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Osteoporosis and Sarcopenia 2 (2016) 170–174

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

Original article

Monthly minodronate inhibits bone resorption to a greater extent than does monthly risedronate

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Received 17 June 2016; revised 3 July 2016; accepted 5 July 2016
Available online 3 August 2016

Abstract

As a bisphosphonate, minodronate (MIN) is one of the strongest inhibitors of bone resorption. However, there have been no reports directly comparing the antiresorptive effects of monthly MIN with those of monthly risedronate (RIS). We enrolled 30 cases of osteoporosis (OP; 16 in the MIN group [mean age: 68.2 years] and 14 in the RIS group [mean age: 68.1 years]) to investigate the early effects of treatment by monthly MIN or RIS over a 4-month period using bone turnover marker values. Only female patients were enrolled to avoid gender bias. Urinary cross-linked N-telopeptide of type I collagen (NTX) before treatment and at 1, 2, and 4 months of therapy, as well as serum bone alkaline phosphatase and alkaline phosphatase before treatment and at 4 months afterwards, were evaluated. All bone turnover marker values were significantly decreased at 4 months in both groups. The changes in urinary NTX at the study end point for RIS and MIN were −30.1% and −63.1%, respectively. From 2 months of treatment, the antiresorptive effects on urinary NTX by MIN were significantly higher than those by RIS, indicating that MIN more immediately and strongly inhibited bone absorption. Thus, monthly MIN seems to suppress bone resorption faster and more strongly than RIS in OP treatment.

Keywords: Minodronate; Osteoporosis; Risedronate

1. Introduction

Bisphosphonates (BPs) are the first-line drugs in osteoporosis (OP) treatment [1]. The goal of OP management is the prevention of fractures and ultimately death caused directly or indirectly by bone fragility fractures; indeed, mortality rate was decreased by BP treatment in patients with femoral neck fractures [2,3], and OP therapy using BPs reduced mortality risk in the elderly [4,5].

First launched outside of Japan, alendronate (ALN) and risedronate (RIS) are common BPs employed in OP treatment. These drugs were approved in Japan in 2001 and have been prescribed in once-daily, -weekly, and -monthly regimens. Currently, weekly and monthly BP courses are most widely used for OP [1]. Moreover, Iwamoto et al. [6] reported that greater than 65% of Japanese osteoporotic patients prefer monthly BPs to daily or weekly BPs.

Developed and recently approved in Japan in 2009, minodronate (minodronic acid hydrate; MIN) is the strongest inhibitor of bone resorption among commercially available BPs [7]. MIN is a potent nitrogen-containing BP manufactured in Japan [8] that has been demonstrated to prevent vertebral fractures in Japanese osteoporotic patients based on a placebo-controlled phase III trial [9].

It is very difficult to directly evaluate the effects of BP therapy on the prevention of fractures and ultimate death caused by fractures. Another means of estimating the efficacy

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Peer review under responsibility of The Korean Society of Osteoporosis.

http://dx.doi.org/10.1016/j.afos.2016.07.002

of osteoporotic treatment is bone mineral density (BMD), although a relatively long follow-up period is required to evaluate changes in BMD. Most OP treatments, including BPs, augment BMD through the inhibition of bone resorption. The antiresorptive effects induced by BPs appear in the early period of administration and can be easily confirmed by the measurement of bone turnover markers. Therefore, in the short-term period of BP treatment, bone turnover markers represent useful surrogate biomarkers to evaluate the therapeutic effects of BPs.

Nowadays, MIN and RIS are used as monthly BP options for OP treatment in Japan. In a phase III study, the inhibitory effects of these drugs on urinary cross-linked N-telopeptide of type I collagen (NTX) at 3–6 months of monthly treatment were over 50% and approximately 30%, respectively [10]. We previously compared the early changes in bone turnover markers between daily MIN and weekly RIS to reveal that daily MIN more strongly inhibited bone turnover [8]. From the results of these studies, the bone resorption-inhibiting effect of MIN has become well recognized as stronger than that of RIS. However, there have been no reports directly comparing the inhibition of bone turnover caused by monthly MIN and RIS regimes. We herein investigated the short-term treatment effects of these drugs using established bone turnover markers. The purpose of this study was to confirm the stronger bone turnover inhibitory effects of MIN, even by monthly administration.

2. Patients and methods

The subjects were patients who had been newly diagnosed as having primary OP between June 2013 and May 2014 based on the primary OP diagnostic criteria (2000 revision) [11]. Written informed consent was obtained from all participants prior to enrollment. The subjects were randomly assigned into a group receiving 50 mg/month of MIN (MIN group) or a group receiving 75 mg/month of RIS (RIS group). When participants were given a diagnosis of OP, we used the envelope method to randomly divide them into the MIN group or RIS group.

A total of 32 cases (17 in the MIN group and 15 in the RIS group) were recruited. One case in each group dropped out of the study before the end point due to an inability to visit our outpatient clinic on scheduled dates. Ultimately, we analyzed the data of 30 cases (16 of MIN and 14 of RIS) obtained just before treatment and at 4 months afterwards. Only female patients were enrolled to avoid gender effects.

As a representative bone resorption marker, urinary NTX was measured before drug administration and at 1, 2, and 4 months after commencement. As bone formation markers, serum bone alkaline phosphatase (BAP) and alkaline phosphatase (ALP) [12] were recorded before the start of administration and 4 months afterwards.

Serum BAP was determined using a chemiluminescent enzyme immunoassay/antibody radioimmunoassay. Serum ALP was measured by a modified JSCC reference method by SRL, Inc. (Tokyo, Japan). Urinary NTX was evaluated by the enzyme-linked immunosorbent assay (ELISA) (Osteomark, Osteox International, Seattle, WA). After overnight fasting, serum and first void urine samples were collected between 8:30 a.m. and 10:00 a.m. Immunoassays were performed by SRL, Inc. (Tokyo, Japan). Serum calcium (Ca) was measured using Arsenazo III (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan). Serum phosphorus (P) was determined by means of the Molybdate direct method by SRL, Inc. (Tokyo, Japan).

Lumbar and bilateral hip bone mineral density (L-BMD and H-BMD, respectively) were measured using a Dual-energy X-ray Absorption (DXA) fan-beam bone densitometer (Lunar Prodigy; GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA) at the L1-4 levels of the posteroanterior spine and bilateral hips, respectively. BMD values were determined for the purpose of diagnosing OP in this study and not for evaluating the effectiveness of BPs. The coefficients of variation for the lumbar spine and femoral neck were 0.7% and 1.1%, respectively.

Value changes of urinary NTX before treatment and at 1, 2, and 4 months of therapy in the MIN and RIS groups were measured and presented as the average ± standard error (SE) (Fig. 1). Comparisons between measurement points and baseline values in each treatment group were done using one-sided paired *t*-tests with Bonferroni correction. Group comparisons at each measurement point were performed using one-sided Welch's *t*-tests. The background data of the MIN and RIS groups just prior to treatment are shown in Table 1 and expressed as mean ± standard deviation (SD). The averaged findings of age, weight, height, L-BMD, H-BMD, urinary NTX, serum BAP, ALP, serum corrected Ca, and P were analyzed using Welch's *t*-tests. Value changes of bone turnover markers before treatment and at 4 months of therapy are presented in Table 2. Bone turnover markers were analyzed using one-sided Welch's *t*-tests, while ALP, Ca, and P were

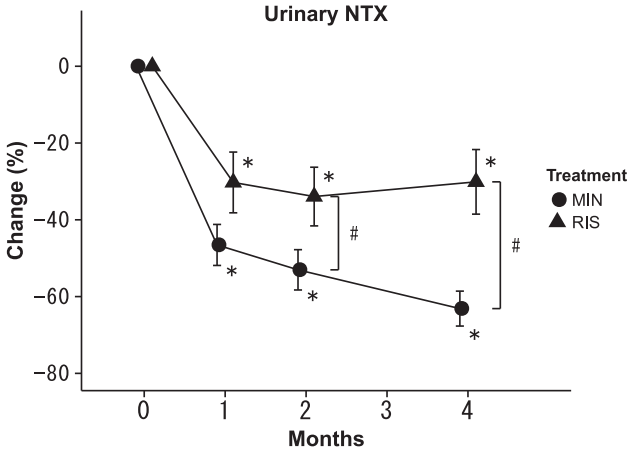

Fig. 1. Value changes of urinary NTX before treatment and at 1, 2, and 4 months of therapy in MIN and RIS groups. Data are shown as average ± SE. *: statistically significant based on one-sided paired *t*-tests with Bonferroni correction. #: statistically significant according to one-sided Welch's *t*-tests. MIN (50 mg/monthly), minodronate; RIS, risedronate (75 mg/monthly); NTX, cross-linked N-telopeptide of type I collagen.