Short-term efficacy and safety of zoledronate acid or denosumab in Japanese patients with postmenopausal osteoporosis

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Abstract

Introduction

We aimed to compare the efficacy after switching from either bisphosphonates (BPs) or non-BPs (NBPs) to combination therapies of denosumab (DMAb) or zoledronic acid (Zol) with eldecalcitol (ELD) in bone mineral density (BMD) and bone metabolism and investigate the prognostic and risk factors of side effects of this therapy.

Materials and Methods

One-hundred forty-eight patients with postmenopausal osteoporosis were recruited; their therapy was switched from BPs or NBPs to Zol or DMAb plus ELD (BP-Zol: 43, NBP-Zol: 32, BP-DMAb: 35, and NBP-DMAb: 38). Longitudinal changes in bone metabolic markers (P1NP and TRACP-5b) and BMD were evaluated.

Results

In the BP-Zol group, P1NP did not change after 6-months and increased by 38.9% after 12-months. TRACP-5b decreased 15.8% after 6-months, but came back to baseline values 12-months after administration. In the rest of the groups, the bone metabolic markers remained suppressed after 6- and 12-months. Compared with baseline, all groups showed increase in BMD after 6- and 12-months. Bone metabolic markers at baseline were correlated with %change in lumbar spine BMD from baseline to 12 months. P1NP and 25-hydroxy vitamin D levels at baseline were identified as potential predictors of development of acute phase reactions.

Conclusions

The combination therapy of Zol or DMAb and ELD may increase BMD at 12 months after the first administration in Japanese patients with postmenopausal osteoporosis, regardless

of BPs pretreatment. Bone metabolic markers at baseline may be useful predictors for reaction to the therapy and side effects caused by these combination therapies in postmenopausal osteoporosis.

Keywords: postmenopausal osteoporosis, eldecalcitol, denosumab, zoledronic acid, bone metabolic marker

Introduction

Osteoporosis is a chronic, progressive condition that requires long-term management. An estimated 9 million new osteoporosis-related fractures were reported worldwide in the year 2000 [1]. It is reported that 75 million people in the United States, Europe, and Japan are affected by osteoporosis [2]. Oral bisphosphonates (BPs) are commonly prescribed for osteoporosis [3]; however, inconvenient dosing regimens and side effects can cause low adherence [4], leading to reduced antifracture efficacy [5,6] and increased health care costs [7]. Therefore, extended dosing intervals could improve adherence and establish drug effects [8,9]. Additionally, due to the COVID-19 pandemic, which caused an unusual cluster of viral pneumonia cases in China that spread globally [10,11], the demand for long-term anti-osteoporosis therapy may increase.

Two injectable antiresorptive agents, denosumab (DMAb) and zoledronic acid (Zol), have been increasingly used for the treatment of osteoporosis. DMAb is injected subcutaneously (60 mg) every 6 months, and Zol is administered intravenously (5 mg) once every 12 months. DMAb, an anti-bone resorptive drug, is a human monoclonal antibody that targets the osteoclast differentiation factor/receptor activator of the NF-kB ligand (RANKL) [12]. Several studies have shown that it causes a greater increase in bone mineral density (BMD) and reduction in bone resorption than BPs [13-15]. Zol is a BP that contains an imidazole ring as a side chain, and is the most potent of all the clinically available BPs [16,17]. In Japan, DMAb and Zol were approved for the treatment of osteoporosis in 2013 and 2016, respectively. Although both drugs have been confirmed for the treatment of osteoporosis in Japanese patients [18-21], there is a lack of clinical evidence regarding a comparison of the efficacy of DMAb and Zol among Japanese patients.

Despite the demonstrated efficacy, several serious adverse effects of DMAb have been reported, including hypocalcemia [22,23] in 2–20% of women with postmenopausal osteoporosis [24,25]. To prevent hypocalcemia, short-term Ca and vitamin D supplements are usually required. Alternatively, Zol, like other BPs, causes acute-phase reactions (APRs), such as pyrexia and myalgia; mostly resolved within 3 days after its infusion [26]. Various risk and protective factors, including race, age, 25-hydroxy vitamin D (25(OH)D) levels, and prior BP use leading to the development of APRs have been identified in previous studies [27]. Although a recent study showed that the use of loxoprofen and prior use of BPs in Japanese patients with primary osteoporosis treated with Zol were protective against APRs [28], there is limited information regarding the association of APRs and use of Zol among Japanese patients.

The primary aim of this study was to compare the efficacy after switching from either non-BPs (NBPs) or BPs to the combination therapies of DMAb or Zol and eldecalcitol (ELD) with respect to change in bone mineral density (BMD) and bone metabolism. ELD has a longer half-life, a lower clearance rate, and increased vitamin D receptor-mediated effects than alfacalcidol [29] among Japanese patients with postmenopausal osteoporosis in a real-world clinical setting. The secondary aim was to investigate the prognostic and risk factors of side effects for patients who switched to DMAb or Zol and ELD.

Materials and Methods

Study design and subjects

This retrospective study was conducted in accordance with the ethical standards of

the Declaration of Helsinki and approved by the Hokkaido University Hospital Institutional Review Board (#020-0188). Total 115 patients with postmenopausal osteoporosis and high risk of fractures who were treated using DMAb (60 mg, subcutaneously every 6 months) in combination with daily oral ELD (0.75

Monitoring of serum Ca and inflammatory reactions was started at 1 or 2 weeks after DMAb and Zol administration to evaluate changes in Ca level and to assess APRs (Fig. 2). The APRs defined in this study were pyrexia, myalgia or arthralgia, headache, malaise, and others with onset within 3 days after Zol administration, as described in a previous study [30].

BMD assessment

Areal BMD of the lumbar spine (LS; L2–L4), femoral neck (FN), and total proximal femur (TPF) were assessed at baseline, 6 months, and 12 months after treatment, using DXA Bone Densitometer (Discovery A, Hologic Inc., Massachusetts, USA). Regions of severe scoliosis, previous vertebral fracture, and postoperative sites were excluded from BMD measurements; at least two of the L2–L4 lumbar vertebrae were evaluated for BMD [31]. Subjects were excluded from BMD assessment if the area was fractured or operated on during the study.

Statistical analysis

Statistical comparisons among the groups were performed using the chi-square test, unpaired *t*-test or a two-way analysis of variance, and Tukey test. Linear regression models adjusted for age, body mass index (BMI), pretreatment with BPs and active vitamin D, 25(OH)D levels, and treatment were established to determine the associations between bone metabolic markers at baseline and %change of BMD from baseline to 12 months. Multivariate logistic regression analysis, adjusted for age, prior treatment with active vitamin D3, BP use, and acetaminophen, were conducted to determine the factors affecting the development of APRs. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Statistics version 23.0) (IBM Corporation, Armonk, NY,

USA), with the significance level set at 0.05.

Results

Clinical characteristics

Table 1 shows the baseline characteristics of the patients. The number of patients who switched from BPs to Zol (BP-Zol), NBPs to Zol (NBP-Zol), BPs to DMAb (BP-DMAb), and NBPs to DMAb (NBP-DMAb) were 43, 32, 35, and 38, respectively. The mean age of patients in the BP-Zol group was significantly higher than that in the NBP-DMAb group ($P = 0.010$). The mean duration of pretreatment in BP-DMAb group was significantly higher than that in the BP-Zol group ($P = 0.034$). Total 32 patients in the BP-Zol group, 16 patients in the NBP-Zol group, 23 patients in the BP-DMAb group, and 10 patients in the NBP-DMAb group used active vitamin D3 before the administration of ELD. Four patients in the BP-Zol group, three patients in the NBP-Zol group, three patients in the BP-DMAb group, and two patients in the NBP-DMAb group received oral Ca before being administered ELD. There were no patients with thyroid or parathyroid abnormalities. The number of patients who experienced fragility fractures were 32, 17, 23, and 21 in the BP-Zol, NBP-Zol, and BP-DMAb groups, respectively. The BP-Zol and BP-DMAb groups exhibited significantly lower P1NP and TRACP-5b levels than the NBP-Zol and NBP-DMAb groups ($P < 0.001$). There were no differences in BMI, Ca levels, 25(OH)D levels, and %YAM, and BMD at baseline between each group. Notably, during treatment, one patient each in the BP-Zol and NBP-DMAb groups, and two patients in the BP-DMAb group experienced fractures.

Longitudinal changes in Ca, P1NP, and TRACP 5b levels

The decrease in serum Ca levels from baseline to 1 or 2 weeks in the NBP groups was significantly higher than that in the BP groups (P = 0.004). There were no significant differences in Ca levels between the DMAb and Zol groups, and no significant interaction was detected between the treatment and pre-treatment groups. Although six patients experienced hypocalcemia (Ca level < 8.4) and one patient experienced hypercalcemia (Ca level > 10.3), none experienced serious side effects related to hypercalcemia (short QT syndrome and renal diabetes insipidus) and hypocalcemia (tonic convulsions and tetany). P1NP and TRACP 5b levels at baseline were associated with decreased serum Ca levels from baseline to 1 or 2 weeks (P1NP: P = 0.003 and TRACP-5b: P = 0.037) (Fig. 3). In the BP-Zol group, P1NP did not change after 6-months and increased by 38.9% after 12-months. TRACP-5b decreased 15.8% after 6-months, but came back to baseline values 12-months after administration. In the rest of the groups, the bone metabolic markers remained suppressed after 6- and 12-months (Fig. 4). Patients in the DMAb groups showed significant suppression of P1NP level at 12 months (P < 0.001) and TRACP-5b level at 6 and 12 months (P = 0.046 and P = 0.003, respectively) compared with those in the Zol groups. The NBP groups showed decreased P1NP and TRACP-5b levels at 6 and 12 months compared with the BP groups (P < 0.001).

Longitudinal changes in BMD

At 6 months after the administration of DMAb or Zol, all the groups showed approximately 2.5–4.3% increase in lumbar spine and femoral neck BMDs compared with the baseline (Fig. 5). All groups showed approximately 1.2–2.7% increase in total proximal femoral BMDs compared with the baseline. At 12 months, the DMAb groups exhibited a

bigger increase in lumbar spine and total proximal femoral BMDs, albeit not significantly, compared with the Zol groups. There were no significant differences in the increase in BMDs at 12 months, between the BP and NBP groups. Total P1NP and TRACP 5b levels at baseline were associated with %change in lumbar spine BMD from baseline to 12 months (total P1NP in Zol group: = 0.339, P = 0.024 and DMAb group: = 0.564, P < 0.001) and TRACP-5b (Zol group: P = 0.036 and DMAb group: P = 0.004) (Fig. 6). However, bone metabolic markers were not associated with %change in the femoral neck and total proximal femur BMDs from baseline to 12 months.

Side effects and APRs

During the observational period, there were no cases of necrosis of the jaw and atypical femoral fracture. Patients in the DMAb group did not have side effects, such as hypocalcemia or hypercalcemia, which required treatment. However, 17 of 75 patients treated using Zol experienced APRs. Although patients in the DMAb groups continued treatment for over 12 months, 8 of 73 patients in the Zol groups discontinued the treatment after 12 months due to side effects (including APRs) and drug eruption involving skin redness and wheal formation. Comparisons of the clinical characteristics at baseline are summarized in Table 2. Patients with APRs were younger than those without APRs (P < 0.001). Although the ratio of prior BP use was lower in patients with APRs compared to those without APRs, there were no significant differences in the ratio of prior use of active vitamin D and acetaminophen between patients with and without APRs. The mean P1NP level of patients with APRs at baseline was higher than that of patients without APRs (P = 0.002). The mean 25(OH)D level in patients with APRs at baseline was lower than that in patients without APRs (P = 0.019). Patients with APRs exhibited higher Ca depletion from

baseline to 1–2 weeks compared to those without APRs (P = 0.030). Patients with APRs exhibited a larger increase in lumbar spine BMD from baseline to 12 months compared to those without APRs.

In the univariate analysis, age, prior BP use, P1NP level, and 25(OH)D level at baseline were identified as potential predictors for the development of APRs (Table 3). Furthermore, the P1NP and 25(OH)D levels at baseline were identified as potential predictors of the development of APRs in the multivariate logistic regression analyses adjusted for age, prior use of active vitamin D3, BP, and acetaminophen.

Discussion

This study showed that the combination therapy of Zol or DMAb and ELD increased lumbar spine and hip BMDs, regardless of pretreatment, thus suggesting that both combination therapies are effective treatments for Japanese patients with postmenopausal osteoporosis. Patients in the DMAb groups exhibited increased lumbar spine and total proximal femoral BMDs, albeit not significantly different compared to that in the Zol groups. This finding is slightly different from those of previous studies comparing DMAb and Zol [32,33]. Since the effect of ELD on the bone is independent of its supplementary effect in vitamin D insufficiency [34], this discrepancy may be explained by the fact that all the patients received combination therapy with ELD.

In this study, patients in the BP-Zol group exhibited attenuation of suppression of bone turnover at 12 months, suppressed by pretreatment. This finding was consistent with those reported in previous studies [33,35]. McClung et al. reported that transition to Zol from oral alendronate attenuated the suppression of bone turnover marker at 12 months; however, bone biopsies at 12 months exhibited decrease in excessive remodeling, as seen in

osteoporosis [35]. In this study, the BP-Zol group exhibited an increase in BMD at 12 months despite the attenuation in suppressed bone turnover. This finding supported the conclusion that patients can be switched from oral BPs to Zol infusion with maintenance of therapeutic effect for at least 12 months. However, because it is unknown whether this attenuation would have positive outcomes in preventing fragility fracture or severely suppressed bone turnover in the future, long-term continuous follow-up is necessary. Patients in the non-BPs groups exhibited increased lumbar spine, albeit not significant, compared with patients in the BPs groups. Further, bone metabolic markers at baseline were associated with changes in BMD from baseline to 12 months. Therefore, previous treatment regimen and bone metabolic markers at baseline may be useful for evaluating BMD during treatment with Zol or DMAb and ELD.

Although mean serum Ca levels decreased 1 or 2 weeks after the first administration of DMAb or Zol in combination with ELD, none of the patients experienced serious side effects related to hypocalcemia. There was a significant decrease in Ca levels in the NBP group compared to that in the BP group. Bone metabolic markers at baseline had significant correlations with changes in serum Ca levels from baseline to 1 or 2 weeks, similar to the results of a previous study regarding denosumab-induced hypocalcemia [36]. Although the DMAb group continued the treatment over 12 months, the Zol group experienced APRs (> 20 %), and 8 of 73 patients discontinued Zol. Therefore, DMAb may have relatively fewer side effects and was easier to administer compared to Zol. However, a systematic review has reported increased risk of multiple vertebral fractures after discontinuation of DMAb [37]; and therefore, strict adherence may be required with DMAb.

Consistent with the previous reports [38,39], we found that age, prior BP use, and lower 25(OH)D levels were associated with APRs. Considering the results from the multivariate analysis, higher P1NP level and lower 25(OH)D at baseline may be risk factors for APRs at the first administration and need to be monitored before the first administration. In contrast to previous reports [40,41], this study showed that acetaminophen use could not prevent APRs. This discrepancy could be explained by the fact that the dose used in this study (200 mg tablets, three times a day) was lower than that used in the previous study [41]. A recent Japanese randomized study reported that Zol-induced APRs could be suppressed by non-steroidal anti-inflammatory drugs (NSAIDs) [28]. Therefore, to prevent these APRs, an appropriate dose of acetaminophen or NSAIDs after the administration may be important in addition to monitoring bone metabolic markers and 25(OH)D levels. Considering that the ratio of APRs (17/75 cases = 22.7%) in this study for all patients who received ELD after infusion of Zol was less, regardless of lower mean 25(OH)D level, compared with that in a previous report [42], ELD could also be effective in preventing APRs. Additionally, since patients with APRs exhibited a greater decrease in Ca levels from baseline to 1–2 weeks than those without APRs, patients with APRs should be strictly monitored for hypocalcemia. Moreover, considering that patients with APRs exhibited significant increase in BMD from baseline to 12 months compared to those without APRs, APRs might have reflected the reaction to the therapy.

There were some limitations in this study. First, this study had a small sample size and a short observation period. Further studies are needed to ascertain whether BMD continuously increases upon treatment with Zol or DMAb and ELD and to what extent fractures can be prevented. Second, this study included pretreatment with various BPs,

including alendronate and risedronate, and pretreatment with active vitamin D3, such as alfacalcidol and ELD, which might have affected the results.

In conclusion, the combination therapy of Zol or DMAb and ELD may increase BMD at 12 months after the first administration, regardless of BP pretreatment, in Japanese patients with postmenopausal osteoporosis. Bone metabolic markers at baseline may be useful predictors for reaction to the therapy and side effects such as APRs and hypocalcemia during these combination therapies in postmenopausal osteoporosis. The prior use of BP is protective against the development of APR.

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Conflict of Interest: Yumejiro Nakamura, Tomohiro Shimizu, Tsuyoshi Asano, Shun Shimodan, Hotaka Ishizu, Daisuke Takahashi, Masahiko Takahata and Norimasa Iwasaki declare that they have no conflict of interest.

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Tables

Table 1 Clinical characteristics at baseline

	Zoledronic acid		Denosumab	
Variable	BPs	NBPs	BPs	NBPs
Number	43	32	35	38
Age (years)	77.6 (1.0)	76.6 (1.7)	74.4 (1.5)	71.8 (1.4) *
BMI (kg/m^2)	22.9 (0.5)	21.8 (0.6)	22.2 (0.6)	22.7 (0.5)
Duration of pretreatment (months)	28.5 (4.0)	NA	43.8 (5.9) *	NA
Prior active vitamin D3 use	32 patients	16 patients	23 patients	10 patients
Prior oral Ca intake	4 patients	3 patients	3 patients	2 patients
History of fragility fracture	32 patients	17 patients	23 patients	21 patients
Ca (mg/dL)	9.39 (0.06)	9.31 (0.06)	9.58 (0.07)	9.47 (0.06)
eGFR (mL/min/1.73 mm^2)	63.7 (2.3)	65.1 (2.3)	69.2 (3.2)	73.4 (2.3) *
P1NP (ng/mL)	28.4 (3.4)	56.5 (7.7) †	21.6 (2.0)	56.3 (5.4) †
TRACP 5b (mU/dL)	307.1 (24.5)	411.1 (35.0) †	279.5 (20.2)	451.0 (27.2) †
25(OH)D (ng/mL)	14.7 (0.8)	14.1 (1.3)	17.0 (1.2)	17.7 (1.0)
Intact PTH (pg/mL)	35.0 (3.3)	38.6 (5.7)	36.8 (2.4)	37.1 (1.1)
%YAM Lumbar (%)	70.9 (1.5)	69.7 (2.1)	71.7 (2.1)	68.5 (2.1)
%YAM FN (%)	64.2 (1.6)	64.3 (1.8)	62.2 (1.6)	61.8 (1.6)
%YAM TPF (%)	70.5 (1.8)	70.2 (2.0)	65.9 (1.9)	68.0 (1.7)

Mean (standard error of the mean) *; $P < 0.05$ vs. zoledronic acid group †; $P < 0.05$ vs. BPs group

BPs: bisphosphonates, NBPs: non bisphosphonates, BMI: body mass index, Cr: creatinine, eGFR: estimated glomerular filtration rate, P1NP: total type 1 procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b, 25(OH)D: 25- hydroxyl vitamin D, PTH: parathyroid hormone, YAM: young adult mean, FN: femoral neck, TPF: total proximal femur

Table 2 Comparisons of clinical characteristics between patients with and without acute phase reaction

Variable	APRs (+)	APRs (-)	P-value
Number	17	58	
Age (years)	70.8 (2.3)	79.8 (1.0)	< 0.001
BMI (kg/m^2)	21.6 (0.8)	22.7 (0.5)	0.273
Prior active vitamin D3 use	10 patients	43 patients	0.223
Prior bisphosphonate use	5 patients	38 patients	0.017
Acetaminophen* use	10 patients	24 patients	0.204
Ca (mg/dL)	9.37 (0.13)	9.35 (0.05)	0.885
eGFR (mL/min/1.73 mm^2)	67.2 (4.4)	63.5 (1.7)	0.357
P1NP (ng/mL)	65.0 (15.1)	33.1 (2.9)	0.002
TRACP 5b (mU/dL)	390.0 (51.6)	337.1 (22.8)	0.324
25(OH)D (ng/mL)	10.7 (1.2)	14.8 (0.9)	0.019
Intact PTH, (pg/mL)	45.6 (9.5)	33.0 (3.0)	0.112
Change in Ca levels (mg/dL)	- 0.45 (0.09)	- 0.18 (0.06)	0.030
%Change in Lumbar BMD (%)	6.96 (1.95)	3.57 (0.71)	0.045
%Change in FN BMD (%)	3.88 (1.51)	3.63 (1.41)	0.925
%Change in TPF BMD TPF (%)	2.52 (0.63)	2.25 (1.01)	0.886

Mean (standard error of the mean)

* Patients took 200 mg tablets three times a day after every meal

APR: acute phase reaction, BMI: body mass index, Cr: creatinine, eGFR: estimated glomerular filtration rate, P1NP: total type 1 procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b, 25(OH)D: 25- hydroxyl vitamin D, PTH: parathyroid hormone, BMD: bone mineral density, FN: femoral neck, TPF: total proximal femur

Table 3 Univariate and multivariate logistic regression analyses of factors affecting development of acute-phase reactions

Factor	Odds ratio	95 % confidence interval		P-value
Univariate analysis				
Age (years)	0.875	0.810	0.945	0.001
Prior active vitamin D3 use	0.498	0.161	1.544	0.227
Prior bisphosphonate use	0.254	0.079	0.082	0.022
Acetaminophen* use	2.024	0.675	6.069	0.208
P1NP (ng/mL)	1.027	1.005	1.048	0.014
TRACP 5b (mU/dL)	1.001	0.999	1.004	0.325
25(OH)D (ng/mL)	0.874	0.776	0.984	0.026
Intact PTH (pg/mL)	0.984	0.960	1.005	0.148
Multivariate analysis#				
P1NP (ng/mL)	1.039	1.005	1.074	0.025
TRACP 5b (mU/dL)	1.001	0.997	1.005	0.640
25(OH)D (ng/mL)	0.851	0.736	0.983	0.029
Intact PTH (pg/mL)	0.998	0.967	1.026	0.911

Mean (standard error of the mean)

*Patients took 200 mg tablets three times a day after every meal

#Adjusted by age, prior active vitamin D3, bisphosphonate use, and acetaminophen use.

APR: acute phase reaction, P1NP: total type 1 procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b, 25(OH)D: 25- hydroxyl vitamin D, PTH: parathyroid hormone, YAM: young adult mean, FN: femoral neck, TPF: total proximal femur

Figure captions

Fig. 1 Study design

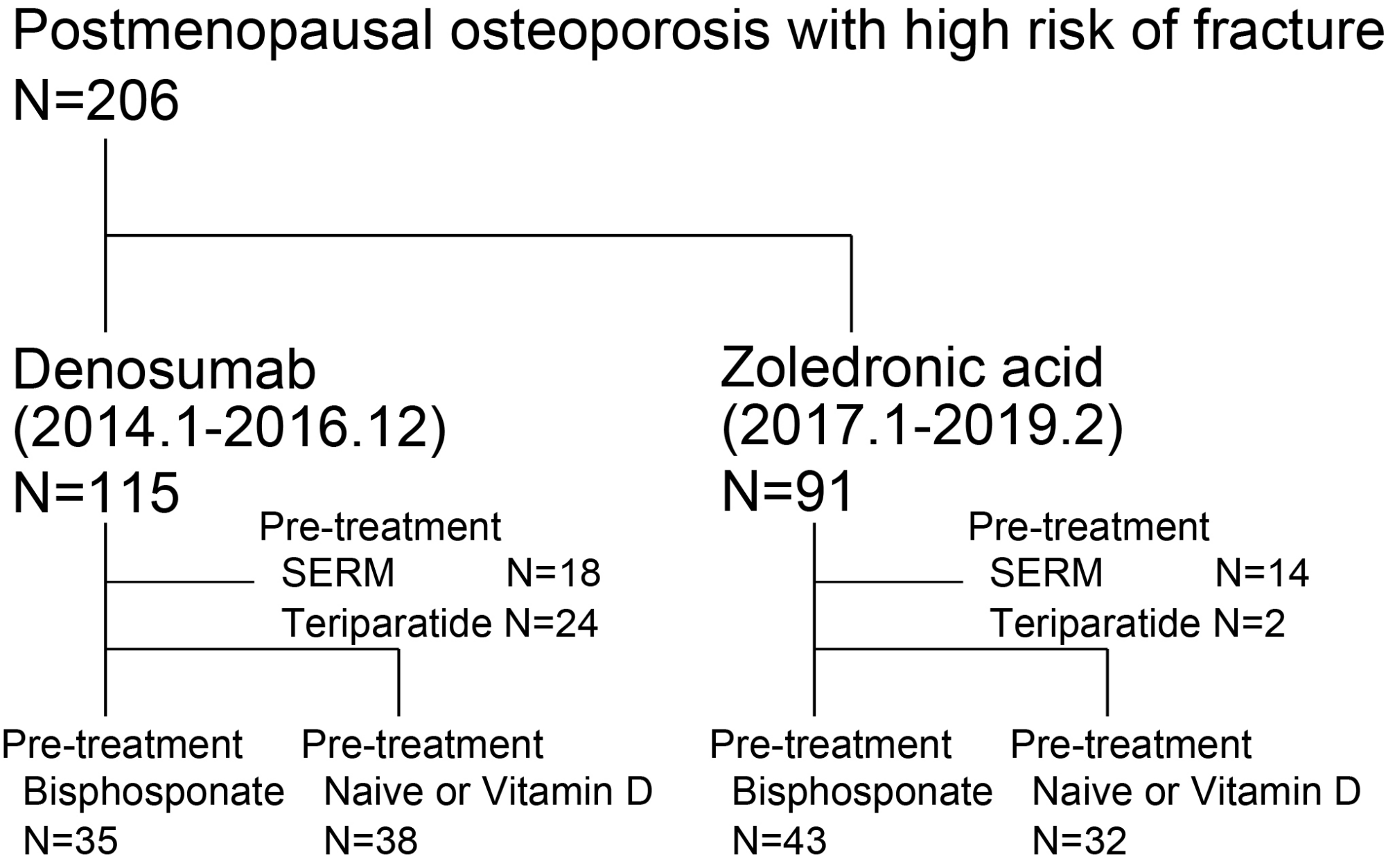
Fig. 2 Clinical protocol

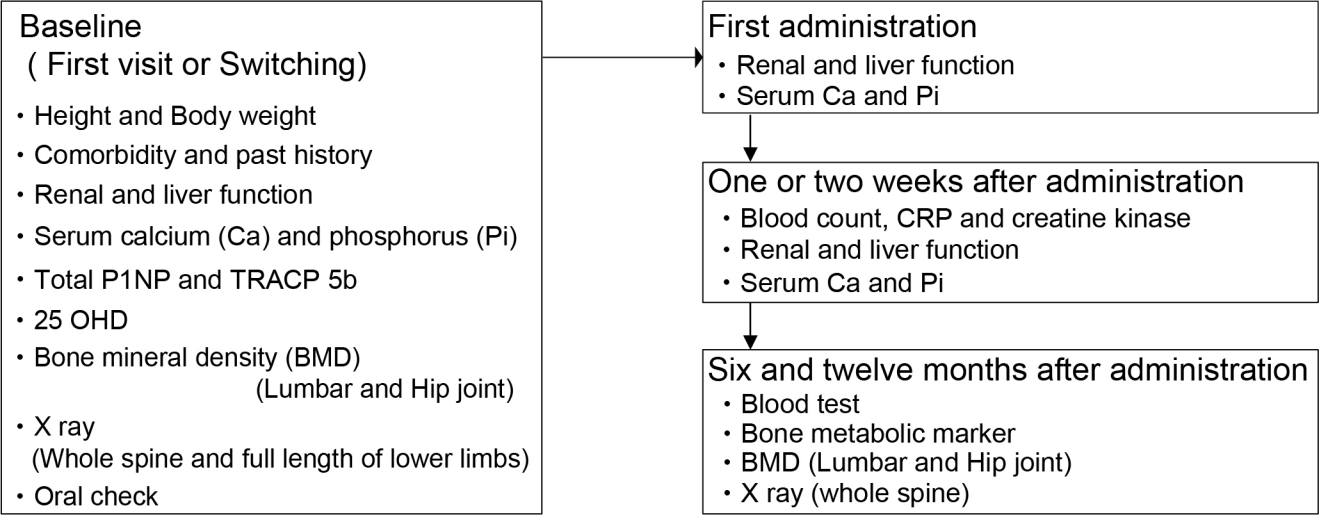
Fig. 3 Correlation between the changes in Ca from baseline to 1-2 weeks after administration ,and total type 1 procollagen-N-propeptide and tartrate-resistant acid phosphatase 5b, P1NP: total type 1 procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b

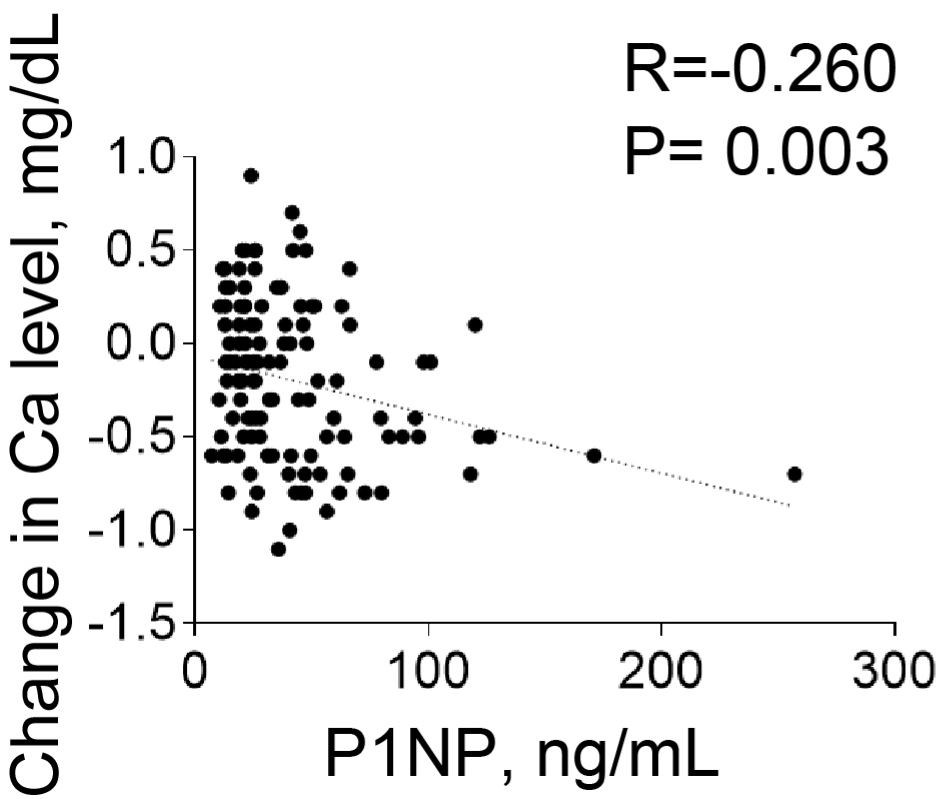
Fig. 4 Comparison of changes in (A) serum P1NP levels and (B) serum TRACP 5b levels at 6- and 12-months post-administration. Data show mean ± SEM, Zol: zoledronate acid, DMAb: denosumab, BPs: bisphosphonates, non-BPs: non bisphosphonates, P1NP: total type 1 procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b

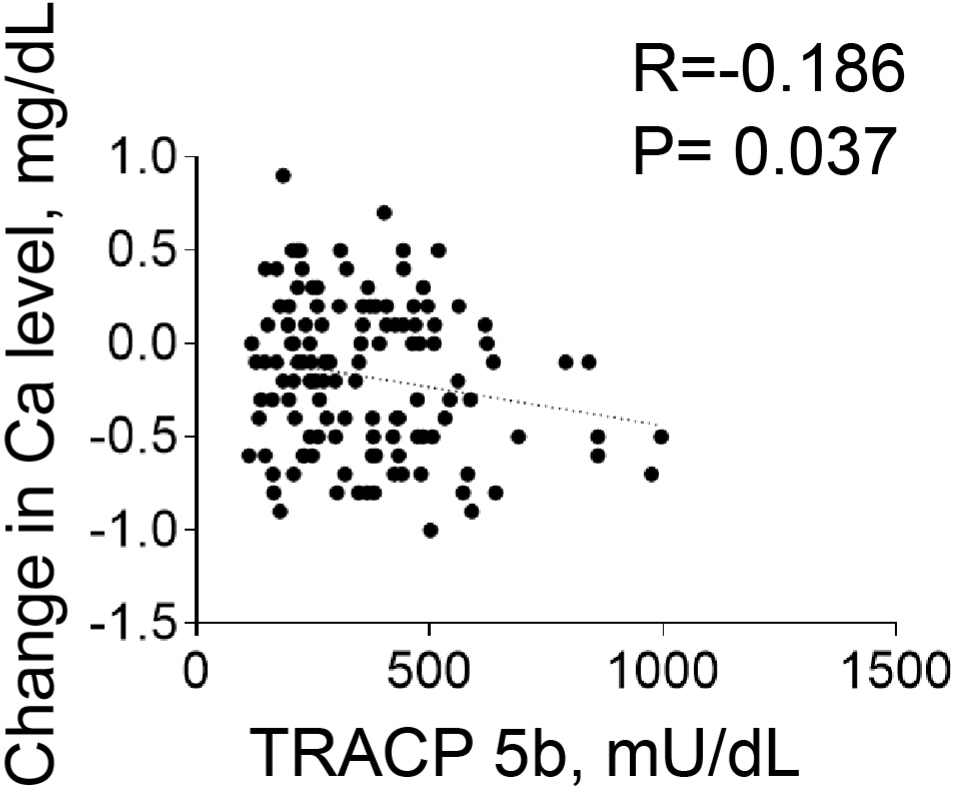
Fig. 5 Longitudinal changes in %change in bone mineral densities of lumbar, femoral neck, and total proximal femur. Data show mean ± SEM

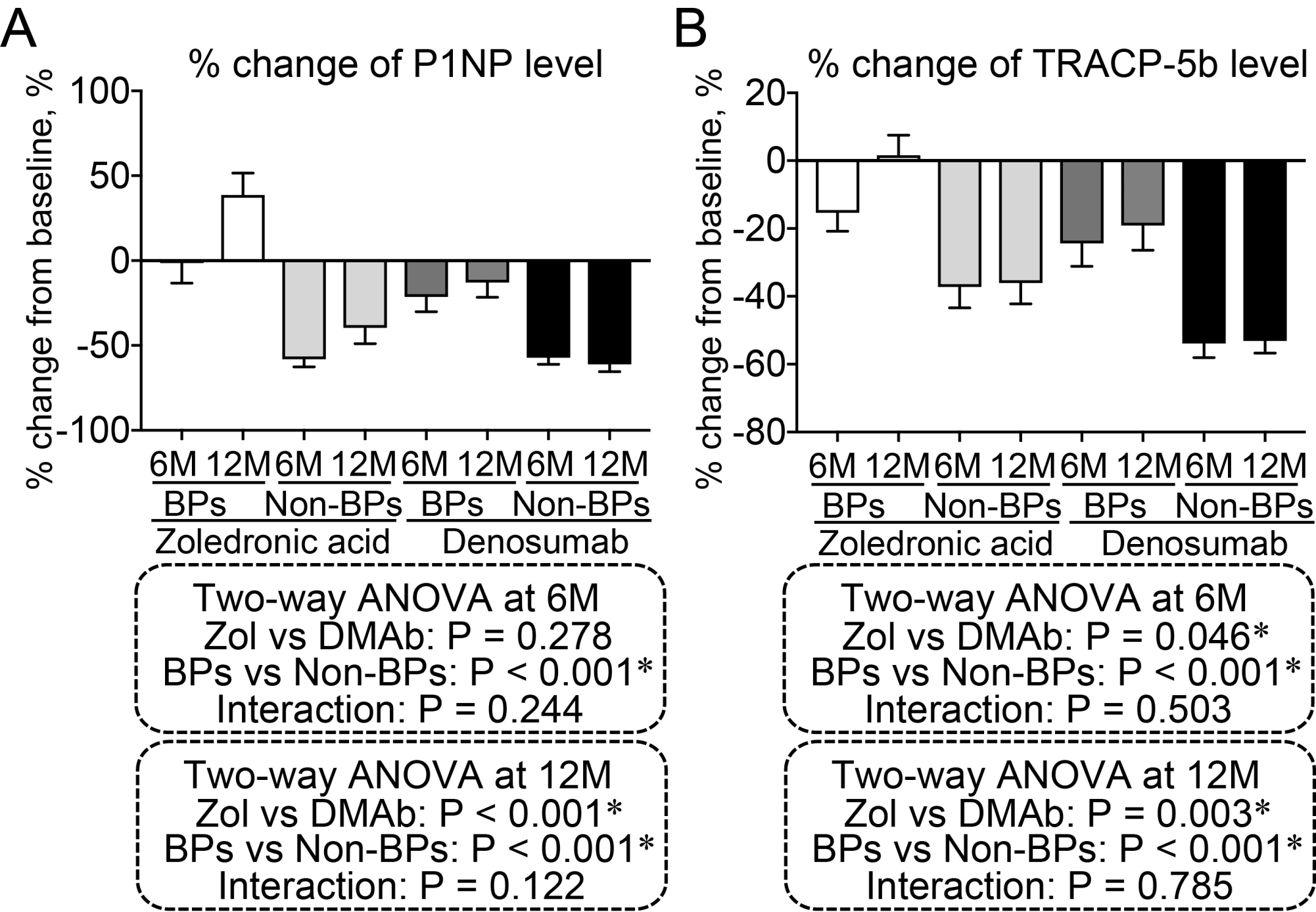
Fig. 6 Correlation between the changes in bone metabolic markers (a) total type 1 procollagen-N-propeptide and (b) tartrate-resistant acid phosphatase 5b) and lumbar bone mineral density. Linear regression models adjusted for age, bone mineral density, pretreatment with bisphosphonate and active vitamin D, 25-dihydroxyvitamin D levels, %young adult mean at baseline, and treatment

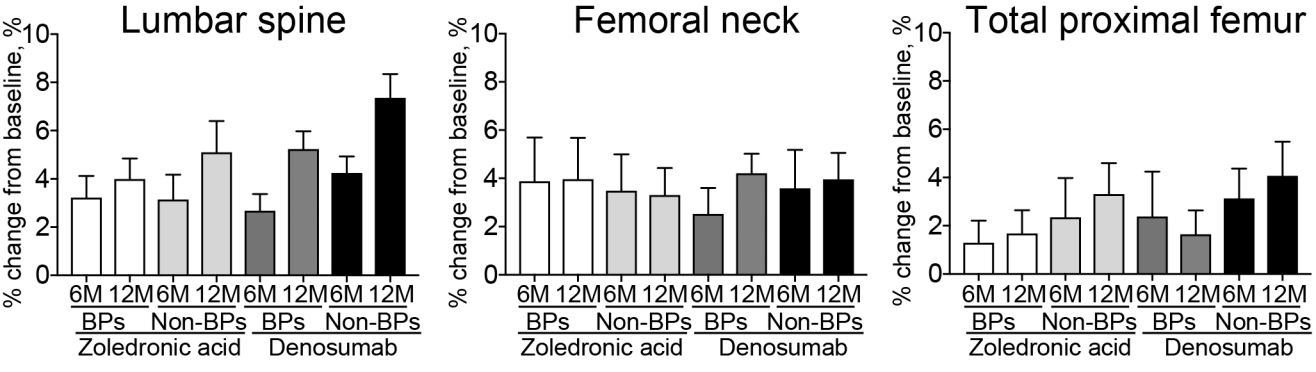

Postmenopausal osteoporosis with high risk of fracture
N=206
Denosumab
(2014.1-2016.12)
N=115
Zoledronic acid
(2017.1-2019.2)
N=91
Pre-treatment
SERM N=18
Teriparatide N=24
Pre-treatment
SERM N=14
Teriparatide N=2
Pre-treatment
Bisphosponate
N=35
Pre-treatment
Naive or Vitamin D
N=38
Pre-treatment
Bisphosponate
N=43
Pre-treatment
Naive or Vitamin D
N=32


Baseline
(First visit or Switching)
・Height and Body weight
・Comorbidity and past history
・Renal and liver function
・Serum calcium (Ca) and phosphorus (Pi)
・Total P1NP and TRACP 5b
・25 OHD
・Bone mineral density (BMD)
(Lumbar and Hip joint)
・X ray
(Whole spine and full length of lower limbs)
・Oral check
First administration
・Renal and liver function
・Serum Ca and Pi
One or two weeks after administration
・Blood count, CRP and creatine kinase
・Renal and liver function
・Serum Ca and Pi
Six and twelve months after administration
・Blood test
・Bone metabolic marker
・BMD (Lumbar and Hip joint)
・X ray (whole spine)


R=-0.260
P= 0.003
Change in Ca level, mg/dL
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
100
200
300
P1NP, ng/mL


R=-0.186
P= 0.037
Change in Ca level, mg/dL
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
500
1000
1500
TRACP 5b, mU/dL


A
% change of P1NP level
% change from baseline, %
100
50
0
-50
-100
6M 12M 6M 12M 6M 12M 6M 12M
BPs Non-BPs BPs Non-BPs
Zoledronic acid Denosumab
Two-way ANOVA at 6M
Zol vs DMAb: P = 0.278
BPs vs Non-BPs: P < 0.001*
Interaction: P = 0.244
Two-way ANOVA at 12M
Zol vs DMAb: P < 0.001*
BPs vs Non-BPs: P < 0.001*
Interaction: P = 0.122
B
% change of TRACP-5b level
% change from baseline, %
20
0
-20
-40
-60
-80
6M 12M 6M 12M 6M 12M 6M 12M
BPs Non-BPs BPs Non-BPs
Zoledronic acid Denosumab
Two-way ANOVA at 6M
Zol vs DMAb: P = 0.046*
BPs vs Non-BPs: P < 0.001*
Interaction: P = 0.503
Two-way ANOVA at 12M
Zol vs DMAb: P = 0.003*
BPs vs Non-BPs: P < 0.001*
Interaction: P = 0.785



Two-way ANOVA at 12M

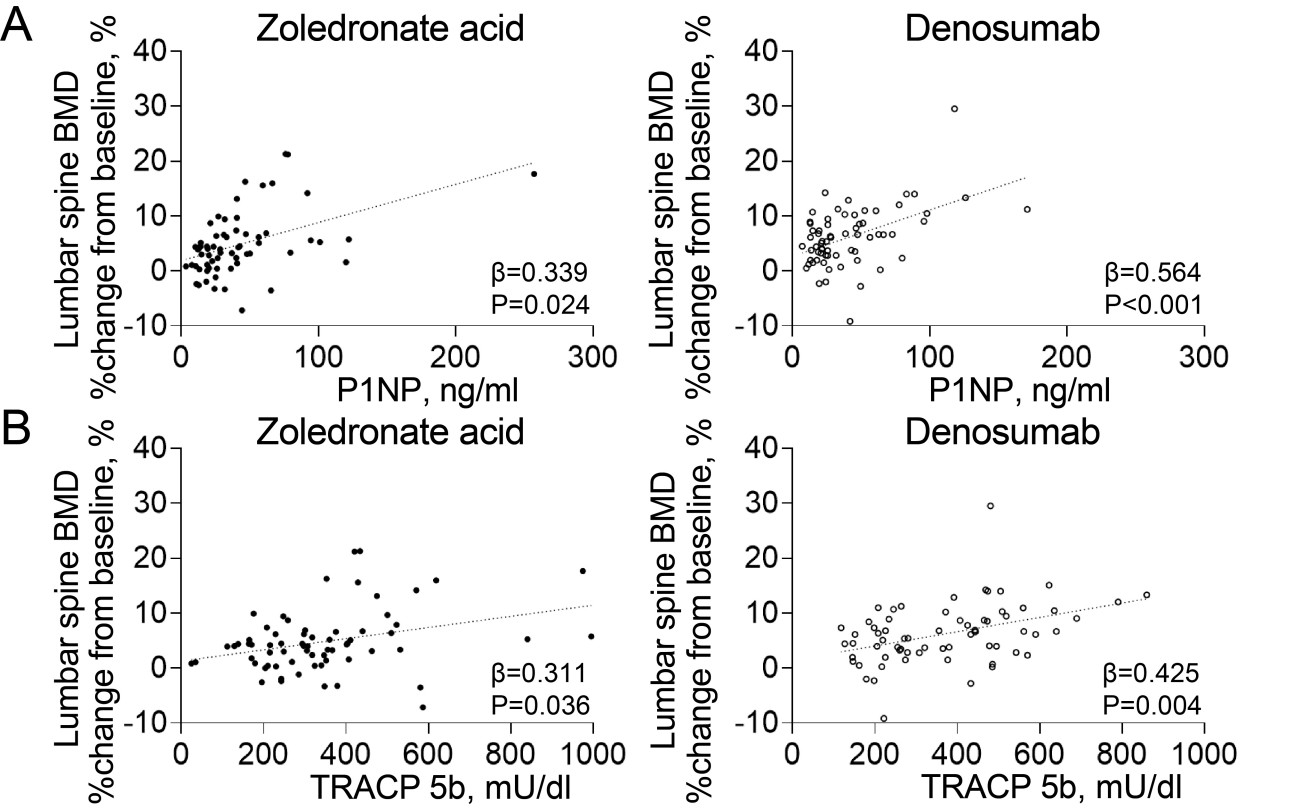
Treatment: P = 0.076
Pre-treatment: P = 0.103
Interaction: P = 0.605

Two-way ANOVA at 12M

Treatment: P = 0.764
Pre-treatment: P = 0.763
Interaction: P = 0.891

Two-way ANOVA at 12M

Treatment: P = 0.098
Pre-treatment: P = 0.742
Interaction: P = 0.768


A
Zoledronate acid
Lumbar spine BMD
%change from baseline, %
40
30
20
10
0
-10
0
100
200
300
P1NP, ng/ml
β=0.339
P=0.024
Denosumab
Lumbar spine BMD
%change from baseline, %
40
30
20
10
0
-10
0
100
200
300
P1NP, ng/ml
β=0.564
P<0.001
B
Zoledronate acid
Lumbar spine BMD
%change from baseline, %
40
30
20
10
0
-10
0
200
400
600
800
1000
TRACP 5b, mU/dl
β=0.311
P=0.036
Denosumab
Lumbar spine BMD
%change from baseline, %
40
30
20
10
0
-10
0
200
400
600
800
1000
TRACP 5b, mU/dl
β=0.425
P=0.004