



Title	Effects of switching weekly alendronate or risedronate to monthly minodronate in patients with rheumatoid arthritis: a 12-month prospective study
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1 1 **Original Article**2 Effects of switching weekly alendronate or risedronate to monthly minodronate in
3 patients with rheumatoid arthritis: a twelve-month prospective study4
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1
2 24 **Abstract**
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5 25 *Purpose*
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8 26 The aim of this prospective, observational study was to evaluate the effects of switching
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10 27 weekly alendronate (ALN 35 mg) or risedronate (RIS 17.5 mg) to monthly minodronate
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12 28 (MIN 50 mg) in patients with rheumatoid arthritis (RA).
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17 29 *Methods*
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20 30 Patient characteristics were as follows: n=172; 155 postmenopausal women; age 65.5
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24 31 (44-87) years; T-score of lumbar spine (LS), -1.4; total hip (TH), -1.8; femoral neck
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27 32 (FN), -2.1; dose and rate of oral prednisolone (2.3 mg/day), 69.1%; prior duration of
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30 33 ALN or RIS, 46.6 months; were allocated, based on their preference, to either the (1)
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34 34 continue group (n=88), (2) switch-from-ALN group (n=44), or (3) switch-from-RIS
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37 35 group (n=40).
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40 36 *Results*
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43 37 After 12 months, increase in BMD was significantly greater in group 3 compared to
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46 38 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
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49 39 -0.5%; $P < 0.05$); and in group 2 compared to group 1: LS (3.2 vs 1.2%; $P < 0.05$) and
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52 40 TH (1.5 vs -0.7%; $P < 0.01$). The decrease in bone turnover markers was significantly
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55 41 greater in group 3 compared to group 1: TRACP-5b (-37.3 vs 2.5%; $P < 0.001$), PINP
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2 42 (-24.7 vs -6.2%; $P < 0.05$), and ucOC (-39.2 vs 13.0%; $P < 0.05$); and in group 2
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5 43 compared to group 1: TRACP-5b (-12.5 vs 2.5%; $P < 0.05$) at 12 months.
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8 44 *Conclusions*
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11 45 Switching weekly ALN or RIS to monthly MIN in patients with RA may be an effective
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14 46 alternative treatment option of oral bisphosphonate treatment.
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21 48 **Keywords**
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24 49 Rheumatoid arthritis; osteoporosis; minodronate; alendronate; risedronate.
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31 51 **Mini Abstract**
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34 52 Switching weekly ALN or RIS to monthly MIN in patients with RA, of whom
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37 53 two-thirds were treated with low-dose PSL, significantly decreased bone turnover
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40 54 markers and increased BMD at 12 months, suggesting that monthly MIN may be an
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43 55 effective alternative treatment option of oral bisphosphonate treatment.
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50 57 **Introduction**
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53 58 Increased risk of fractures in patients with rheumatoid arthritis (RA) compared to
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56 59 non-RA controls has been reported, with risk ratios (RR) varying from 2.0 to 3.0 at the
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2 60 hip and 2.4 to 6.2 at the spine [1-3]. Pro-inflammatory cytokines, such as tumor necrosis
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4 61 factor-alpha (TNF- α), interleukin (IL)-1, IL-6, and IL-17, are strongly involved in the
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6 62 pathogenesis of RA, and also concerned with osteoclastogenesis and consequent bone
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8 63 loss [4-7]. Indeed, high bone turnover and inflammation is associated with bone loss of
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11 64 the femoral neck (FN) in postmenopausal RA patients [8]. Moreover, glucocorticoids
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13 65 are often used to treat RA, which induce apoptosis of osteoblasts and osteocytes, and
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16 66 result in increased fracture risk [9, 10]. Minodronate (MIN) is an oral
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18 67 nitrogen-containing bisphosphonate (BP) developed in Japan which has a stronger
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21 68 inhibitory effect on farnesyl pyrophosphate synthase in osteoclasts compared with
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24 69 alendronate (ALN) or risedronate (RIS) [11]. It has been shown that switching daily or
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27 70 weekly BP (mainly ALN and RIS) to monthly MIN increased bone mineral density
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30 71 (BMD) of the lumbar spine (LS) and distal radius, and also decreased bone turnover
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33 72 markers in patients with osteoporosis [12]. There are still considerable number of
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36 73 patients who desire oral osteoporosis treatment, and we hypothesized that MIN can be a
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39 74 convenient candidate of alternative oral BP treatment in patients with RA treated by
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42 75 ALN and RIS, which may be more effective in decreasing bone turnover and increasing
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45 76 BMD. The aim of this prospective study was to clarify the effect of switching weekly
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48 77 ALN (35 mg) or RIS (17.5 mg) to monthly minodronate (50 mg) in patients with RA.

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5 79 **Materials and methods**
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8 80 *Study design and subjects*
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11 81 This twelve-month observational study was conducted based on a two-center,
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14 82 prospective, open-label design. A total of 172 patients with RA who were treated with
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17 83 oral weekly ALN or RIS **in proportion to the Japanese guidelines for prevention and**
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20 84 **treatment of osteoporosis 2011 [13]** and the guidelines on the management and
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23 85 **treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and**
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26 86 **Mineral Research 2004 [14]**, were enrolled in the study (Fig. 1). RA was diagnosed
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29 87 based on the 1987 revised American College of Rheumatology (ACR) criteria [15].
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32 88 C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), and the Disease
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35 89 Activity Score assessing 28 joints with CRP (DAS28-CRP) were evaluated as the
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38 90 parameters reflecting inflammation as well as the disease activity of RA [16, 17].
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41 91 Registered patients were asked their preference for a change to monthly oral BP
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44 92 treatment and were allocated based on their preferences to either the “continue” group
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47 93 (n=88), consisting of patients who wanted to continue their current therapies, or the
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50 94 “switch-from-ALN” group (n=44) or “switch-from-RIS” group (n=40), consisting of
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53 95 patients who were willing to switch over to MIN 50 mg from their current therapies.
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2 96 Other combined osteoporosis treatments, such as active vitamin D, vitamin K₂, and
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4 97 **calcium** were continued during the study period. Patients' treatment persistence and
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6 98 satisfaction levels with the therapies were assessed using a self-administered
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8 99 questionnaire at 12 months (Table 1). **Patients were asked for their drug adherence every**
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10 100 **time visiting outpatient clinic (every 1-3 months), and patients who didn't take their**
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12 101 **medications more than twice of their interval (more than 2 weeks for weekly ALN or**
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14 102 **RIS, and more than 2 months for monthly MIN) were considered as drop-out.**
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24 103 This observational study was conducted in accordance with the ethical standards of the
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27 104 Declaration of Helsinki and was approved by ethical review boards at the clinical center
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30 105 (approval number 11273-2; Osaka University, Graduate School of Medicine). Written
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33 106 informed consent was obtained from individual patients included in the study.
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40 108 **BMD assessment**
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43 109 Areal BMD in the LS (L2-L4), total hip (TH), and femoral neck (FN) were assessed by
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46 110 dual-energy x-ray absorptiometry (Discovery A, Hologic, Inc., Waltham, MA, USA) at
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49 111 baseline and after 6 and 12 months of treatment. Regions of severe scoliosis, vertebral
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52 112 fracture, and operated sites were excluded from BMD measurements as previously
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55 113 described [18].
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5 115 *Biochemical markers of bone turnover*
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8 116 Bone turnover markers were measured in serum obtained from each patient at
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11 117 approximately the same time in the morning after overnight fasting. The bone formation
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14 118 marker, N-terminal type I procollagen propeptide (PINP); inter-assay coefficient of
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17 119 variation (CV), 3.2%-5.2%, (Intact UniQ assay; Orion Diagnostica, Espoo, Finland),
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20 120 and bone resorption marker, isoform 5b of tartrate-resistant acid phosphatase
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23 121 (TRACP-5b); inter-assay CV, 5.0%-9.0%, (Immunodiagnostic Systems Ltd., Boldon,
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26 122 UK) were measured by ELISA as previously described [19]. Levels of
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29 123 undercarboxylated osteocalcin (ucOC) were measured by a solid-phase enzyme
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32 124 immunoassay kit; inter-assay CV, 5.2%-8.3%, (Takara Bio, Shiga, Japan) with a
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35 125 sensitivity of 0.25 ng/mL. **UcOC reflects not only vitamin K deficiency, but also total**
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38 126 **bone turnover, as it is released from both osteoblasts and absorbed bone extracellular**
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41 127 **matrix by osteoclast as previously described [20, 21]. Intact- parathyroid hormone**
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44 128 (PTH) was measured using a two-site immunoradiometric assay; inter-assay CV 8.4%,
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47 129 (Nichols Institute Diagnostics, Valencia, USA).
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56 131 *Statistical analysis*
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2 132 The normal distributions of the data were examined by the Shapiro-Wilk test.
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5 133 Differences between each study group were tested using analysis of variance for
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8 134 normally distributed data and the nonparametric Kruskal-Wallis test was used for
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11 135 non-normally distributed data. Changes in BMD and ranked bone turnover marker data
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14 136 from baseline to specified time points within each study group were compared using the
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17 137 nonparametric Wilcoxon signed-rank test. Results are expressed as the mean \pm standard
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20 138 error. A *P* value < 0.05 indicated statistical significance. All tests were performed using
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24 139 IBM SPSS Statistics version 22 software (IBM, Armonk, NY, USA).
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31 141 **Results**
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34 142 Baseline characteristics are shown in Table 2. Of the 172 study patients, 84 (48.8%)
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37 143 were willing to switch to MIN 50 mg. No significant differences were observed in
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40 144 baseline age, combined dose and prescription rate of active vitamin D or vitamin K₂ or
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43 145 calcium or prednisolone (PSL), BMD, or disease activity of RA between the groups.
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46 146 Duration of prior BP therapy at baseline was significantly longer in the
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49 147 switch-from-ALN group (57.2 months) compared to the continue group (43.6 months; *P*
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52 148 < 0.05) and the switch-from-RIS group (41.0 months; *P* < 0.05). Baseline serum
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55 149 TRACP-5b levels in the switch-from-ALN group were significantly lower compared to

1 150 the switch-from-RIS group (244.5 vs 309.8 mU/dL; $P < 0.05$). Eventually, 95.5%
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5 151 (84/88) of patients in the continue group (2 patients were lost to follow up and 2
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8 152 patients desired to change the medication) and 94.0% (79/84) of patients in the switch
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11 153 group (3 patients were lost to follow up and 2 patients desired to change the medication)
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14 154 completed the twelve-month trial (Fig. 1).
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21 156 *Change in BMD*

24 157 BMD was monitored every 6 months (Fig. 2). Both the switch groups showed a
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27 158 significant increase in LS and TH BMD from baseline to 6 and 12 months, while only
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30 159 the switch-from-RIS group showed a significant increase in FN BMD from baseline to 6
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33 160 and 12 months. Moreover, the switch-from-RIS group showed a significantly greater
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36 161 increase compared to the continue group in the LS from 6 months (2.3 vs 0.6%; $P <$
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38 162 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
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40 163 < 0.01) to 12 months (2.0 vs -0.7%; $P < 0.01$), and in the FN from 6 months (2.0 vs
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43 164 -0.4%; $P < 0.05$) to 12 months (2.7 vs -0.5%; $P < 0.05$), respectively. On the other hand,
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46 165 the switch-from-ALN group showed a significantly greater increase compared to the
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49 166 continue group in LS BMD at 12 months (3.2 vs 1.2%; $P < 0.05$) and in the TH from 6
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52 167 months (1.2 vs -0.5%; $P < 0.01$) to 12 months (1.5 vs -0.7%; $P < 0.01$). The

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2 168 switch-from-RIS group showed a significantly greater increase compared to the
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4 169 switch-from-ALN group in the FN from 6 months (2.1 vs -0.3%; $P < 0.05$) to 12 months
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6 170 (2.7 vs -0.6%; $P < 0.05$).
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12 172 *Bone turnover markers*
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15 173 Percent changes in bone turnover markers from baseline are shown in Fig. 3. The
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17 174 switch-from-RIS group showed a significantly greater decrease compared to the
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20 175 continue group in TRACP-5b levels from 6 months (-35.8 vs 1.3%; $P < 0.001$) to 12
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23 176 months (-37.3 vs 2.5%; $P < 0.001$), in PINP levels from 6 months (-22.2 vs -3.3%; $P <$
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26 177 0.05) to 12 months (-24.7 vs -6.2%; $P < 0.05$), and in ucOC levels from 6 months (-22.2
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29 178 vs 12.4%; $P < 0.05$) to 12 months (-39.2 vs 13.0%; $P < 0.05$). On the other hand, the
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31 179 switch-from-ALN group showed a significantly greater decrease compared to the
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34 180 continue group only in TRACP-5b levels from 6 months (-14.6 vs 1.3%; $P < 0.01$) to 12
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37 181 months (-12.5 vs 2.5%; $P < 0.05$). The switch-from-RIS group showed a significantly
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40 182 greater decrease than the minimum significant change of serum TRACP-5b, PINP, and
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43 183 ucOC levels, while the switch-from-ALN group showed only in the serum TRACP-5b
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46 184 at 12 months. There were no greater changes than the minimum significant change of
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49 185 serum TRACP-5b, PINP, and ucOC levels in the continue group. **The absolute value of**

1 186 bone turnover markers are shown in Fig. 4. The average value of TRACP-5b, PINP, and
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5 ucOC in all the groups were all within the reference value.
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12 189 *Rate of fragility fracture*
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15 190 During the twelve-month period, the continue group patients experienced 3 vertebral
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17 and 1 non-vertebral clinical fragility fractures (4.5%). The switch-from-ALN group
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19 experienced 1 vertebral and 1 non-vertebral clinical fragility fractures (4.5%), and no
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21 clinical fragility fracture was observed in the switch-from-RIS group (0.0%). No
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23 statistically significant difference in the total clinical fragility fracture rate was observed
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31 between the groups.
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37 197 *Patient preference after switching to MIN 50 mg*
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40 198 Patient preference after switching to monthly MIN 50 mg is shown in Fig. 5. The
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42 questionnaire revealed that 80.8% of patients were satisfied with the switch to monthly
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44 therapy and 88.7% preferred to continue the monthly treatment. The main reasons for
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46 desiring continuation of monthly dosing was both the decreased frequency (69.8%) and
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2 204 **Discussion**
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5 205 In this study, we have demonstrated for the first time that in patients with RA, of whom
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8 206 two-thirds were treated with low-dose PSL (< 10 mg/day), switching from weekly ALN
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11 207 or RIS to monthly MIN was effective in increasing BMD and decreasing bone turnover
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14 208 markers at 12 months. In addition, no previous studies have demonstrated the difference
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17 209 of the effects of switching, by the difference of prior BP therapies.
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21 210 In nitrogen-containing BP treatment, mineral binding affinities may influence their
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24 211 distribution within bone and the period till anti-fracture effects are shown, and
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27 212 inhibition of farnesyl diphosphate synthase (FPPS) may affect their anti-resorptive
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30 213 effects by inducing apoptosis of osteoclasts [22].
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34 214 It has been shown that ALN possesses a stronger binding affinity to hydroxyapatite
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37 215 compared to RIS, while RIS possesses a stronger FPPS inhibition compared to ALN
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40 216 [22]. Consequently, weekly ALN (70 mg) showed a greater increase in BMD and
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43 217 decrease in bone turnover markers compared to weekly RIS (35 mg) in patients with
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46 218 postmenopausal osteoporosis [23], while RIS showed lower rates of hip and
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49 219 non-vertebral fractures than ALN during the first year of therapy [24].
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53 220 Previous reports have demonstrated that MIN showed stronger FPPS inhibition [11] and
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56 221 a weaker binding affinity to hydroxyapatite compared to ALN and RIS [25], which
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2 222 suggests that MIN inhibits bone resorption more strongly and is more quickly
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4 223 distributed within the bone compared to ALN and RIS. Indeed, MIN suppressed bone
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7 224 remodeling of cancellous and cortical bone more strongly than ALN in vitro [26], as
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9 225 well as in ovariectomized cynomolgus monkeys in vivo [27]. **In the previous human**
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11 226 **study, switching ALN or RIS to monthly MIN for 6 months increased BMD +1.1% in**
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13 227 **LS, and the reduction rate of serum TRACP-5b was approximately 35% in the**
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15 228 **switching from RIS group at 6 months [12], which were consistent with our study.**
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18 229 Finally, glucocorticoids have been shown to induce apoptosis of osteocytes, and BPs
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20 230 inhibit osteocyte apoptosis in vitro [28] as well as in glucocorticoid-treated animals [29].
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23 231 A systematic review and meta-analysis revealed that BPs can preserve bone mass and
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26 232 reduce the incidence of vertebral fractures in patients with rheumatic disease, mainly for
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28 233 those who are being treated with glucocorticoids [30], and both ALN and RIS strongly
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31 234 decreased the fracture risk associated with glucocorticoid-induced osteoporosis (GIO)
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34 235 [31, 32]. In this study, monthly MIN 50 mg resulted in a greater BMD increase and
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37 236 bone turnover decrease when patients were switched from ALN or RIS, which suggests
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40 237 its effectiveness not only in primary osteoporosis, but also in GIO.
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1 240 patients showed remission or low disease activity in this study, the effects of switching
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5 241 on high disease activity patients should be assessed in further study. Although most
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8 242 patients were postmenopausal, some male patients were included in this study.
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11 243 **Concerning medication, the dose of ALN and RIS allowed in Japan is the half of**
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14 244 **Caucasians, and the duration of prior BP therapy was significantly longer in switch-to**
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17 245 **ALN group compared to other groups. In addition, only a small number of patients were**
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20 246 **combined with calcium formulation, and total calcium intake couldn't be monitored.**
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23 247 In conclusion, switching weekly ALN or RIS to monthly MIN in patients with RA, of
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26 248 whom two-thirds were treated with low-dose PSL, significantly decreased bone
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29 249 turnover markers and increased BMD at 12 months, suggesting that monthly MIN may
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32 250 be an effective alternative treatment option of oral BP treatment.
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38 252 **Acknowledgments**
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44 254
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47 255 **Authors' roles**
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50 256 Study design: KE, MH, JH, and HY. Study conduct: KE, TN, MH, and SK. Data
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53 257 collection: KE, TN, SK, and MY. Data analysis: KE, TN, and MH. Data interpretation:
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2 258 KE and MH. Drafting the manuscript: KE and MH. Approving final version of the
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4
5 259 manuscript: KE, TN, MH, JH, SK, and HY. KE takes responsibility for the integrity of
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8 260 the data analysis.
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15 262 **Conflicts of interest**
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17
18 263 This research was funded by Astellas Pharma, Inc. The funder had no role in the study
19
20
21 264 design, data collection, data analysis, decision to publish, or preparation of the
22
23
24 265 manuscript. Kosuke Ebina, Takaaki Noguchi, Makoto Hirao, Jun Hashimoto, Shoichi
25
26
27 266 Kaneshiro, Masao Yukioka, and Hideki Yoshikawa declare that they have no conflict of
28
29
30 267 interest.
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2 371 **Figure legends**
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8 373 Figure 1. Study design and schedule. Patients were asked for their willingness to switch
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11 374 to monthly MIN 50 mg. Bone mineral density and bone turnover markers were
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14 375 evaluated every 6 months in all the patients. The switch group patients were asked to
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17 376 complete a patient preference questionnaire at 12 months.
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24 378 Figure 2. Mean \pm standard error (SE) change from baseline in bone mineral density
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27 379 (BMD) at the lumbar spine (panel a), total hip (panel b), and femoral neck (panel c). *P
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30 380 < 0.05 , $^{**}P < 0.01$, $^{***}P < 0.001$ change from baseline within each treatment group. $^{\#}P <$
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34 381 < 0.05 , $^{##}P < 0.01$, $^{###}P < 0.001$ continue group versus switch-from-RIS group. $^{\dagger}P <$
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37 382 0.05, switch-from-ALN group versus switch-from-RIS group.
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44 384 Figure 3. Mean \pm standard error (SE) change from baseline in serum concentration of
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47 385 bone turnover markers TRAP-5b (panel a), PINP (panel b), and ucOC (panel c).
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50 386 TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; PINP, type I collagen
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53 387 N-terminal propeptide; ucOC, undercarboxylated osteocalcin; $^*P < 0.05$, $^{##}P < 0.01$,
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56 388 $^{###}P < 0.001$ continue group versus each switch group. $^*P < 0.05$, $^{**}P < 0.01$
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2 389 switch-from-ALN group versus switch-from-RIS group.
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8 391 **Figure 4.** Mean \pm standard error (SE) absolute value of bone turnover markers TRAP-5b
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10 392 (panel a), PINP (panel b), and ucOC (panel c). TRAP-5b, isoform 5b of tartrate-resistant
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14 393 acid phosphatase; PINP, type I collagen N-terminal propeptide; ucOC,
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18 394 undercarboxylated osteocalcin; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ continue group
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21 395 versus each switch group. $^{\ast}P < 0.05$ switch-from-ALN group versus switch-from-RIS
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24 396 group.
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31 398 **Figure 5.** Patient satisfaction, preference, and reasons for preference after switching
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34 399 weekly ALN or RIS to monthly MIN 50 mg treatment at 12 months.
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1 Table 1. Patient preference questionnaire

1. Rate your satisfaction with the current once-monthly dosing schedule ^{a)}

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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

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

3 b) Multiple answers allowed.

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15 Table 2. Baseline clinical characteristics

Variable	Continue (n=88)	Switch-from-ALN (n=44)	Switch-from-RIS (n=40)
Age, (mean \pm SE years)	64.9 \pm 0.9	64.9 \pm 1.6	67.3 \pm 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 \pm 0.4	21.2 \pm 0.6	22.2 \pm 0.6
Prior BP, ALN n/N(%)	58/88 (65.9%)		
Duration of prior BP therapy (months)	43.6 \pm 2.1	57.2 \pm 4.6*	41.0 \pm 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 \pm 0.017	0.861 \pm 0.028	0.858 \pm 0.019
Lumbar spine BMD (T-score)	-1.4 \pm 0.1	-1.3 \pm 0.2	-1.4 \pm 0.2
Femoral neck BMD (g/cm ²)	0.584 \pm 0.027	0.546 \pm 0.015	0.584 \pm 0.016
Femoral neck BMD (T-score)	-2.1 \pm 0.1	-2.3 \pm 0.1	-2.0 \pm 0.1
Total hip BMD (g/cm ²)	0.698 \pm 0.028	0.658 \pm 0.017	0.677 \pm 0.018
Total hip BMD (T-score)	-1.8 \pm 0.1	-1.9 \pm 0.1	-1.8 \pm 0.2
T-score < -2.5, n/N(%)	45/88 (51.1%)	22/44 (50.0%)	16/40 (40.0%)
PINP (μ g/l)	34.2 \pm 2.7	29.7 \pm 2.7	34.5 \pm 2.5
TRACP-5b (mU/dl)	258.1 \pm 11.2	244.5 \pm 17.6	309.8 \pm 22.7†
ucOC (ng/ml)	2.7 \pm 0.3	3.6 \pm 0.9	3.7 \pm 0.6
Intact-PTH (pg/ml)	48.9 \pm 2.4	51.5 \pm 3.7	45.6 \pm 2.6
eGFR (ml/min/1.73m ²)	77.2 \pm 2.5	73.6 \pm 3.5	74.9 \pm 3.3
Duration of disease (years)	17.6 \pm 1.0	18.3 \pm 1.6	15.1 \pm 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 \pm 0.1	0.6 \pm 0.1	0.5 \pm 0.1
MMP-3 (ng/ml)	158.4 \pm 16.2	118.1 \pm 16.4	118.2 \pm 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%)

16 Mean ± Standard Error (SE), unless otherwise noted.

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

18 ALN, Alendronate; RIS, Risedronate; BP, Bisphosphonate; PINP, Type I collagen N-terminal propeptide;
19 TRAP-5b, Isoform 5b of tartrate-resistant acid phosphatase; ucOC, Undercarboxylated osteocalcin; PTH,
20 parathyroid hormone; eGFR, Estimated glomerular filtration rate; RF, Rheumatoid factor; ACPA, Anti-
21 cyclic citrullinated peptide antibody; CRP, C-reactive protein; MMP-3, Matrix metalloproteinase-3;
22 DAS28-CRP, Disease activity score assessing 28 joints with CRP; MHAQ, Modified Health Assessment
23 Questionnaire; MTX, Methotrexate.

24 Differences between the groups were determined by ANOVA or chi-square test. *P<0.05 vs Continue
25 group. **P<0.01 vs Continue group. †P<0.05 vs Switch-from-ALN group. ††P<0.01 vs
26 Switch-from-ALN group.

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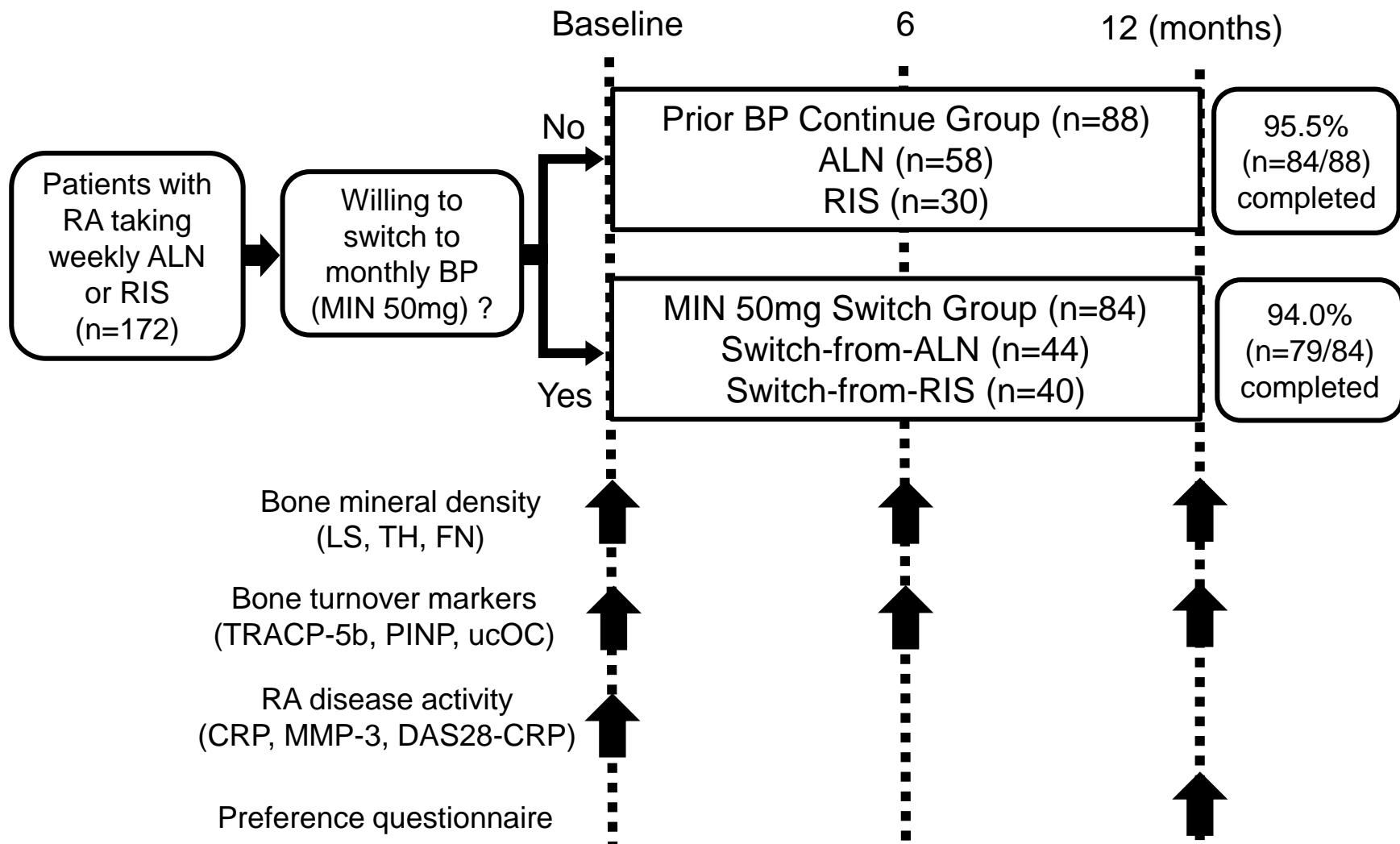
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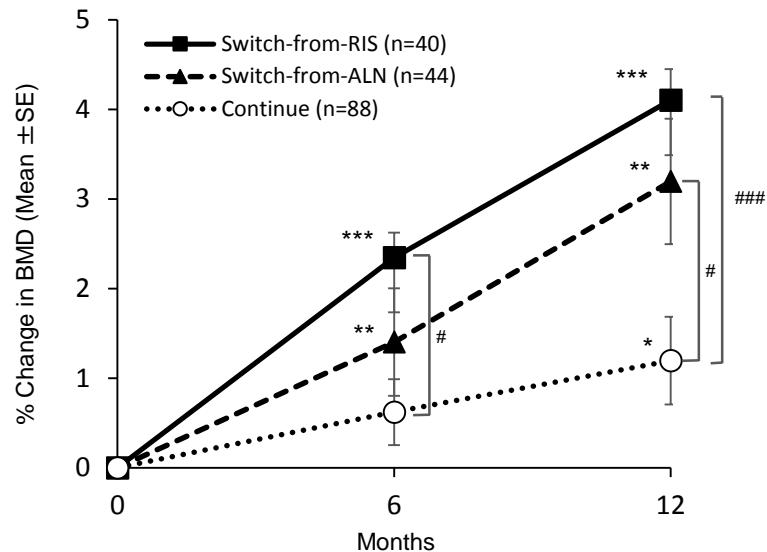
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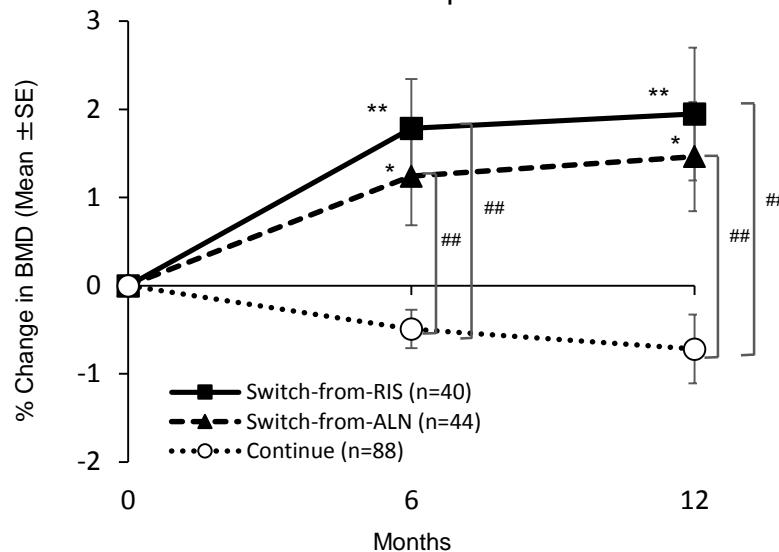
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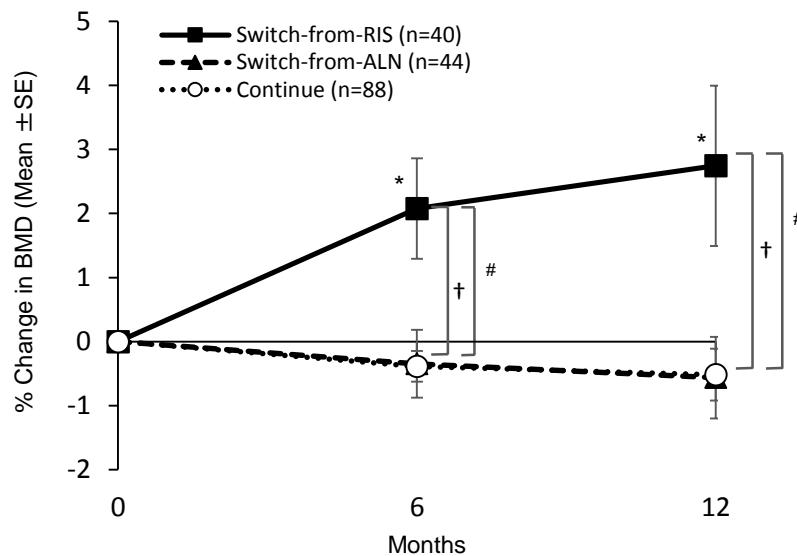
a Lumbar Spine

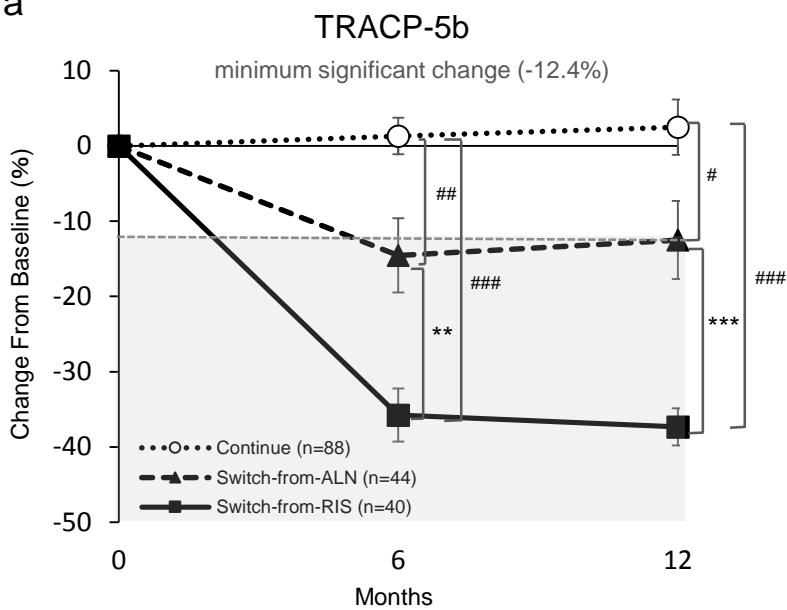
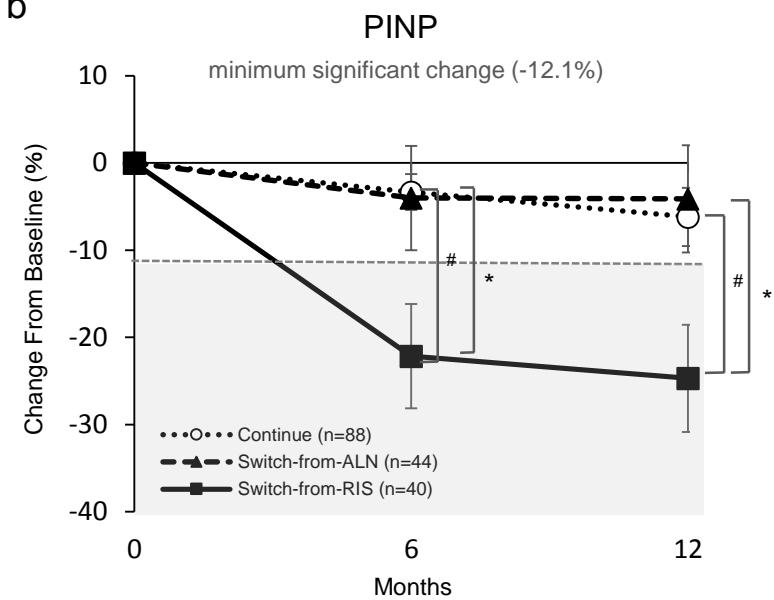
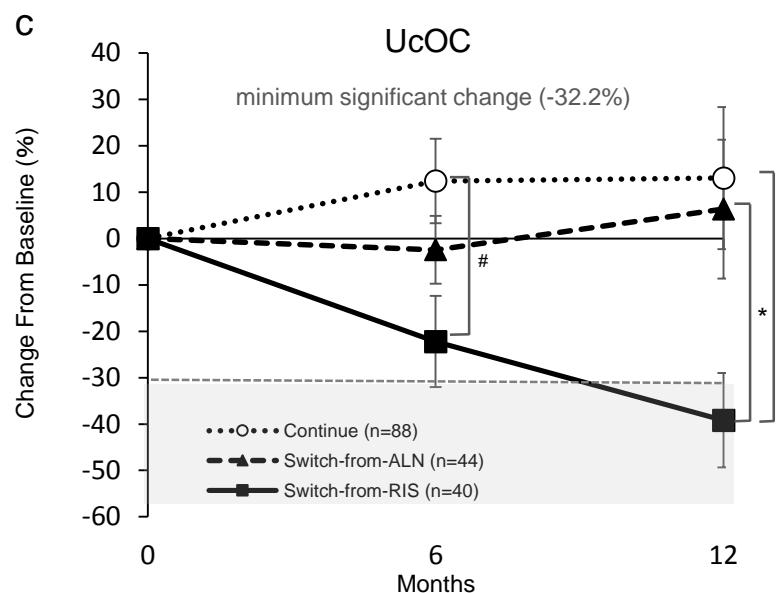


b Total Hip



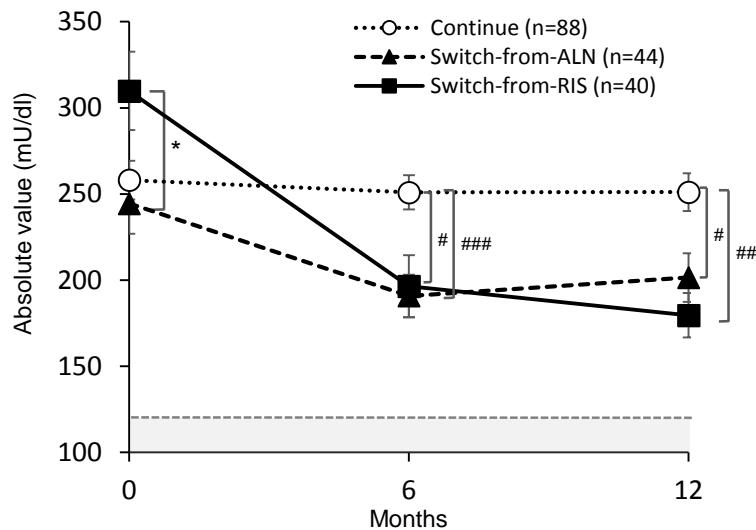
c Femoral neck



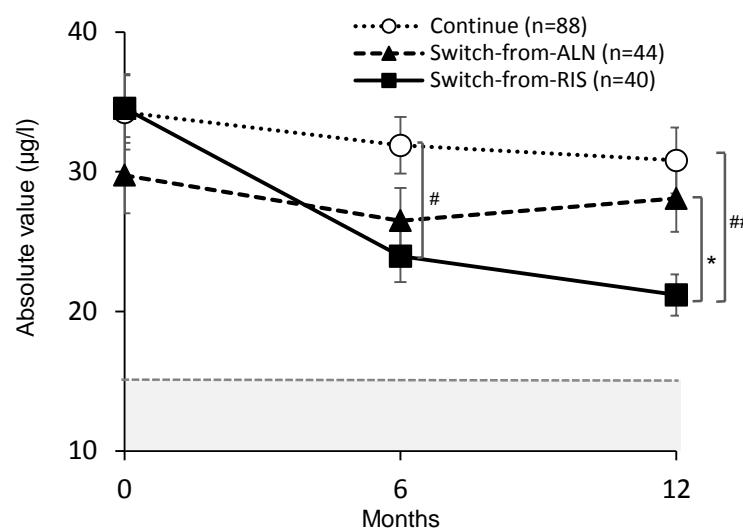
a**b****c**

a**TRACP-5b**

reference range: 120-420 mU/dl

**b****PINP**

reference range: 14.9-68.8 µg/l

**c****UcOC**

reference range: <4.5 ng/ml

