

Original article

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

Mikio Kamimura<sup>a</sup>, Yukio Nakamura<sup>b,\*</sup>, Shota Ikegami<sup>b</sup>, Masatoshi Komatsu<sup>b</sup>,  
Shigeharu Uchiyama<sup>b</sup>, Hiroyuki Kato<sup>b</sup>

<sup>a</sup> Center for Osteoporosis and Spinal Disorders, Kamimura Orthopedic Clinic, Nagano, Japan

<sup>b</sup> Department of Orthopaedic Surgery, Shinshu University School of Medicine, Nagano, Japan

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## 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.

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**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

\* Corresponding author. Department of Orthopaedic Surgery, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto 390-8621, Nagano, Japan  
E-mail address: [yxn14@aol.jp](mailto:yxn14@aol.jp) (Y. Nakamura).

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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 regimens. 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  $\pm$  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  $\pm$  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

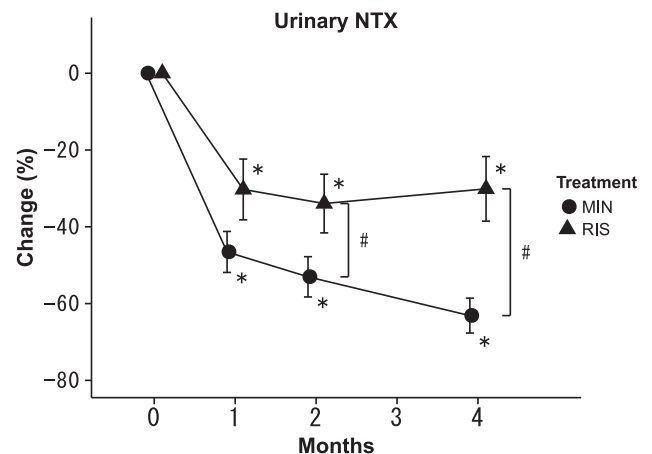


Fig. 1. Value changes of urinary NTX before treatment and at 1, 2, and 4 months of therapy in MIN and RIS groups. Data are shown as average  $\pm$  SE. \*: statistically significant based on one-sided paired *t*-tests with Bonferroni correction. #: statistically significant according to one-sided Welch's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

Table 1  
Background data of MIN and RIS groups before treatment.

	MIN group	RIS group	p value
	(n = 16)	(n = 14)	
Age (years)	68.2 ± 8.2	68.1 ± 6.2	0.986
Height (cm)	153.9 ± 5.4	151.8 ± 6.0	0.332
Weight (kg)	50.9 ± 5.5	48.8 ± 4.1	0.239
L-BMD (g/cm <sup>2</sup> )	0.828 ± 0.050	0.861 ± 0.096	0.248
H-BMD (g/cm <sup>2</sup> )	0.770 ± 0.090	0.723 ± 0.066	0.118
Urinary NTX (nmol BCE/ mmol Cr)	55.3 ± 18.9	59.1 ± 17.6	0.573
Serum BAP (µg/L)	17.5 ± 5.3	19.5 ± 4.9	0.297
ALP (U/L)	245.3 ± 47.3	273.6 ± 53.2	0.139
Serum corrected Ca (mg/dL)	9.30 ± 0.54	8.96 ± 0.38	0.057
P (mg/dL)	3.20 ± 0.42	3.47 ± 0.35	0.064

Values are expressed as mean ± SD.

The mean data for age, weight, height, L-BMD, H-BMD, urinary NTX, serum BAP, ALP, serum corrected Ca, and P were analyzed using Welch's *t*-tests.

MIN, minodronate; RIS, risedronate; BMD, bone mineral density; NTX, cross-linked N-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; ALP, alkaline phosphatase; Ca, Calcium; P, Phosphorus.

analyzed by two-sided tests. Values are expressed as mean ± SE. The comparative data of percent changes between the MIN and RIS groups are shown in Table 3. Bone turnover markers were analyzed by one-sided Welch's *t*-tests, while ALP, Ca, and P were analyzed using two-sided tests. Values are expressed as mean ± SE. A *p* value of <0.05 was considered statistically significant, and indicated as \* or # in the Figure and Tables.

This study was approved by the Institutional Ethics Committee at Showa-Inan General Hospital (Proctol No.: 2015-

18) and carried out in accordance with the revised 2014 Declaration of Helsinki.

### 3. Results

The backgrounds of the patients in the MIN and RIS groups before treatment are shown in Table 1. There were no significant differences between the groups with regard to age, height, weight, BMD, or bone turnover markers. Both groups had satisfactory drug compliance and exhibited no major adverse events from BP therapy.

#### 3.1. Bone resorption marker

At 1 month of treatment, urinary NTX values were significantly decreased by 46.5% in the MIN group and 30.3% in the RIS group as compared with pre-treatment levels. NTX findings were further decreased at −53.0% at 2 months and −63.1% at 4 months in the MIN group. On the other hand, these values plateaued at −33.9% at 2 months and −30.1% at 4 months in the RIS group (Fig. 1). With respect to the increasing ratio (IR), there was a significant difference between the groups from 2 months (*p* = 0.025) to 4 months of after treatment (*p* = 0.001).

In the MIN group, urinary NTX was significantly decreased at 4 months as compared with baseline values, from 55.3 ± 4.7 to 20.2 ± 3.0 (nmol BCE/mmol Cr) (*p* < 0.001), with an IR of −63.1% (*p* < 0.001) (Tables 2 and 3). In the RIS group, urinary NTX was also significantly decreased at 4 months versus

Table 2  
Value changes of bone turnover markers before treatment and at 4 months afterwards.

	MIN group			RIS group		
	Before treatment	After 4 months	p value	Before treatment	After 4 months	p value
Urinary NTX (nmol BCE/mmol Cr)	55.3 ± 4.7	20.2 ± 3.0	<0.001*	59.1 ± 4.7	41.2 ± 5.6	0.003*
Serum BAP (µg/L)	17.5 ± 1.3	10.4 ± 0.8	<0.001*	19.5 ± 1.3	13.6 ± 0.9	<0.001*
ALP (U/L)	245.3 ± 11.8	195.3 ± 18.3	0.018*	273.6 ± 14.2	227.4 ± 13.9	<0.001*
Serum corrected Ca (mg/dL)	9.30 ± 0.13	9.11 ± 0.12	0.065	8.96 ± 0.10	8.95 ± 0.09	0.897
P (mg/dL)	3.20 ± 0.11	2.79 ± 0.14	0.061	3.47 ± 0.09	3.16 ± 0.07	0.033*

Values are expressed as mean ± SE.

Bone turnover markers were analyzed by one-sided Welch's *t*-tests, while ALP, Ca, and P were analyzed using two-sided tests.

MIN, minodronate; RIS, risedronate; NTX, cross-linked N-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; ALP, alkaline phosphatase; Ca, Calcium; P, Phosphorus.

\*Statistically significant.

Table 3  
Percent change and comparison of MIN and RIS groups.

	MIN	p value	RIS	p value	Group comparison p value
Urinary NTX	−63.1 ± 4.5%	<0.001*	−30.1 ± 8.4%	0.020*	0.001*
Serum BAP	−38.2 ± 4.2%	<0.001*	−28.4 ± 3.8%	<0.001*	0.046*
ALP	−19.4 ± 7.3%	0.009*	−16.7 ± 2.9%	<0.001*	0.369
Serum corrected Ca	−2.0 ± 1.0%	0.036*	0.0 ± 1.2%	0.970	0.236
P	−10.9 ± 5.8%	0.039*	−7.8 ± 3.7%	0.028*	0.652

Values are expressed as mean ± SE.

Bone turnover markers were analyzed by one-sided Welch's *t*-tests, while ALP, Ca, and P were analyzed using two-sided tests.

MIN, minodronate; RIS, risedronate; NTX, cross-linked N-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; ALP, alkaline phosphatase; Ca, Calcium; P, Phosphorus.

\*Statistically significant.

baseline values, from  $59.1 \pm 4.7$  to  $41.2 \pm 5.6$  (nmol BCE/mmol Cr) ( $p = 0.003$ ), with an IR of  $-30.1\%$  ( $p = 0.020$ ) (Tables 2 and 3). MIN had reduced urinary NTX significantly more than had RIS at the study end point ( $p = 0.001$ ) (Table 3).

### 3.2. Bone formation markers

In the MIN group, serum BAP was significantly decreased at 4 months as compared with baseline values, from  $17.5 \pm 1.3$  to  $10.4 \pm 0.8$  ( $\mu\text{g/L}$ ) ( $p < 0.001$ ), with an IR of  $-38.2\%$  ( $p < 0.001$ ) (Tables 2 and 3). In RIS patients, serum BAP was significantly decreased at 4 months versus pre-treatment values, from  $19.5 \pm 1.3$  to  $13.6 \pm 0.9$  ( $\mu\text{g/L}$ ) ( $p < 0.001$ ), with an IR of  $-28.4\%$  ( $p < 0.001$ ) (Tables 2 and 3). The decrease in BAP by MIN was significantly greater than that by RIS ( $p = 0.046$ ) (Table 3).

In both test groups, serum ALP values before drug administration were similar and had significantly decreased at 4 months of BP treatment ( $p = 0.018$  and  $p < 0.001$ , respectively) (Table 2). The IR of ALP was  $-19.4\%$  for MIN ( $p = 0.009$ ) and  $-16.7\%$  for RIS ( $p < 0.001$ ), which were comparable (Table 3).

### 3.3. Calcium and phosphorus

In the MIN group, serum Ca was decreased at 4 months as compared with baseline values, from  $9.30 \pm 0.13$  to  $9.11 \pm 0.12$  (mg/dL) ( $p = 0.065$ ), with an IR of  $-2.0\%$  ( $p = 0.036$ ) (Table 2). This parameter did not change remarkably for RIS ( $p = 0.970$ ). The IR of Ca was  $-2.0\%$  for MIN and  $0.0\%$  for RIS, which were not significantly different (Table 3).

Serum P tended to be decreased at 4 months in the MIN group ( $p = 0.061$ ), with a significant change in IR of  $-10.9\%$  ( $p = 0.039$ ). In the RIS group, serum P was significantly decreased at 4 months, from  $3.47 \pm 0.09$  to  $3.16 \pm 0.07$  (mg/dL) ( $p = 0.033$ ), with an IR of  $-7.8\%$  ( $p = 0.028$ ). The IR of P was  $-10.9\%$  for MIN and  $-7.8\%$  for RIS, which were not significantly different (Table 3).

## 4. Discussion

Iwamoto et al. have described that Japanese osteoporotic patients strongly prefer monthly BP (65.2–73.0%) to weekly BP (13.9–15.7%) since the former was more convenient in the MARTO study [6], wherein “dosing schedule fits lifestyle better” was the most common reason for the preference. This was similar to findings in Western patients [6,10,13]. Nowadays, monthly BPs are the mainstay of drug treatment for OP.

It is well recognized that MIN inhibits bone resorption to a greater extent than does RIS [6,10,13]. However, to our knowledge, there have been no reports directly comparing the data of monthly MIN and monthly RIS. This study showed that monthly MIN significantly and more strongly inhibited bone resorption than did monthly RIS. We observed that urinary NTX had decreased by an IR of  $-30.1\%$  at 4 months by

RIS treatment. Similarly, the inhibitory effects on NTX after 3–6 months of RIS treatment were approximately 30% in a phase III trial in Japan [8]. The changes in NTX at 2 and 4 months of treatment with MIN were  $-53.3\%$  and  $-63.1\%$ , respectively. In the Japanese phase III study, monthly MIN therapy produced comparable alterations at 3–6 months of over 50% [8]. Based on the above data, the changes in urinary NTX in this study were in accordance with accepted values for MIN and RIS treatments.

BPs are deposited on hydroxyapatite (HAP) and function after being absorbed by osteoclasts. The binding affinities of BPs to HAP in rank order have been reported as: zoledronate > ALN > ibandronate > RIS > etidronate [15,16]. The binding affinity of MIN to HAP is very similar to that of RIS [17].

Both MIN and RIS are third-generation nitrogen-containing BPs that inhibit farnesyl pyrophosphate synthetase (FPPS) in the mevalonate pathway in osteoclasts. This inhibition suppresses the function of osteoclasts and induces their apoptosis, thereby inhibiting osteoclastic activity [18]. When the inhibitory effect on bone resorption of etidronate is set as “1”, that of RIS is 1,000–10,000 and that of MIN is more than 10,000 [19]. It is known that the 50% inhibitory concentration of FPPS is considerably lower for MIN than for RIS, indicating a stronger inhibitory action of the former [18]. In a recent report on BP binding to FPPS, MIN bound more strongly in pockets for BP side chains and occupied more binding sites as compared with ALN or RIS [18,19]. Here, MIN also exhibited strong effects on bone resorption inhibition that were particularly apparent in considerations with RIS. The results of this study supported the notion of MIN's stronger binding force with FPPS.

Overseas, comparisons of daily (5 mg) and monthly (150 mg) RIS demonstrated no significant difference in BMD increases between the regimes. Thereafter, monthly RIS has been approved at 150 mg doses [18]. Similar findings were witnessed in Japan for daily (2.5 mg) and monthly (75 mg) RIS [14]. On the other hand, comparative studies of RIS indicated that the suppression of bone turnover markers by monthly dosing were significantly weaker than that by daily dosing both in Japan and abroad [14]. Daily (1 mg) versus monthly (30 or 50 mg) MIN has been examined in the phase III trial. Interestingly, monthly 50 mg MIN evoked the same bone metabolic effects and improved BMD values as did daily 1 mg MIN, and thus monthly 50 mg MIN has been approved in this country [19]. Comparative studies of monthly MIN (50 mg) and monthly RIS (75 mg), which had been approved in Japan, were also performed this time. The dosages of daily RIS (5 mg) and monthly RIS (150 mg) approved by FDA are double those approved in Japan. The differences in administered doses of MIN and RIS might have affected the bone inhibitory effects caused by the drugs in this study.

When we evaluate the early phase treatment effects of BPs in clinical practice, bone turnover markers are useful surrogate markers of patient response. Here, we confirmed that MIN more strongly inhibited bone resorption than did RIS at monthly doses. Accordingly, monthly MIN seems to suppress

bone resorption faster and more strongly than RIS in OP treatment.

## 5. Conclusion

Our findings showed that monthly MIN more immediately and strongly inhibited bone resorption than did monthly RIS to represent a more favorable anti-absorptive drug option for OP treatment.

## 6. Limitations

The limitations of this study were a relatively small sample size, no evaluation of the efficacy of the drugs on BMD values or fracture prevention, the exclusion of male patient data.

## Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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