the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) and the serum levels of alkaline phosphatase (ALP), and modestly increased the SOS. To date, however, very few studies have examined the effects of minodronate on the SOS in postmenopausal women with osteoporosis. The aim of the present clinical practice-based observational study was to examine the effects of 12 months of minodronate treatment on the SOS and on the levels of bone turnover markers in Japanese postmenopausal women with an increased risk of fractures.

2. Methods

2.1. Ethics approval

The present study was performed at Hiyoshi Medical Clinic (Kanagawa, Japan). The protocol was approved by the Ethics Committee of Hiyoshi Medical Clinic (Kanagawa, Japan).

2.2. Study participants

Forty-two Japanese postmenopausal women with an increased risk of fractures who had been treated with a 50-mg monthly dose of minodronate for > 12 months were recruited at the outpatient clinic of Hiyoshi Medical Clinic (Kanagawa, Japan) during a 5-month period between January 7, 2014 and June 3, 2014. The dose of minodronate used in this study is the dose used in Japan to treat osteoporosis in postmenopausal women, and its safety and efficacy have been demonstrated.[2] Patients were eligible if they had postmenopausal osteoporosis or osteopenia with a clinical risk factor for fractures. The clinical risk factors for fractures included current smoking, a maternal history of hip fractures, and daily alcohol consumption of $\geq$ 2 units.[8] According to the Japanese diagnostic criteria,[9,10] osteoporosis is defined as (1) BMD < 70% of the young adult mean (YAM) or the "presence" of osteopenia on X-ray images of the spine and (2) BMD of 70−80% of the YAM or "possible" osteopenia on X-ray images of the spine and a history of osteoporotic fractures. Dual-energy X-ray absorptiometry of the spine is useful for monitoring osteoporosis in Japanese women and QUS is apparently less useful,[11] therefore osteoporosis the was diagnosed by using the SOS (i.e., < 70% of the YAM or 70−80% of the YAM and a history of osteoporotic fractures) and the X-ray findings of the spine (i.e., "presence" of osteopenia or "possible" osteopenia along with a history of osteoporotic fractures). Osteopenia was defined as a BMD between 70% and 80% of the YAM but without any history of osteoporotic fractures.[9,10] Patients were excluded if they had a history of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, renal failure, or bone diseases such as cancer-induced bone loss because of aromatase inhibitors, primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, multiple myeloma, Paget's disease of the bone, rheumatoid arthritis, or osteogenesis imperfecta.

The assessment before the start of minodronate treatment included a medical history, physical examination, plain radiography of the thoracic and lumbar spine, measurement of the SOS of the calcaneus, and biochemical tests of the blood (e.g., serum calcium, phosphorus, and ALP) and urine (e.g., NTX). The urinary NTX levels were also measured at 3 months after the start of treatment. The serum levels of calcium, phosphorus, and ALP, and the SOS of the calcaneus were measured every 6 months after the start of treatment. We evaluated the outcome of minodronate treatment after 12 months. The compliance of all patients for 12-month minodronate treatment was > 90%.

2.3. Assessment of morphometric vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained at the start of treatment to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture is defined in accordance with the vertebral height on lateral X-ray films.[9,10] In brief, the vertebral height is measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body. A vertebral fracture is defined as (1) a $\geq$ 20% reduction in the vertebral height (A, C, and P), compared to the height of the adjacent vertebrae; (2) a C/A or C/P ratio of < 0.8; or (3) an A/P ratio of < 0.75. Vertebral fractures were assessed at the T4−L4 level.

2.4. Assessment of clinical vertebral and nonvertebral fractures

Low-traumatic osteoporotic clinical fractures were assessed. Clinical vertebral fractures were determined by the clinical symptoms and findings on radiographic or magnetic resonance images of the lumbar and thoracic spine. Nonvertebral fractures such as major osteoporotic fractures of the distal radius, proximal humerus, and hip were determined by clinical symptoms and radiographic images of the wrist, shoulder, and hip joints, respectively.