Osteoporos Int (2016) 27:351–359
DOI 10.1007/s00198-015-3369-6

ORIGINAL ARTICLE

Effects of switching weekly alendronate or risedronate to monthly minodronate in patients with rheumatoid arthritis: a 12-month prospective study

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Received: 31 July 2015 / Accepted: 7 October 2015 / Published online: 16 October 2015

Abstract
Summary Switching weekly ALN or RIS to monthly MIN in patients with RA, of whom two-thirds were treated with low-dose PSL, significantly decreased bone turnover markers and increased BMD at 12 months, suggesting that monthly MIN may be an effective alternative treatment option of oral bisphosphonate treatment.
Introduction The aim of this prospective, observational study was to evaluate the effects of switching weekly alendronate (ALN 35 mg) or risedronate (RIS 17.5 mg) to monthly minodronate (MIN 50 mg) in patients with rheumatoid arthritis (RA).
Methods Patient characteristics were as follows: n=172; 155 postmenopausal women, age 65.5 (44–87)years; T-score of lumbar spine (LS), −1.4; total hip (TH), −1.8; femoral neck (FN), −2.1; dose and rate of oral prednisolone (2.3 mg/day), 69.1 %; prior duration of ALN or RIS, 46.6 months; were allocated, based on their preference, to either the (1) continue group (n=88), (2) switch-from-ALN group (n=44), or (3) switch-from-RIS group (n=40).
Results After 12 months, increase in BMD was significantly greater in group 3 compared to group 1: LS (4.1 vs 1.2 %; P<0.001), TH (1.9 vs −0.7 %; P<0.01), and FN (2.7 vs −0.5 %; P<0.05); and in group 2 compared to group 1: LS (3.2 vs 1.2 %; P<0.05) and TH (1.5 vs −0.7 %; P<0.01). The decrease in bone turnover markers was significantly greater in group 3 compared to group 1: TRACP-5b (−37.3 vs 2.5 %; P<0.001), PINP (−24.7 vs −6.2 %; P<0.05), and ucOC (−39.2 vs 13.0 %; P<0.05); and in group 2 compared to group 1: TRACP-5b (−12.5 vs 2.5 %; P<0.05) at 12 months.
Conclusions Switching weekly ALN or RIS to monthly MIN in patients with RA may be an effective alternative treatment option of oral bisphosphonate treatment.

Keyword Alendronate · Minodronate · Osteoporosis · Rheumatoid arthritis · Risedronate

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Introduction

Increased risk of fractures in patients with rheumatoid arthritis (RA) compared to non-RA controls has been reported, with risk ratios (RR) varying from 2.0 to 3.0 at the hip and 2.4 to 6.2 at the spine [1–3]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-17, are strongly involved in the pathogenesis of RA and also concerned with osteoclastogenesis and consequent bone loss [4–7]. Indeed, high bone turnover and inflammation is associated with bone loss of the femoral neck (FN) in postmenopausal RA patients [8]. Moreover, glucocorticoids are often used to treat RA, which induce apoptosis of osteoblasts and osteocytes, and result in increased fracture risk [9, 10]. Minodronate (MIN) is an oral nitrogen-containing bisphosphonate (BP) developed in Japan which has a stronger inhibitory effect on farnesyl pyrophosphate synthase in osteoclasts

compared with alendronate (ALN) or risedronate (RIS) [11]. It has been shown that switching daily or weekly BP (mainly ALN and RIS) to monthly MIN increased bone mineral density (BMD) of the lumbar spine (LS) and distal radius, and also decreased bone turnover markers in patients with osteoporosis [12]. There are still considerable number of patients who desire oral osteoporosis treatment, and we hypothesized that MIN can be a convenient candidate of alternative oral BP treatment in patients with RA treated by ALN and RIS, which may be more effective in decreasing bone turnover and increasing BMD. The aim of this prospective study was to clarify the effect of switching weekly ALN (35 mg) or RIS (17.5 mg) to monthly minodronate (50 mg) in patients with RA.

Table 1 Patient preference questionnaire

1. Rate your satisfaction with the current once-monthly dosing schedule[a]
   1 2 3 4 5
   1-Low satisfaction 5-High satisfaction
2. Which dosing schedule do you prefer?
   a. Once weekly b. Once monthly c. No preference
3. If you prefer once-monthly dosing schedule, check all the statements you agree with[b]
   a. This dosing schedule impose less burden of frequency
   b. This dosing schedule has less worry to forget
   c. I feel this dosing schedule is more effective
   d. I expect less side effects with this dosing schedule
   e. Others

[a] Answer 4 and 5 are evaluated as satisfied, 3 as no preference, and 1 and 2 as not satisfied

[b] Multiple answers allowed

Materials and methods

Study design and subjects

This 12-month observational study was conducted based on a two-center, prospective, open-label design. A total of 172 patients with RA who were treated with oral weekly ALN or RIS in proportion to the Japanese guidelines for prevention and treatment of osteoporosis 2011 [13] and the guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research 2004 [14], were enrolled in the study (Fig. 1). RA was diagnosed based on the 1987 revised American College of Rheumatology (ACR) criteria [15]. C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), and the Disease Activity Score assessing 28 joints with CRP (DAS28-CRP) were evaluated as the parameters reflecting inflammation as well as the disease activity of RA [16, 17]. Registered patients were asked their preference for a change to monthly oral BP treatment and were allocated based on their preferences to either the "continue" group (n=88), consisting of patients who wanted to continue their current therapies, or the "switch-from-ALN" group (n=44) or "switch-from-RIS" group (n=40), consisting of patients who were willing to switch over to MIN 50 mg from their current therapies. Other combined osteoporosis treatments, such as active vitamin D, vitamin K_2, and calcium were continued during the study period. Patients' treatment persistence and satisfaction levels with the therapies were assessed using a self-administered questionnaire at 12 months (Table 1). Patients were asked for their drug adherence every time visiting outpatient clinic (every 1–3 months), and patients who did not take their medications more than twice of their interval (more than

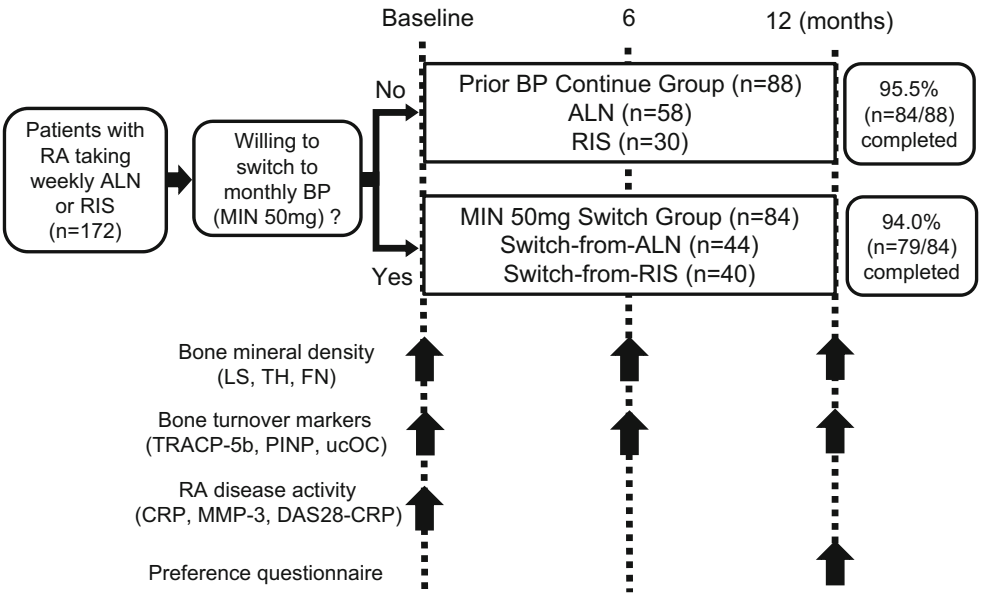

Fig. 1 Study design and schedule. Patients were asked for their willingness to switch to monthly MIN 50 mg. Bone mineral density and bone turnover markers were evaluated every 6 months in all the patients. The switch group patients were asked to complete a patient preference questionnaire at 12 months

Table 2 Baseline clinical characteristics

Variable	Continue (*n*=88)	Switch-from-ALN (*n*=44)	Switch-from-RIS (*n*=40)
Age, (mean±SE years)	64.9±0.9	64.9±1.6	67.3±1.6
Gender, females (%)	81/88 (92.0 %)	40/44 (90.9 %)	38/40 (95.0 %)
Postmenopausal, *n*/*N* (%)	80/88 (90.9 %)	38/44 (86.4 %)	37/40 (92.5 %)
Body mass index (kg/m^2)	21.9±0.4	21.2±0.6	22.2±0.6
Prior BP, ALN *n*/*N* (%)	58/88 (65.9 %)		
Duration of prior BP therapy (months)	43.6±2.1	57.2±4.6*	41.0±5.5†
Combined vitamin D, n/N (%)	46/88 (52.3 %)	26/44 (59.1 %)	25/40 (62.5 %)
Combined vitamin K_2, *n*/*N* (%)	21/88 (23.9 %)	12/44 (27.3 %)	10/40 (25.0 %)
Combined calcium, *n*/*N* (%)	5/88 (5.7 %)	3/44 (6.8 %)	3/40 (7.5 %)
Prior vertebral fracture(s), *n*/*N* (%)	25/88 (28.4 %)	9/44 (20.5 %)	8/40 (20.0 %)
Prior non-vertebral fracture(s), *n*/*N* (%)	22/88 (25.0 %)	10/44 (22.7 %)	7/40 (17.5 %)
Bone mineral density (BMD)			
Lumbar spine BMD (g/cm^2)	0.856±0.017	0.861±0.028	0.858±0.019
Lumbar spine BMD (T-score)	−1.4±0.1	−1.3±0.2	−1.4±0.2
Femoral neck BMD (g/cm^2)	0.584±0.027	0.546±0.015	0.584±0.016
Femoral neck BMD (T-score)	−2.1±0.1	−2.3±0.1	−2.0±0.1
Total hip BMD (g/cm^2)	0.698±0.028	0.658±0.017	0.677±0.018
Total hip BMD (T-score)	−1.8±0.1	−1.9±0.1	−1.8±0.2
T-score<–2.5, *n*/*N* (%)	45/88 (51.1 %)	22/44 (50.0 %)	16/40 (40.0 %)
PINP (μg/l)	34.2±2.7	29.7±2.7	34.5±2.5
TRACP-5b (mU/dl)	258.1±11.2	244.5±17.6	309.8±22.7†
ucOC (ng/ml)	2.7±0.3	3.6±0.9	3.7±0.6
Intact-PTH (pg/ml)	48.9±2.4	51.5±3.7	45.6±2.6
eGFR (ml/min/1.73 m^2)	77.2±2.5	73.6±3.5	74.9±3.3
Duration of disease (years)	17.6±1.0	18.3±1.6	15.1±1.5
RF positivity, *n*/*N* (%)	73/88 (83.0 %)	41/44 (93.2 %)	35/40 (87.5 %)
ACPA positivity, *n*/*N* (%)	75/88 (85.2 %)	40/44 (90.9 %)	34/40 (85.0 %)
CRP (mg/dl)	0.7±0.1	0.6±0.1	0.5±0.1
MMP-3 (ng/ml)	158.4±16.2	118.1±16.4	118.2±30.1
DAS28-CRP	2.6±0.1	2.5±0.1	2.4±0.1
Remission (<2.3), *n*/*N* (%)	41/88 (46.6 %)	22/44 (50.0 %)	22/40 (55.0 %)
Low disease activity (<2.7), *n*/*N* (%)	16/88 (18.2 %)	11/44 (25.0 %)	7/40 (17.5 %)
Moderate disease activity (2.7–4.1), *n*/*N* (%)	26/88 (29.5 %)	10/44 (22.7 %)	9/40 (22.5 %)
High disease activity (>4.1), *n*/*N* (%)	5/88 (5.7 %)	1/44 (2.3 %)	2/40 (5.0 %)
MHAQ	0.5±0.1	0.4±0.1	0.6±0.1
Prednisolone dose (mg/day)	2.5±0.3	2.2±0.3	1.7±0.4
Prednisolone usage, *n*/*N* (%)	62/88 (70.5 %)	32/44 (72.7 %)	25/40 (62.5 %)
MTX dose (mg/week)	5.0±0.4	5.6±0.6	4.7±0.6
MTX usage, *n*/*N* (%)	63/88 (71.6 %)	35/44 (79.5 %)	28/40 (70.0 %)
Biologics usage, *n*/*N* (%)	20/88 (25.7 %)	8/44 (18.2 %)	9/40 (22.5 %)

Mean±Standard Error (SE), unless otherwise noted

n/*N* (%) number of patients with measurements / total number of patients (%)

ALN alendronate, *RIS* risedronate *BP* bisphosphonate, *PINP* type I collagen N-terminal propeptide, *TRAP-5b* isoform 5b of tartrate-resistant acid phosphatase, *ucOC* undercarboxylated osteocalcin, *PTH* parathyroid hormone, *eGFR* estimated glomerular filtration rate, *RF* rheumatoid factor, *ACPA* anti-cyclic citrullinated peptide antibody, *CRP* C-reactive protein, *MMP-3* matrix metalloproteinase-3, *DAS28-CRP* disease activity score assessing 28 joints with CRP, *MHAQ* modified health assessment questionnaire, *MTX* methotrexate

Differences between the groups were determined by ANOVA or chi-square test. *P<0.05 vs Continue group. †P<0.05 vs Switch-from-ALN group.

2 weeks for weekly ALN or RIS and more than 2 months for monthly MIN) were considered as dropout.

This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by ethical review boards at the clinical center (approval number 11273-2; Osaka University, Graduate School of Medicine). Written informed consent was obtained from individual patients included in the study.

BMD assessment

A real BMD in the LS (L2–L4), total hip (TH), and femoral neck (FN) were assessed by dual-energy X-ray absorptiometry (Discovery A, Hologic, Inc., Waltham, MA, USA) at baseline and after 6 and 12 months of treatment. Regions of severe scoliosis, vertebral fracture, and operated sites were excluded from BMD measurements as previously described [18].

Biochemical markers of bone turnover

Bone turnover markers were measured in serum obtained from each patient at approximately the same time in the morning after overnight fasting. The bone formation marker, N-terminal type I procollagen propeptide (PINP); inter-assay coefficient of variation (CV), 3.2 %–5.2 %, (Intact UniQ assay, Orion Diagnostica, Espoo, Finland), and bone resorption marker, isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b); inter-assay CV, 5.0 %–9.0 %, (Immunodiagnostic Systems Ltd., Boldon, UK) were measured by ELISA as previously described [19]. Levels of undercarboxylated osteocalcin (ucOC) were measured by a solid-phase enzyme immunoassay kit; inter-assay CV, 5.2 %–8.3 %, (Takara Bio, Shiga, Japan) with a sensitivity of 0.25 ng/mL. UcOC reflects not only vitamin K deficiency, but also total bone turnover, as it is released from both osteoblasts and absorbed bone extracellular matrix by osteoclast as previously described [20, 21]. Intact parathyroid hormone (PTH) was measured using a two-site immunoradiometric assay; inter-assay CV 8.4 %, (Nichols Institute Diagnostics, Valencia, USA).

Statistical analysis

The normal distributions of the data were examined by the Shapiro-Wilk test. Differences between each study group

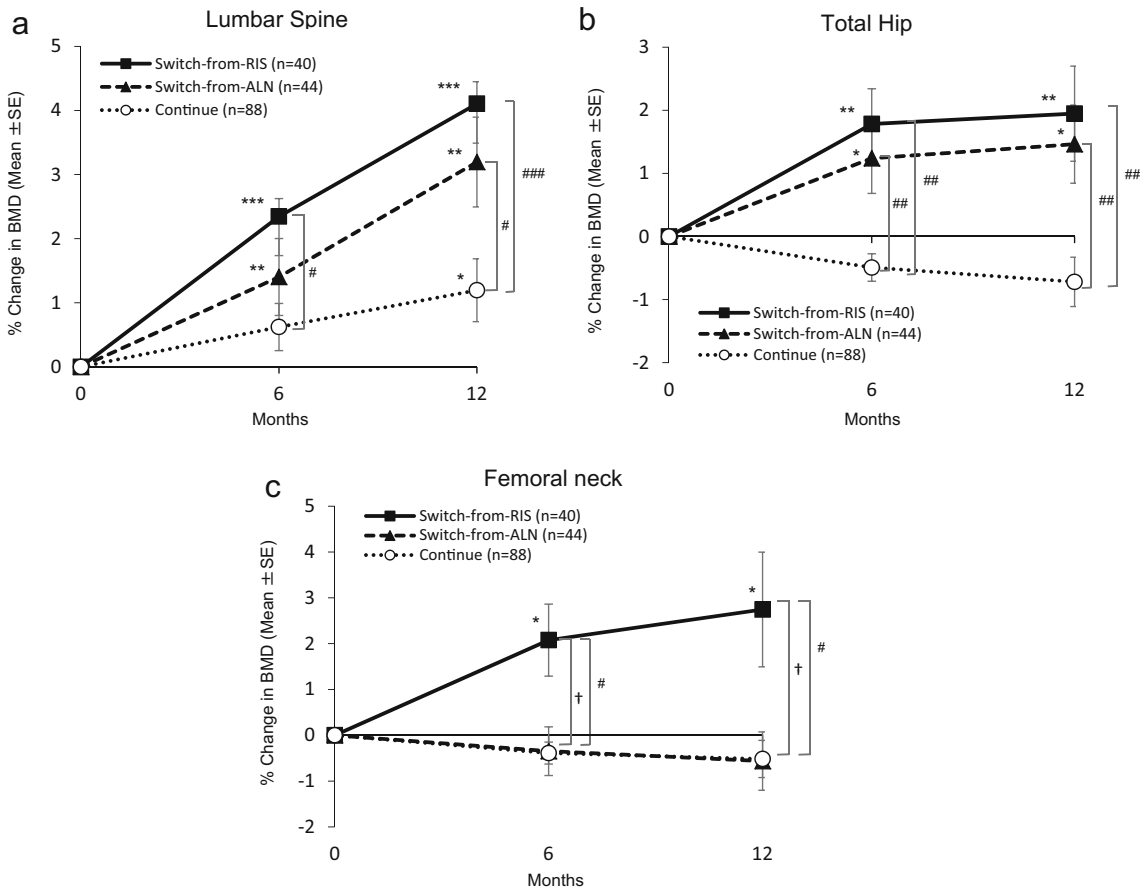

Fig. 2 Mean±standard error (SE) change from baseline in bone mineral density (BMD) at the lumbar spine (**a**), total hip (**b**), and femoral neck (**c**). *$P<0.05$, **$P<0.01$, ***$P<0.001$ change from baseline within each treatment group. $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$ continue group versus switch-from-RIS group. $^{\dagger}P<0.05$, switch-from-ALN group versus switch-from-RIS group

were tested using analysis of variance for normally distributed data and the nonparametric Kruskal-Wallis test was used for non-normally distributed data. Changes in BMD and ranked bone turnover marker data from baseline to specified time points within each study group were compared using the non-parametric Wilcoxon signed-rank test. Results are expressed as the mean±standard error. A P value <0.05 indicated statistical significance. All tests were performed using IBM SPSS Statistics version 22 software (IBM, Armonk, NY, USA).

Results

Baseline characteristics are shown in Table 2. Of the 172 study patients, 84 (48.8 %) were willing to switch to MIN 50 mg. No significant differences were observed in the baseline age, combined dose, and prescription rate of active vitamin D or vitamin K_2 or calcium or prednisolone (PSL), BMD, or disease activity of RA between the groups.

Duration of prior BP therapy at baseline was significantly longer in the switch-from-ALN group (57.2 months) compared to the continue group (43.6 months; $P< 0.05$) and the switch-from-RIS group (41.0 months; $P< 0.05$). Baseline serum TRACP-5b levels in the switch-from-ALN group were significantly lower compared to the switch-from-RIS group (244.5 vs 309.8 mU/dL; $P< 0.05$). Eventually, 95.5 % (84/88) of patients in the continue group (2 patients were lost to follow up and 2 patients desired to change the medication) and 94.0 % (79/84) of patients in the switch group (3 patients were lost to follow up and 2 patients desired to change the medication) completed the 12-month trial (Fig. 1).

Change in BMD

BMD was monitored every 6 months (Fig. 2). Both the switch groups showed a significant increase in LS and TH BMD from baseline to 6 and 12 months, while only the switch-from-RIS group showed a significant increase in FN BMD from baseline to 6 and 12 months. Moreover, the switch-from-RIS group showed a significantly greater increase compared to the continue group in the LS from 6 months (2.3 vs

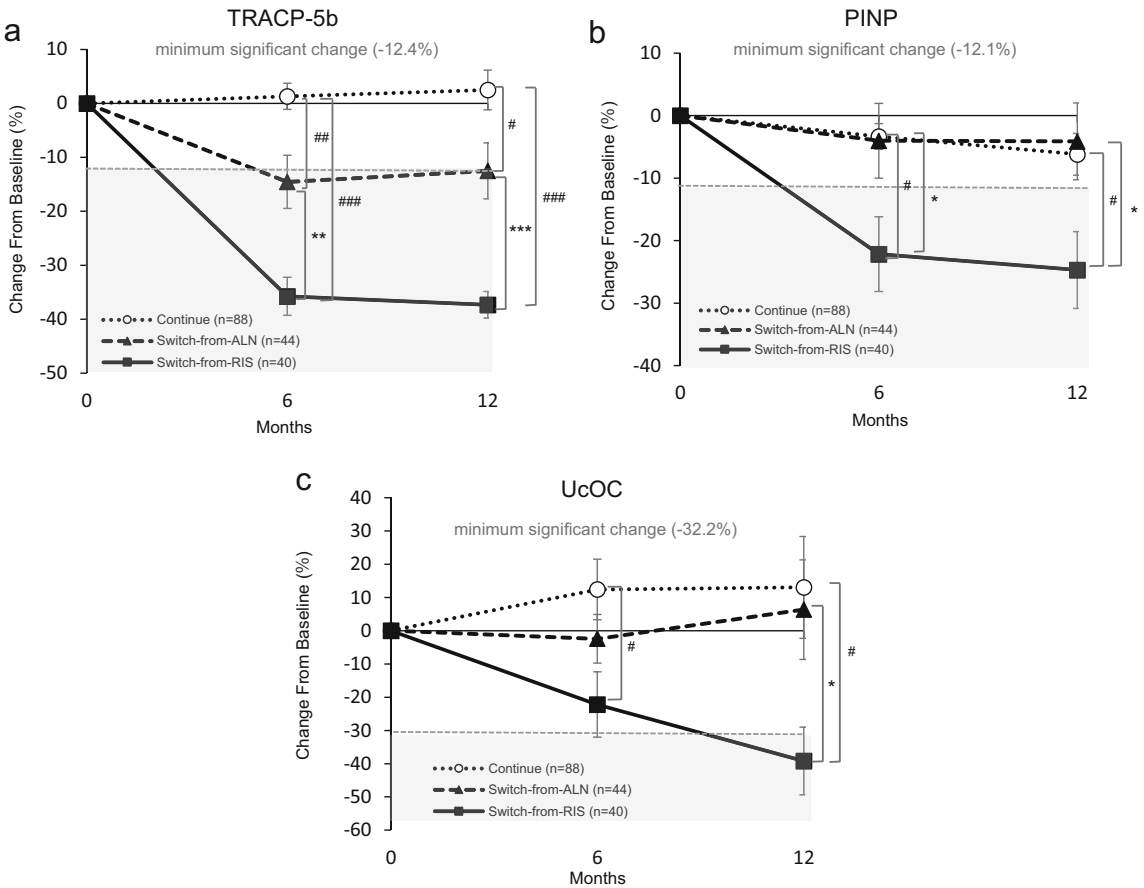

Fig. 3 Mean±standard error (SE) change from baseline in serum concentration of bone turnover markers TRAP-5b (**a**), PINP (**b**), and ucOC (**c**). TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; PINP, type I collagen N-terminal propeptide; ucOC, undercarboxylated osteocalcin; $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$ continue group versus each switch group. $*P<0.05$, $**P<0.01$ switch-from-ALN group versus switch-from-RIS group

0.6 %; $P<0.05$) to 12 months (4.1 vs 1.2 %; $P<0.001$), in the TH from 6 months (1.8 vs –0.5 %; $P<0.01$) to 12 months (2.0 vs –0.7 %; $P<0.01$), and in the FN from 6 months (2.0 vs –0.4 %; $P<0.05$) to 12 months (2.7 vs –0.5 %; $P<0.05$), respectively. On the other hand, the switch-from-ALN group showed a significantly greater increase compared to the continue group in LS BMD at 12 months (3.2 vs 1.2 %; $P<0.05$) and in the TH from 6 months (1.2 vs –0.5 %; $P<0.01$) to 12 months (1.5 vs –0.7 %; $P<0.01$). The switch-from-RIS group showed a significantly greater increase compared to the switch-from-ALN group in the FN from 6 months (2.1 vs –0.3 %; $P<0.05$) to 12 months (2.7 vs –0.6 %; $P<0.05$).

Bone turnover markers

Percent changes in bone turnover markers from baseline are shown in Fig. 3. The switch-from-RIS group showed a significantly greater decrease compared to the continue group in TRACP-5b levels from 6 months (–35.8 vs 1.3 %; $P<0.001$) to 12 months (–37.3 vs 2.5 %; $P<0.001$), in PINP levels from 6 months (–22.2 vs –3.3 %; $P<0.05$) to 12 months (–24.7 vs –6.2 %; $P<0.05$), and in ucOC levels from 6 months (–22.2 vs 12.4 %; $P<0.05$) to 12 months (–39.2 vs 13.0 %; $P<0.05$). On the other hand, the switch-from-ALN group showed a significantly greater decrease compared to the continue group only in TRACP-5b levels from 6 months (–14.6 vs 1.3 %; $P<0.01$) to 12 months (–12.5 vs 2.5 %; $P<0.05$). The switch-from-RIS group showed a significantly greater decrease than the minimum significant change of serum TRACP-5b, PINP, and ucOC levels, while the switch-from-ALN group showed only in the serum TRACP-5b at 12 months. There were no greater changes than the minimum significant change of serum TRACP-5b, PINP, and ucOC levels in the continue group. The absolute value of bone turnover markers are shown in Fig. 4. The average value of TRACP-5b, PINP, and ucOC in all the groups were all within the reference value.

Rate of fragility fracture

During the 12-month period, the continue group patients experienced three vertebral and one non-vertebral clinical

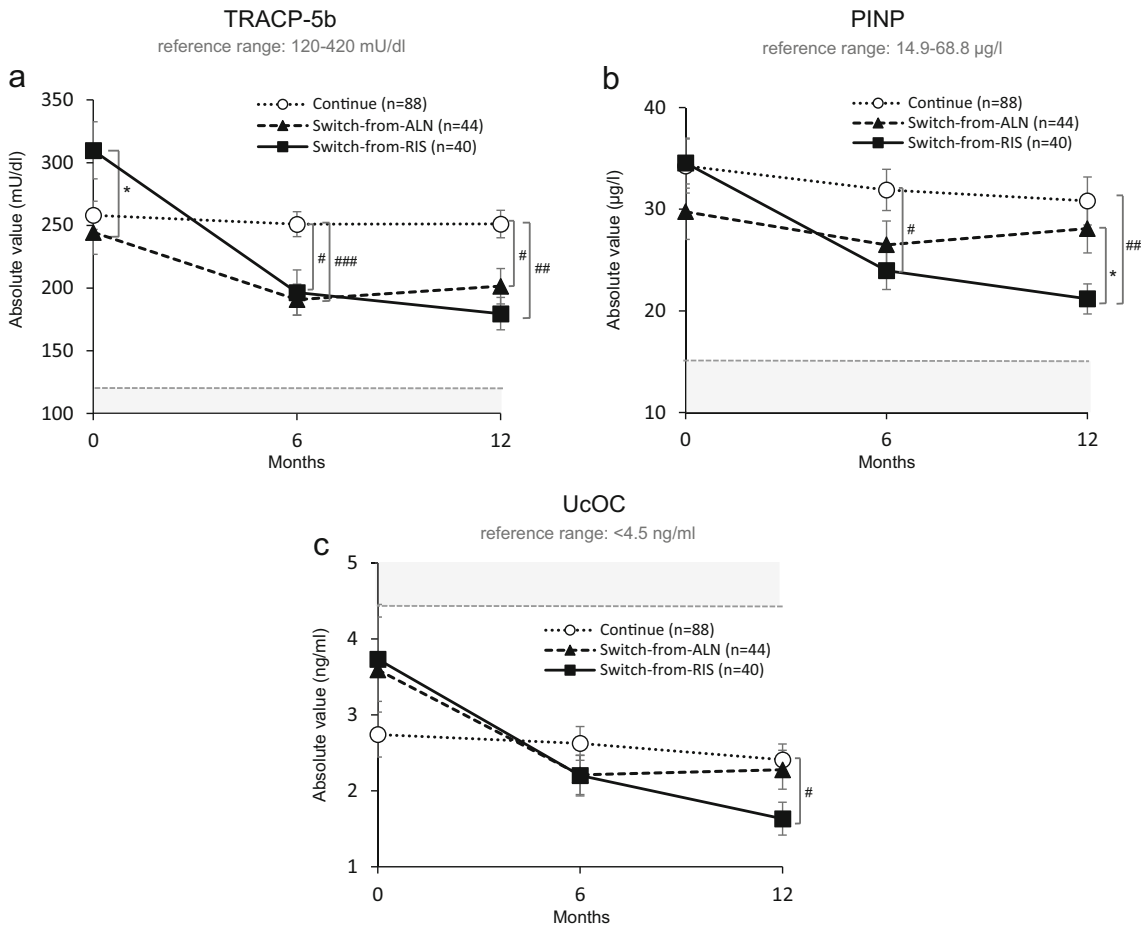

Fig. 4 Mean±standard error (SE) absolute value of bone turnover markers TRAP-5b (**a**), PINP (**b**), and ucOC (**c**). *TRAP-5b* isoform 5b of tartrate-resistant acid phosphatase, *PINP* type I collagen N-terminal propeptide, *ucOC* undercarboxylated osteocalcin. $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$ continue group versus each switch group. $^{*}P<0.05$ switch-from-ALN group versus switch-from-RIS group

fragility fractures (4.5 %). The switch-from-ALN group experienced one vertebral and one non-vertebral clinical fragility fractures (4.5 %), and no clinical fragility fracture was observed in the switch-from-RIS group (0.0 %). No statistically significant difference in the total clinical fragility fracture rate was observed between the groups.

Patient preference after switching to MIN 50 mg

Patient preference after switching to monthly MIN 50 mg is shown in Fig. 5. The questionnaire revealed that 80.8 % of patients were satisfied with the switch to monthly therapy and 88.7 % preferred to continue the monthly treatment. The main reasons for desiring continuation of monthly dosing was both the decreased frequency (69.8 %) and less worry about forgetting doses (47.2 %), thus a perception of less overall burden.

Discussion

In this study, we have demonstrated for the first time that in patients with RA, of whom two-thirds were treated with low-dose PSL (<10 mg/day), switching from weekly ALN or RIS to monthly MIN was effective in increasing BMD and decreasing bone turnover markers at 12 months. In addition, no previous studies have demonstrated the difference of the effects of switching by the difference of prior BP therapies.

In nitrogen-containing BP treatment, mineral-binding affinities may influence their distribution within bone and the period till anti-fracture effects are shown, and inhibition of farnesyl diphosphate synthase (FPPS) may affect their antiresorptive effects by inducing apoptosis of osteoclasts [22].

It has been shown that ALN possesses a stronger binding affinity to hydroxyapatite compared to RIS, while RIS possesses a stronger FPPS inhibition compared to ALN [22]. Consequently, weekly ALN (70 mg) showed a greater increase in BMD and decrease in bone turnover markers compared to weekly RIS (35 mg) in patients with postmenopausal osteoporosis [23], while RIS showed lower rates of hip and non-vertebral fractures than ALN during the first year of therapy [24].

Previous reports have demonstrated that MIN showed stronger FPPS inhibition [11] and a weaker binding affinity to hydroxyapatite compared to ALN and RIS [25], which suggests that MIN inhibits bone resorption more strongly and is more quickly distributed within the bone compared to ALN and RIS. Indeed, MIN suppressed bone remodeling of cancellous and cortical bone more strongly than ALN in vitro [26] as well as in ovariectomized cynomolgus monkeys in vivo [27]. In the previous human study, switching ALN or RIS to monthly MIN for 6 months increased BMD + 1.1 % in LS, and the reduction rate of serum TRACP-5b was approximately 35 % in the switching from RIS group at 6 months [12], which were consistent with our study.

Finally, glucocorticoids have been shown to induce apoptosis of osteocytes, and BPs inhibit osteocyte apoptosis in vitro [28] as well as in glucocorticoid-treated animals

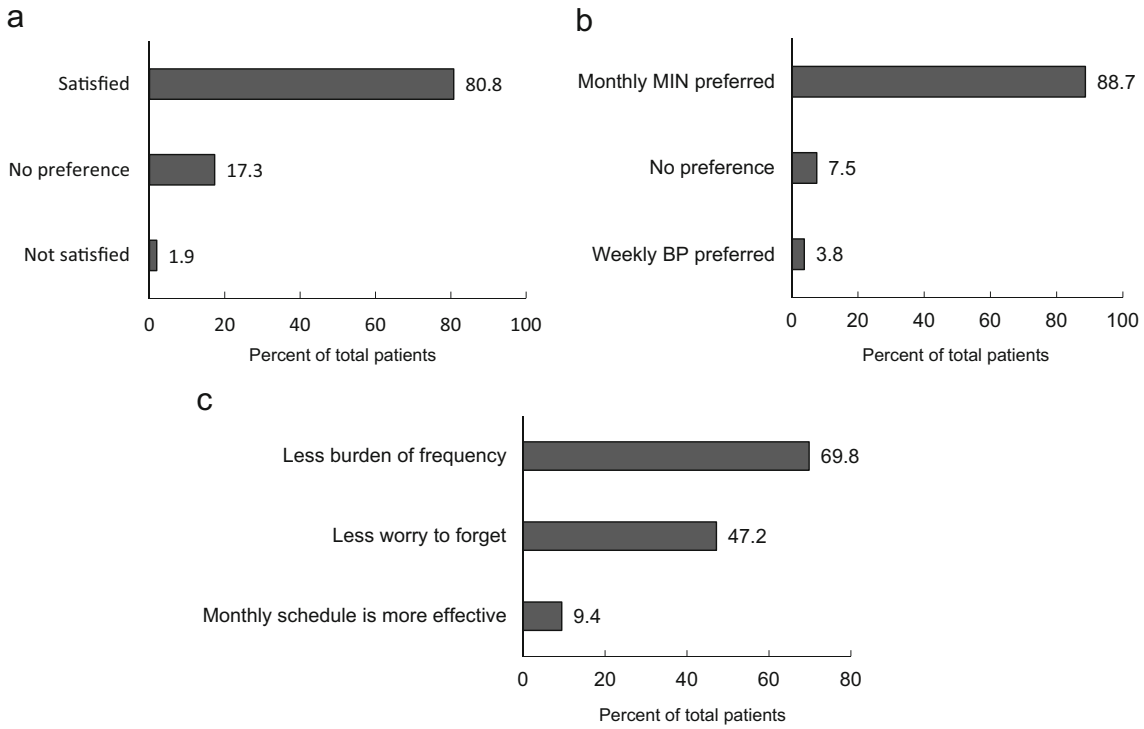

Fig. 5 Patient satisfaction, preference, and reasons for preference after switching weekly ALN or RIS to monthly MIN 50 mg treatment at 12 months

[29]. A systematic review and meta-analysis revealed that BPs can preserve bone mass and reduce the incidence of vertebral fractures in patients with rheumatic disease, mainly for those who are being treated with glucocorticoids [30], and both ALN and RIS strongly decreased the fracture risk associated with glucocorticoid-induced osteoporosis (GIO) [31, 32]. In this study, monthly MIN 50 mg resulted in a greater BMD increase and bone turnover decrease when patients were switched from ALN or RIS, which suggests its effectiveness not only in primary osteoporosis, but also in GIO.

There are several limitations to this study. Due to the small number of subjects, fracture risk comparisons should be assessed in a randomized, larger cohort. As most of the patients showed remission or low disease activity in this study, the effects of switching on high disease activity patients should be assessed in further study. Although most patients were postmenopausal, some male patients were included in this study. Concerning medication, the dose of ALN and RIS allowed in Japan is the half of Caucasians, and the duration of prior BP therapy was significantly longer in switch-to-ALN group compared to other groups. In addition, only a small number of patients were combined with calcium formulation, and total calcium intake could not be monitored.

In conclusion, switching weekly ALN or RIS to monthly MIN in patients with RA, of whom two-thirds were treated with low-dose PSL, significantly decreased bone turnover markers and increased BMD at 12 months, suggesting that monthly MIN may be an effective alternative treatment option of oral BP treatment.

Acknowledgments The authors thank Dr. Kenrin Shi for his excellent cooperation in conducting the study.

Compliance with ethical standards This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by ethical review boards at the clinical center (approval number 11273-2; Osaka University, Graduate School of Medicine). Written informed consent was obtained from individual patients included in the study.

Conflicts of interest This research was funded by Astellas Pharma, Inc. The funder had no role in the study design, data collection, data analysis, decision to publish, or preparation of the manuscript. Kosuke Ebina, Takaaki Noguchi, Makoto Hirao, Jun Hashimoto, Shoichi Kaneshiro, Masao Yukioka, and Hideki Yoshikawa declare that they have no conflict of interest.

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