

Title	Impact of switching oral bisphosphonates to denosumab or daily teriparatide on the progression of radiographic joint destruction in patients with biologic-naïve rheumatoid arthritis
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2 3	1	Original Article
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8 9	3	progression of radiographic joint destruction in patients with biologic-naïve rheumatoid
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### 22 Abstract

23 Purpose

The aim of this study was to clarify the effects of switching oral bisphosphonates (BPs) to denosumab (DMAb) or daily teriparatide (TPTD) on the progression of radiographic joint destruction in patients with biologic-naïve rheumatoid arthritis (RA).

27 Methods

A retrospective, case-controlled study involving 90 female RA patients (mean age 68.2 years, 96.7% postmenopausal, disease activity score assessing 28 joints with CRP (DAS28-CRP) 2.4, methotrexate treatment 81.1%, prednisolone treatment 68.9%, and prior BP treatment 44.8 months), who were allocated depending on each patient's and physician's wishes, to (1) the BP-continue group (n=30), (2) the switch-to-DMAb group (n=30), or (3) the switch-to-TPTD group (n=30), was conducted. Patients were retrospectively selected to minimize the difference of possible clinical backgrounds that may affect the joint destruction of RA. The primary endpoint was to clarify the change of the modified total Sharp score (mTSS) from baseline to 12 months. 

37 Results

After 12 months, the mean changes of the modified Sharp erosion score were significantly lower in the switch-to-DMAb group  $(0.2\pm0.1; \text{mean}\pm\text{standard error})$  than

40	in the switch-to-TPTD group (1.3 $\pm$ 0.5; <i>P</i> < 0.05), and mTSS was significantly lower in
41	the switch-to-DMAb group (0.3±0.2) than in the BP-continue group (1.0±0.3; $P < 0.05$ )
42	and the switch-to-TPTD group (1.7 $\pm$ 0.6; P < 0.05). The logistic regression analysis
43	showed that mTSS changes were significantly associated with the percent changes of
44	TRACP-5b at 6 months ( $\beta$ =0.30, 95% CI=0.002-0.016; <i>P</i> < 0.01).
45	Conclusions
46	Changes of systemic bone turnover induced by switching BPs to DMAb or TPTD may
47	affect not only systemic bone mass, but also local joint destruction, and its clinical
48	relevance should be considered comprehensively.
49	
50	Keywords
51	Bisphosphonate; denosumab; joint destruction; rheumatoid arthritis; teriparatide
52	
53	Mini Abstract
54	In biologic-naïve female RA patients, switching oral BPs to DMAb significantly
55	reduced radiographic joint destruction compared to continuing oral BPs or switching to
56	TPTD at 12 months, which were significantly associated with a decrease of a bone
57	resorption marker at 6 months.
58	

#### 59 Introduction

Rheumatoid arthritis (RA) is characterized by systemic inflammation, which is associated with increased osteoclast activity leading to bone erosion and joint destruction [1, 2]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin (IL)-1, IL-6, and IL-17, are strongly involved in receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) induction, which is essential for osteoclast differentiation and activation [3]. Moreover, previous reports demonstrated that increased bone turnover [4, 5] and low bone mineral density (BMD) [6] is associated with future radiographic joint destruction in RA, suggesting the significance of inhibiting bone turnover and obtaining high BMD to protect against joint destruction. Bisphosphonates (BPs), which induce apoptosis of osteoclasts by inhibiting farnesyl diphosphate synthase, play pivotal roles in the treatment of both primary and secondary osteoporosis [7]. However, the efficacy of switching BPs to denosumab (DMAb), an anti-RANKL antibody that strongly inhibits bone resorption [8], or daily teriparatide (TPTD), a bone anabolic agent that strongly induces bone formation [9], has been reported in primary osteoporosis. In addition, we have recently reported that switching BPs to DMAb significantly inhibited bone turnover [10], and Takeuchi et al. demonstrated that DMAb inhibited progression of the bone erosion of RA [11]. On the other hand, switching BPs to daily TPTD induced overshoot of the bone turnover of RA[10, 12].

Taken together, we hypothesized that the change of bone turnover induced by these osteoporosis agents may have some effects on the progression of joint destruction (especially on bone erosion) in RA. The aim of this retrospective, case-controlled study was to clarify the effects of switching BPs to DMAb or TPTD on radiographic joint destruction in biologic-naïve female patients with RA.

### 85 Materials and methods

#### 86 Study design and subjects

This 12-month retrospective, case-controlled study was conducted based on a two-center, open-label design. A total of 155 biologic-naïve female (96.7% postmenopausal) patients with RA, who were treated with an oral BP according to the Japanese guidelines for prevention and treatment of osteoporosis 2011 [13] or the guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research 2004 [14], were enrolled. RA was diagnosed based on the 1987 revised American College of Rheumatology (ACR) criteria [15]. Registered patients were allocated based on each physician's discretion and 

95	patients' preference to the "BP-continue" group (n=63), the "switch-to-DMAb" group
96	(n=61), or the "switch-to-TPTD" group (n=31). Calcium (50-610 mg/day) and vitamin
97	D (0.25-10 $\mu$ g/day) supplements were provided, and dosing was adjusted by the
98	attending physician. Patients who completed 12 months of osteoporosis treatment
99	without biologic disease-modifying antirheumatic drugs (bDMARDs) of the three
100	groups were matched with the following parameters, including baseline age, disease
101	duration, rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA)
102	positivity, serum levels of bone turnover markers (BTMs), C-reactive protein (CRP),
103	Disease Activity Score assessing 28 joints with CRP (DAS28-CRP), and the modified
104	Total Sharp Score (mTSS), which may affect the progression of joint destruction as
105	previously described [16]. BP-continue group (n=63) and switch-to-DMAb group (n=61)
106	were independently matched with these parameters to switch-to-TPTD group (n=31) with
107	propensity score matching, using 1:1 optimal matching without replacement as previously
108	described [17]. Finally, the "BP-continue" group (n=30), the "switch-to-DMAb" group
109	(n=30), and the "switch-to-TPTD" group (n=30) were evaluated.
110	This study was conducted in accordance with the ethical standards of the Declaration of
111	Helsinki and was approved by the ethical review board at the clinical center (approval

number 13231-2; Osaka University, Graduate School of Medicine). Written, informed

113 consent was obtained from each individual patient included in the study.

#### 115 Radiographic assessment of the modified Sharp score

The hand and foot radiographs were taken at baseline and at 12 months when switching osteoporosis therapies or starting observation. Two rheumatologists independently assessed the images blinded to patients' clinical information, and the average scores of the two were used in the analysis, as previously described [18]. The primary endpoint was the change from baseline in the modified Sharp erosion (ERO) score, the modified Sharp joint space narrowing (JSN) score, and the modified total Sharp score (mTSS) at 12 months [11]. The cumulative probability of the progression of mTSS per year  $(\Delta mTSS/year)$  and the clinically relevant radiological progression rate (CRRP;  $\Delta mTSS/year \ge 3$ ) were evaluated [19]. 

#### 126 BMD and trabecular bone score (TBS) assessment

Areal BMDs in the lumbar spine (LS; L2-L4), total hip (TH), and femoral neck (FN)
were assessed by dual-energy X-ray absorptiometry (Discovery, Hologic, Inc., Waltham,
MA, USA) at baseline and after 12 months of treatment. Regions of severe sclerosis,
vertebral fractures, and operated sites were excluded from BMD measurements, as

previously described [20]. The trabecular bone score (TBS) was assessed at the same
regions used for LS DXA scans, using the TBS iNsight Software v1.7 (Med-Imaps,
Bordeaux, France), as previously described [21].

135

## Biochemical markers of bone turnover

BTMs were measured in serum obtained from each patient in the morning after overnight fasting. As for 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 as for bone resorption marker, 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 [12]. Previous report demonstrated that TRACP-5b is a useful marker which shows higher clinical sensitivity and signal-to-noise ratio compared to serum collagen type 1 cross-linked C-telopeptide (CTX) [22]. Serum intact parathyroid hormone (PTH) levels was measured using a two-site immunoradiometric assay (inter-assay CV, 8.4%; Quest Diagnostics Nichols Institute, California, USA).

148 Statistical analysis

Differences among study groups 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 were compared within each study group using the nonparametric Wilcoxon signed-rank test. Patients' clinical background characteristics that showed significant correlations with 12-month mTSS change as evaluated by Spearman correlation coefficients were selected as predictor variables, and multivariate logistic regression analysis with a forward stepwise procedure was performed to identify significant indicators of 12-month mTSS change. The 95% confidence intervals (CIs) for correlation coefficients were calculated based on Fisher's z-transformation. Results are expressed as means  $\pm$  standard error. A P value < 0.05 was considered significant. All tests were performed using IBM SPSS Statistics version 22 software (IBM, Armonk, NY, USA). 

### **Results**

The patients' baseline characteristics and changes after 12 months are shown in Table 1.
No significant differences were observed in baseline age, body mass index, disease
duration of RA, RF and ACPA positivity, mTSS, CRP, swollen/tender joint count, and

DAS28-CRP. In addition, no significant changes and no differences between the groups were observed in the swollen/tender joint count and DAS28-CRP after 12 months. The patients' medications and bone metabolism-related parameters are shown in Table 2. No significant differences were observed in combined prednisolone (PSL) or methotrexate (MTX) doses and usage rates, areal BMD (T-scores), trabecular bone score (TBS), serum intact-PTH levels (which increase in response to a low serum 25-hydroxycholecalciferol [25(OH)D)] level and low calcium intake [23]), and BTMs. On the other hand, the switch-to-TPTD group showed longer prior BP therapy duration and a lower rate of combined vitamin D use compared to the BP-continue group and the switch-to-DMAb group. The switch-to-DMAb group had a higher rate and dose of calcium and native vitamin D (cholecalciferol; VD3) administration compared to both the BP-continue group and the switch-to-TPTD group. There was no significant difference in the prescription rate of active vitamin D (alfacalcidol [ALF] and eldecalcitol [ELD]) between the BP-continue group and the switch-to-TPTD group. 

182 Bone turnover markers

183 Percent changes in BTMs from baseline are shown in Fig 1a and 1b. The
184 switch-to-DMAb group showed a significantly greater decrease compared to the

185	BP-continue group in both PINP levels (-28.7% vs 0.9%; $P < 0.05$ ) and TRACP-5b
186	levels (-29.0% vs -4.6%; $P < 0.01$ ) at 6 months. On the other hand, the switch-to-TPTD
187	group showed a significantly greater increase compared to the BP-continue group in
188	PINP levels from 6 months (218.6% vs 0.9%; $P < 0.001$ ) to 12 months (165.5% vs
189	5.8%; P < 0.001), and in TRACP-5b levels from 6 months (64.9% vs -4.6%; $P$ < 0.001)
190	to 12 months (63.5% vs -6.4%; <i>P</i> < 0.001).
191	
192	Changes in BMD and TBS
193	Changes in BMD and TBS are shown in Table 2. The switch-to-TPTD group showed
194	the highest increases in LS BMD, TBS, and BTMs. On the other hand, the
195	switch-to-DMAb group tended to show the highest increases in FN and TH BMD
196	compared to the other two groups.
197	
198	Effects of switching osteoporosis therapy on joint space narrowing and bone erosion
199	The mean changes from baseline at 12 months in the radiographic modified Sharp
200	erosion score are shown in Fig 2. The changes from baseline in the modified Sharp JSN
201	score at 12 months showed no significant difference among the three groups (Fig 2a).
202	On the other hand, as shown in Fig 2b, the change from baseline in the modified Sharp

erosion score at 12 months was significantly lower in the switch-to-DMAb group than in the switch-to-TPTD group ( $0.2\pm0.1$  vs  $1.3\pm0.5$ ; P < 0.05). Consequently, the changes from baseline in the mTSS at 12 months were significantly lower in the switch-to-DMAb group than in the BP-continue group ( $0.3\pm0.2$  vs  $1.0\pm0.3$ ; P < 0.05) and the switch-to-TPTD group  $(0.3\pm0.2 \text{ vs } 1.7\pm0.6; P < 0.05)$  (Fig 2c). Cumulative probability plots for changes in the modified Sharp JSN score (Fig 3a), the modified Sharp ERO score (Fig 3b), and mTSS (Fig 3c) at 12 months are shown. The clinically relevant radiological progression rate (CRRP;  $\Delta mTSS/year \ge 3$ ) [19] was significantly lower in the switch-to-DMAb group than in the switch-to-TPTD group (3.3% vs 20.0%; P < 0.05). In addition, the structural remission rate ( $\Delta mTSS$ /year  $\leq$ 0.5) [18] tended to be higher in the switch-to-DMAb group than in the BP-continue group (76.7% vs 53.3%; P = 0.06) and the switch-to-TPTD group (76.7% vs 56.7%; P =0.10). Significant predictor variables of 12-month mTSS progression on multivariate linear

*regression analysis* 

Spearman correlation coefficients of possible clinical background characteristics
(including baseline age, disease duration, modified Sharp score, DAS28-CRP, combined

221	PSL and MTX dose, prior BP therapy duration, RF and ACPA titers, areal BMD, TBS,
222	and baseline and change of BTMs) with 12-month mTSS progression were investigated
223	for all patients (Table 3), and all significant ( $P < 0.05$ ) predictors (DAS28-CRP, ACPA
224	positivity, and $\Delta$ 6-month TRACP-5b (%)) were identified and subjected to stepwise
225	multivariable linear regression analysis to investigate significant predictors of 12-month
226	mTSS progression. The significant predictor of 12-month mTSS progression was $\Delta$
227	6-month TRACP-5b (%).
228	
229	Discussion
230	To the best of our knowledge, this is the first report demonstrating the effect of
231	switching oral BPs to DMAb or daily TPTD on the progression of radiographic joint
232	destruction in biologic-naïve patients with RA. Previous reports showed that increased
233	bone turnover is associated with future radiographic joint destruction in RA [4, 5],
234	suggesting the critical role of bone turnover in joint destruction, especially in
235	osteoclast-induced periarticular bone erosion.
236	Factors affecting the progression of joint destruction (especially bone erosion) in RA
237	have been reported. Syversen et al. demonstrated that baseline RF and ACPA positivity,
238	high disease activity, and female sex were independent predictors of progression of

mTSS in a 10-year prospective study [24]. Another cross-sectional study showed that the presence of bone erosions in RA correlates with low BMD levels [25]. In the present study, to investigate the effects of osteoporosis treatments, these factors affecting the progression of joint destruction were controlled between the groups. In addition, 12-month mTSS progression was significantly associated with baseline DAS28-CRP, ACPA positivity, and  $\Delta 6$ -month TRACP-5b (%), in accordance with previous reports. Finally, multivariate linear regression analysis showed that  $\Delta 6$ -month TRACP-5b (%) was the significant factor associated with 12-month mTSS progression. Concerning BPs, zoledronate is one of the BPs that most strongly induces apoptosis of osteoclasts [26], and a previous animal study showed that the combination of zoledronate and MTX prevented bone erosion in collagen-induced arthritis of rats [27]. On the other hand, human prospective, randomized trials failed to show the positive effects of zoledronate monotherapy on bone erosion in patients with psoriatic arthritis [28] and tophaceous gout [29]. Taken together, BP monotherapy may be insufficient, but its combination with MTX may have some positive effects on inhibition of bone erosion in arthritis. Takeuchi et al. reported that DMAb significantly inhibited the progression of bone 

erosion compared with placebo in Japanese RA patients who had bone erosions or

C-reactive protein (CRP)  $\geq 1.0$  mg/dL, and who were also never treated by BPs or biologics at baseline [11]. This population may be relatively rare compared to the real-world use of DMAb, since most patients are considered to be treated by BPs at first line according to the osteoporosis guidelines [13, 14]. Moreover, the placebo group was not treated by any bone resorption inhibitors such as BPs in this study. So the effects of switching BPs to DMAb on bone erosion of RA still remained unclear. Recently, Solomon et al. demonstrated that 1-year daily TPTD treatment failed to show significant effects on bone erosion of the hands or wrists compared to a control group in RA, who were all strictly controlled by TNF inhibitors and not taking osteoporosis treatment [30]. Taken together, TPTD may not reduce or enhance bone erosion compared to a non-osteoporosis treatment group, but its effects on bone erosion compared to BPs or DMAb still remained unclear. The present study demonstrated for the first time that switching oral BPs to DMAb significantly reduced  $\Delta 12$ -month mTSS compared to continuing oral BPs or switching

to TPTD, which were significantly associated with a decrease of a bone resorption marker. It has been reported that low BMD and thinning at the cortical site was significantly associated with bone erosions of RA[31]. DMAb showed positive effects in improving cortical porosity compared to BPs [32], while TPTD failed to show 

positive effects on cortical sites in the short-term treatment [33, 34]. Taken together, the
differential effects of each agent on both cortical bone and bone turnover may affected
the results.

There are several limitations to this study. First, since this was a small cohort, retrospective study, we could not completely match all the clinical backgrounds between the groups, and a large, prospective study is required to confirm the results. Second, as the treatment assignment was dependent on each patient's and physician's wishes, the initial treatment selection may affected the results. Third, since TPTD is recommended to patients at high fracture risk, the switch-to-TPTD group showed a tendency of higher rate and dose of PSL, with a longer duration of prior BP prescription than other groups. Fourth, there was significant difference in the form of vitamin D among the groups, because only active vitamin D combination is allowed in the treatment of BP or TPTD in our country. Fifth, the switch-to-TPTD group was treated with a lower rate of calcium and vitamin D supplementation compared to other groups, because of the recommendation of careful consideration in calcium and active vitamin D supplementation due to the risk of hypercalcemia in our country. Sixth, although mean serum intact-PTH levels of the three groups at baseline were all within the reference range (<65 pg/ml), we didn't monitor serum 25OH(D) levels and other standard bone 

turnover markers.

In conclusion, the changes of systemic bone turnover induced by switching BPs to DMAb or TPTD may affect not only systemic bone mass, but also local joint destruction, and its clinical relevance should be comprehensively considered by factors such as RA disease activity and fracture risk. 

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#### **Authors' roles**

Study design: KE, MH, JH, and HY. Study conduct: KE and MH. Data collection: KE, MH, and JH. Data analysis: KE, MH, HM, TI, RC, YE, and GO. Data interpretation: KE, MH, JH, HM, TI, RC, YE, GO, and AM. Drafting the manuscript: KE and MH. 

Approving final version of the manuscript: KE, MH, JH, HM, TI, RC, YE, GO, AM, 

and HY. KE takes responsibility for the integrity of the data analysis. 

#### **Conflicts of interest**

311	K Ebina, M Hirao, J Hashimoto, and H Yoshikawa have received research grants from
312	Astellas Pharma and Eisai Co. Ltd. K Ebina, M Hirao, and H Yoshikawa have received
313	research grants from Daiichi Sankyo. H Yoshikawa has received research grants from
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315	Pharmaceutical, Eisai Co. Ltd., Ono Pharmaceutical, Daiichi Sankyo, and Eli Lily. H
316	Matsuoka, T Iwahashi, R Chijimatsu, Y Etani, G Okamura, and A Miyama declare that
317	they have no conflicts of interest.

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#### 427 Figure legends

Fig 1. Mean changes in serum concentrations of bone turnover markers, PINP (panel a) and TRAP-5b (panel b). BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; PINP, type I collagen N-terminal propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase. Bars indicate standard errors.  $^{\#\#}P < 0.01$ ,  $^{\#\#\#}P < 0.01$ 0.001 BP-continue group versus switch-to-TPTD group. \*P < 0.05, \*\*P < 0.01BP-continue group versus switch-to-DMAb group.  $^{\dagger\dagger\dagger}P < 0.001$  switch-to-DMAb group versus switch-to-TPTD group. Fig 2. Mean changes in the radiographic score evaluated by the van der Heijde-modified Sharp method at 12 months. Modified Sharp joint space narrowing (JSN) score (panel a), Modified Sharp erosion (ERO) score (panel b), and Modified total Sharp score (mTSS) (panel c). BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide. Bars indicate standard errors. N.S., not significant, \*P 

441 < 0.05.

Fig 3. Cumulative probability plots of the changes from baseline at 12 months.
Modified Sharp joint space narrowing (JSN) score (panel a), Modified Sharp

2 3 1	445	erosion (ERO) score (panel b), and Modified total Sharp score (mTSS) (panel c).
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V/a	BP-continue group	Switch-to-DMAb	Switch-to-TPTD
variable	(n=30)	group (n=30)	group (n=30)
Age (mean ± SE years)	67.6±1.8	68.5±1.8	67.9±1.5
Postmenopausal (%)	96.7	93.3	100
Body mass index (kg/m <sup>2</sup> )	22.2±0.6	20.5±0.6	21.4±0.6
Duration of RA (years)	18.3±1.9	18.2±2.4	17.6±1.5
RF positivity (%)	90.0	90.0	80.0
RF titer (U/ml)	102.0±23.2	130.0±45.1	110±33.2
ACPA positivity (%)	90.0	86.7	80.0
ACPA titer (U/ml)	$194.4 \pm 50.8$	161.5±42.0	221.5±70.4
Modified Sharp erosion score	33 7+7 0	32 7+7 6	37 5+6 0
(0–280)	55.7±7.0	52.1±1.0	57.5±0.0
Modified Sharp JSN score (0–168)	55.8±7.3	45.1±6.6	56.2±6.6
Modified total Sharp score (0-448)	89.5±13.7	77.8±13.9	93.7±12.2
Baseline			
CRP (mg/dl)	1.1±0.3	$0.6 \pm 0.2$	$0.8\pm0.2$
Swollen joint count (0–28)	2.0±0.4	1.4±0.3	1.8±0.5
Tender joint count (0–28)	1.1±0.3	0.8±0.3	1.0±0.2
DAS28-CRP	2.5±0.2	2.2±0.2	2.3±0.2
Remission (< 2.3) (%)	46.7	56.7	46.7
Low (< 2.7) (%)	16.7	13.3	20.0
Moderate (≤4.1) (%)	33.3	30.0	30.0
High (> 4.1) (%)	3.3	0.0	3.3
12 months			
CRP (mg/dl)	1.1±0.3	$0.5 \pm 0.1$	0.6±0.2
Swollen joint count (0–66)	1.8±0.6	1.1±0.3	1.6±0.4
Tender joint count (0–68)	1.5±0.5	0.7±0.3	$0.8\pm0.2$
DAS28-CRP	2.4±0.1	2.0±0.2	2.0±0.1
Remission (< 2.3) (%)	46.7	60.0	63.3
Low (< 2.7) (%)	26.7	16.7	16.7
Moderate (≤4.1) (%)	23.3	23.3	20.0
High (> 4.1) (%)	3.3	0.0	0.0

1 Table 1. Patients' clinical characteristics at baseline and after 12 months of 2 treatment

3 Mean  $\pm$  standard error (SE), unless otherwise noted. % = number of patients with measurements / total

4 number of patients.

5 BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; RF, rheumatoid factor; ACPA, anti-cyclic

6	citrullinated peptide antibody; JSN, joint space narrowing; CRP, C-reactive protein; DAS28-CRP, disease
7	activity score assessing 28 joints with CRP.
8	Differences between the groups were determined by ANOVA or the chi-squared test.
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Variable	BP-continue group	Switch-to-DMAb	Switch-to-TPTD
Variable	(n=30)	group (n=30)	group (n=30)
	Weekly ALN	Weekly ALN	Weekly ALN
	(n=14; 46.7%)	(n=15; 50.0%)	(n=17; 56.7%)
	Weekly RIS	Weekly RIS	Weekly RIS
РПОГ БР шегару	(n=4; 13.3%)	(n=2; 6.7%)	(n=13; 43.3%) <sup>###, †††</sup>
	Monthly MIN	Monthly MIN	
	(n=12; 40.0%)	(n=13; 43.3%)	
	Total (36.6±4.2)	Total (40.5±5.4)	Total (57.4±5.5) <sup>#,††</sup>
Duration of prior BP therapy	ALN (32.7±2.7)	ALN (35.9±7.1)	ALN (59.1±6.7) <sup>##,†</sup>
(months)	RIS (27.3±7.3)	RIS (48.5±41.5)	RIS (55.2±9.3) <sup>#</sup>
	MIN (44.3±9.6)	MIN (44.5±8.1)	
Concomitant medication			
Baseline			
Vitamin D (%)	93.3	100.0	66.7 <sup>#, ††</sup>
ALF / ELD / VD3 (%)	73.3 / 20.0 / 0.0	40.0** / 16.7 /	60.0 / 6.7 / 0.0***
ALF / ELD / VD3 (µg/day)	0 8+0 1 / 0 8+0 0 /	+3.5 0 9+0 1/ 0 8+0 0 /	0.5+0.0###,††† /
	0.0+0.0	10.0+0.0***	0 8+0 0 / 0 0+0 0 <sup>†††</sup>
Calcium (%)	13.3	90.0***	6.7 <sup>†††</sup>
Calcium (mg/day)	51.3+40.1	300.3+50.6***	5.2+3.8 <sup>†††</sup>
Prednisolone dose (mg/day)	2 8+0 5	2.8+0.6	4 4+0 6
Prednisolone usage (%)	60.0	66.7	80.0
MTX dose (mg/week)	5 2+0 7	61+06	5 3+0 7
MTX usage (%)	76.7	867	80.0
12 months	70.7	0017	0010
Vitamin D (%)	80.0	100.0	53.3 <sup>#, †††</sup>
ALF / ELD / VD3 (%)	63.3 / 16.7 / 0.0	40.0 / 16.7 / 43.3***	50.0 / 3.3 / 0.0 <sup>†††</sup>
ALF / ELD / VD3 (%)	0.9+0.1 / 0.8+0.0 /	0.9+0.1/ 0.8+0.0 /	0.5+0.1###, ††† /
	0.0+0.0	10.0+0.0***	0.8+0.0 / 0.0+0.0 <sup>†††</sup>
Calcium (%)	10.0	83.3***	6.7 <sup>†††</sup>
Calcium (mg/dav)	48.7±40.2	294.2±51.6***	5.2±3.8 <sup>†††</sup>
Prednisolone dose (mg/day)	2.6±0.5	2.1±0.5	3.8±0.7 <sup>†</sup>
Prednisolone usage (%)	56.7	56.7	70.0
MTX dose (mg/week)	5.5+0.8	5.3±0.6	5.4±0.8

# **Table 2. Patients' medications and bone metabolism-related parameters**

MTX usage (%)	73.3	76.7	70.0		
Baseline					
Lumbar spine BMD (T-score)	-1.7±0.2	-2.0±0.3	-2.3±0.2		
Femoral neck BMD (T-score)	-2.2±0.2	-2.6±0.1	-2.6±0.2		
Total hip BMD (T-score)	-2.0±0.2	-2.4±0.2	-2.3±0.2		
Trabecular bone score	$1.4{\pm}0.0$	1.3±0.0	1.3±0.0		
Intact-PTH (pg/ml)	41.4±3.1	49.2±3.8	50.1±3.6		
Corrected calcium (mg/dl)	9.2±0.1	9.3±0.1	9.2±0.1		
eGFR (ml/min/1.73 m <sup>2</sup> )	75.0±4.4	71.3±3.6	75.3±4.1		
PINP (µg/l)	26.8±2.4	40.4±5.2	39.3±3.8		
TRACP-5b (mU/dl)	245.5±23.2	326.9±38.2	304.8±31.0		
12-month change (%)					
Lumbar spine BMD	3.2±0.9	4.9±1.0	5.3±1.1		
Femoral neck BMD	1.2±0.9	4.5±1.5	$1.7{\pm}1.4$		
Total hip BMD	$1.4{\pm}1.0$	2.9±0.8	1.1±0.9		
Trabecular bone score	-0.4±0.7	$0.2\pm0.6$	1.6±0.7		
PINP (µg/l)	5.8±13.0	-24.9±7.8	$165.5{\pm}40.0^{\#\#,\uparrow\uparrow\uparrow}$		
TRACP-5b (mU/dl)	-6.4±6.6	-24.7±7.6	63.5±14.9 <sup>###, †††</sup>		

27 Mean  $\pm$  standard error (SE), unless otherwise noted. % = number of patients with measurements / total

28 number of patients.

29 BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; ALN, alendronate; RIS, risedronate; MIN,

30 minodronate; ALF, alfacalcidol; ELD, eldecalcitol; VD3, cholecalciferol; MTX, methotrexate; BMD,

31 bone mineral density; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate; PINP, Type

32 I collagen N-terminal propeptide; TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase.

33 Differences between the groups were determined by ANOVA or the chi-squared test.

34 \*\*\* P<0.001; BP continue group vs Switch-to-DMAb group.

35 *\** P<0.05, *\*\*\** P<0.01, *\*\*\*\** P<0.001; BP continue group vs Switch-to-TPTD group.

36 <sup>†</sup>P<0.05, <sup>††</sup>P<0.01, <sup>†††</sup>P<0.001; Switch-to-DMAb group vs Switch-to-TPTD group.

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Table 3. Spearman correlation coefficients between changes in the 12-month
 modified total Sharp score and patients' clinical parameters, and significant
 predictor variables evaluated by multivariate linear regression analysis

	Parameter	r	P-value
Baseline	Age	0.01	0.90
	Body mass index	0.07	0.50
	Disease duration of RA	-0.08	0.48
	DAS28-CRP	0.22	0.04*
	Modified Sharp erosion score	0.20	0.06
	Modified Sharp JSN score	0.08	0.44
	Modified total Sharp score	0.14	0.19
	RF positivity	0.11	0.30
	ACPA positivity	0.32	0.01**
	Duration of prior BP therapy	-0.03	0.76
	Lumbar spine BMD (T-score)	-0.08	0.45
	Femoral neck BMD (T-score)	-0.02	0.89
	Total hip BMD (T-score)	-0.04	0.69
	Trabecular bone score	0.01	0.95
	Prednisolone dose (mg/day)	0.06	0.57
	PINP (µg/l)	-0.003	0.98
	TRACP-5b (mU/dl)	-0.12	0.29
6 months	$\Delta \text{PINP}(\%)$	0.16	0.15
	$\Delta$ TRACP-5b (%)	0.23	0.04*
12 months	$\Delta \text{PINP}(\%)$	0.09	0.45
	$\Delta$ TRACP-5b (%)	0.12	0.32

	Parameter	β	95% CI	P-value
$\Delta 12$ -month	$\Delta 6$ -month TRACP-5b (%)	0.30	0.002 to 0.016	0.009**
mTSS				

47 RA, rheumatoid arthritis; DAS28-CRP, disease activity score assessing 28 joints with CRP; JSN, joint 48 space narrowing; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; BP, 49 bisphosphonate; BMD, bone mineral density; PINP, Type I collagen N-terminal propeptide; TRAP-5b, 50 isoform 5b of tartrate-resistant acid phosphatase.  $\Delta$ , change; mTSS, modified total Sharp score;  $\beta$ , 51 standardized coefficient; 95%CI, 95%confidence intervals. \* P<0.05, \*\* P<0.01.





