Original Article

The effects of switching daily teriparatide to oral bisphosphonates or denosumab in patients with primary osteoporosis

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Abstract

Purpose

The aim of this twelve-month, observational study was to compare the effects of switching daily teriparatide (TPTD) to oral bisphosphonates (BP) therapy or denosumab (DMAb) therapy in patients with primary osteoporosis.

Methods

Patients (n=78; 71 postmenopausal women and 7 men; mean age 76.3 [64-94] years; mean duration of prior daily TPTD therapy 20.1 [6-24] months) were allocated to either the (1) "switch-to-BP" group (n=36; weekly alendronate 35 mg [n=19], weekly risedronate 17.5 mg [n=12], monthly minodronate 50 mg [n=5]) or (2) "switch-to-DMAb" group (n=42; 60 mg sc every 6 months) based on each physicians' decision. Changes in bone mineral density (BMD) and serum bone turnover markers were monitored every 6 months.

Results

No significant difference was observed in baseline clinical characteristics between the groups. After 12 months, the increase in BMD was significantly greater in the switch-to-DMAb group compared to the switch-to-BP group: lumbar spine (6.2 vs 2.6%; $P < 0.01$), total hip (4.2 vs 1.1%; $P < 0.05$), and femoral neck (3.5 vs 1.4%; $P <$

0.05). In addition, the patients in the switch-to-DMAb group showed a significant decrease compared to those in the switch-to-BP group in TRACP-5b (-55.8 vs -32.8%; $P < 0.01$) and ucOC (-85.5 vs -65.0%; $P < 0.001$), while no significant difference was observed in PINP (-67.5 vs -62.1%).

Conclusions

Switching daily TPTD to DMAb significantly increased BMD and decreased bone resorption marker compared to switching to oral BP at 12 months, and thus may provide an effective sequential treatment option after daily TPTD treatment.

Keywords

primary osteoporosis, daily teriparatide, oral bisphosphonates, denosumab

Introduction

In daily teriparatide (TPTD) treatment, osteoblastic differentiation and increase of bone formation markers is strongly induced [1], which is also associated with receptor activator of NF-κB ligand (RANKL) production from bone marrow cells [2]. RANKL induces osteoclasts differentiation and bone resorption which may mitigate bone anabolic effects of TPTD [3]. The early treatment period of TPTD in which

osteoanabolic effects overwhelm osteocatabolic effects is called the “anabolic window” [3]. A previous study demonstrated that adding alendronate (ALN) to TPTD after 9 months of initiation resulted in higher increase in bone mineral density (BMD) compared to TPTD monotherapy, suggesting that reopening the anabolic window by bone resorption inhibition is effective in increasing BMD [4]. Furthermore, daily TPTD treatment is associated with “cortical porosity,” which is one of the concerns to attenuate bone strength [5]. Denosumab (DMAb), a fully human monoclonal antibody to RANKL, has shown a greater reduction in bone resorption compared to bisphosphonates (BP) such as ALN [6], ibandronate [7], or risedronate (RIS) [8], and also reduces cortical porosity by greater inhibition of intracortical remodeling compared to ALN [9, 10]. From these observations, we hypothesized that greater inhibition of bone resorption (especially intracortical remodeling) by DMAb may be a more effective sequential treatment compared to oral BP after daily TPTD treatment.

The aim of this observational study was to compare the switching effect of daily TPTD to oral BP and DMAb in patients with primary osteoporosis.

Materials and methods

Study design and subjects

This twelve-month observational study was carried out at 2 centers. A total of 78 patients with primary osteoporosis who were treated with daily TPTD in proportion to the Japanese guidelines for prevention and treatment of osteoporosis 2011 [11] were enrolled in the study (Fig. 1). Patients were allocated to either the "switch-to-BP" group (n=36), consisting of patients who were switched to an oral BP, or the "switch-to-DMAb" group (n=42), consisting of patients who were switched to subcutaneous DMAb 60 mg every 6 months, depending on each physicians' decision. Patients who finished TPTD before DMAb came onto the market of Japan (June, 2013) were switched to oral BP. After DMAb became available, patients were mainly switched to DMAb. Most patients were treated with active or native vitamin D during the study (Table 1).

This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by ethical review boards at each clinical center (approval number 13231-2; Osaka University, Graduate School of Medicine) and posted on the hospital homepage with informed consent obtained from individual patients included in the study.

BMD assessment

Areal BMD in the lumbar spine (LS, L2–L4), total hip (TH), and femoral neck (FN) were assessed by dual-energy x-ray absorptiometry (Discovery A, Hologic, Inc., Waltham, MA, USA) at baseline and after 6 and 12 months of treatment. Regions of severe scoliosis, previous vertebral fracture, and postoperative sites were excluded from BMD measurements, and at least 2 of the lumbar vertebrae L2–L4 had to be evaluable for BMD. Subjects were excluded from the BMD analyses if the area was fractured or operated on during the study as previously described [12-14].

Biochemical markers of bone turnover

Bone turnover markers were measured in serum obtained from each patient at approximately the same time in the morning after overnight fasting. The bone formation marker, N-terminal type I procollagen propeptide (PINP); inter-assay coefficient of variation [CV] 3.2%−5.2% (Intact UniQ assay, Orion Diagnostica, Espoo, Finland) and bone resorption marker, isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b); inter-assay CV 5.0%−9.0% (Immunodiagnostic Systems Ltd., Boldon, UK) were measured by ELISA as previously described [12, 14, 15]. Levels of undercarboxylated osteocalcin (ucOC) were measured by a solid-phase enzyme immunoassay kit; inter-assay CV 5.2%–8.3% (Takara Bio, Shiga, Japan) with a sensitivity of 0.25 ng/mL.

UcOC reflects not only vitamin K deficiency, but also total bone turnover, as it is released from both osteoblasts and absorbed bone extracellular matrix by osteoclast as previously described [14, 16]. Intact parathyroid hormone (PTH) was measured using a two-site immunoradiometric assay; inter-assay CV 8.4% (Nichols Institute Diagnostics, Valencia, USA).

Radiographs

Spinal radiographs were obtained at baseline and also at unscheduled times if subjects had symptoms suggestive of clinical vertebral fracture. For incidental non-vertebral fractures, radiographs were assessed by the investigator if subjects had symptoms.

Statistical analysis

Differences between each study group were tested using the Mann-Whitney U test or the chi-square test. Changes in BMD and ranked bone turnover marker data from baseline to specified time points within each study group were compared using the nonparametric Wilcoxon signed-rank test. Results are expressed as the mean ± standard error. Bone turnover markers that showed a significant correlation with the twelve-month BMD change in LS, TH, and FN, as evaluated using the Spearman

correlation, were selected as predictor variables, and multivariable linear regression analysis with a forward stepwise procedure was performed to select significant indicators of twelve-month BMD change. A *P* value < 0.05 indicated statistical significance. All tests were performed using IBM SPSS Statistics version 22 software (IBM, Armonk, NY, USA).

Results

Baseline characteristics are shown in Table 1. Type of BP switched from daily TPTD was as follows: oral weekly alendronate 35 mg (n=19), weekly risedronate 17.5 mg (n=12), and monthly minodronate 50 mg (n=5). No significant difference was observed in the baseline age, body mass index, rate of prior vertebral fracture, areal BMD, or bone turnover markers between the groups, but the switch-to-DMAb group was combined with higher rate of calcium formulation compared to the switch-to-BP group (88.1 vs 25.0%; *P* < 0.001).

91.7% (33/36) in the switch-to-BP group (3 patient were lost to follow up), and 92.9% (39/42) in the switch-to-DMAb group (1 patient was lost to follow up and 2 patients desired to change the medication) completed 12 months of therapy with no significant differences in dropout rates between the groups (Fig. 1). During the twelve-month

period, in the switch-to-BP group, 1 patient experienced a clinical vertebral fragility fracture (2.8%), and in the switch-to-DMAb group 2 patients experienced a clinical vertebral fragility fracture (4.8%). All the fractures were associated with fall, and no statistically significant difference in the fracture rate was observed between the groups.

Change in BMD

BMD was monitored every 6 months (Fig. 2). The switch-to-DMAb group showed a significant increase in BMD from baseline to 6 months and 12 months in the LS (4.6%; $P < 0.001$ and 6.2%; $P < 0.001$), TH (2.6%; $P < 0.01$ and 4.2%; $P < 0.001$), and FN (2.2%; $P < 0.05$ and 3.5%; $P < 0.01$), respectively. On the other hand, the switch-to-BP group showed a significant increase in BMD from baseline to 12 months in the LS (2.6%; $P < 0.01$) and TH (1.1%; $P < 0.01$), but not in the FN.

Moreover, the switch-to-DMAb group showed a significantly greater BMD increase compared to the switch-to-BP group in the LS from 6 months (4.6 vs 0.8%; $P < 0.01$) to 12 months (6.2 vs 2.6%; $P < 0.01$), in the TH at 12 months (4.2 vs 1.1%; $P < 0.05$), and in the FN at 12 months (3.5 vs 1.4%; $P < 0.05$), respectively.

Bone turnover markers

Percent changes in bone turnover markers from baseline are shown in Fig. 3. The switch-to-DMAb group showed a significantly greater decrease compared to the switch-to-BP group in TRACP-5b levels from 6 months (-55.6 vs -32.1%; $P < 0.01$) to 12 months (-55.8 vs -32.8%; $P < 0.01$), and in ucOC levels from 6 months (-79.7 vs -51.6%; $P < 0.001$) to 12 months (-85.5 vs -65.0%; $P < 0.001$). In addition, serum absolute intact PTH levels were significantly lower in the switch-to-DMAb group compared to the switch-to-BP group from 6 months (35.6 vs 50.6 pg/mL; $P < 0.05$) to 12 months (35.0 vs 56.5 pg/mL; $P < 0.05$).

On the other hand, no significant difference was observed between the switch-to-DMAb group and the switch-to-BP group with regard to the change in serum PINP levels from 6 months (-67.8 vs -55.4%) to 12 months (-67.5 vs -62.1%). The absolute values of bone turnover markers are shown in Fig. 4. The average value of TRACP-5b, PINP, and ucOC from 6 to 12 months in both groups were all within the reference value.

Association between changes in BMD and bone turnover markers

Spearman correlation coefficients between bone turnover markers and twelve-month BMD changes (%) for all patients are shown in Table 2. Generally, higher decreasing rates of TRACP-5b, ucOC, and PINP were associated with a greater increase in the

BMD of the LS and TH. On the other hand, absolute intact PTH levels showed a significant negative correlation with FN BMD increase.

All significant predictors were selected and put into multivariable linear regression analysis to select significant predictors of twelve-month BMD change in the LS, TH, and FN (Table 3). The significant indicator of BMD change for the LS and TH was the percent change in TRACP-5b at 12 months, and the significant indicator for the FN was the absolute intact PTH levels at 12 months.

Discussion

In this study, we have demonstrated that switching daily TPTD to DMAb significantly increased BMD and decreased serum TRACP-5b, ucOC, and intact PTH levels, while maintained serum PINP levels to the same extent compared to switching to oral BP. Multivariable linear regression analysis revealed that BMD increase of the LS and TH was significantly associated with the percent decrease of TRACP-5b, and that of FN was negatively associated with absolute intact PTH levels.

A recent report demonstrated that an increase in BMD may be obtained by a combination of 3 elements: remodeling closure (inhibition of bone resorption), secondary mineralization (related to calcium and vitamin D metabolism), and bone

204 modeling without bone resorption [17].

205 The greater inhibition of bone resorption by DMAb than BP may be explained by the
206 differences in their mechanisms of action. Nitrogen-containing BP is internalized into
207 only mature bone-resorbing osteoclasts by endocytosis and induce apoptosis of
208 osteoclasts [18]. On the other hand, DMAb inhibits not only mature osteoclasts, but also
209 the RANKL-induced osteoclastogenesis from precursors [10]. Daily TPTD treatment is
210 associated with "cortical porosity", which is one of the concerns to attenuate bone
211 strength [5]. Concentrations of BP is lower in cortical than trabecular bone because of
212 its high affinity to hydroxyapatite and less blood supply [10]. By contrast, DMAb
213 circulates freely to bone surfaces and may inhibits remodeling more rapidly and strongly,
214 especially in cortical bone [10].

215 Considering secondary mineralization related to calcium and vitamin D metabolism,
216 patients with DMAb had lower serum intact PTH levels than patients with BP, which
217 was negatively correlated with FN BMD increase. One previous report demonstrated
218 that in ovariectomized monkeys, either DMAb or ALN treatment with calcium and
219 vitamin D supplementation altered serum intact PTH levels [9]. However, Joo et al
220 reported that lower dietary calcium intake was significantly associated with higher
221 serum PTH levels and lower FN BMD, and also demonstrated that low calcium intake

222 cannot be compensated by high serum 25-hydroxy vitamin D levels [19]. In this study,
223 although most patients were combined with vitamin D, the proportion of patients taking
224 calcium supplementation was significantly higher in the switch-to-DMAb group
225 compared to the switch-to-BP group (88.1 vs 25.0%; $P < 0.001$), and also oral calcium
226 intake couldn't be monitored. Taken together, total calcium intake may have influenced
227 the serum intact PTH levels and consequent FN BMD change, although the significance
228 of calcium supplementation after TPTD treatment should be investigated in further
229 studies.
230 Considering bone modeling, there are several reports suggesting the reasons for the
231 discrepancy between relatively maintained bone formation marker and strongly reduced
232 bone resorption marker in DMAb compared to oral BP treatment. Osteoprotegerin
233 (OPG), a physiological soluble decoy receptor for RANKL [20], prevents Tumor
234 Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL)-induced apoptosis of
235 osteoblasts [21] and also promotes osteoblastic differentiation of murine bone marrow
236 cells [22]. In addition, Inage et al reported that serum PINP levels were preserved while
237 TRACP-5b levels were significantly reduced after induction of DMAb at 1 month in
238 postmenopausal osteoporosis patients [23]. Although further investigation is required,
239 these findings may support the results of relatively maintained PINP levels and strongly

reduced TRACP-5b levels in DMAb compared to oral BP treatment. As for ucOC, baseline levels were relatively higher in switch-to-DMAb group compared to switch-to-BP group, and were significantly decreased by DMAb compared to oral BP. Consequently, absolute serum ucOC value converged to similar levels. Taken together, DMAb may decrease serum ucOC levels stronger than oral BP, which may represent stronger reduction of total bone turnover.

Previous studies demonstrated that 12 months administration of DMAb approximately increased BMD by 5.3-6.5% in LS, 3.5% in TH, and 2.4-2.7% in FN, and also decreased TRACP-5b by 45%, and PINP by 68-72% in patient with osteoporosis who were mostly not previously treated by TPTD [6, 24-26]. Compared with these studies, increase of BMD in TH and FN, and decrease of TRACP-5b was relatively higher, although decrease of PINP was similar in this study. Considering high bone turnover levels in the baseline of this study, DMAb after TPTD treatment may be equal to or more effective in patients without previous TPTD treatment.

There are several limitations to this study. Due to the small number of subjects, whether greater change in BMD and bone turnover markers induced by DMAb than that of oral BP may reduce fracture risk should be assessed in a larger cohort. Oral intake of calcium could not be assessed, and also the difference in the calcium supplementation

rate between the groups may have affected the results. Although the number was small, some male patients were included in this study.

In conclusion, switching daily TPTD to DMAb significantly increased BMD and decreased bone resorption markers while maintained bone formation marker compared to switching to oral BP at 12 months, which may provide an effective sequential treatment option after daily TPTD treatment.

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Conflicts of interest

K Ebina has received payments for lectures from Daiichi Sankyo. J Hashimoto, M Kashii, M Hirao, S Kaneshiro, T Noguchi, Y Tsukamoto, and H Yoshikawa declare that they have no conflicts of interest.

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Figure legends

Fig. 1 Study design and schedule. Patients were allocated to either the (1) switch-to-BP group (n=36; oral weekly alendronate 35 mg, n=19; oral weekly risedronate 17.5 mg n=12; or oral monthly minodronate 50 mg, n=5) or (2) switch-to-DMAb group (n=42; subcutaneous 60 mg/6 months) based on each physicians' decision. Bone mineral density and bone turnover markers were evaluated every 6 months in all patients.

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

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

389 treatment group.

390

391 Fig. 4 Mean ± standard error (SE) absolute value of bone turnover markers TRAP-5b

392 (Panel a), PINP (Panel b), and ucOC (Panel c). TRAP-5b, isoform 5b of

393 tartrate-resistant acid phosphatase; PINP, type I collagen N-terminal propeptide; ucOC,

394 undercarboxylated osteocalcin. $^{\#\#}P < 0.01$ switch-to-BP group versus switch-to-DMAb

395 group.

396

Table 1. Baseline clinical characteristics

Variable	Switch-to-BP (n=36)	Switch-to-DMAb (n=42)	*P* value
Switched treatment	Oral weekly ALN (35mg; n=19) Oral weekly RIS (17.5mg; n=12) Oral monthly MIN (50mg; n=5)	DMAb sc 60mg/6months	
Prior TPTD treatment (months)	21.1	19.2	N.S.
Age, (years)	73.5±1.1	78.7±0.9	N.S.
Gender, Females, n/N (%)	33/36 (91.7%)	39/42 (92.9%)	N.S.
Postmenopausal, n/N (%)	33/36 (91.7%)	39/42 (92.9%)	N.S.
Body mass index (kg/m^2)	21.3±0.6	21.7±0.4	N.S.
Prior vertebral fracture(s), n/N(%)	25/36 (69.4%)	31/42 (73.8%)	N.S.
Lumbar spine BMD (g/cm^2)	0.814±0.025	0.795±0.020	N.S.
Lumbar spine BMD (T-score)	-2.6±0.2	-2.5±0.2	N.S.
Total hip BMD (g/cm^2)	0.680±0.023	0.624±0.018	N.S.
Total hip BMD (T-score)	-2.1±0.2	-2.4±0.2	N.S.
Femoral neck BMD (g/cm^2)	0.618±0.022	0.566±0.018	N.S.
Femoral neck BMD (T-score)	-2.2±0.1	-2.5±0.2	N.S.
Corrected Ca (mg/dl)	9.5±0.1	9.3±0.1	N.S.
Intact-PTH (pg/ml)	42.4±3.1	38.5±3.1	N.S.
PINP (μg/l)	80.0±11.6	99.5±12.0	N.S.
TRACP-5b (mU/dl)	460.2±44.1	517.3±46.6	N.S.
ucOC (ng/ml)	7.3±1.4	11.7±2.2	N.S.
eGFR ($ml/min/1.73m^2$)	71.6±2.9	65.8±3.4	N.S.
Combined vitamin D, n/N (%) (Native : Alfacalcidol: Eldecalcitol)	33/36 (91.7%) 0:24:9	42/42 (100.0%) 18:24:0	N.S.
Combined Ca, n/N (%)	9/36 (25.0%)	37/42 (88.1%)	< 0.001

Data are expressed as the mean ± standard error (SE), unless otherwise noted.

BP, Bisphosphonates; DMAb, Denosumab; ALN, Alendronate; RIS, Risedronate; MIN, Minodronate; sc, subcutaneous; TPTD, daily teriparatide; N.S., not significant; n/N (%) = number of patients with measurements / total number of patients (%). Bone mineral density; BMD, Ca, caicium; PTH, parathyroid hormone; PINP, Type I collagen N-terminal propeptide; TRAP-5b, Isoform 5b of tartrate-resistant acid phosphatase; ucOC, Undercarboxylated osteocalcin; eGFR, Estimated glomerular filtration rate; Differences between the groups were determined by Mann-Whitney U-test or chi-square test.

Table 2. Spearman correlation coefficients between changes in bone turnover markers and percent change in bone mineral density (BMD) of the lumbar spine (LS), total hip (TH), and femoral neck (FN) at 12 months

Bone turnover markers	Months	12 months BMD change (%)		
		LS	TH	FN
TRACP-5b	0	0.26*	-0.03	-0.06
	Δ6 (%)	-0.51***	-0.31*	0.07
	Δ12 (%)	-0.51***	-0.32**	-0.02
ucOC	0	0.27*	0.23	-0.04
	Δ6 (%)	-0.41**	-0.31*	-0.23
	Δ12 (%)	-0.45**	-0.34*	-0.16
PINP	0	0.34*	0.25	-0.01
	Δ6 (%)	-0.43**	-0.42**	-0.12
	Δ12 (%)	-0.43**	-0.41**	-0.05
Intact-PTH	0	-0.14	0.09	-0.28*
	6	0.09	0.09	-0.33*
	12	0.01	-0.004	-0.32*

*P<0.05, **P<0.01, ***P<0.001; correlation coefficients.

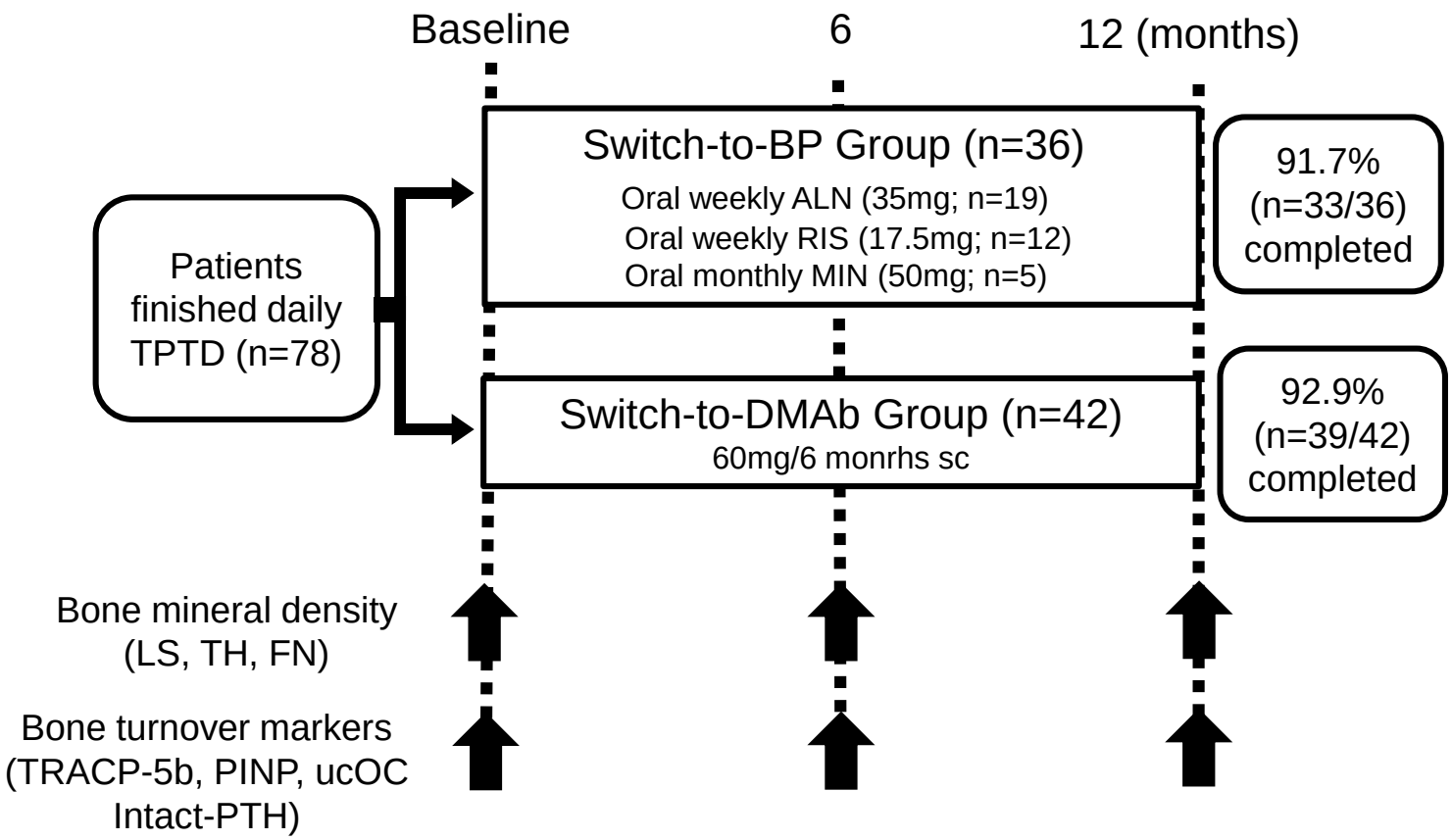
Time 0, baseline concentration of bone turnover marker versus bone mineral density (BMD) at 12 months; Δ 6, change in marker at 6 month (%) versus BMD at 12 months; Δ12, change in marker at 12 months (%) versus BMD at 12 months; Time 6 and 12, concentration of intact-PTH versus bone mineral density (BMD) at 6 and 12 months; TRACP-5b, Isoform 5b of tartrate-resistant acid phosphatase; ucOC, Undercarboxylated osteocalcin; PINP, Type I collagen N-terminal propeptide; PTH, Parathyroid hormone.

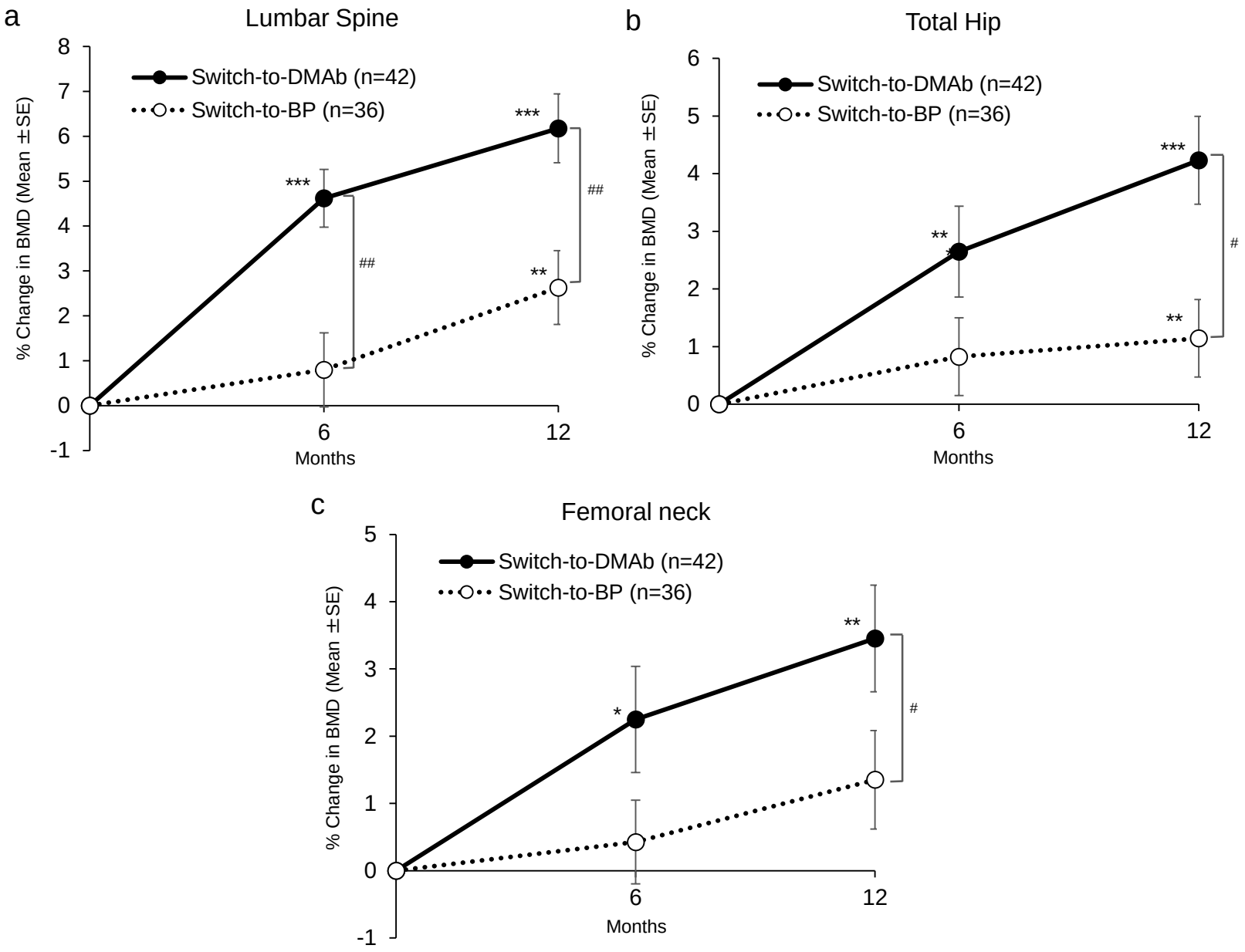
Table 3. Significant predictor variables of bone turnover markers investigated by multivariate linear regression analysis, which showed significant correlation with the 12-month bone mineral density (BMD) change (%) of the lumbar spine (LS), total hip (TH), and femoral neck (FN)

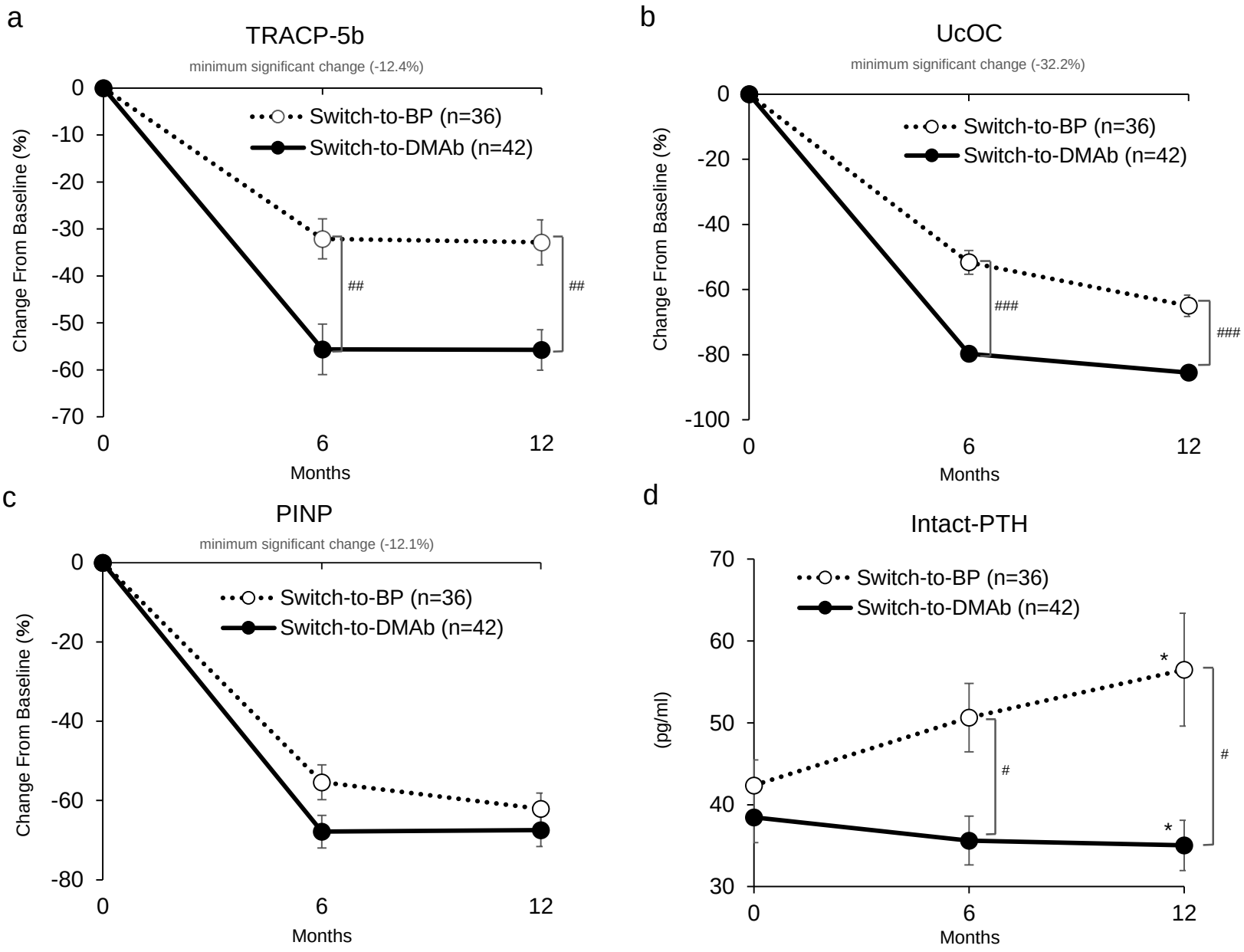
Δ12 BMD	parameters	β	95% CI	*P* value
LS	Δ12 TRACP-5b (%)	-0.54	0.05 to 0.13	< 0.001
TH	Δ12 TRACP-5b (%)	-0.45	0.03 to 0.10	< 0.001
FN	12 intact-PTH	-0.33	0.01 to 0.09	< 0.05

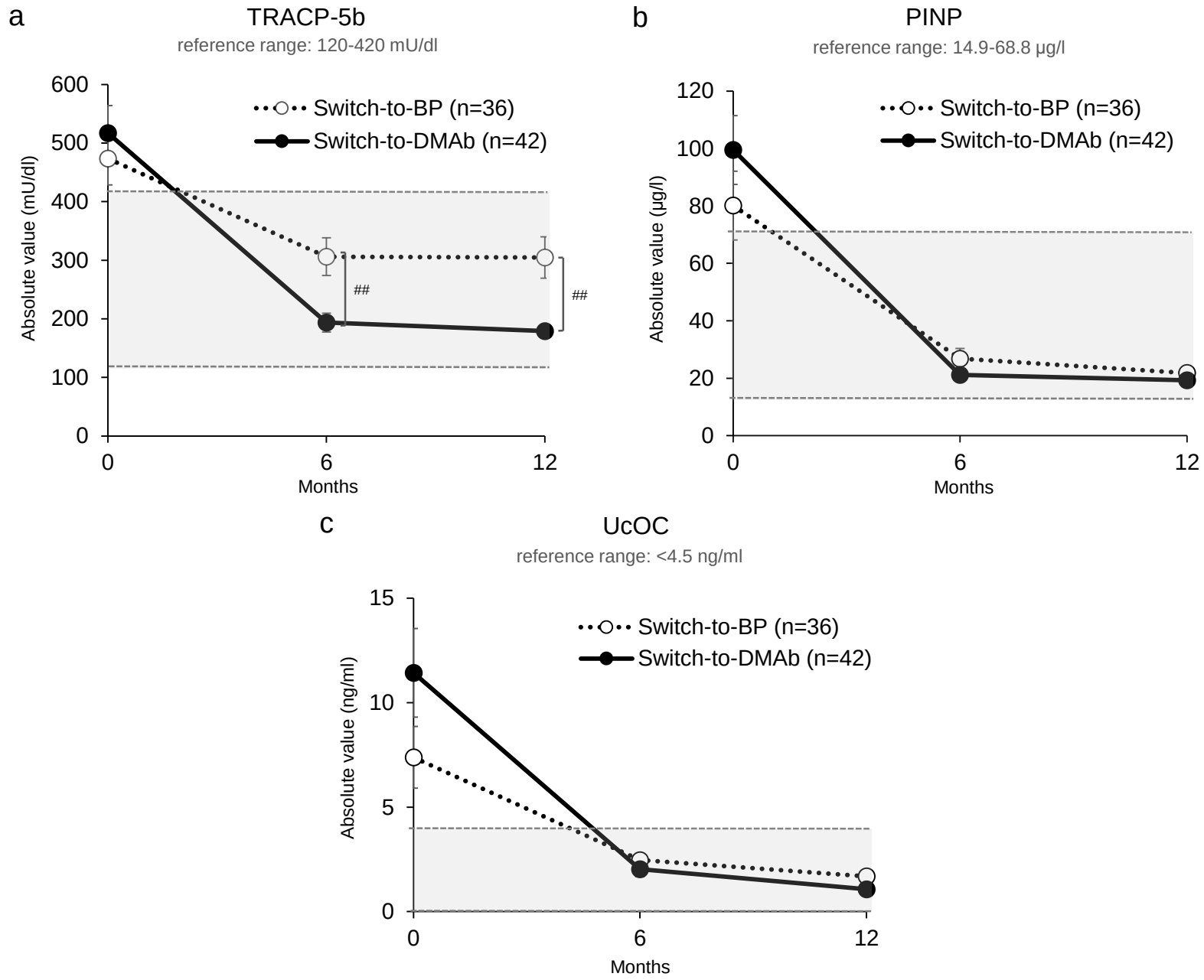
Δ12 BMD, percent change in BMD from baseline at 12 months; β, standardized coefficient; 95% CI, 95% confidence intervals (CIs). Δ12, percent change in bone turnover marker at 12 months; TRACP-5b, Isoform 5b of tartrate-resistant acid phosphatase; PTH, Parathyroid hormone.

Figure


Baseline
6
12 (months)
Switch-to-BP Group (n=36)
Oral weekly ALN (35mg; n=19)
Oral weekly RIS (17.5mg; n=12)
Oral monthly MIN (50mg; n=5)
91.7% (n=33/36) completed
Patients finished daily TPTD (n=78)
Switch-to-DMAb Group (n=42)
60mg/6 monrhs sc
92.9% (n=39/42) completed
Bone mineral density (LS, TH, FN)
Bone turnover markers (TRACP-5b, PINP, ucOC Intact-PTH)


a
Lumbar Spine
Switch-to-DMAb (n=42)
Switch-to-BP (n=36)
% Change in BMD (Mean ±SE)
Months
***
***
**
##
##
b
Total Hip
Switch-to-DMAb (n=42)
Switch-to-BP (n=36)
% Change in BMD (Mean ±SE)
Months
**
***
**
#
c
Femoral neck
Switch-to-DMAb (n=42)
Switch-to-BP (n=36)
% Change in BMD (Mean ±SE)
Months
*
**
#


a
TRACP-5b
minimum significant change (-12.4%)
Change From Baseline (%)
0
-10
-20
-30
-40
-50
-60
-70
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
##
##
0
6
12
Months
b
UcOC
minimum significant change (-32.2%)
Change From Baseline (%)
0
-20
-40
-60
-80
-100
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
###
###
0
6
12
Months
c
PINP
minimum significant change (-12.1%)
Change From Baseline (%)
0
-20
-40
-60
-80
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
0
6
12
Months
d
Intact-PTH
(pg/ml)
70
60
50
40
30
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
*
*
#
#
0
6
12
Months


a
TRACP-5b
reference range: 120-420 mU/dl
Absolute value (mU/dl)
600
500
400
300
200
100
0
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
##
##
0
6
12
Months
b
PINP
reference range: 14.9-68.8 µg/l
Absolute value (µg/l)
120
100
80
60
40
20
0
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
0
6
12
Months
c
UcOC
reference range: <4.5 ng/ml
Absolute value (ng/ml)
15
10
5
0
Switch-to-BP (n=36)
Switch-to-DMAb (n=42)
0
6
12
Months