

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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1 **Original Article**

2 Impact of switching oral bisphosphonates to denosumab or daily teriparatide on the  
3 progression of radiographic joint destruction in patients with biologic-naïve rheumatoid  
4 arthritis

5

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22 **Abstract**

23 *Purpose*

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

27 *Methods*

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

37 *Results*

38 After 12 months, the mean changes of the modified Sharp erosion score were  
39 significantly lower in the switch-to-DMAb group (0.2±0.1; mean±standard error) than

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2 40 in the switch-to-TPTD group ( $1.3\pm 0.5$ ;  $P < 0.05$ ), and mTSS was significantly lower in  
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5 41 the switch-to-DMAb group ( $0.3\pm 0.2$ ) than in the BP-continue group ( $1.0\pm 0.3$ ;  $P < 0.05$ )  
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8 42 and the switch-to-TPTD group ( $1.7\pm 0.6$ ;  $P < 0.05$ ). The logistic regression analysis  
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11 43 showed that mTSS changes were significantly associated with the percent changes of  
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14 44 TRACP-5b at 6 months ( $\beta=0.30$ , 95% CI=0.002-0.016;  $P < 0.01$ ).  
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#### 17 45 *Conclusions*

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21 46 Changes of systemic bone turnover induced by switching BPs to DMAb or TPTD may  
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24 47 affect not only systemic bone mass, but also local joint destruction, and its clinical  
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27 48 relevance should be considered comprehensively.  
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#### 31 50 **Keywords**

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37 51 Bisphosphonate; denosumab; joint destruction; rheumatoid arthritis; teriparatide  
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#### 41 53 **Mini Abstract**

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46 54 In biologic-naïve female RA patients, switching oral BPs to DMAb significantly  
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49 55 reduced radiographic joint destruction compared to continuing oral BPs or switching to  
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52 56 TPTD at 12 months, which were significantly associated with a decrease of a bone  
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56 57 resorption marker at 6 months.  
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2 **59 Introduction**  
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5 60 Rheumatoid arthritis (RA) is characterized by systemic inflammation, which is  
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8 61 associated with increased osteoclast activity leading to bone erosion and joint  
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11 62 destruction [1, 2]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha  
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14 63 (TNF- $\alpha$ ), interleukin (IL)-1, IL-6, and IL-17, are strongly involved in receptor activator  
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18 64 of nuclear factor kappa B (RANK) ligand (RANKL) induction, which is essential for  
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21 65 osteoclast differentiation and activation [3]. Moreover, previous reports demonstrated  
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24 66 that increased bone turnover [4, 5] and low bone mineral density (BMD) [6] is  
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27 67 associated with future radiographic joint destruction in RA, suggesting the significance  
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31 68 of inhibiting bone turnover and obtaining high BMD to protect against joint destruction.  
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34 69 Bisphosphonates (BPs), which induce apoptosis of osteoclasts by inhibiting farnesyl  
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37 70 diphosphate synthase, play pivotal roles in the treatment of both primary and secondary  
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40 71 osteoporosis [7]. However, the efficacy of switching BPs to denosumab (DMAb), an  
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43 72 anti-RANKL antibody that strongly inhibits bone resorption [8], or daily teriparatide  
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46 73 (TPTD), a bone anabolic agent that strongly induces bone formation [9], has been  
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50 74 reported in primary osteoporosis. In addition, we have recently reported that switching  
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53 75 BPs to DMAb significantly inhibited bone turnover [10], and Takeuchi et al.  
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56 76 demonstrated that DMAb inhibited progression of the bone erosion of RA [11]. On the  
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2 77 other hand, switching BPs to daily TPTD induced overshoot of the bone turnover of RA  
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5 78 [10, 12].  
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8 79 Taken together, we hypothesized that the change of bone turnover induced by these  
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11 80 osteoporosis agents may have some effects on the progression of joint destruction  
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14 81 (especially on bone erosion) in RA. The aim of this retrospective, case-controlled study  
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18 82 was to clarify the effects of switching BPs to DMAb or TPTD on radiographic joint  
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21 83 destruction in biologic-naïve female patients with RA.  
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## 25 26 27 85 **Materials and methods**

### 28 29 86 *Study design and subjects*

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33 87 This 12-month retrospective, case-controlled study was conducted based on a  
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37 88 two-center, open-label design. A total of 155 biologic-naïve female (96.7%  
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40 89 postmenopausal) patients with RA, who were treated with an oral BP according to the  
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43 90 Japanese guidelines for prevention and treatment of osteoporosis 2011 [13] or the  
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46 91 guidelines on the management and treatment of glucocorticoid-induced osteoporosis of  
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49 92 the Japanese Society for Bone and Mineral Research 2004 [14], were enrolled. RA was  
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52 93 diagnosed based on the 1987 revised American College of Rheumatology (ACR)  
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55 94 criteria [15]. Registered patients were allocated based on each physician's discretion and  
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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 µg/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  
112 number 13231-2; Osaka University, Graduate School of Medicine). Written, informed



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

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115 *Radiographic assessment of the modified Sharp score*

116 The hand and foot radiographs were taken at baseline and at 12 months when switching  
117 osteoporosis therapies or starting observation. Two rheumatologists independently  
118 assessed the images blinded to patients' clinical information, and the average scores of  
119 the two were used in the analysis, as previously described [18]. The primary endpoint  
120 was the change from baseline in the modified Sharp erosion (ERO) score, the modified  
121 Sharp joint space narrowing (JSN) score, and the modified total Sharp score (mTSS) at  
122 12 months [11]. The cumulative probability of the progression of mTSS per year  
123 ( $\Delta$ mTSS/year) and the clinically relevant radiological progression rate (CRRP;  
124  $\Delta$ mTSS/year  $\geq$  3) were evaluated [19].

125

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

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

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

134

135 *Biochemical markers of bone turnover*

136 BTMs were measured in serum obtained from each patient in the morning after  
137 overnight fasting. As for bone formation marker, N-terminal type I procollagen  
138 propeptide (PINP) (inter-assay coefficient of variation (CV), 3.2%-5.2%; Intact UniQ  
139 assay; Orion Diagnostica, Espoo, Finland), and as for bone resorption marker,  
140 tartrate-resistant acid phosphatase (TRACP)-5b (inter-assay CV, 5.0%-9.0%;  
141 Immunodiagnostic Systems Ltd., Boldon, UK), were measured by ELISA, as previously  
142 described [12]. Previous report demonstrated that TRACP-5b is a useful marker which  
143 shows higher clinical sensitivity and signal-to-noise ratio compared to serum collagen type 1  
144 cross-linked C-telopeptide (CTX) [22]. Serum intact parathyroid hormone (PTH) levels was  
145 measured using a two-site immunoradiometric assay (inter-assay CV, 8.4%; Quest Diagnostics  
146 Nichols Institute, California, USA).

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148 *Statistical analysis*

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149 Differences among study groups were tested using analysis of variance for normally  
150 distributed data, and the nonparametric Kruskal-Wallis test was used for non-normally  
151 distributed data. Changes in BMD and ranked bone turnover marker data from baseline  
152 to specified time points were compared within each study group using the  
153 nonparametric Wilcoxon signed-rank test. Patients' clinical background characteristics  
154 that showed significant correlations with 12-month mTSS change as evaluated by  
155 Spearman correlation coefficients were selected as predictor variables, and multivariate  
156 logistic regression analysis with a forward stepwise procedure was performed to  
157 identify significant indicators of 12-month mTSS change. The 95% confidence intervals  
158 (CIs) for correlation coefficients were calculated based on Fisher's z-transformation.  
159 Results are expressed as means  $\pm$  standard error. A *P* value  $<$  0.05 was considered  
160 significant. All tests were performed using IBM SPSS Statistics version 22 software  
161 (IBM, Armonk, NY, USA).

162

163 **Results**

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

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167 DAS28-CRP. In addition, no significant changes and no differences between the groups  
168 were observed in the swollen/tender joint count and DAS28-CRP after 12 months.

169 The patients' medications and bone metabolism-related parameters are shown in Table 2.

170 No significant differences were observed in combined prednisolone (PSL) or  
171 methotrexate (MTX) doses and usage rates, areal BMD (T-scores), trabecular bone  
172 score (TBS), serum intact-PTH levels (which increase in response to a low serum  
173 25-hydroxycholecalciferol [25(OH)D]) level and low calcium intake [23]), and BTMs. On the  
174 other hand, the switch-to-TPTD group showed longer prior BP therapy duration and a  
175 lower rate of combined vitamin D use compared to the BP-continue group and the  
176 switch-to-DMAb group. The switch-to-DMAb group had a higher rate and dose of  
177 calcium and native vitamin D (cholecalciferol; VD3) administration compared to both  
178 the BP-continue group and the switch-to-TPTD group. There was no significant  
179 difference in the prescription rate of active vitamin D (alfacalcidol [ALF] and  
180 eldecalcitol [ELD]) between the BP-continue group and the switch-to-TPTD group.

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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

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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%;  $P < 0.001$ ).

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

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203 erosion score at 12 months was significantly lower in the switch-to-DMAb group than  
204 in the switch-to-TPTD group ( $0.2\pm 0.1$  vs  $1.3\pm 0.5$ ;  $P < 0.05$ ). Consequently, the changes  
205 from baseline in the mTSS at 12 months were significantly lower in the  
206 switch-to-DMAb group than in the BP-continue group ( $0.3\pm 0.2$  vs  $1.0\pm 0.3$ ;  $P < 0.05$ )  
207 and the switch-to-TPTD group ( $0.3\pm 0.2$  vs  $1.7\pm 0.6$ ;  $P < 0.05$ ) (Fig 2c).

208 Cumulative probability plots for changes in the modified Sharp JSN score (Fig 3a), the  
209 modified Sharp ERO score (Fig 3b), and mTSS (Fig 3c) at 12 months are shown. The  
210 clinically relevant radiological progression rate (CRRP;  $\Delta mTSS/year \geq 3$ ) [19] was  
211 significantly lower in the switch-to-DMAb group than in the switch-to-TPTD group  
212 (3.3% vs 20.0%;  $P < 0.05$ ). In addition, the structural remission rate ( $\Delta mTSS/year \leq$   
213 0.5) [18] tended to be higher in the switch-to-DMAb group than in the BP-continue  
214 group (76.7% vs 53.3%;  $P = 0.06$ ) and the switch-to-TPTD group (76.7% vs 56.7%;  $P =$   
215 0.10).

216

217 *Significant predictor variables of 12-month mTSS progression on multivariate linear*  
218 *regression analysis*

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

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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 (%).

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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

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239 mTSS in a 10-year prospective study [24]. Another cross-sectional study showed that  
240 the presence of bone erosions in RA correlates with low BMD levels [25]. In the present  
241 study, to investigate the effects of osteoporosis treatments, these factors affecting the  
242 progression of joint destruction were controlled between the groups. In addition,  
243 12-month mTSS progression was significantly associated with baseline DAS28-CRP,  
244 ACPA positivity, and  $\Delta$ 6-month TRACP-5b (%), in accordance with previous reports.  
245 Finally, multivariate linear regression analysis showed that  $\Delta$ 6-month TRACP-5b (%)  
246 was the significant factor associated with 12-month mTSS progression.

247 Concerning BPs, zoledronate is one of the BPs that most strongly induces apoptosis of  
248 osteoclasts [26], and a previous animal study showed that the combination of  
249 zoledronate and MTX prevented bone erosion in collagen-induced arthritis of rats [27].  
250 On the other hand, human prospective, randomized trials failed to show the positive  
251 effects of zoledronate monotherapy on bone erosion in patients with psoriatic arthritis  
252 [28] and tophaceous gout [29]. Taken together, BP monotherapy may be insufficient, but  
253 its combination with MTX may have some positive effects on inhibition of bone erosion  
254 in arthritis.

255 Takeuchi et al. reported that DMAb significantly inhibited the progression of bone  
256 erosion compared with placebo in Japanese RA patients who had bone erosions or



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257 C-reactive protein (CRP)  $\geq 1.0$  mg/dL, and who were also never treated by BPs or  
258 biologics at baseline [11]. This population may be relatively rare compared to the  
259 real-world use of DMAb, since most patients are considered to be treated by BPs at first  
260 line according to the osteoporosis guidelines [13, 14]. Moreover, the placebo group was  
261 not treated by any bone resorption inhibitors such as BPs in this study. So the effects of  
262 switching BPs to DMAb on bone erosion of RA still remained unclear.

263 Recently, Solomon et al. demonstrated that 1-year daily TPTD treatment failed to show  
264 significant effects on bone erosion of the hands or wrists compared to a control group in  
265 RA, who were all strictly controlled by TNF inhibitors and not taking osteoporosis  
266 treatment [30]. Taken together, TPTD may not reduce or enhance bone erosion  
267 compared to a non-osteoporosis treatment group, but its effects on bone erosion  
268 compared to BPs or DMAb still remained unclear.

269 The present study demonstrated for the first time that switching oral BPs to DMAb  
270 significantly reduced  $\Delta 12$ -month mTSS compared to continuing oral BPs or switching  
271 to TPTD, which were significantly associated with a decrease of a bone resorption  
272 marker. It has been reported that low BMD and thinning at the cortical site was  
273 significantly associated with bone erosions of RA[31]. DMAb showed positive effects  
274 in improving cortical porosity compared to BPs [32], while TPTD failed to show

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

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

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293 turnover markers.

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

298

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302

303 **Authors' roles**

304 Study design: KE, MH, JH, and HY. Study conduct: KE and MH. Data collection: KE,  
305 MH, and JH. Data analysis: KE, MH, HM, TI, RC, YE, and GO. Data interpretation:  
306 KE, MH, JH, HM, TI, RC, YE, GO, and AM. Drafting the manuscript: KE and MH.  
307 Approving final version of the manuscript: KE, MH, JH, HM, TI, RC, YE, GO, AM,  
308 and HY. KE takes responsibility for the integrity of the data analysis.

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310 **Conflicts of interest**

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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**

428 **Fig 1. Mean changes in serum concentrations of bone turnover markers, PINP**  
429 **(panel a) and TRAP-5b (panel b).** BP, bisphosphonate; DMAb, denosumab; TPTD,  
430 teriparatide; PINP, type I collagen N-terminal propeptide; TRACP-5b, isoform 5b of  
431 tartrate-resistant acid phosphatase. Bars indicate standard errors.  $^{##}P < 0.01$ ,  $^{###}P <$   
432  $0.001$  BP-continue group versus switch-to-TPTD group.  $^{*}P < 0.05$ ,  $^{**}P < 0.01$   
433 BP-continue group versus switch-to-DMAb group.  $^{+++}P < 0.001$  switch-to-DMAb group  
434 versus switch-to-TPTD group.

435

436 **Fig 2. Mean changes in the radiographic score evaluated by the van der**  
437 **Heijde-modified Sharp method at 12 months. Modified Sharp joint space**  
438 **narrowing (JSN) score (panel a), Modified Sharp erosion (ERO) score (panel b),**  
439 **and Modified total Sharp score (mTSS) (panel c).** BP, bisphosphonate; DMAb,  
440 denosumab; TPTD, teriparatide. Bars indicate standard errors. N.S., not significant,  $^{*}P$   
441  $< 0.05$ .

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



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445 **erosion (ERO) score (panel b), and Modified total Sharp score (mTSS) (panel c).**

446 BP, bisphosphonate; DMAB, denosumab; TPTD, teriparatide.

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

Variable	BP-continue group (n=30)	Switch-to-DMAb group (n=30)	Switch-to-TPTD 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±50.8	161.5±42.0	221.5±70.4
Modified Sharp erosion score (0–280)	33.7±7.0	32.7±7.6	37.5±6.0
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
<b>Baseline</b>			
CRP (mg/dl)	1.1±0.3	0.6±0.2	0.8±0.2
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
<b>12 months</b>			
CRP (mg/dl)	1.1±0.3	0.5±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±0.2
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

3 Mean ± 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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26 **Table 2. Patients' medications and bone metabolism-related parameters**

Variable	BP-continue group (n=30)	Switch-to-DMAb group (n=30)	Switch-to-TPTD group (n=30)
Prior BP therapy	Weekly ALN (n=14; 46.7%)	Weekly ALN (n=15; 50.0%)	Weekly ALN (n=17; 56.7%)
	Weekly RIS (n=4; 13.3%)	Weekly RIS (n=2; 6.7%)	Weekly RIS (n=13; 43.3%) <sup>###, †††</sup>
	Monthly MIN (n=12; 40.0%)	Monthly MIN (n=13; 43.3%)	
	<b>Total (36.6±4.2)</b>	<b>Total (40.5±5.4)</b>	<b>Total (57.4±5.5)<sup>#, ††</sup></b>
Duration of prior BP therapy (months)	ALN (32.7±2.7)	ALN (35.9±7.1)	ALN (59.1±6.7) <sup>###, †</sup>
	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)	
<b>Concomitant medication</b>			
<b>Baseline</b>			
Vitamin D (%)	93.3	100.0	66.7 <sup>#, ††</sup>
ALF / ELD / VD3 (%)	73.3 / 20.0 / 0.0	40.0 <sup>**</sup> / 16.7 / 43.3 <sup>***</sup>	60.0 / 6.7 / 0.0 <sup>†††</sup>
ALF / ELD / VD3 (µg/day)	0.8±0.1 / 0.8±0.0 / 0.0±0.0	0.9±0.1 / 0.8±0.0 / 10.0±0.0 <sup>***</sup>	0.5±0.0 <sup>###, †††</sup> / 0.8±0.0 / 0.0±0.0 <sup>†††</sup>
Calcium (%)	13.3	90.0 <sup>***</sup>	6.7 <sup>†††</sup>
Calcium (mg/day)	51.3±40.1	300.3±50.6 <sup>***</sup>	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	6.1±0.6	5.3±0.7
MTX usage (%)	76.7	86.7	80.0
<b>12 months</b>			
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 <sup>***</sup>	50.0 / 3.3 / 0.0 <sup>†††</sup>
ALF / ELD / VD3 (µg/day)	0.9±0.1 / 0.8±0.0 / 0.0±0.0	0.9±0.1 / 0.8±0.0 / 10.0±0.0 <sup>***</sup>	0.5±0.1 <sup>###, †††</sup> / 0.8±0.0 / 0.0±0.0 <sup>†††</sup>
Calcium (%)	10.0	83.3 <sup>***</sup>	6.7 <sup>†††</sup>
Calcium (mg/day)	48.7±40.2	294.2±51.6 <sup>***</sup>	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

MTX usage (%)	73.3	76.7	70.0
<b>Baseline</b>			
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±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
<b>12-month change (%)</b>			
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±1.4
Total hip BMD	1.4±1.0	2.9±0.8	1.1±0.9
Trabecular bone score	-0.4±0.7	0.2±0.6	1.6±0.7
PINP (µg/l)	5.8±13.0	-24.9±7.8	165.5±40.0 <sup>##, †††</sup>
TRACP-5b (mU/dl)	-6.4±6.6	-24.7±7.6	63.5±14.9 <sup>###, †††</sup>

27 Mean ± 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 † P<0.05, †† P<0.01, ††† P<0.001; Switch-to-DMAB group vs Switch-to-TPTD group.

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42 **Table 3. Spearman correlation coefficients between changes in the 12-month**  
 43 **modified total Sharp score and patients' clinical parameters, and significant**  
 44 **predictor variables evaluated by multivariate linear regression analysis**  
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	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 ( $\mu\text{g/l}$ )	-0.003	0.98
	TRACP-5b (mU/dl)	-0.12	0.29
6 months	$\Delta$ PINP (%)	0.16	0.15
	$\Delta$ TRACP-5b (%)	0.23	0.04*
12 months	$\Delta$ PINP (%)	0.09	0.45
	$\Delta$ TRACP-5b (%)	0.12	0.32

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

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.

Figure 1

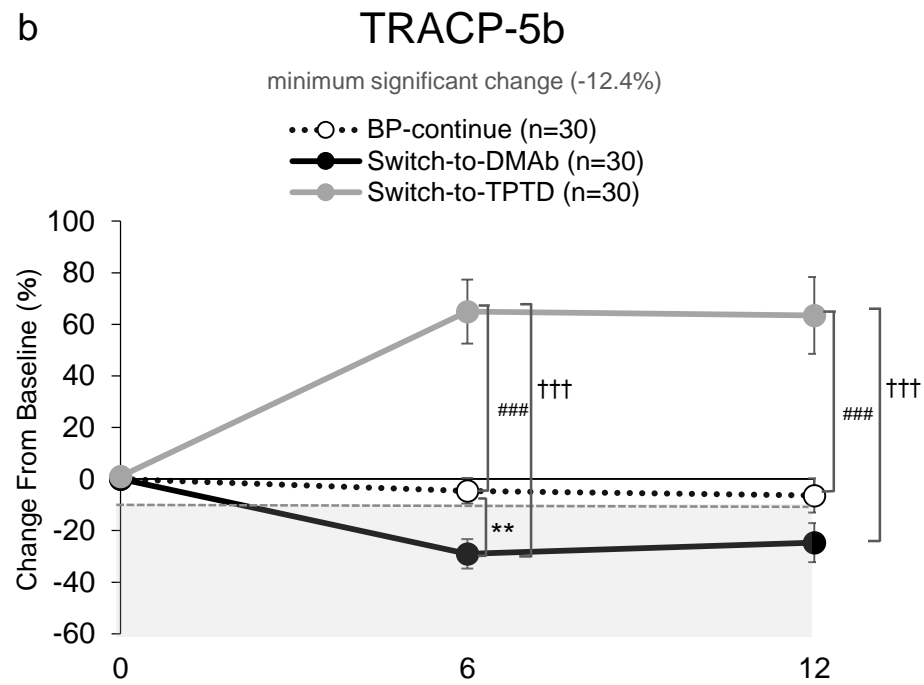
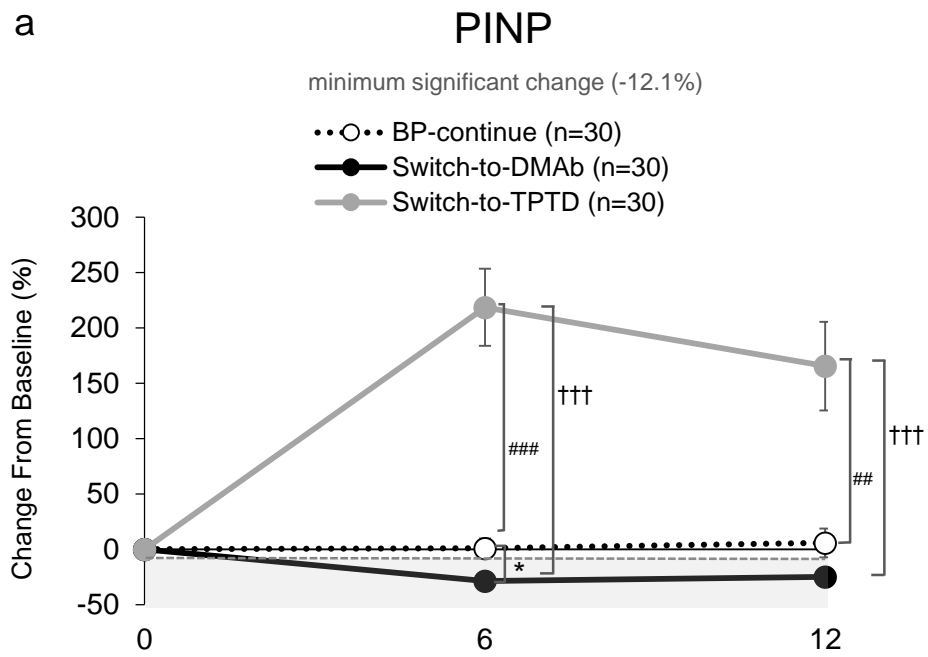


Figure 2

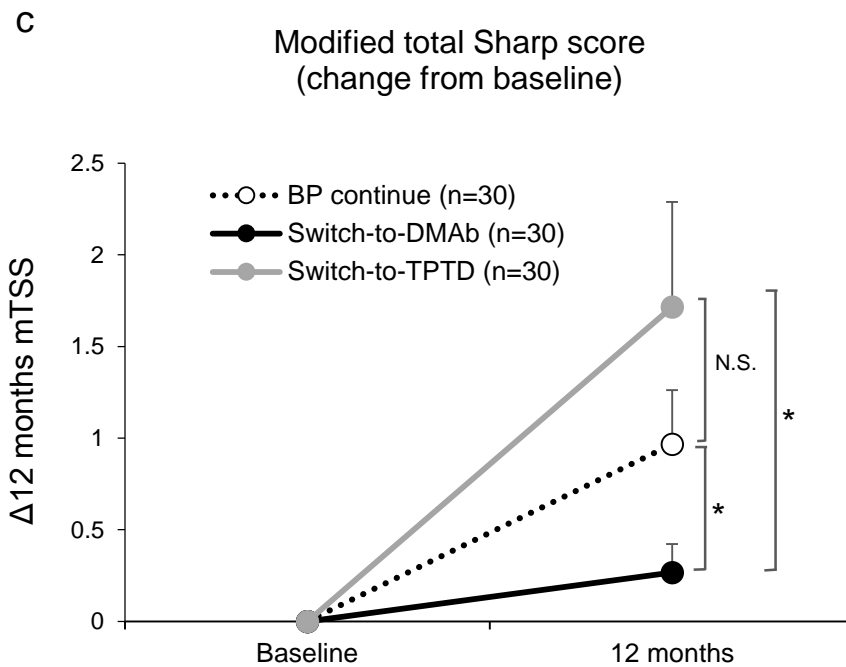
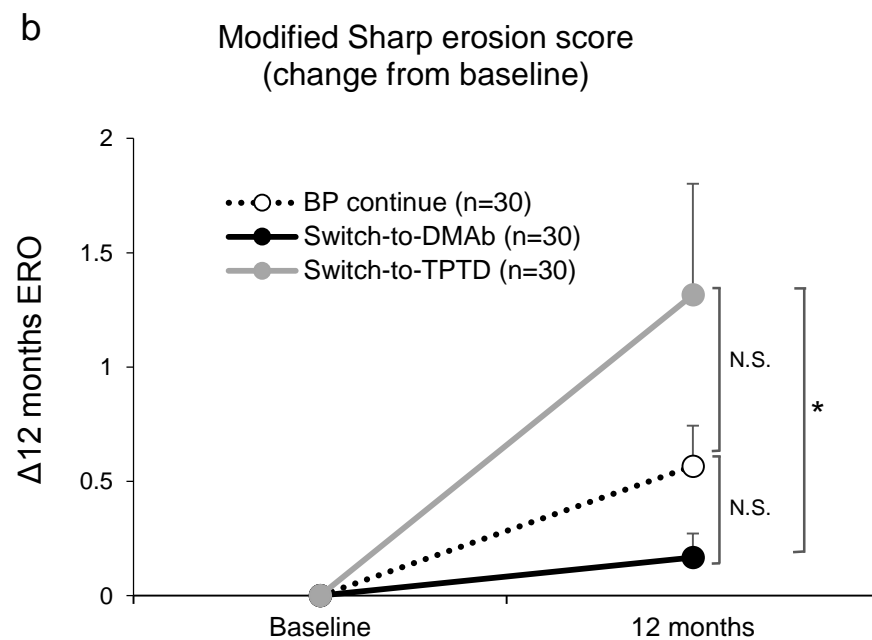
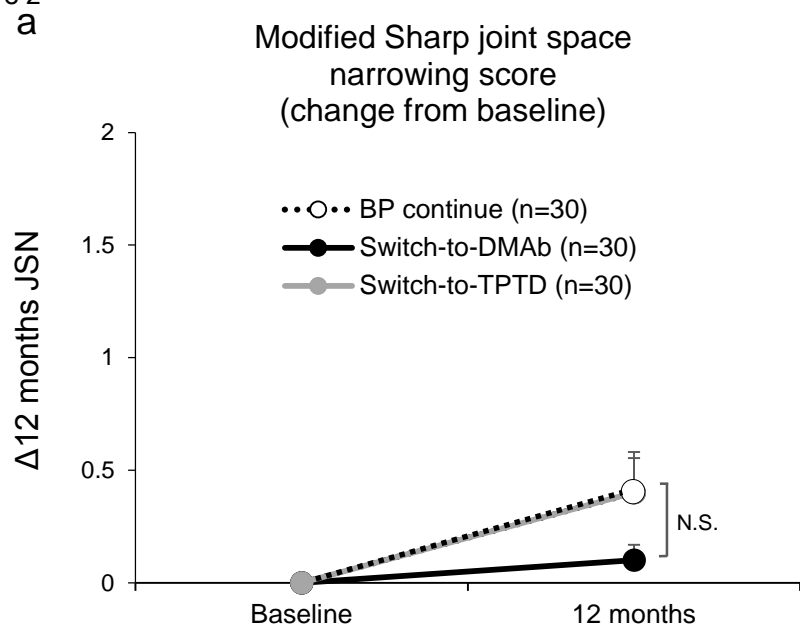
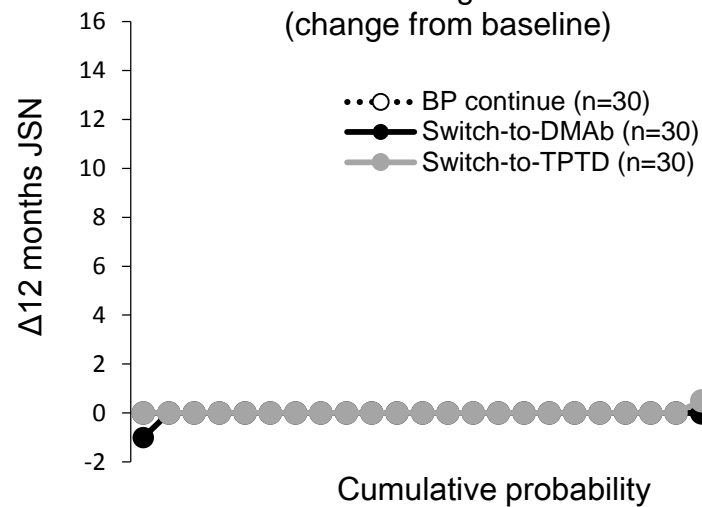




Figure 3

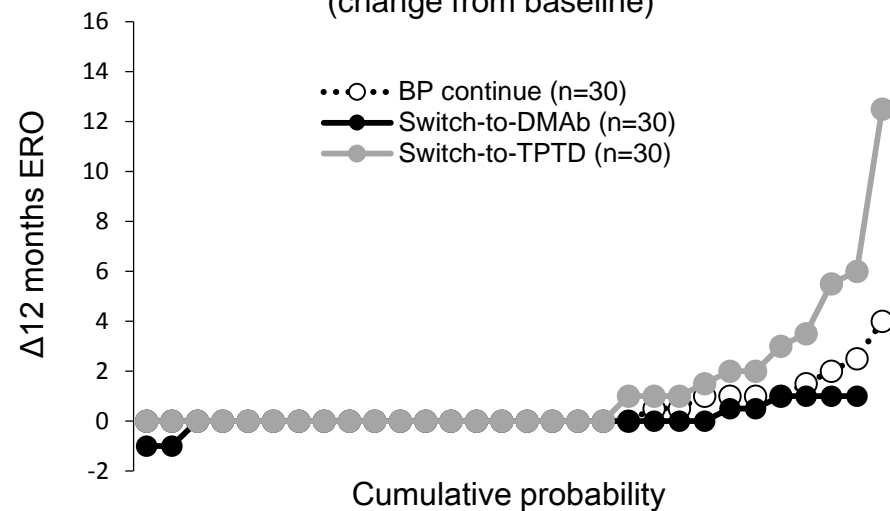
a

Modified Sharp joint space narrowing score  
(change from baseline)



b

Modified Sharp erosion score  
(change from baseline)



c

Modified total Sharp score  
(change from baseline)

