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# Original Article

Effects of follow-on therapy after denosumab discontinuation in patients with postmenopausal osteoporosis

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## Abstract

### Objectives

To clarify the effects of follow-on therapy after denosumab (DMAb) discontinuation.

### Methods

In this retrospective, multicenter study, postmenopausal patients with osteoporosis who were previously treated by oral bisphosphonates (BP) (n=26) or teriparatide (TPTD) (n=27) were switched to DMAb (administered 2.6 times), and then discontinued. Patients (73.1 years, T-scores of the lumbar spine [LS] -2.7 and femoral neck [FN] -2.2) were switched to either (1) raloxifene (RAL) (n=13) or BP [(2) weekly or monthly BP (wmBP) (n=29) or (3) zoledronate (ZOL) (n=11)], based on each physician's decision (mean interval after final DMAb administration was 7.2 months). Bone mineral density (BMD) at final DMAb administration were set as baseline.

### Results

Changes in LS BMD at 1.5 years after final DMAb administration were -2.7% in the RAL, 0.7% in the wmBP, and 1.9% in the ZOL (P=0.31 between groups), and in FN BMD were -3.8%, -0.8%, and 1.8%, respectively (P=0.02 between the RAL and ZOL; P=0.048 between the RAL and BP). Clinical vertebral fracture incidence during 1.5 years after final DMAb

administration was 23.1% in the RAL, 3.4% in the wmBP, and 0.0% in the ZOL (P=0.048 between the RAL and ZOL; P=0.015 between the RAL and BP). No significant differences were observed in these parameters between the wmBP and ZOL.

## Conclusions

These results may contribute to the selection of adequate follow-on therapy after DMAb discontinuation, although further investigations are required.

## Keywords

Bisphosphonate; denosumab; discontinuation; follow-on treatment; postmenopausal osteoporosis

## Introduction

Denosumab (DMAb) is a monoclonal anti-RANKL antibody that acts on bone as a potent antiresorptive agent and is associated with reduced vertebral and non-vertebral fracture risk of patients with osteoporosis [1]. However, discontinuation of DMAb is associated with a substantial increase in bone turnover markers above pretreatment levels [2], as well as bone mineral density (BMD) loss and increased vertebral fracture risk [3, 4].

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2 68 To protect patients from the rapid effects that may occur after discontinuation of DMAb,  
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5 69 follow-on treatments with bisphosphonates (BP) have been investigated. Previous reports  
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8 70 demonstrated some positive effects of treatment with alendronate (ALN) [5] or zoledronate  
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11 71 (ZOL) [6]. However, another case report showed that treatment with raloxifene (RAL) was  
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14 72 associated with multiple vertebral fractures [7], and treatment with teriparatide (TPTD) was  
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17 73 associated with transient loss of BMD [8]. In addition, a previous study showed that serum  
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20 74 collagen type 1 cross-linked C-telopeptide (CTX) levels of patients with prior exposure to BP  
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23 75 remained in the postmenopausal range after DMAb discontinuation [9], suggesting the  
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26 76 importance of prior treatment before DMAb. Collectively, most of these previous studies were  
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29 77 relatively small case series, and the ideal prior and follow-on treatments of DMAb are still  
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32 78 unknown.

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37 79 Taken together, the aim of this retrospective study was to clarify the effects of follow-on  
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40 80 therapy after DMAb discontinuation on bone resorption, BMD, and clinical fracture risk.  
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## 45 46 47 82 **Materials and methods**

### 48 49 83 *Study design and subjects* 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65

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2 84 This non-randomized, retrospective study was conducted in 6 centers according to the Japanese  
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5 85 Guidelines for Prevention and Treatment of Osteoporosis 2011 [10]. A total of 129  
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8 86 postmenopausal patients with osteoporosis who were treated with and discontinued DMAb were  
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11 87 enrolled (Fig. 1). Among them, patients who were lost to follow-up 1.5 years after final DMAb  
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14 88 administration, who did not receive follow-on treatment or were treated by TPTD, who did not  
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17 89 undergo dual-energy x-ray absorptiometry (DXA) or spinal radiograph, or without bone  
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21 90 resorption marker data were excluded. To minimize the patients' variance, only patients who  
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24 91 were treated with oral BP or TPTD before DMAb, and followed by ALN, RIS, or IBN as BP  
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27 92 were included. Finally, 53 patients were included, whose physicians chose to treat them with  
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30 93 RAL (60 mg/day; n=13) or BP (n=40) [weekly or monthly BP (wmBP; ALN, RIS, or IBN)  
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33 94 (dose varies by agent used; n=29) or ZOL (5 mg/year IV; n=11)].  
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#### 43 44 45 96 *Ethical statement*

46 97 This study was conducted in accordance with the ethical standards of the Declaration of  
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49 98 Helsinki and was approved by the institutional ethical review board of Osaka University  
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52 99 Graduate School of Medicine (approval number 18258; Osaka University, Graduate School of  
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55 100 Medicine) and each institute. The board waived the requirement for patients' informed consent  
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58 101 because of the anonymous nature of the data.  
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103 *BMD assessment*

104 Areal BMD in the lumbar spine (LS; L2-L4) and femoral neck (FN) were assessed by DXA

105 (Discovery, Hologic, Inc., Waltham, MA, USA) at baseline (ie, final DMAb administration) and

106 1.5 years after final DMAb administration. Regions of severe sclerosis, vertebral fracture, and

107 surgical sites were excluded from BMD measurements, as previously described [11].

108

109 *Biochemical markers of bone resorption*

110 The bone resorption marker, isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b)

111 (inter-assay coefficient of variation, 5.0-9.0%) (Immunodiagnostic Systems Ltd., Boldon, UK)

112 was measured by enzyme-linked immunosorbent assay in the morning after overnight fasting, as

113 previously described [12]. A previous report demonstrated that TRACP-5b levels are a useful

114 marker that show higher clinical sensitivity and signal-to-noise ratio compared to serum CTX

115 levels [13]. Serum 25-hydroxycholecalciferol (25(OH)D) levels were measured by

116 electrochemiluminescence using the Elecsys system (Roche Diagnostics, Basel, Switzerland).

117

118 *Radiographs*

119 Spinal radiographs were obtained at final DMAb administration and at unscheduled times if  
 120 subjects had symptoms suggestive of clinical vertebral fractures during the 1.5-years follow-up.  
 121 For incidental non-vertebral fractures, radiographs were assessed by the investigator if subjects  
 122 had symptoms.  
 123  
 124 *Statistical analysis*  
 125 The differences between study groups were tested using the Mann-Whitney U test (for 2  
 126 groups) or by non-parametric Kruskal-Wallis test (for 3 groups) for continuous variables, and  
 127 Pearson's chi-squared test (for 2 groups) or Fisher's exact test (for 3 groups) for categorical  
 128 variables, and multi-way analysis of variance. Changes in BMD and serum TRACP-5b levels  
 129 from baseline to specified time points within each study group were compared using the  
 130 non-parametric Wilcoxon signed-rank test. Multivariate logistic regression analysis with a  
 131 forward stepwise procedure was performed to identify significant indicators of LS or FN BMD  
 132 change. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical  
 133 University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical  
 134 Computing, Vienna, Austria) [14]. A *P* value < 0.05 was considered significant.

## Results

Patients' clinical backgrounds before DMAb discontinuation are shown in Table 1. Of the 53 study patients, 49.1% (n=26) were previously treated with an oral BP, and 50.9% (n=27; 19 daily and 6 weekly) were previously treated by TPTD before DMAb administration. There were no significant differences between groups in prior therapy duration before DMAb (mean, 18.9 months), serum TRACP-5b levels before DMAb administration (347.2 mU/dl), and the number of times that DMAb was administered (2.6 times) between groups. Reasons for discontinuation of DMAb, as evaluated by each physician, were as follows: patients' preference, 20.8%; toxic reasons (malignancy, eruption, itching, swelling of gums, renal failure, and hypocalcemia), 13.2%; ineffectiveness, 13.2%; need for dental care, 7.5%; adequate BMD achieved (mostly LS BMD T-score > -2.5), 7.5%; and other nontoxic reasons, 35.8%. Results of these backgrounds separated by the RAL group (n=13) and the BP group (n=40) are shown in supplemental Table 1. No significant differences were observed between the groups.

Table 2 shows patients' clinical backgrounds at switching from DMAb to other therapy and BMD at final DMAb administration. There were no significant differences between groups in interval between final DMAb administration and start of follow-on treatment (7.2 months), combined active vitamin D (92.5%) and calcium (11.3%) rate, age (73.1 years), body mass index (20.5 kg/m<sup>2</sup>), estimated glomerular filtration rate (eGFR) (71.9 ml/min/1.73 m<sup>2</sup>), serum

154 25(OH)D (13.8 ng/ml) or serum TRACP-5b levels (192.8 mU/dl), LS T-score (-2.7), FN  
155 T-score (-2.2), and prior vertebral (50.9%) and non-vertebral (26.4%) fracture rate. Results of  
156 these backgrounds separated by the RAL group (n=13) and the BP group (n=40) are shown in  
157 supplemental Table 2. The RAL group showed lower eGFR (P=0.04) and higher rate of prior  
158 non-vertebral fracture (P=0.010) compared to the BP group.

159

160 *Bone resorption marker*

161 Percent changes in serum TRACP-5b levels from baseline (before DMAb administration) to  
162 each time point are shown in Figure 2a. All groups showed similar and significant reductions in  
163 TRACP-5b levels at final DMAb administration (RAL, -38.5%; wmBP, -35.3%; and ZOL, -  
164 31.2%) (P=0.32 between groups). However, the RAL group tended to show marked increases  
165 (52.9%), whereas the wmBP (14.2%) and ZOL (9.1%) groups showed a similar restoration to  
166 pre-DMAb levels at 1.5 years after final DMAb administration (P=0.50 between groups).  
167 Results of these parameters separated by the RAL group (n=13) and the BP group (n=40) are  
168 shown in supplemental Figure 1a.

169

170 *Changes in BMD*

171 Changes in LS BMD from final DMAb administration (baseline) to 1.5 years after final DMAb  
172 administration are shown in Figure 2b. The wmBP (+0.7%) and ZOL (+1.9%) groups  
173 maintained levels, whereas the RAL group (−2.7%) tended to show a decrease in levels 1.5  
174 years after DMAb discontinuation (P=0.31 between groups).

175 Changes in FN BMD from final DMAb administration (baseline) to 1.5 years after final DMAb  
176 administration are shown in Figure 2c. The wmBP (−0.8%) and ZOL (+1.8%) groups  
177 maintained levels, whereas the RAL group (−3.8%) showed a significant decrease from baseline  
178 (P=0.02) and a significant decrease compared to the ZOL group (+1.8%) (P=0.02).

179 No significant differences were observed in these parameters between the wmBP and ZOL, and  
180 also between wmBP (ALN, RIS, and IBN; data not shown). Results of these parameters  
181 separated by the RAL group (n=13) and the BP group (n=40) are shown in supplemental Figure  
182 1b and 1c, respectively. In FN BMD changes, the BP group maintained significantly higher  
183 levels (−0.1%) compared to that of the RAL group (−3.8%) (P=0.048).

184

185 *Effects of prior treatment before DMAb and follow-on treatment after DMAb discontinuation on*  
186 *bone resorption and BMD changes*

Multi-way analysis of variance was conducted to evaluate the effects of prior treatment before DMAB and follow-on treatment after DMAB discontinuation on serum TRACP-5b levels and BMD changes after DMAB discontinuation (Figure 3a-3c). Patients previously treated by TPTD tended to be protected by bone resorption increases and BMD decreases compared to those previously treated by a BP, especially in the RAL group, although there were no statistically significant differences. Finally, the difference of follow-on treatment after DMAB discontinuation remained a significant factor for FN BMD changes after adjusting for the difference of prior treatment (P=0.043). Results of these parameters separated by the RAL group (n=13) and the BP group (n=40) are shown in supplemental Figure 2a-2c, respectively. The difference of follow-on treatment (RAL or BP) after DMAB discontinuation remained a significant factor for FN BMD changes after adjusting for the difference of prior treatment (P=0.033).

*Effects of number of DMAB treatment and follow-on treatment after DMAB discontinuation on bone resorption and BMD changes*

Multi-way analysis of variance was conducted to evaluate the effects of number of DMAB treatments and follow-on treatment after DMAB discontinuation on serum TRACP-5b levels (Figure 4a) and FN BMD changes (Figure 4b) after DMAB discontinuation. There were no

significant differences between patients who were treated 1 to 2 times with DMAb (n=31) and

those previously treated more than 3 times with DMAb (n=22) in the change of serum

TRACP-5b levels (F-value=0.59, P=0.45) and FN BMD (F-value=0.0022, P=0.96). Results of

these parameters separated by the RAL group (n=13) and the BP group (n=40) are shown in

supplemental Figure 3a and 3b, respectively. Patients who were treated by BP tended to be

protected by FN BMD decrease compared to that of RAL (F-value=3.65, P=0.063).

#### *Significant predictor variables of the change in LS or FN BMD*

The possible clinical backgrounds [including baseline age, body mass index, prior therapy

before DMAb, number of DMAb administration, interval after final DMAb administration,

baseline BMD (LS or FN T-score), the difference of follow-on therapy after DMAb

{categorized as RAL (1), wmBP (2), and ZOL (3)}, and the change of TRACP-5b (%) at 1.5

years after final DMAb administration] were subjected to stepwise multivariable linear

regression analysis to investigate significant predictors of BMD changes at 1.5 years after final

DMAb administration. As for LS BMD change, the only significant predictor was the difference

of follow-on therapy after DMAb (partial regression coefficient=+3.72, P=0.022). As for FN

BMD change, the significant predictors were the difference of follow-on therapy after DMAb

(partial regression coefficient=+3.66, P=0.0035), the change of TRACP-5b (%) (partial

regression coefficient=-0.027, P=0.0032), and the baseline FN T-score (partial regression coefficient=-2.58, P=0.013).

#### *Rate of clinical fragility fracture*

Figure 4 shows clinical vertebral (Fig. 4c) and non-vertebral (Fig. 4d) fracture rates during the 1.5 years period after final DMAb administration. RAL showed the highest rate of clinical vertebral fractures (23.1%) compared to wmBP (3.4%) or ZOL (0.0%) (P=0.048; RAL vs. ZOL), as well as that of non-vertebral clinical fractures (7.7%) compared to wmBP (3.4%) or ZOL (0.0%) (P=0.71 between groups), although differences were not statistically significant. Results of these parameters when separated by the RAL group (n=13) and the BP group (n=40) are shown in supplemental Figure 3c and 3d, respectively. The RAL group showed higher rate of clinical vertebral fractures (23.1%) compared to that of the BP group (2.5%) (P=0.015). The grades of vertebral fracture, evaluated by a semiquantitative method, were grade 2 (n=1) and grade 3 (n=2) in the RAL group, and grade 3 vertebral fracture (n=1) in the wmBP group [15]. There were no patients who had multiple vertebral fractures after DMAb discontinuation. Seventy-five percent of patients who suffered clinical vertebral fracture were treated by oral BP before DMAb (n=3/4).



## Discussion

Previous studies concerning follow-on therapy after DMAb discontinuation revealed several factors affecting treatment effectiveness.

First, in terms of the protective effects of prior exposure to BP, Uebelhart et al. reported that serum CTX levels of patients with prior exposure to BP remained in the postmenopausal range after DMAb discontinuation [9]. In this study, 49.1% of patients were treated by oral BP, and 50.9% were treated by TPTD before DMAb administration. Patients previously treated by TPTD tended to be protected by bone resorption increase and BMD decreases compared to those previously treated by BP, especially in the RAL group. There are no previous reports evaluating the effect of prior TPTD treatment on DMAb discontinuation, although some positive effects may be expected, as we previously reported that prior TPTD treatment followed by DMAb treatment showed beneficial results for continuous increases in BMD [16].

Second, patients with a low number of DMAb treatments (especially a single treatment) were also protected from bone resorption increase [9]. In this study, there were no significant differences in the change of bone resorption marker and FN BMD between patients who were treated 1 to 2 times with DMAb (n=31) and those previously treated more than 3 times with

257 **DMAb (n=22).** This finding may be due to the relatively small number of patients and the small  
258 number of DMAb treatments (mean, 2.6 times).

259 Third, in terms of the strength of bone-resorption inhibition of follow-on treatment, a previous  
260 report demonstrated that ZOL was more effective in improving BMD and reducing bone  
261 turnover compared to weekly oral ALN [17], and RIS tended to show lower BMD preservation  
262 compared to ZOL after DMAb discontinuation [6]. However, no significant differences were  
263 observed in the change of BMD and TRACP-5b levels between the wmBP and ZOL, and also  
264 between wmBP (ALN, RIS, and IBN; data not shown) in this study. In addition, Freemantle et  
265 al. reported that switching DMAb to ALN maintained BMD in DAPS study [5], although  
266 another case report demonstrated that ALN was not effective in preventing multiple vertebral  
267 fractures after DMAb discontinuation [18]. Taken together, the follow-on effect due to the  
268 difference of BP remains controversial. On the other hand, a case report showed that follow-on  
269 RAL treatment was associated with bone resorption increase after DMAb discontinuation [7]. In  
270 this study, the increase in the TRACP-5b level and decrease in the FN BMD were more  
271 apparent in the RAL group compared to the BP group, which suggests that RAL may have little  
272 effect on inhibiting bone resorption increase and preserving FN BMD.

273 Fourth, in terms of the timing of follow-on treatment, Horne et al. reported that most of the  
274 BMD gain obtained with DMAb was preserved with delayed administration of ZOL (7 to 8

275 months after last DMAb administration) [6]. This may be partially due to the fact that BP uptake  
 276 into the bone is expected to increase as a result of increased bone turnover. In this study, we  
 277 conducted multi-way analysis of variance to clarify whether the treatment interval after DMAb  
 278 [within 6 months (n=37) vs. more than 7 months (n=16)] may influence the change in bone  
 279 resorption marker or BMD. Finally, no significant differences were observed between groups  
 280 (data not shown).

281 Fifth, the difference of combined vitamin D should be considered. In this study, most patients  
 282 were treated by active vitamin D, which may be different from a previous study [6]. Previous  
 283 studies demonstrated that alfacalcidol (active vitamin D) in combination with ALN [19] or  
 284 DMAb [20] showed a higher increase in BMD compared to that of combination with native  
 285 vitamin D. However, we should note that RAL in combination with active vitamin D failed to  
 286 protect against bone turnover increase and FN BMD loss after DMAb discontinuation.

287 There are several limitations to this study. Because of the small number of patients, the  
 288 statistical power of the results (especially for the fracture incidence) may be attenuated. As  
 289 spinal X-ray was not routinely performed at 1.5 years after final DMAb administration,  
 290 subclinical vertebral fractures could not be monitored. There was no control group of patients  
 291 without follow-on treatment, and we could not monitor the early change of serum TRACP-5b  
 292 levels and bone formation marker after DMAb discontinuation. When switching DMAb to other

agents, the RAL group tended to show higher age, lower eGFR, lower serum TRACP-5b levels, and higher LS T-score compared to other groups. These backgrounds may potentially affect physicians' treatment selection and following effects. Larger, randomized studies with longer follow-up periods should be conducted in the future.

In conclusion, in this short-term follow-up of postmenopausal patients with osteoporosis who discontinued DMAb, switching to BP showed better FN BMD preservation, as well as prevention of clinical vertebral fractures compared to switching to RAL. No significant differences were observed in these parameters between the wmBP and ZOL. These results may contribute to the selection of adequate follow-on therapy after DMAb discontinuation, although further investigations are required.

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**Conflicts of interest**

K. Ebina is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, which is supported by Taisho. K. Ebina, M. Hirao,

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## **Figure legends**

### **Figure 1. Study design, schedule, and patient flow.**

Treatment of patients was changed based on each physician's discretion to the DMAB to RAL group (n=13) or the DMAB to BP group (n=40) [weekly or monthly BP group (n=29) or the DMAB to yearly ZOL group (n=11)]. Bone mineral density, TRACP-5b levels, and clinical fracture incidence were evaluated at each time point. TPTD, teriparatide; DXA, dual-energy

x-ray absorptiometry; BP, bisphosphonate; DMAb, denosumab; ALN, alendronate; RIS, risedronate; IBN, ibandronate; RAL, raloxifene; ZOL, zoledronate; LS, lumbar spine; FN, femoral neck; TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase.

**Figure 2. Mean changes of serum TRAP-5b levels (a), changes of BMD in the lumbar spine (b) and femoral neck (c).** TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; DMAb, denosumab; RAL, raloxifene; BP, bisphosphonate; ZOL, zoledronate; BMD, bone mineral density. Bars indicate standard errors (SE). <sup>#</sup>P < 0.05 change from final DMAb administration within each treatment group. \*P < 0.05 RAL group versus ZOL group.

**Figure 3. Multi-way analysis of variance for prior treatment before DMAb and follow-on treatment after DMAb discontinuation on serum TRACP-5b levels (a), lumbar spine BMD (b), and femoral neck BMD (c) changes.**

TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; DMAb, denosumab; RAL, raloxifene; wmBP, weekly or monthly bisphosphonate; ZOL, zoledronate. Bars indicate standard deviations (SD).

**Figure 4. Multi-way analysis of variance of number of DMAb treatments and follow-on treatment after DMAb discontinuation on serum TRACP-5b levels (a) and femoral neck BMD (b) changes. Incidence rate of clinical vertebral fracture (c) and non-vertebral fracture (d) from final DMAb administration to 1.5 years after final DMAb administration.**

TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; DMAb, denosumab; RAL, raloxifene; wmBP, weekly or monthly bisphosphonate; ZOL, zoledronate; BMD, bone mineral density. Bars indicate standard deviations (SD). \*P < 0.05 RAL group versus yearly ZOL group.

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1    **Table 1. Patients’ clinical backgrounds before discontinuation of DMAb**

Variable	RAL group (n=13)	Weekly or monthly BP group (n=29)	ZOL group (n=11)	P-value
		Weekly or monthly oral BP (n=14)	Weekly or monthly oral BP (n=6)	
	Weekly or monthly oral BP (n=6)	[ALN 35 mg/week (n=7)]	[ALN 35 mg/week (n=3)]	
Prior therapy before DMAb	[ALN 35 mg/week (n=4)]	RIS 17.5 mg/week (n=4)	RIS 17.5 mg/week (n=1)	1.00
	MIN 50 mg/month (n=2)]	MIN 50 mg/month (n=3)]	IBN 100 mg/month (n=2)]	
	TPTD (n=7) [daily (n=4) weekly (n=3)]	TPTD (n=15) [daily (n=13) weekly (n=2)]	TPTD (n=5) [daily (n=4) weekly (n=1)]	
Prior therapy duration before DMAb (months)	17.1±12.1	19.0±15.6	21.0±21.9	0.84
TRACP-5b level before DMAb (mU/dl)	361.9±167.2	347.2±155.0	332.4±99.7	0.88
DMAb administration (no. of times)	2.5±1.1	2.4±1.5	3.3±2.3	0.50
Reasons for discontinuation of DMAb	Adequate BMD achieved (n=1)  Patient’s preference	Adequate BMD achieved (n=2)  Patient’s preference	Adequate BMD achieved (n=1)  Patient’ preference	N.A.

(n=2)	(n=8)	(n=1)
Dental care (n=3)	Dental care (n=2)	
Other nontoxic reasons (n=3)	Other nontoxic reasons (n=10)	Other nontoxic reasons (n=6)
Ineffectiveness (n=1)	Ineffectiveness (n=3)	Ineffectiveness (n=3)
Toxic reasons (itching, swelling of gum, renal failure) (n=3)	Toxic reasons (malignancy, eruption, renal failure, hypocalcemia) (n=4)	

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- 2 Mean  $\pm$  standard deviation; N.A. = not applicable.
- 3 DMAB, denosumab; RAL, raloxifene; BP, bisphosphonate; ZOL, zoledronate; ALN, alendronate; RIS,
- 4 risedronate; IBN, ibandronate; MIN, minodronate; TPTD, teriparatide; TRACP-5b, isoform 5b of
- 5 tartrate-resistant acid phosphatase; BMD, bone mineral density.
- 6 Differences between the groups were determined by Kruskal-Wallis test or Fisher's exact test.

1    **Table 2. Patients’ clinical background at time of switch from DMAb to other treatment**

Variable	RAL group (n=13)	Weekly or monthly BP group (n=29)	ZOL group (n=11)	P-value
Interval after final DMAb administration (months)	7.0±1.7 (range, 6-11)	7.4±3.7 (range, 5-16)	6.8±2.4 (range, 5-14)	0.85
Switched therapy from DMAb	RAL 60 mg/day PO  (n=13)	ALN 35 mg/week PO  (n=11)	ZOL 5 mg/year IV (n=11)	N.A.
		ALN 900 ug/month IV  (n=3)		
		RIS 17.5 mg/week PO  (n=9)		
		IBN 100 mg/month PO  (n=4)		
		IBN 1 mg/month IV  (n=2)		
Combined active vitamin D	Total (92.3%; n=12)	Total (89.7%; n=26)	Total (100.0%; n=11)	0.80
	ALF (n=7)	ALF (n=23)		
	ELD (n=5)	ELD (n=3)	ALF (n=11)	
Combined Ca, n/N (%)	15.4% (n=2)	10.3% (n=3)	9.1% (n=1)	0.47
Age (years)	77.1±7.9	71.6±11.5	72.8±8.5	0.23
Body mass index	19.7±2.5	20.7±2.7	21.2±1.2	0.19

(kg/m<sup>2</sup>)

eGFR (ml/min/1.73 m <sup>2</sup> )	60.5±22.6	75.3±22.5	76.8±13.3	0.10
Corrected serum Ca (mg/dl)	9.3±0.6	9.3±0.5	9.2±0.4	0.64
Serum 25(OH)D levels (ng/ml)	7.9±3.3	14.4±4.1	16.5±0.4	0.13
TRACP-5b (mU/dl)	160.9±108.1	186.3±141.6	239.1±81.8	0.18
Lumbar spine BMD (T-score)	-2.3±0.9	-2.7±1.4	-2.8±1.8	0.46
Femoral neck BMD (T-score)	-2.2±0.8	-2.2±0.8	-2.3±1.1	0.93
Prior vertebral fracture	46.2% (n=6)	51.7% (n=15)	54.5% (n=6)	0.98
Prior non-vertebral fracture	53.8% (n=7)	17.2% (n=5)	18.2% (n=2)	0.10

2 Mean ± standard deviation; N.A. = not applicable.

3 DmAb, denosumab; RAL, raloxifene; BP, bisphosphonate; ZOL, zoledronate; PO, oral; IV, intravenous;

4 ALN, alendronate; RIS, risedronate; IBN, ibandronate; ALF, alfacalcidol; ELD, eldecalcitol; Ca, calcium;

5 eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxy vitamin D; TRACP-5b, isoform 5b of

6 tartrate-resistant acid phosphatase; BMD, bone mineral density.

7 Differences between the groups were determined by Kruskal-Wallis test or Fisher's exact test.

8

Figure 1

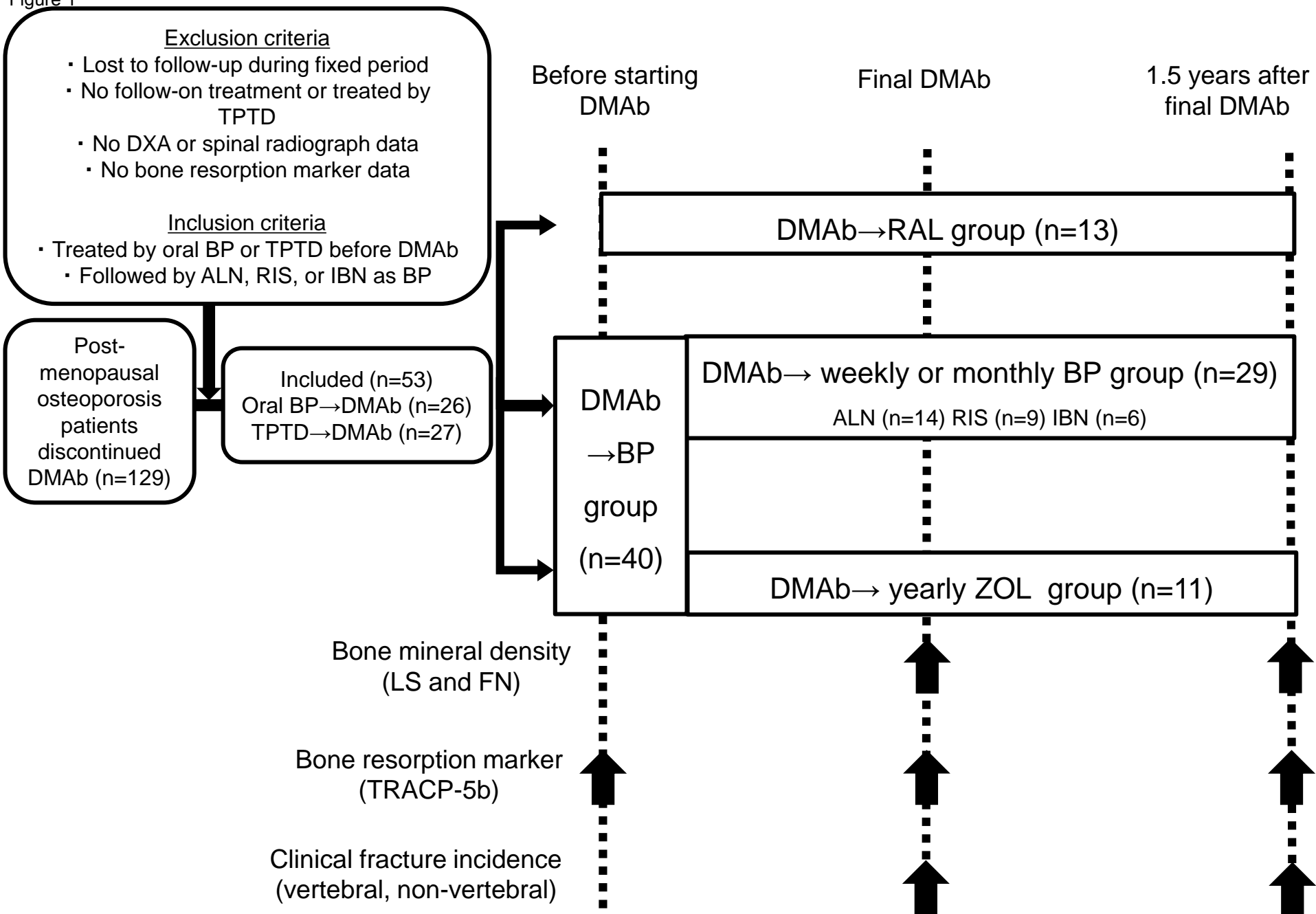
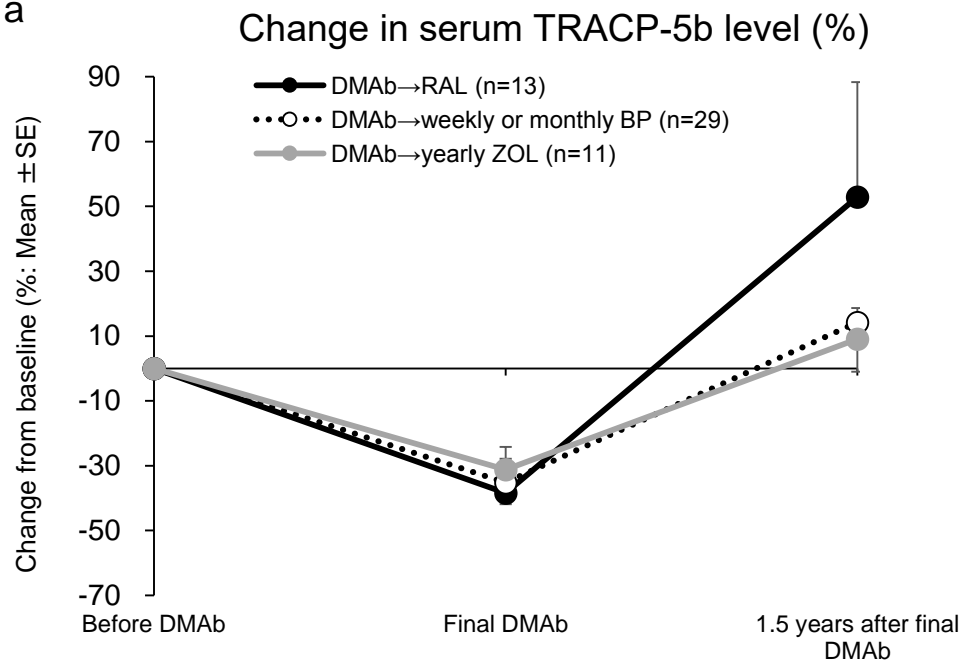
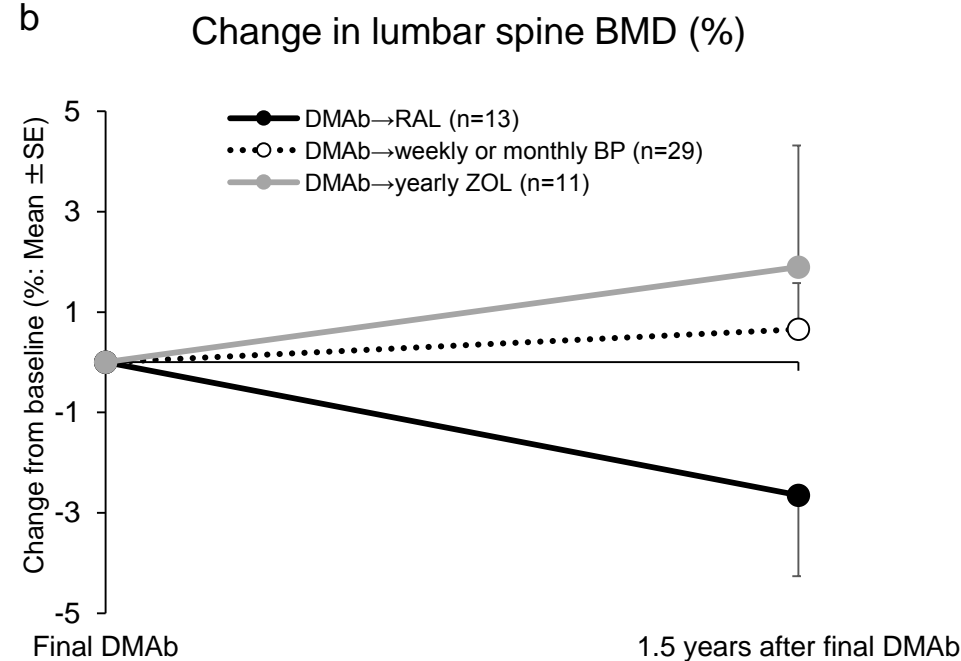


Figure 2

a



b



c

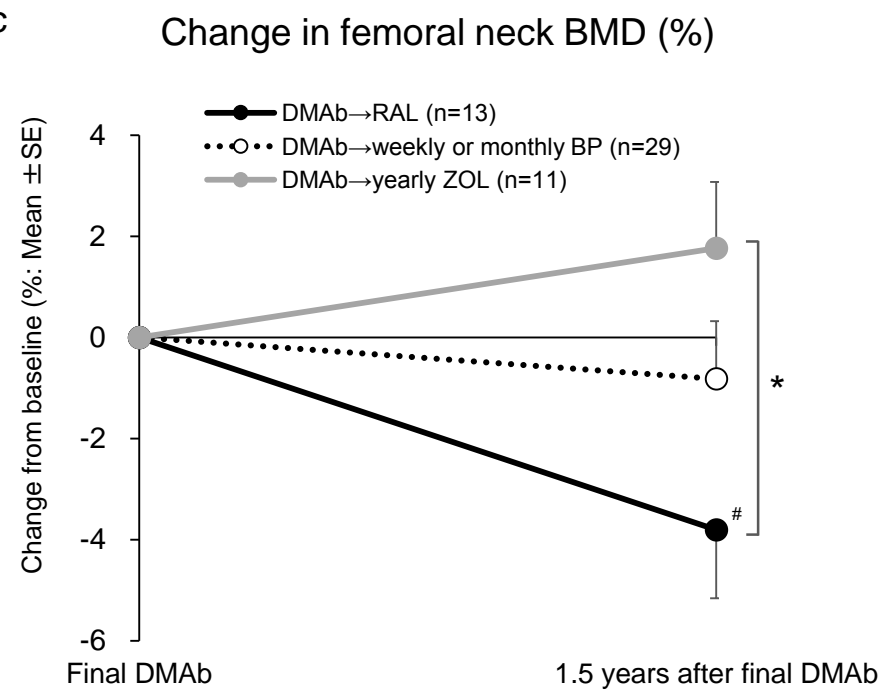


Figure 3

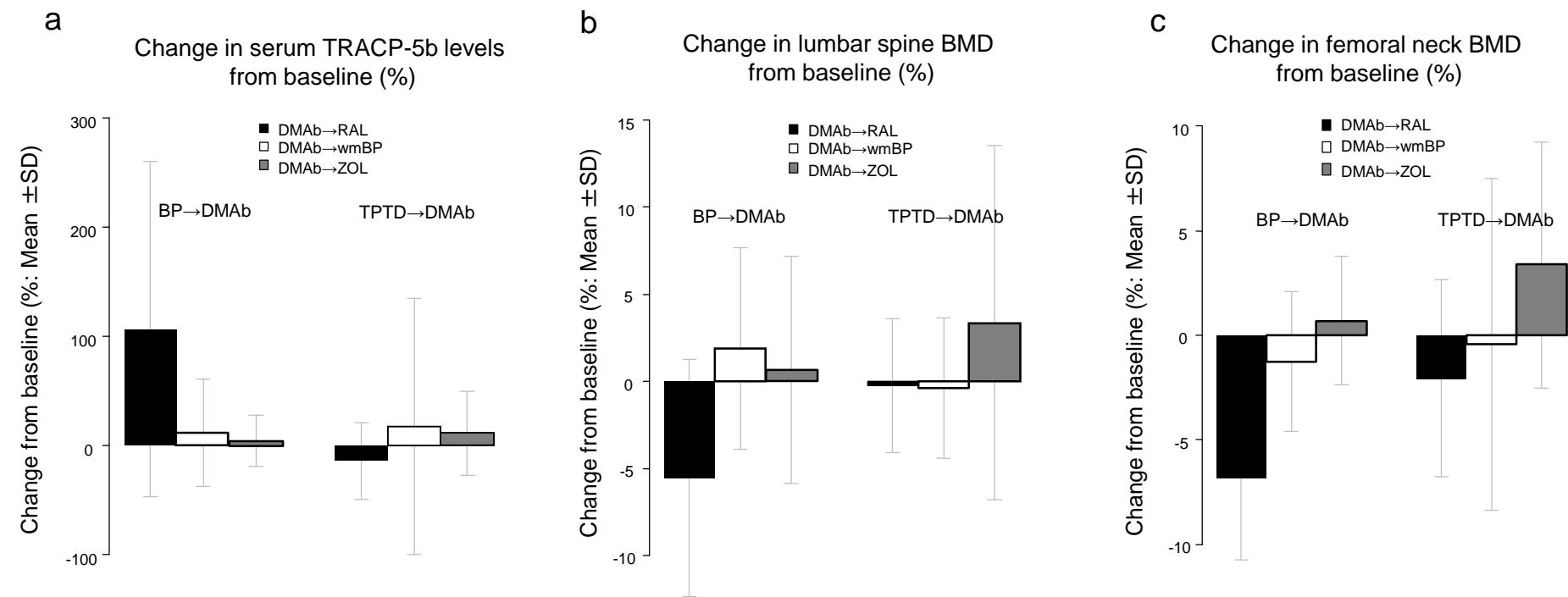




Figure 4

