Osteoporosis and Sarcopenia 5 (2019) 122–127

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

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

Original article

Effects of monthly minodronate with or without eldecalcitol addition in osteoporosis patients with rheumatoid arthritis: An 18-month prospective study

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ARTICLE INFO

Article history:
Received 27 June 2019
Received in revised form
24 October 2019
Accepted 26 November 2019
Available online 16 December 2019

Keywords:
Bone mineral density
Eldecalcitol
Minodronate
Osteoporosis
Rheumatoid arthritis

ABSTRACT

Objectives: Increasing bone mineral density (BMD) to reduce fracture risk is a primary goal of osteoporosis treatment. This prospective, observational study evaluates the effects of monthly minodronate (MIN; 50 mg) with or without eldecalcitol (ELD) addition in osteoporosis patients with rheumatoid arthritis (RA) during 18 months.

Methods: The cohort was prospectively and randomly split into the MIN monotherapy group (14 cases) and MIN plus ELD group (combination group; 14 cases) due to no reports on the effectiveness and safety of MIN therapy in relation to ELD addition for comparisons of serum tartrate-resistant acid phosphatase (TRACP)-5b, bone alkaline phosphatase (BAP), and BMD of the lumbar 1–4 vertebrae (L-BMD), bilateral total hips (H-BMD; the mean value of the right and left hips), and bilateral femoral necks (FN-BMD) at baseline and at 6, 12, and 18 months of treatment.

Results: Baseline values were comparable between the groups apart from a tendency for higher TRACP-5b in the combination group. Seven of 14 patients in the combination group had received previous bisphosphonate treatment. BAP was significantly more reduced in the monotherapy group at 6 months, with no other remarkable differences for TRACP5b, L-BMD, H-BMD, or FN-BMD during the observation period.

Conclusions: The above findings suggest that regardless of ELD addition, MIN potentially improves BMD during 18 months in osteoporosis patients with RA.

1. Introduction

Osteoporosis is a metabolic bone disorder characterized by skeletal fragility and deterioration of bone structure that most commonly affects elderly people. Fragility fractures caused by osteoporosis can occur following minimal trauma or, in some cases, without any at all. The ultimate goal of osteoporosis treatment is the prevention of fractures to extend healthy life expectancy. Although multiple antiresorptive and bone-forming drugs are available for osteoporosis, this condition remains the most common bone disease in humans [1].

Minodronate (MIN) is a third-generation nitrogen-containing bisphosphonate (BP) that was originally developed in Japan. Several studies have demonstrated that MIN can increase bone mineral density (BMD) and decrease fracture risk in the treatment of primary osteoporosis [2,3], with similar effects reported by Hasegawa et al. [4] in glucocorticoid-induced osteoporosis. However, few reports exist on the efficacy or adverse events of MIN in osteoporosis patients with rheumatoid arthritis (RA). Moreover, none have addressed the additive effects of active vitamin D during MIN treatment.

Vitamin D supplementation is often provided with the first-line osteoporosis drug, BP treatment. In Japan, vitamin D supplementation is covered by national health insurance only for combined use with another representative osteoporosis drug, denosumab. Thus, additional vitamin D in patients with BP therapy is not typically recognized in the daily clinical setting, and vitamin D

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Peer review under responsibility of The Korean Society of Osteoporosis.

https://doi.org/10.1016/j.afos.2019.11.004

supplementation generally cannot be used in the clinical research of BPs in Japan. We have previously reported that vitamin D supplementation is required for denosumab or ibandronate (IBN) [5,6]. As vitamin D analogues, 1-α hydroxycholecalciferol (alfacalcidol; ALF) and 1α,25-dihydroxy-2β-(3-hydroxypropyloxy) vitamin D_3 (eldecalcitol; ELD) have been approved for osteoporosis in Japan [7] and are frequently used in osteoporosis management. However, there are a few reports on combined therapy using a BP and active vitamin D, and the precise effects of active vitamin D on BP treatment for osteoporosis is controversial [8–11]. Furthermore, little is known on the role of ELD during MIN treatment of osteoporosis patients with RA.

In most clinical osteoporosis trials and especially those for antiresorptive drugs, vitamin D and calcium were administered to both placebo/control groups and drug groups [12]. In fact, the Japanese Ministry of Health's 1999 *Guidelines for the Prevention and Treatment of Osteoporosis* clearly state that whenever a placebo group is used as a control against a drug group, sufficient calcium and vitamin D should be administered as baseline therapy. Thus, calcium and vitamin D supplementation is routinely used in osteoporosis research in Japan and abroad, although little is known on the specific additive effects or risks of active vitamin D during BP treatment.

This study investigates the efficacy of MIN with or without ELD, an active vitamin D_3 derivative, in osteoporosis patients with RA.

2. Methods

Twenty-eight Japanese female osteoporosis patients with low-to-moderate RA disease activity (2.6 < disease activity score [DAS]28 $\leq$ 5.1) were prospectively recruited from Shinshu University School of Medicine and Showa-Inan General Hospital between May 2016 and August 2017. The inclusion criteria for the study were osteoporosis patients with low bilateral hip and/or lumbar 1–4 BMD (less than −2.5 standard deviation [SD]) who were complicated with RA [13]. The exclusion criteria were chronic renal failure (estimated glomerular filtration rate < 45 mL/min/1.73 m^2) and bone metabolic disorders or diabetes mellitus that could affect osteoporosis. The cohort was randomly divided into 2 groups: 14 patients treated with MIN alone in the MIN monotherapy group and 14 patients receiving MIN and vitamin D supplementation in the combination group. Subjects who were BP-naïve or had a BP washout period of at least 24 months subsequently received MIN or MIN plus vitamin D supplementation. Group selection was performed by simple randomization using an enveloped method (Table 1). All patients were diagnosed as having osteoporosis with RA. The diagnosis of osteoporosis was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research [14]. Seven of 14 patients in the combination group had been treated with BPs (4 with alendronate [ALN] and 3 with risedronate [RIS]) that were discontinued for at least 24 months prior to the study (Table 1). During the treatment period, each patient received monthly oral MIN (50 mg), with the addition of daily oral ELD (0.75 μg) in the combination group.

Each marker was measured just before MIN administration and at 6, 12, and 18 months of MIN treatment. The percent changes in serum whole parathyroid hormone (PTH) 1–84 and the active form of vitamin D, $1,25(OH)_2D_3$, were measured by immunoradiometric assays. Immunoassays were carried out by SRL Diagnostics (Tokyo, Japan). The percent changes in serum bone alkaline phosphatase (BAP) were measured as a bone formation marker using a chemiluminescent enzyme immunoassay. The percent changes in serum tartrate-resistant acid phosphatase (TRACP)-5b were measured as a bone resorption marker with an enzyme-linked immunosorbent assay. The percent changes in serum 25-hydroxyvitamin D (25(OH)D) were measured using an electrochemiluminescence immunoassay.

The percent changes in BMD were calculated by means of a dual-energy X-ray absorption fan-beam bone densitometer (Lunar Prodigy; GE Healthcare, Waukesha, WI, USA) at the lumbar 1–4 levels of the posteroanterior spine (L-BMD) and as the mean values of the right and left hips (H-BMD) and bilateral femoral necks (FN-BMD). All BMD data were presented up to 3 digits after the decimal. For statistical analysis, comparisons of markers and BMD at each measurement point were conducted using paired *t*-tests with Bonferroni correction. Comparisons of markers between the groups

Table 1
Baseline patient characteristics.

Variables	MIN monotherapy (n = 14)	Combination (n = 14)	P-value
Age, yr	65.8 ± 4.0	68.7 ± 3.1	0.57
Body mass index, kg/m^2	20.1 ± 0.5	20.4 ± 0.7	0.72
Serum albumin-corrected Ca, mg/dL	9.4 ± 0.1	9.6 ± 0.2	0.32
Serum phosphorus, mg/dL	3.4 ± 0.1	3.3 ± 0.1	0.52
Serum BAP, μg/L	14.5 ± 1.3	13.2 ± 1.3	0.53
Serum TRACP-5b, mU/dL	481.9 ± 57.1	378.5 ± 42.5	0.16
Serum whole PTH, pg/mL	25.7 ± 2.1	31.9 ± 4.8	0.25
Serum $1,25(OH)_2D_3$, pg/mL	43.5 ± 4.1	47.9 ± 3.3	0.41
Serum 25(OH)D, pg/mL	13.2 ± 0.7	14.0 ± 0.8	0.44
eGFR, mL/min/1.73m^2	70.0 ± 3.6	63.9 ± 5.0	0.33
Duration of BP use, yr	–	2.1 ± 0.8 (7)	–
Methotrexate, mg/wk (n)	6.5 ± 1.0 (8)	7.5 ± 0.7 (8)	0.43
PSL, mg/day (n)	5.1 ± 1.2 (7)	6.4 ± 1.7 (6)	0.52
L1-4 BMD, g/cm^2	0.929 ± 0.044	0.904 ± 0.040	0.67
Total hip BMD, g/cm^2	0.688 ± 0.034	0.698 ± 0.037	0.85
Femoral neck BMD, g/cm^2	0.668 ± 0.022	0.673 ± 0.038	0.91
MMP3, IU/mL	129.0 ± 35.9	299.0 ± 93.8	0.11
DAS28-CRP	2.7 ± 0.4	2.8 ± 0.3	0.77
SDAI	7.5 ± 2.6	9.5 ± 1.5	0.52
HAQ-DI	0.9 ± 0.3	0.8 ± 0.2	0.97

Values are presented as mean ± standard error of the mean.
A P-value of <0.05 was considered significant.
MIN, minodronate; Ca, calcium; BAP, bone alkaline phosphatase; TRACP-5b, tartrate-resistant acid phosphatase 5b; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate; BP, bisphosphonate; PSL, prednisolone; L, lumbar; BMD, bone mineral density; MMP-3, matrix metalloproteinase-3; DAS28-CRP, disease activity score 28 using C-reactive protein; SDAI, simplified disease activity index; HAQ-DI, health assessment questionnaire without disability index.

were performed by Welch's *t*-test. Statistical analyses were performed using the statistical package R, ver. 3.5.1 (available at http://www.r-project.org). A P-value of < 0.05 was considered statistically significant. On the basis of a SD of 2.5% and a sample size of 14 in each group, we calculated that the study had 80% power to detect at least a 5% difference between the groups.

The study protocol was approved by Ethics Committee of Shinshu University School of Medicine (Matsumoto, Japan) and Showa-Inan General Hospital (Komagane, Japan). This investigation was carried out in accordance with the ethical standards set forth in the Declaration of Helsinki (2014 revision). The UMIN registration number was UMIN000022364 and the date of registration was 20 May 2016. Written informed consent was obtained from all patients.

Oral medications for RA including methotrexate and prednisolone were evaluated in this study. Disease activity indicators for RA including matrix metalloproteinase-3, disease activity score 28, C-reactive protein, simplified disease activity index, and health assessment questionnaire without disability index were assessed.

3. Results

The percent changes in serum albumin-corrected calcium, phosphorus, and bone turnover markers are shown in Figures 1 and 2. There were no remarkable differences in baseline parameters between the groups except for a BP pretreatment history in half of the combination group and a tendency for lower TRACP-5b (Table 1). No serious adverse events, such as hypocalcemia or bone fracture, occurred during the study period.

3.1. Serum albumin-corrected calcium and phosphorus

The percent changes in serum calcium and phosphorus did not differ remarkably for either group compared with baseline levels or with respect to each other at any time point (Fig. 1A and B).

3.2. Serum whole PTH and 1,25(OH)$_2$D$_3$

The percent changes in serum PTH and 1,25(OH)$_2$D$_3$ initially increased in the MIN monotherapy group, but remained around baseline levels in the combination group throughout the study period. The 1,25(OH)$_2$D$_3$ level at 6 months was significantly higher in the MIN monotherapy group than in the combination group (Fig. 1C and D).

3.3. Markers of bone turnover

3.3.1. Marker of bone resorption

The percent changes in serum TRACP-5b were suppressed significantly and comparably from baseline in both groups from 6 to 18 months (Fig. 2A).

3.3.2. Marker of bone formation

The percent changes in serum BAP were significantly decreased in the MIN monotherapy group only from 6 to 18 months. A significant difference was noted at 6 months between the groups (Fig. 2B).

3.4. Serum 25(OH)D

The percent changes in serum 25(OH)D initially increased, but remained around baseline levels in the MIN monotherapy group. Serum 25(OH)D tended to be increased at 18 months in the combination group (Fig. 3A).

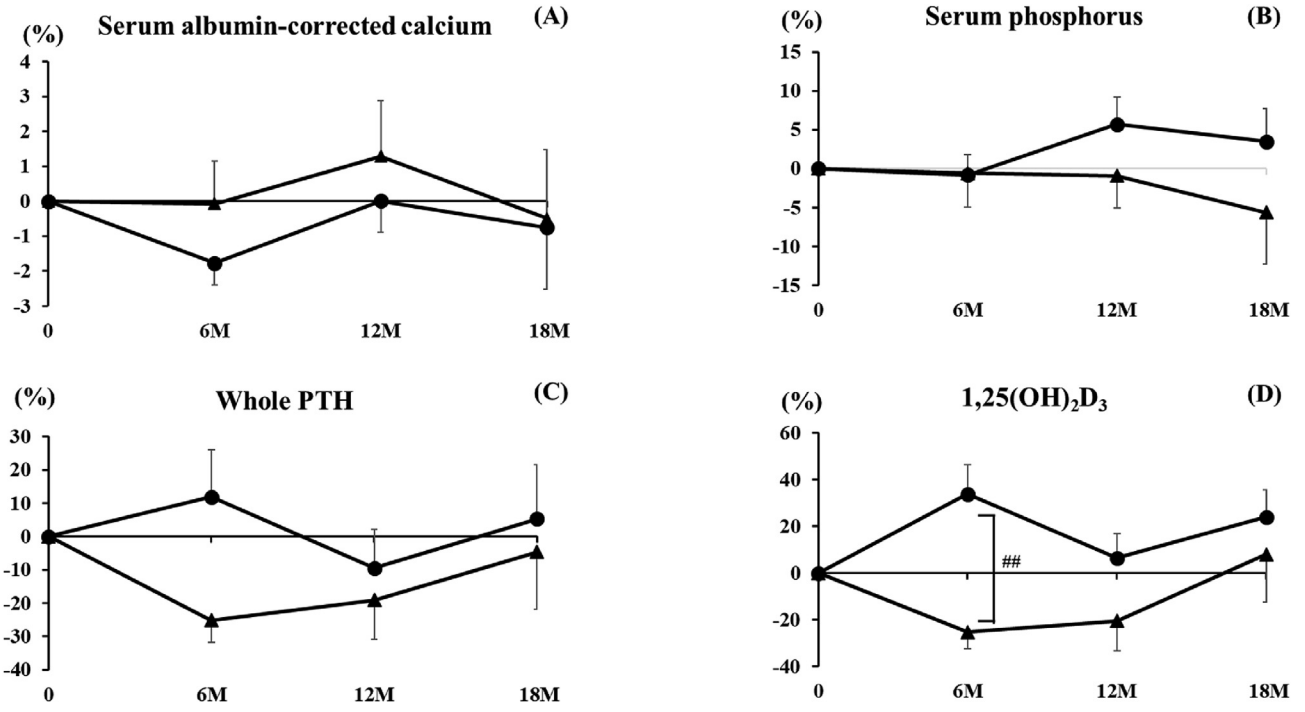

Fig. 1. Percent changes in serum albumin-corrected calcium, phosphorus, whole PTH, and 1,25(OH)$_2$D$_3$. The percent changes in serum calcium (A) and phosphorus (B) were comparable between the groups. There were no significant differences between either parameter and baseline values any time point. The percent changes in serum PTH (C) and 1,25(OH)$_2$D$_3$ (D) tended to increase in the MIN monotherapy group but remained around baseline levels in the combination group. A significant difference was noted at 6 months between the groups for 1,25(OH)$_2$D$_3$. Circles indicate the MIN monotherapy group and triangles indicate the combination group. Double hashtags denote a significant difference ($P < 0.01$) between the MIN monotherapy and combination groups. PTH, parathyroid hormone; MIN, minodronate; 6M, 6 months; 12M, 12 months; 18M, 18 months.

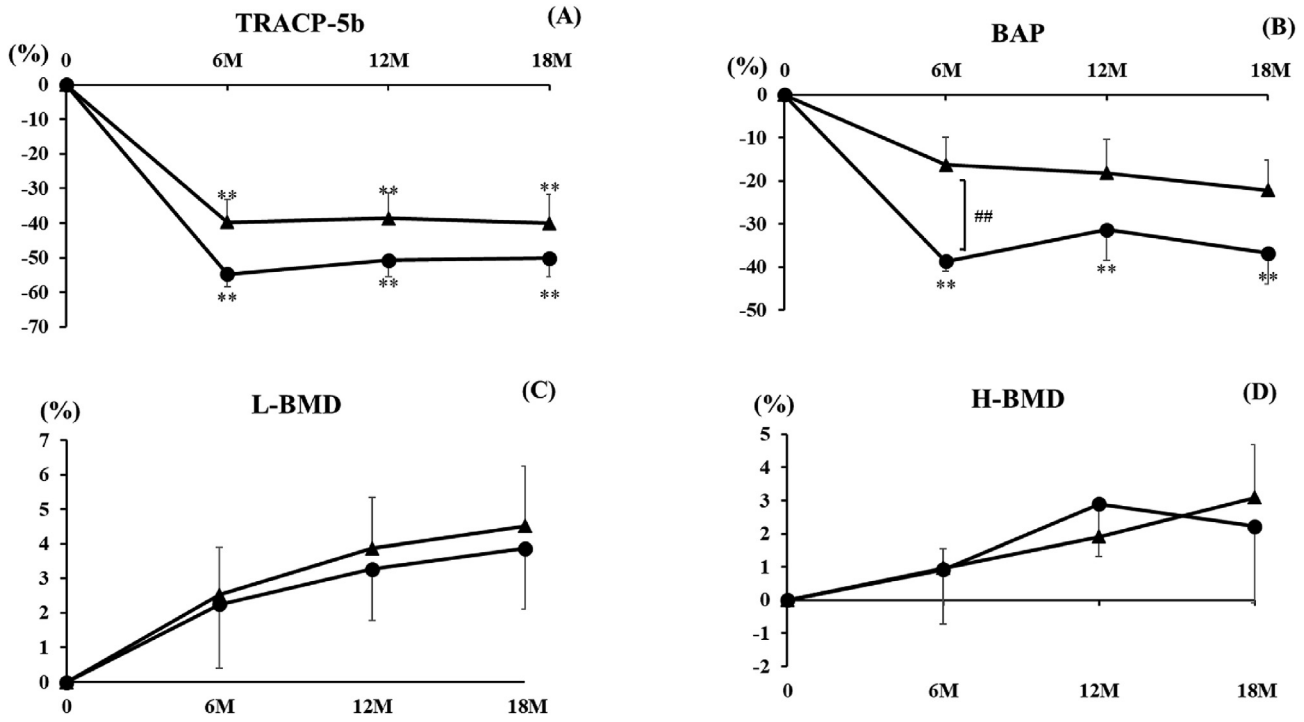

Fig. 2. Percent changes in serum TRACP-5b, BAP, L-BMD, and H-BMD. (A) The percent changes in serum TRACP-5b were suppressed significantly and comparably in both groups from 6 to 18 months. (B) The percent changes in serum BAP decreased significantly from 6 to 18 months in the MIN monotherapy group only. A significant difference was noted at 6 months between the groups. (C, D) The percent changes in L-BMD and H-BMD increased steadily and comparably for 12 months in both groups. Circles indicate the MIN monotherapy group and triangles indicate the combination group. Double asterisks denote a significant difference ($P < 0.01$) with baseline values. Double hashtags denote a significant difference ($P < 0.01$) between the MIN monotherapy and combination groups. TRACP-5b, tartrate-resistant acid phosphatase-5b; BAP, bone alkaline phosphatase; L-BMD, lumbar 1–4 bone mineral density; H-BMD, bilateral total hip bone mineral density.

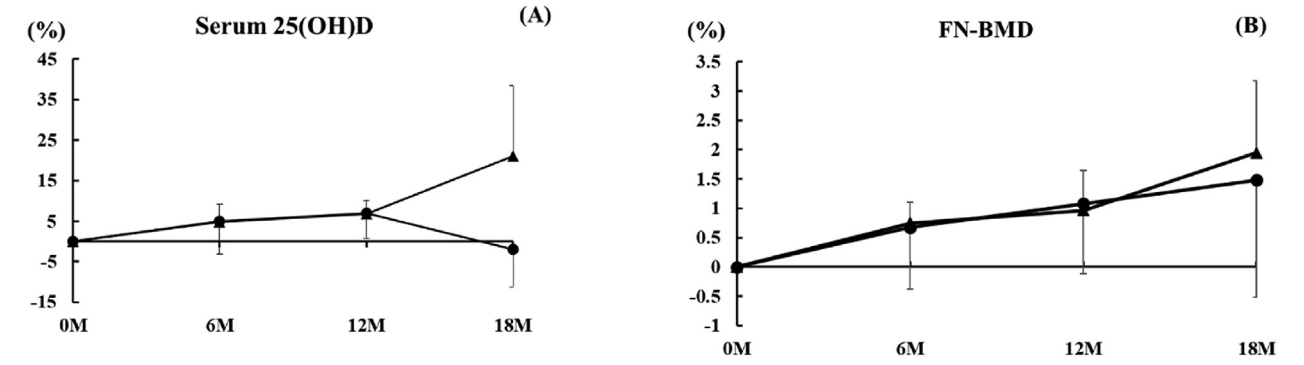

Fig. 3. Percent changes in serum 25(OH)D and FN-BMD. The percent changes in serum 25(OH)D (A) and FN-BMD (B) were comparable between the groups. There were no significant differences between either parameter and baseline values any time point 25(OH)D, 25-hydroxyvitamin D; FN-BMD, femoral neck bone mineral density.

3.5. L-BMD, H-BMD, and FN-BMD

The percent changes in L-BMD, H-BMD, and FN-BMD increased steadily and comparably for 18 months in both groups (Figures 2C, 2D, 3B).

4. Discussion

This is the first report providing comparative data between MIN treatment with or without ELD, an active vitamin D_3 derivative, in Japanese osteoporosis patients with RA. In relation to MIN monotherapy, combination therapy of MIN and active vitamin D appeared to mitigate an early decrease in serum calcium, although similar BMD gains were seen at 18 months.

Several reports have described the efficacy of MIN for osteoporosis. Okimoto et al. [15] observed that when compared with weekly ALN, daily MIN improved bone turnover and BMD and reduced back pain and bone metabolism markers. Monthly MIN also induced fewer upper gastrointestinal symptoms after a BP switch [16,17]. Hagino et al. [18] reported that the effects on L-BMD and H-BMD and the safety profile of MIN were comparable to those of ALN. Furthermore, Kumagai et al. [19] found that MIN imparted the same effects as RIS on an increase in BMD and a stronger effect on bone resorption inhibition than RIS in osteoporosis patients with RA in a randomized study. The above findings suggest that MIN is a convenient and effective therapeutic option, which may enhance treatment adherence.

There were significant differences for the percent changes in

serum BAP and $1,25(OH)_2D_3$ between the groups at 6 months. Although no remarkable differences in serum albumin-corrected calcium level were observed, this parameter tended to be decreased at 6 months in the monotherapy group. The above alterations may have been associated with a decrease in serum albumin-corrected calcium levels, as we earlier reported [6].

We previously described the additive effects of ALF during IBN therapy in postmenopausal Japanese women with osteoporosis. Bone formation and resorption markers were significantly decreased in both IBN monotherapy and ALF combination groups during 4–18 months, with greater suppression in the combination group. L-BMD and H-BMD were also significantly increased in the combination group over the monotherapy group [5]. Furthermore, we have demonstrated that when compared with denosumab monotherapy, combination therapy of denosumab with vitamin D and calcium mitigated the decrease in calcium caused by denosumab, inhibited bone metabolism to a greater extent, and increased BMD, especially at the hips [6]. The addition of active vitamin D can therefore be considered more effective than monotherapy during IBN or denosumab treatment for osteoporosis. Ebina et al. [20] found that MIN plus ELD combination therapy resulted in the highest BMD increase as compared with MIN monotherapy and MIN plus vitamin K combination therapy in patients with primary osteoporosis. On the other hand, BMD increases were comparable regardless of vitamin D addition during BP therapy in postmenopausal osteoporosis or glucocorticoid-induced osteoporosis patients [10,21,22], which were similar to the findings of this study. Although the mechanism for such discrepancies is unknown, the following reasons may be possible: (1) In the combination group, half of the patients had received BP pretreatment. However, we considered that this did not remarkably affect BMD gains. (2) The RA patients might have had a more complex patient background as compared with earlier primary osteoporosis-only patient groups. Thus, MIN monotherapy might still be an option for osteoporosis patients with RA from the viewpoint of comparable BMD increases, although ELD addition is generally advised during BP therapy.

The main limitations of this study were a small sample size, short observation period, and the inclusion of BP-pretreated patients only in the combination group, which may have added bias to the results. Further investigation is required to confirm if BMD increases continue under MIN treatment, to what extent fractures can be prevented, and the future occurrence of adverse effects.

5. Conclusions

No adverse events were seen for MIN monotherapy or MIN plus ELD. As BMD gains were comparable between the groups, MIN monotherapy may also be considered for osteoporosis patients with RA.

Author contributions

All authors have read the manuscript and have approved this submission.

Study design: TS and YN.
Study conduct: TS, HK and YN.
Data collection and analysis: TS.
Data interpretation: TS and YN.
Drafting manuscript: TS, HK and YN.
Revising manuscript content: TS, HK and YN.
Approving final version of manuscript: TS, HK and YN.
TS takes responsibility for the integrity of the data analysis.

Conflicts of interest

This study was funded by Ono Pharmaceutical Co., Ltd., Japan.

Acknowledgments

We thank Mr. Yuji Takanashi for his data collection, and Mr. Trevor Ralph for his English editing. **ORCID.** Takako Suzuki: 0000-0002-2174-3343. Yukio Nakamura: 0000-0002-3911-7180. Hiroyuki Kato: 0000-0002-4996-632X.

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