

# Effects of minodronate in postmenopausal women with osteoporosis who received prior treatment with raloxifene

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**Background:** In clinical practice, patients with postmenopausal osteoporosis have often shown a poor response to treatment with an antiresorptive agent for several years. The purpose of this study was to investigate the efficacy of switching raloxifene with minodronate in patients who responded poorly to the treatment of postmenopausal osteoporosis with raloxifene.

**Patients and methods:** This observational study was conducted based on a single-arm, non-randomized, open-label design and was approved by the institute's institutional review board. Postmenopausal women with osteoporosis who became unresponsive in terms of bone mineral density (BMD) after being administered raloxifene for two or more years were enrolled. Patients were treated with 1 mg minodronate daily or 50 mg minodronate monthly. Changes in BMD and serum bone turnover markers were monitored at baseline, 6, 12, and 24 months after switching treatment.

**Results:** Twenty-seven patients were enrolled. Two discontinued treatment because of adverse events related to the study drug. Among the remaining 25 patients, lumbar BMD significantly increased by 3.67%, 5.08%, and 6.97% at 6, 12, and 24 months, respectively, and femoral neck BMD increased by 1.63%, 2.18%, and 3.85% at 6, 12, and 24 months, respectively. Serum bone-specific alkaline phosphatase showed a significant reduction of 30.35% from the baseline ( $p < 0.0001$ ) within the first 6 months, suggesting a stronger antiresorptive effect of minodronate. Serum N-terminal telopeptide of type I collagen showed a tendency to decrease.

**Conclusion:** Switching raloxifene with minodronate is effective in poor responders of osteoporosis treatment and should be considered as one of the treatment options for osteoporosis.

**Keywords:** osteoporosis, minodronate, raloxifene, switching therapy

## Introduction

Postmenopausal osteoporosis is the most common bone disease and is related to a low bone mineral density (BMD) and pathological fractures, which lead to significant morbidity.<sup>1</sup> In addition, the risk of osteoporotic fracture associated with surgical menopause has proven to be increased compared with that in women who have intact ovaries, even in elderly women after menopause.<sup>2</sup> These osteoporotic fractures and pain caused by postmenopausal estrogen deficiency have a long-term serious influence on health-related quality of life. In a rapidly increasing aged population worldwide, a reduction of the burden of osteoporosis in the coming years is clearly needed.

Therapeutic treatments recommended for osteoporosis include bisphosphonates (alendronate [ALN], risedronate [RIS], minodronate [MIN]), selective estrogen-receptor modulators (raloxifene [RAL], bazedoxifene), a full human monoclonal antibody to RANKL (denosumab), active vitamin D<sub>3</sub> derivatives (alfacalcidol, eldcalcitol), and

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recombinant parathyroid hormone (teriparatide).<sup>3</sup> Of these, RAL, a nonsteroidal benzothioephene derivative of the selective estrogen receptor-modulator class, has been shown to reduce the relative risk of vertebral fractures by up to 69% in postmenopausal Caucasian women with osteoporosis after 3 years of treatment, compared with placebo.<sup>4</sup> However, in clinical practice, it has often been reported that some women with postmenopausal osteoporosis have a decreased BMD while taking RAL constantly. Indeed, in a large-scale postmarketing surveillance of RAL in Japan, lumbar BMD increased significantly compared with baseline at 6, 12, 24, and 36 months (2.51%, 2.85%, 4.76%, and 3.51%, respectively).<sup>5</sup> This study demonstrated that a considerable number of patients experienced decreased BMDs after 2-years of treatment with RAL; however, few studies have reported on the timing on when to switch treatment drugs. MIN is an oral nitrogen-containing bisphosphonate developed in Japan, which has a stronger inhibitory effect on farnesyl pyrophosphate synthase in osteoclasts, compared with other bisphosphonates.<sup>6</sup> With regard to bone resorption inhibition, MIN is 1,000 times more effective than etidronate and 10–100 times more effective than ALN.<sup>7</sup> A randomized placebo-controlled trial showed that MIN treatment reduced vertebral fractures by 59% without serious adverse events in Japanese postmenopausal women.<sup>8</sup>

With these in mind, we aimed to analyze the effects of MIN on BMD and bone turnover markers in postmenopausal women with osteoporosis who had received prior treatment with RAL and to investigate the validity of switching from RAL to MIN.

## Patients and methods

### Patients and study design

This observational study was conducted based on a single-arm, non-randomized, open-label design. The women in this study were naturally or surgically menopausal (>12 months since the last menstrual period or after oophorectomy). All were Japanese, aged 36–77 years and from a middle-class community in the northern part of Osaka prefecture in Japan. Lumbar (at the L2–L4 vertebral site) and femoral BMDs were measured by dual-energy X-ray absorptiometry (DXA) (Discovery-A, Hologic, Bedford, MA, USA). The coefficient of variance was <1.0% for the lumbar spine in our institution. Based on their BMDs, patients with osteoporosis (below –2.5 SD of the mean value of healthy 20–44-year-old Japanese women) were diagnosed, and 60 mg RAL (Lilly Co., Ltd., Indianapolis, IN, USA) was prescribed as prior treatment. After at least a 2-year treatment with RAL,

patients whose BMD did not increase, or whose BMD increased initially but who became unresponsive after RAL administration were asked to participate in this study. This study was conducted in accordance with the ethical standards of the Helsinki II Declaration, was approved by the institutional review boards at Academic Clinical Research Center of Osaka University, and registered as a clinical study in UMIN (UMIN000013916). Patients were excluded for the following reasons: 1) concomitant use of other agents for osteoporosis, 2) concomitant use of other agents that potentially affect bone turnover, 3) presence of esophageal stricture or achalasia, 4) inability to remain upright for 30 min after dosing, 5) hypersensitivity to MIN or other bisphosphonate, 6) hypocalcemia, 7) aphagia, esophagitis, gastritis, duodenitis, or ulcers, 8) severe nephropathy, and 9) inappropriate to participate in the study. Participant recruitment was done between September 2010 and February 2015.

After written informed consent were provided, the patients were treated with 1 mg MIN (Astellas Pharma Inc., Tokyo, Japan) once a day or 50 mg MIN (Astellas Pharma Inc.) once a month for 24 months. Participants were instructed to take the tablets with 200 mL water at least 30 min before breakfast and not to lie down within 30 min after taking the medication. Other supplemental osteoporosis treatments, such as active vitamin D and calcium, were continued during the study period. Adverse events were recorded at all post and baseline visits, and their severity and relationship to treatment were evaluated by the investigators.

### BMD measurement

BMDs of the lumbar spine (L2–L4) in the posteroanterior projections and of the femoral neck were measured by dual-energy X-ray absorptiometry (Discovery-A) at baseline, 6, 12, and 24 months after the treatment.

### Biochemical bone markers

At baseline and at 6, 12, and 24 months, the bone absorptive parameter, serum N collagen-type *N*-telopeptide (NTX), was measured by enzyme-linked immunosorbent assay (SRL [Tokyo, Japan]; normal range for women: 7.5–16.5 nmol BCE/L [ $\leq 45$  years], 10.7–24.0 nmol BCE/L [ $> 45$  years]). The bone formation marker, serum bone-specific alkaline phosphatase (BAP), was measured by enzyme immunoassay (SRL; normal range: 9.6–35.4 U/L) until March 2011, and chemiluminescent enzyme immunoassay (SRL; normal range for women: 2.9–14.5  $\mu\text{g/L}$  [ $\leq 45$  years], 3.8–22.6  $\mu\text{g/L}$  [ $> 45$  years]) since April 2011. BAP values were converted based on the compensation formula supplied by the manufacturer.

## Statistical analysis

Paired Student's *t*-test was used to make baseline comparisons of the BMD and bone turnover markers. Results were considered significant at  $p < 0.05$ . All analyses were performed using JMP Pro 10 (SAS Institute Inc., Cary, NC, USA).

## Results

### Patient characteristics

This study enrolled 27 subjects. Baseline characteristics are summarized in Table 1. The median age of the participants was 66 years (range, 37–77 years), and the mean body mass index was  $20.3 \pm 3.0$  kg/m<sup>2</sup>. Four patients (14.8%) were previously treated with other bisphosphonates (etidronate [n=2], ALN [n=2]) before RAL treatment. Two patients (7.4%) discontinued treatment because of adverse events related to the study drug (one experienced epigastric distress at one month, and the other experienced anorexia at four months), and 25 patients completed 24 months of treatment. During the study period, no patient experienced new clinical fractures.

### BMD

Switching RAL to MIN significantly increased lumbar BMD rapidly during the first 6 months ( $3.67\% \pm 3.32\%$ ) and gradually increased thereafter ( $5.08\% \pm 3.81\%$  at 12 months, and  $6.97\% \pm 4.12\%$  at 24 months), whereas it decreased by  $2.61\% \pm 2.32\%$  on prior treatment with RAL after 12 months (Figure 1A). Switching RAL to MIN similarly increased femoral neck BMD by  $1.63\% \pm 3.25\%$ ,  $2.18\% \pm 6.19\%$ ,  $3.85\% \pm 5.96\%$  at 6, 12, and 24 months, respectively, whereas

it decreased by  $1.27\% \pm 3.47\%$  during 12 months of pretreatment with RAL (Figure 1B).

### Bone turnover marker

Percentage change in bone turnover markers from the baseline are shown in Figure 2. Switching RAL to MIN induced a reduction of serum NTX by  $12.95\% \pm 21.60\%$  from baseline ( $p = 0.0305$ ) at 6 months; however, no significant changes were seen after 12 and 24 months (Figure 2A). For serum BAP, it caused a significant reduction of  $30.35\% \pm 16.92\%$ ,  $33.56\% \pm 20.72\%$ , and  $28.01\% \pm 27.20\%$  from the baseline at 6, 12 ( $p < 0.0001$ ) and 24 months ( $p = 0.0016$ ), respectively (Figure 2B). In contrast, prior treatment with RAL did not significantly affect serum NTX and BAP values.

## Discussion

RAL, which has been used to treat postmenopausal osteoporosis in Japan since May 2004 (60 mg tablets), has been shown to increase lumbar spine BMD, improve bone strength, and prevent vertebral fractures, as well as reduce the risk of invasive breast cancers.<sup>9–11</sup> Thus, RAL remains one of the first treatment options for postmenopausal osteoporosis. However, we often encounter women with postmenopausal osteoporosis whose BMDs decrease despite the constant use of RAL. In the present study, we report that switching RAL to MIN in these patients significantly increased their lumbar and femoral BMDs, accompanied by a significant decrease of bone turnover marker, serum BAP. Particularly, lumbar spine BMD significantly increased by  $5.08\% \pm 3.81\%$  and  $6.97\% \pm 4.12\%$  at 12 and 24 months, respectively, which showed a comparable effect as a primary treatment by MIN administration for postmenopausal osteoporosis in a large prospective study ( $6.1\%$  at 12 months).<sup>12</sup>

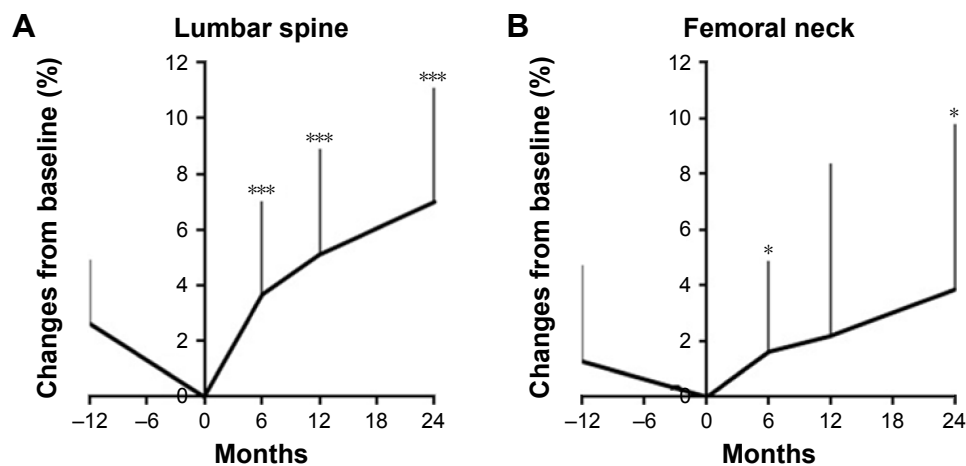
It remains a clinical issue whether the treatment drug should be altered in women with osteoporosis treated long-term with antiresorptive agents, such as bisphosphonates (ALN, RIS, or MIN) or selective estrogen-receptor modulators (bazedoxifene, RAL) when they are not responding to these agents. Although RAL is known to continuously exert the preventive effect against vertebral fractures for at least 3 years,<sup>9</sup> decreased BMD might lead to poor compliance from patients in clinical practice if they are informed about this information. Thus, the protocol of alternative treatment options would be meaningful to have and should be prepared; however, no protocols have conclusively been determined. Although several studies regarding switching therapies have been reported, many of them are focusing on teriparatide rather than antiresorptive agents because it is

**Table 1** Demographics and baseline characteristics of the study population

Characteristics	Values
Age (years), median (range)	66 (36–77)
Height (cm)	154.7±5.6
Weight (kg)	48.5±7.0
Body mass index (kg/m <sup>2</sup> )	20.3±3.0
Lumbar BMD (g/cm <sup>2</sup> )	0.719±0.113
Femoral neck BMD (g/cm <sup>2</sup> )	0.543±0.091
Serum NTX (nmol BCE/L)	15.44±4.93
Serum BAP (U/L)	13.02±3.46
Previous HRT, n (%)	5 (18.5)
Previous bisphosphonate use, n (%)	4 (14.8)
Etidronate	2 (7.4)
Alendronate	2 (7.4)
Risedronate	0 (0.0)

**Note:** Data are expressed as mean ± SD, unless otherwise noted.

**Abbreviations:** BMD, bone mineral density; NTX, N collagen-type N-telopeptide; BAP, bone-specific alkaline phosphatase; HRT, hormone replacement therapy; BCE, bone collagen equivalent.



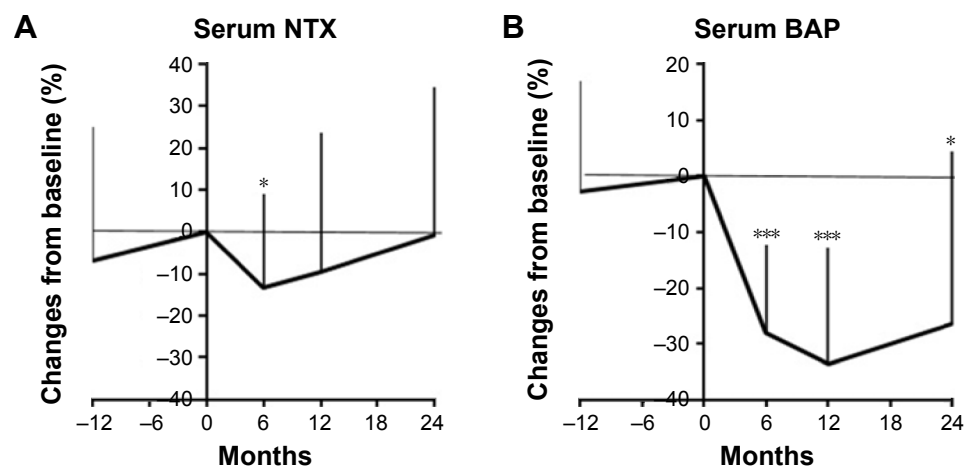
**Figure 1** Percentage change of BMD of the lumbar spine (L2–4) (A) and femoral neck (B) from the baseline during the follow-up period.

**Notes:** Points: mean, vertical lines: standard deviation, \* $p < 0.05$  and \*\*\* $p < 0.001$  versus baseline.

**Abbreviation:** BMD, bone mineral density.

the only anabolic agent available and indicated for the treatment of men and postmenopausal women with osteoporosis who are at high risk for fracture, including those who have failed or are intolerant of previous osteoporosis therapy.<sup>13–15</sup> However, teriparatide is usually used as a second-line treatment for patients with severe osteoporosis who are at high risk for fracture or have osteoporotic fractures and is therefore, not indicated for every patient.<sup>16</sup> Eiken and Vestergaard recently reviewed eleven prospective studies that assessed switching treatment after ALN or RIS in women with postmenopausal osteoporosis. All studies were of short duration (all 24 months or less) and none of the studies had the statistical power to assess fracture-reduction efficacy.<sup>17</sup> Thus, they concluded that further long-term studies were needed, although transitioning to other therapies is a very frequent occurrence in clinical practice.

Among various bisphosphonates clinically available in Japan, we chose MIN in this study. MIN is reported to show the strongest inhibition of bone resorption among all the bisphosphonates used for osteoporosis treatment in Japan.<sup>7</sup> Sakai et al recently reported that 50 mg MIN monthly indeed alleviated low back pain, reduced bone turnover markers, increased bone density, and induced fewer upper gastrointestinal symptoms after switching from prior bisphosphonate treatment.<sup>18</sup> More recently, switching weekly ALN or RIS to monthly 50 mg MIN in patients with rheumatoid arthritis significantly increased lumbar and femoral neck BMDs at 12 months, indicating that switching to MIN may be an alternative treatment option.<sup>19</sup> To the best of our knowledge, the present study is the first to evaluate the efficacy of switching therapy from RAL to MIN in patients with osteoporosis who no longer responded to RAL.



**Figure 2** Percentage change of biochemical bone markers, serum NTX (A) and BAP (B) from the baseline during the follow-up period.

**Notes:** Points: mean, vertical lines: standard deviation, \* $p < 0.05$  and \*\*\* $p < 0.001$  versus baseline.

**Abbreviations:** NTX, Ncollagen-type N-telopeptide; BAP, bone-specific alkaline phosphatase.

## Limitations

This study has limitations. This is an open-label observational study involving a small number of patients, and patients are not randomized. It is pivotal to make an appropriate control to prove the efficacy, which we were unable to do. Further studies would be needed to confirm the findings in the present study.

## Conclusion

Switching RAL to MIN significantly increased lumbar and femoral neck BMDs after 24 months, accompanied by the significant reduction of bone turnover marker, serum BAP, suggested that MIN is effective in RAL poor responders in clinical practice and should be considered as one of the treatment options for osteoporosis.

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## Disclosure

The authors report no conflicts of interest in this work.

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