Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Benefits of Denosumab vs Zoledronate in Postmenopausal Women Previously Treated with Alendronate: A Two-Year Retrospective Study

Ziyuan Wang[1,*], Yazhao Mei[1,*], Li Shen[2], Jiemei Gu[1], Na Ren[1], Ya Wang[1], Zhenlin Zhang[1], Chun Wang[1]

[1]Shanghai Clinical Research Center of Bone Disease, Department of Osteoporosis and Bone Diseases, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [2]Clinical Research Center, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chun Wang; Zhenlin Zhang, Shanghai Clinical Research Center of Bone Disease, Department of Osteoporosis and Bone Diseases, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 600 Yi-Shan Road, Shanghai, 200233, People's Republic of China, Email wangchun66@sjtu.edu.cn; zhangzl@sjtu.edu.cn

Purpose: Due to various clinical considerations, postmenopausal osteoporosis patients initially treated with oral alendronate (ALN) therapy can later transition to either Denosumab (Dmab) or Zoledronate (ZOL). Using a two-year retrospective cohort, this study sought to thoroughly assess and contrast the frequency of osteoporotic fractures and fluctuations in bone mineral density (BMD) among patients switching from ALN therapy to either Dmab or ZOL.

Patients and Methods: This retrospective cohort study enrolled 294 postmenopausal osteoporosis patients who transitioned from oral ALN to either Dmab or ZOL. The primary endpoint was new-onset osteoporotic fractures within 24 months, confirmed via clinical records and imaging (X-ray/CT/MRI). Secondary endpoint included annual percentage changes in BMD at the lumbar spine, total hip, and femoral neck.

Results: There were no discernible variations between the Dmab and ZOL groups in terms of baseline BMD or prior fracture history. The median age of the Dmab group was higher than that of the ZOL group. In comparison to the ZOL group, the overall incidence of new-onset fractures was significantly lower in the Dmab group (3.79% vs 10.39%, raw p value = 0.028; FDR-adjusted p value = 0.028), especially for vertebral fractures (1.52% vs 8.44%, raw p value = 0.023; FDR-adjusted p value = 0.028). Furthermore, although BMD increased from baseline in both groups, the Dmab group improved much more than the ZOL group.

Conclusion: In postmenopausal osteoporosis patients transitioning from oral ALN to other antiresorptive therapies, Dmab is demonstrated superior efficacy over ZOL in lowering risk of new-onset vertebral and overall fractures and sustaining BMD improvements over 24 months. These findings suggest that Dmab may represent a preferential strategy for optimizing clinical outcomes in sequential anti-osteoporosis treatment protocols.

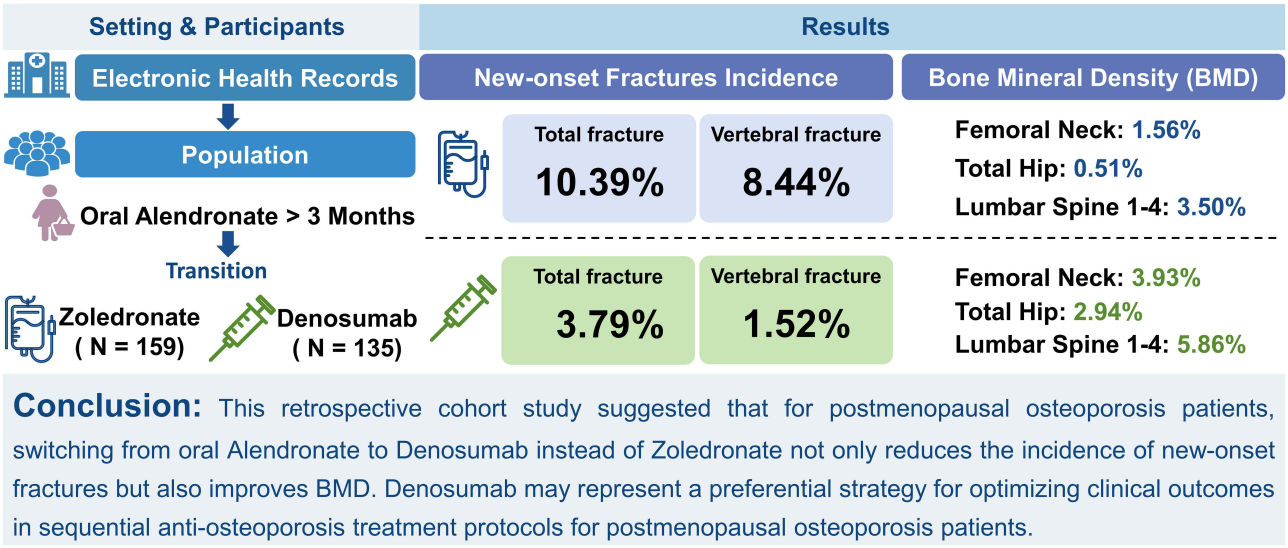
Keywords: transitioned therapy, denosumab, zoledronate, new-onset fracture

Introduction

Osteoporosis is a systemic bone disorder marked by reduced bone density and structural degradation, leading to heightened fragility and susceptibility to fractures.[1,2] For postmenopausal women, oral bisphosphonates (BPs) are the most often prescribed antiresorptive agent. However, owing to the adverse effects of oral BPs, inconvenience, poor adherence, and lack of visible benefits, clinicians may suggest transitioning to other antiresorptive agents.[3,4] An essential therapeutic approach for treating osteoporosis is switching from oral anti-osteoporosis medications to injectable anti-resorptive drugs with longer dosage intervals. Zoledronate (ZOL) and Denosumab (Dmab) are both antiresorptive agents that enhances bone mineral density (BMD) and significantly reduces osteoporotic fracture risk.[5–8]

Received: 23 May 2025
Accepted: 31 October 2025
Published: 15 November 2025

Graphical Abstract



An international multicenter RCT conducted in 2016 examined the effectiveness of Dmab and ZOL after a year of treatment in postmenopausal osteoporosis (PMOP) patients who had previously taken oral BPs.[9] In addition to showing a much higher percentage change in BMD at different skeletal sites, patients who received Dmab treatment also showed a significantly lower level of bone turnover markers (BTMs). Additionally, adverse effects were similar for both medications, with atypical femoral fractures (AFFs) occurring. In 2020, a combined review of four studies assessed the effectiveness and safety of switching postmenopausal women from oral BPs to Dmab or alternative BPs.[10] Although these studies confirmed the better efficacy of Dmab treatment, osteoporotic fractures were not formally examined as a primary endpoint event.[10]

Therefore, we conducted a two-year retrospective cohort study to compare the incidence of new-onset fractures in PMOP patients who switched from oral ALN to ZOL or to Dmab. Additionally, we compared the differences in BMD and BTMs after treatment with ZOL or Dmab. This study aimed to present clinical data supporting the optimization of personalized therapeutic strategies for PMOP patients.

Materials and Methods

Study Subjects

All the data were obtained from the electronic health records (EHRs) of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

The inclusion criteria for this study were as follows: (1) patients diagnosed with PMOP who ≥ 50 years old; (2) oral ALN treatment for more than 3 months; (3) for various reasons (side effects, poor compliance or curative effect), the anti-osteoporosis treatment was changed to Dmab (60mg, subcutaneously) every six months for at least two times or ZOL (5mg, intravenously) once a year for at least one time; and (4) baseline serum beta cross-linked carboxy-terminal telopeptide of type I collagen (β-CTX) was less than 500 pg/mL.[9]

The exclusion criteria were as follows: (1) treatment with Dmab or ZOL at any time in the past; (2) treatment with PTH or PTH derivatives at any time in the past; (3) indications of different metabolic or inherited bone diseases; (4) treatment with glucocorticoids for >3 months during therapy; (5) any diseases, therapy, or circumstance that might contribute to low bone mass without being genetic.

All subjects took at least 600 mg of oral elemental calcium and 400 IU of vitamin D_3 daily.

This study was approved by the Ethics Committee of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (2023-KY-093). The informed consent was obtained from the study participants prior to study commencement.

New-Onset Fracture Assessment

New-onset fractures were defined as nontraumatic fractures that occurred within 24 months from baseline (ALN switches to ZOL or Dmab). Fractures included vertebral, hip, wrist, and humeral fractures. Vertebral fractures were assessed by comparing vertebral morphological changes at baseline with those at month 24 via the Genant semiquantitative technique.[11] All patients underwent vertebral X-ray examinations at 2 years after enrollment, with the examination time window set at 24±3 months. Patients who did not complete BMD and BTMs follow-up examination in our hospital, we conducted telephone follow-ups and requested them to undergo vertebral X-ray examinations at local hospitals. If the actual examination time of a patient exceeded this range, the patient was considered to be outside the time window and excluded from the data analysis cohort of this 2-year X-ray examination. Hip fractures were identified via X-ray examination and surgical records[12] and hip fractures were differentiated from atypical femoral fractures (AFF).[13] Wrist and humeral fractures were determined via X-ray examination.

BMD and BTMs Assessments

The same Lunar Prodigy dual energy X-ray absorptiometry (DXA) (GE Healthcare, Madison, WI, USA) densitometer was used to evaluate BMD of femoral neck and total hip, and lumbar spine 1–4 (L1-L4). The analysis was conducted with Prodigy encore (ver. 6.70, standard-array mode; GE Healthcare, Madison, WI, USA).

The DXA measures at total hip, femoral neck, and L1-L4 showed root–mean–square coefficient of variation (RMS-% CV) values of 0.70%, and 2.22% and 1.39%, respectively. Body weight and height were assessed with standardized instruments. BMI calculation was based on the formula weight/height squared, expressed as kg/m^2.

BMDs were taken at baseline, as well as 12 and 24 months into the course of treatment. The levels of serum β-CTX, osteocalcin (OC) were measured at baseline, month 6, month 12, month 18 and month 24. Serum biochemical indexes including calcium (Ca), phosphorus (P), intact parathyroid hormone (PTH), and 25-hydroxyvitamin D [25(OH)D] were assessed at baseline. Automated analyzers were used to measure the serum levels of Ca and P. Automated Roche's electrochemiluminescence system (E170, Roche, Germany) assessed β-CTX, OC, 25(OH)D, and PTH serum concentrations. All these serum biochemical indexes were measured in Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

Outcome

The primary endpoint was the incidence of new-onset fragility fractures across the 24-month study period. The percentage change in BMD at femoral neck, total hip, L1-L4, and percentage change in BTMs from baseline to month 12 were the main secondary endpoints. Additional secondary endpoints included the percentage change in BMD and BTMs from baseline to month 24.

Statistical Analyses

Descriptive statistics were included as mean (standard deviation) or median (interquartile range, IQR). Normality of the data distribution was evaluated using the Shapiro–Wilk test. And Levene's test was used to assess the homogeneity of variances. When the variances were not homogeneous, Welch's *t*-test was applied. The significant difference was analyzed using *t*-test / Welch's *t*-test for normally distributed variables or the Mann–Whitney *U*-test for non-normally distributed variables.

The overall fracture-free period was defined as the time from the first treatment date to the date of new-onset fracture, or the date of the last visit, up to 24 months, whichever occurred first. Patients who remained fracture-free at their final follow-up were censored. A Log rank test was used to compare time to new-onset fracture between the Dmab group and the ZOL group. Cox proportional hazard models were used to evaluate the contribution of the two treatment groups to new-onset fractures up to 24 months, adjusting for age at baseline, duration of oral ALN therapy, and baseline 25(OH)D

level. The proportional hazards assumption was evaluated using Schoenfeld residuals, which quantify the discrepancy between observed and expected event times for each covariate. Analyses were conducted in R (Version 3.5.1). Schoenfeld residual plots were shown in Supplementary Figure 1.

The relationship between treatment group and the incidence of new-onset fractures was first examined using univariate logistic regression, followed by multivariate logistic regression adjusting for covariates including baseline age, duration of oral ALN therapy and baseline 25(OH)D level. Patients who exceeded the pre-specified examination time window were excluded from the analysis. Analyses were conducted in R (Version 3.5.1).

A sensitivity analysis was performed using Firth regression, with the same covariates as in the multivariate logistic regression. Additionally, the propensity-based sensitivity analysis was performed to effectively reduce the influence of confounding bias between two groups on the results of new-onset fractures and to improve the robustness of the conclusions. We used full matching for propensity score matching, with the caliper and ratio equal to 0.3 and 1, respectively. Age at baseline, duration of oral ALN therapy and baseline serum level of 25(OH)D were included as matching variables. Analyses were conducted in R (Version 3.5.1).

The mean percentage change in BMD from the initial measurement to the 12- and 24-month follow-ups was determined through multiple linear regression analysis. This model accounted for several covariates, including participants' baseline age, duration of prior oral ALN therapy, baseline BMD value, and serum 25(OH)D concentrations at baseline. Homoscedasticity analysis was performed in the linear regression analysis; if heteroscedasticity occurred, HC3 robust standard errors were used to correct for it.

Based on the outcome measures and testing aims of this study, all hypothesis tests were grouped into 8 independent hypothesis families. The number of tests included in each family, along with the rationale for their grouping, was provided in the Supplementary Table 1. To account for multiple comparisons, false discovery rate (FDR) adjusted p values implementing the Benjamini-Hochberg method were included. FDR-adjusted p values <0.05 were considered significant. The p value adjustments were performed using R (Version V.3.5.1). All p values and adjusted p values are grouped by hypothesis families and presented in Supplementary Table 2.

The Mann–Whitney *U*-test or *t*-test was used to compare the median/mean percentage changes in β-CTX and OC after treatment between two groups.

Spearman correlation analysis was used to analyze the association between the incidence of new-onset fractures and the percentage change from baseline to month 12 in the β-CTX and OC in the Dmab and ZOL groups, respectively.

Statistical analyses were performed using SPSS unless otherwise indicated.

Results

Baseline Demographics and Clinical Characteristics

In this study, after rigorous screening, a total of 294 subjects with postmenopausal osteoporosis previously treated with ALN followed by Dmab or ZOL were selected from among patients who were routinely monitored at the Osteoporosis and Bone Diseases outpatient clinic. Among them, 135 subjects were treated with Dmab (Dmab group), and 159 subjects were treated with ZOL (ZOL group). In the Dmab group, all the subjects (135 subjects) received Dmab treatment for 12 month and completed follow-up examinations of BMD and BTMs, among whom 46 finished 24 months of treatment and completion of BMD and BTMs follow-up examination. In the ZOL group, all the subjects (159 subjects) received ZOL treatment for 12 month and completed follow-up examinations of BMD and BTMs, among whom 65 finished 24 months of treatment and completion of BMD and BTMs follow-up examination. Figure 1 shows the detailed information of subject disposition. Table 1 provides a summary of the baseline demographics of total 294 subjects.

The median ages (IQRs) of the Dmab group and ZOL group were 73 (66,78) and 70 (65, 75), respectively ($p = 0.008$). The median durations of previous oral ALN therapy in the Dmab group and ZOL group were 36 (16, 54) months and 20 (10, 35) months, respectively ($p < 0.001$).

At baseline, 66 subjects (48.89%) in the Dmab group had osteoporotic fractures, whereas 92 subjects (57.86%) in the ZOL group had osteoporotic fractures. The two groups experienced fractures at comparable rates ($p = 0.129$).

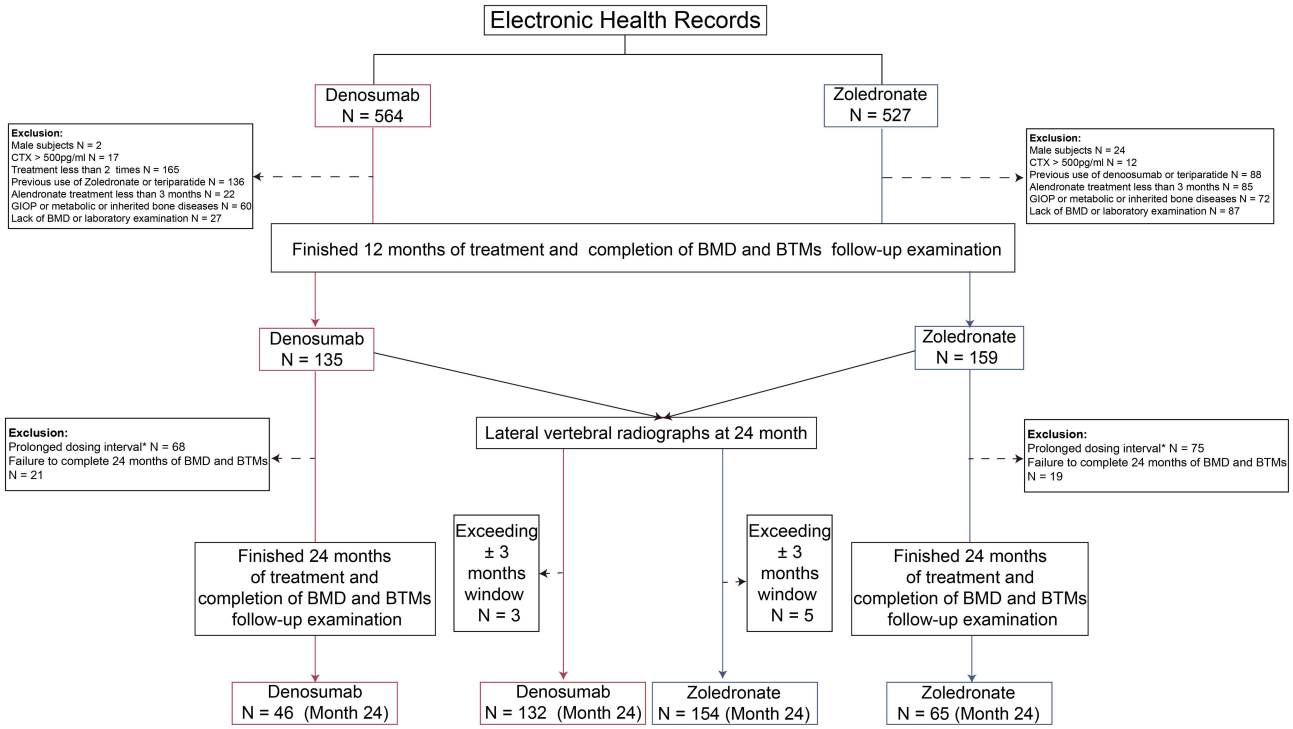


Figure 1 Subject disposition. *Prolonged dosing interval: the situation where the treatment intervals of Dmab and ZOL exceed 7 months and 13 months, respectively.

At baseline, the two groups' BMDs for the femoral neck, total hip, and L1-L4 did not differ significantly. Similar serum concentrations of BTMs, Ca, P and PTH were noted across both groups. Although the serum level of 25(OH)D were maintained above 30ng/mL in both two groups, the Dmab group showed noticeably greater 25(OH)D concentrations than the ZOL group (p = 0.01). Table 1 provides a summary of the detailed clinical features.

Table 1 Baseline Demographics and Clinical Characteristics

	Dmab (N=135)	ZOL (N=159)	p value
Age, year, median (Q1, Q3)	73 (66, 78)	70 (65, 75)	0.008
BMI, mean ± SD	22.49±3.22	22.48±3.46	0.990
Prior oral ALN treatment duration, month, median (Q1, Q3)	36 (16, 54)	20 (10, 35)	<0.001
Osteoporotic fracture (%)	66 (48.89%)	92 (57.86%)	0.129
Vertebral	55 (40.74%)	79 (49.69%)	0.129
Hip	5 (3.70%)	5 (3.14%)	1.000
Radius	13 (9.63%)	11 (6.92%)	0.307
BMD, median (Q1, Q3)			
L1-L4, g/cm^2	0.786 (0.713, 0.868)	0.768 (0.693, 0.830)	0.069
Femoral neck, g/cm^2	0.643 (0.566, 0.712)	0.633 (0.588, 0.692)	0.665
Total hip, g/cm^2	0.694 (0.655, 0.765)	0.694 (0.611, 0.756)	0.209
Serum β-CTX, pg/mL, median (Q1, Q3)	223.5 (133.7, 352.2)	234.0 (159.7, 329.5)	0.618
Serum OC, pg/mL, median (Q1, Q3)	12.80 (10.27, 16.28)	12.46 (9.91, 16.71)	0.868
Serum PTH, pg/mL, median (Q1, Q3)	38.27 (29.19, 45.23)	39.45 (31.04, 53.90)	0.064
Serum Ca, mmol/L, mean ± SD	2.35±0.10	2.34±0.09	0.224
Serum P, mmol/L, mean ± SD	1.11±0.14	1.10±0.13	0.372
Serum 25(OH)D, ng/mL, median (Q1, Q3)	33.44±9.75	30.63±8.9	0.010

Abbreviations: ALN, alendronate; L1-L4, Lumbar spine 1–4.

https://doi.org/10.2147/DDDT.S533224

New-Onset Fractures During the 24-Month Treatment

In this study, 286 patients completed vertebral X-ray examinations within the time window during the 24-month follow-up, while 8 patients underwent vertebral X-ray examinations outside the time window. The detailed information is shown in Figure 1.

The Dmab group had fewer new-onset fractures than the ZOL group (Dmab: 3.79%, 5/132 vs ZOL: 10.39%, 16/154). Table 2 showed the information of new-onset fracture of two groups.

The Cox regression model revealed that, after adjusting for baseline age, duration of oral ALN therapy, and baseline serum 25(OH)D level, patients in the ZOL group had a considerably higher chance of getting new-onset fractures compared to those in the Dmab group (HR = 3.23, 95% CI = 1.13–9.23; raw p value = 0.028; FDR-adjusted p value = 0.028; Table 3). The median fracture-free times was 23.54 months with Dmab and 23.12 months with ZOL (Log rank test p value = 0.025; FDR-adjusted p value = 0.028). Vertebral fractures accounted for the majority of new-onset fractures, with 2 out of 5 in the Dmab group and 13 out of 16 in the ZOL group. After adjusting for the same covariates using the Cox regression model, a similar trend of an elevated risk of developing new-onset vertebral fracture in the ZOL group compared to the Dmab group was seen (HR = 5.88, 95% CI=1.27–27.12; raw p value = 0.023; FDR-adjusted p value = 0.028; Table 3). The median new-onset vertebral fracture-free times were 23.81 months with Dmab and 23.22 months with ZOL (Log rank test p value = 0.007; FDR-adjusted p value = 0.028).

Univariate logistic regression showed that compared with the Dmab group, the ZOL group had a higher incidence of overall new-onset fractures (OR = 2.94; 95% CI = 1.12–9.21; raw p value = 0.040, FDR-adjusted p value = 0.040). After adjusting for baseline age, duration of oral ALN therapy, and baseline serum 25(OH)D level, the risk of overall new-onset fractures in the ZOL group was higher than that in the Dmab group (OR = 3.20; 95% CI = 1.15–10.50; raw p value = 0.036; FDR-adjusted p value = 0.040). Univariate logistic regression showed that compared with the Dmab group, the ZOL group had a higher incidence of vertebral fractures (OR = 5.99; 95% CI = 1.62–38.80; raw p value = 0.020; FDR-

Table 2 New-Onset Fracture Information of Dmab and ZOL Treatment

	Dmab (N = 132)	**ZOL (N = 154)**
Number of subjects	5 (3.79%)	16 (10.39%)
Number of fractures	5	17
Vertebra	2	13
Radius	3	2
Femoral neck	0	2

Table 3 HR, 95% CI and p Value of Cox Regression

Variables	**HR**	**95% CI**	**Raw p Value**	**FDR-Adjusted p Value**
Total fracture incidence				
Treatment Group	3.23	(1.13, 9.23)	0.028	0.028
Age at baseline	1.01	(0.95, 1.08)	0.676	0.856
Duration of oral alendronate therapy	1.00	(0.99, 1.02)	0.648	0.856
Baseline serum level of 25(OH)D	1.00	(0.95, 1.04)	0.856	0.856
Vertebral fracture incidence				
Treatment Group	5.88	(1.27, 27.12)	0.023	0.028
Age at baseline	0.99	(0.92, 1.06)	0.741	0.856
Duration of oral alendronate therapy	1.01	(0.99, 1.03)	0.572	0.856
Baseline serum level of 25(OH)D	0.97	(0.92, 1.03)	0.361	0.856

Abbreviation: FDR, false discovery rate.

adjusted p value = 0.040). After adjusting for covariates, the risk of new-onset vertebral fractures in the ZOL group was also higher than that in the Dmab group (OR = 5.86; 95% CI = 1.49–39.20; raw p value = 0.026; FDR-adjusted p value = 0.040). The detailed information was presented in supplementary Table 3.

Owing to the limited number of new-onset fracture events, there is a potential risk of rare event bias. Thus, Firth's penalized logistic regression was additionally utilized for sensitivity analysis. The results of Firth's penalized logistic regression were consistent with the primary outcome, which indicated that after controlling for rare event biases, the results of this study remain robust. The ORs, 95% CIs, and p values from both logistic regression and Firth's penalized logistic regression, along with a detailed comparison between the two methods, are presented in Supplementary Table 3.

In addition to validating the robustness of the new-onset fracture using Firth's penalized logistic regression, we further verified these results through propensity score sensitivity analysis. Propensity score matching was performed based on the complete sample. Using full matching, a total of 278 subjects were successfully matched (124 in the Dmab group and 154 in the ZOL group). Except for baseline age, the standardized mean differences (SMDs) of the other two covariates (duration of oral ALN therapy and baseline serum 25(OH)D level) were < 0.1 after matching. The absolute values of SMDs before and after matching are presented in Supplementary Table 4. Although the absolute value of the SMD for baseline age was still greater than 0.1 after matching, it is evident that the SMD had decreased compared with that before matching (Figure 2). Univariate and multivariate Logistic regression, along with Cox regression analyses, were conducted on the matched patient cohort. Univariate Logistic regression results showed that the risks of new-onset overall fractures and vertebral fractures in the ZOL group were both higher than those in the Dmab group (overall: OR = 2.76, 95% CI: 1.05–8.64, p = 0.054; vertebral: OR = 5.65, 95% CI: 1.27–25.02, p = 0.023); after adjusting for the covariate of baseline age, the results remained highly consistent (overall: OR = 2.88, 95% CI: 1.08–9.16, p = 0.048; vertebral: OR = 5.52, 95% CI: 1.23–24.71, p = 0.025), with specific values available in Supplementary Table 5. Cox regression analysis revealed that the ZOL group had a significantly higher risk of both new-onset overall fractures and vertebral fractures compared with the Dmab group (overall: HR = 2.79, 95% CI: 1.03–7.62, p = 0.045; vertebral: HR = 5.62, 95% CI: 1.51–36.40, p = 0.025). Results from propensity score matching were largely consistent with the primary outcome, demonstrating that even after accounting for baseline confounders and excluding samples without matched pairs, the Dmab group still reduced the incidence of new-onset fractures, thereby confirming the robustness of the conclusion.

No significant variance in nonvertebral (hip or radius) fracture rates was observed across the two groups.

BMD and BTMs Levels at Month 12

At month 12, femoral neck BMD rose by 2.22% (95% CI = 1.38–3.07%) with Dmab versus 0.74% (95% CI = −0.12–1.60%) with ZOL (raw p = 0.021; FDR-adjusted p = 0.045) from baseline. At total hip, BMD rose by 1.24% (95% CI = 0.52–1.96%) with Dmab versus 0.30% (95% CI = −0.34–0.94%) with ZOL (raw p = 0.059; FDR-adjusted p =

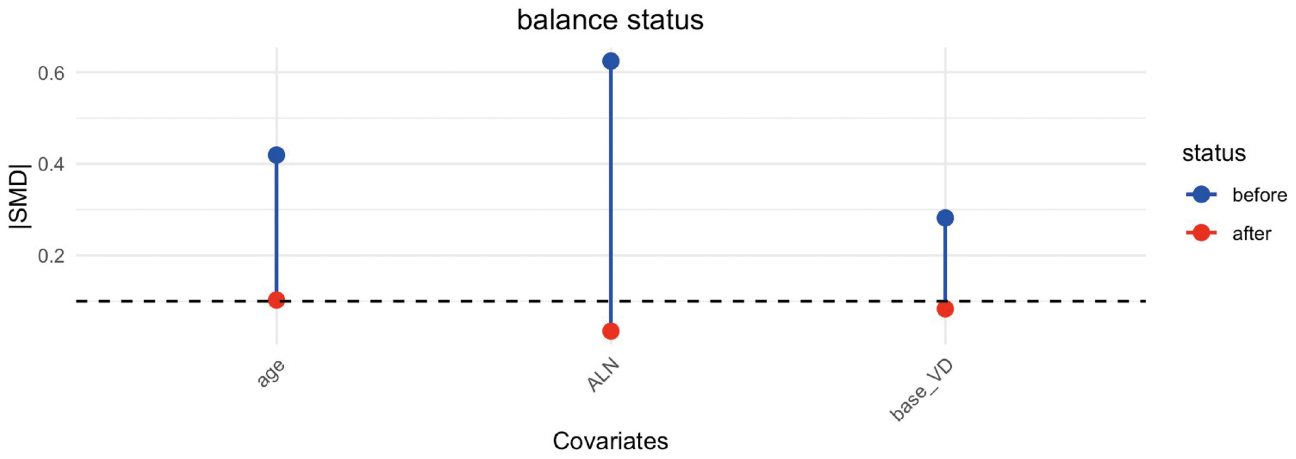


Figure 2 Covariate balance before and after propensity score matching. Absolute values of standardized mean differences (SMD) of covariates before and after propensity score matching. Age means age at baseline; ALN means duration of previous ALN therapy; base_VD means the level of 25(OH)D at baseline.

https://doi.org/10.2147/DDDT.S533224

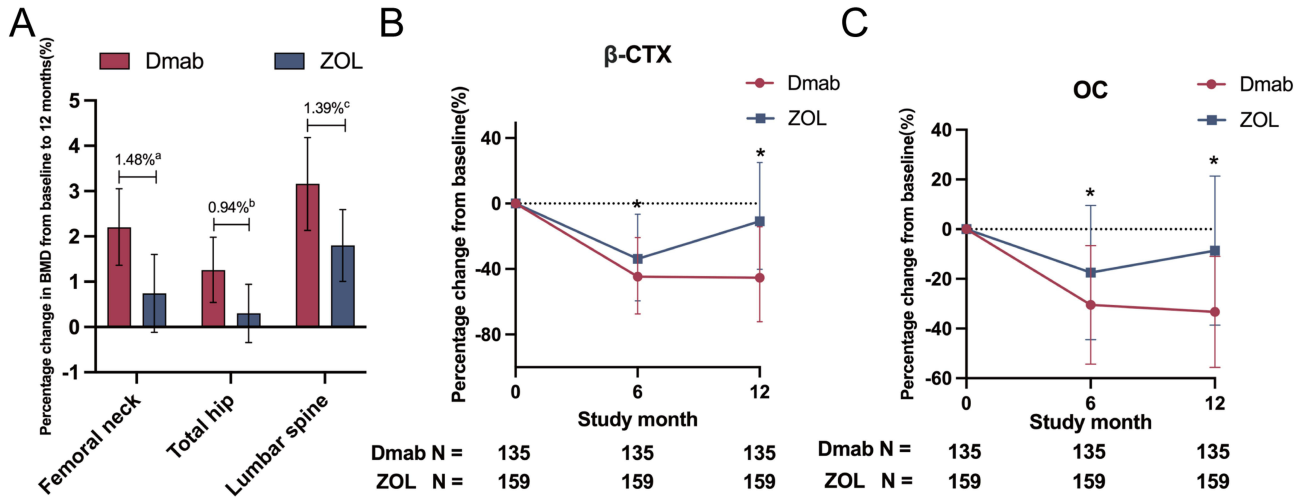


Figure 3 The percentage change in BMD and BTMs after 12 months of treatment. (**A**) Mean percentage change in BMD based on an analysis of multiple linear regression adjusted for age at baseline, duration of prior oral ALN treatment, baseline BMD value and baseline 25(OH)D. a, raw p value = 0.021, FDR-adjusted p value = 0.045; b, raw p value = 0.059, FDR-adjusted p value = 0.076; c, raw p value = 0.011, FDR-adjusted p value = 0.033; (**B**) percentage change in serum β-CTX, shown as medians and IQRs; * indicates raw p and FDR-adjusted p < 0.05. The raw p values and FDR-adjusted p values of the percentage change in serum β-CTX from baseline to month 6 and to month 12 were 0.014 (FDR-adjusted p: 0.024) and 0.001 (FDR-adjusted p = 0.002). (**C**) percentage change in the serum OC concentration shown as the mean and standard deviation; * indicates raw p and FDR-adjusted p < 0.05. The raw p values and FDR-adjusted p values of percentage change in serum OC from baseline to month 6 and to month 12 were 0.001 (FDR-adjusted p: 0.002).

0.076). L1-L4 BMD rose by 3.19% (95% CI = 2.17–4.22%) with Dmab versus 1.80% (95% CI = 1.01–2.59%) with ZOL (raw p= 0.011; FDR-adjusted p = 0.033) (Figure 3A).

The Dmab group's median percentage change in serum β-CTX from baseline was substantially higher than the ZOL group's at both month 6 (Dmab: −44.66%, IQR: −67.49%, −20.87% vs ZOL: −33.81%, IQR: −59.47%, −6.60%; raw p = 0.014; FDR-adjusted p = 0.024) and month 12 (Dmab: −45.31%, IQR: −72.20%, −14.19% vs ZOL: −10.83%, IQR: −40.21%, 25.11%; raw p < 0.001; FDR-adjusted p = 0.002). Similarly, in month 6 and 12, the Dmab group's OC levels were noticeably lower than those of the ZOL group (raw p < 0.001; FDR-adjusted p = 0.002) (Figure 3B and C).

According to the previously reported methodologies,[14] the serum β-CTX levels at baseline were stratified into tertiles (≤165pg/mL, >165pg/mL to 285pg/mL, and >285 pg/mL), revealing a positive correlation between β-CTX tertile categories and BMD improvement. The detailed information was presented in Figure 4. In the highest tertiles of baseline

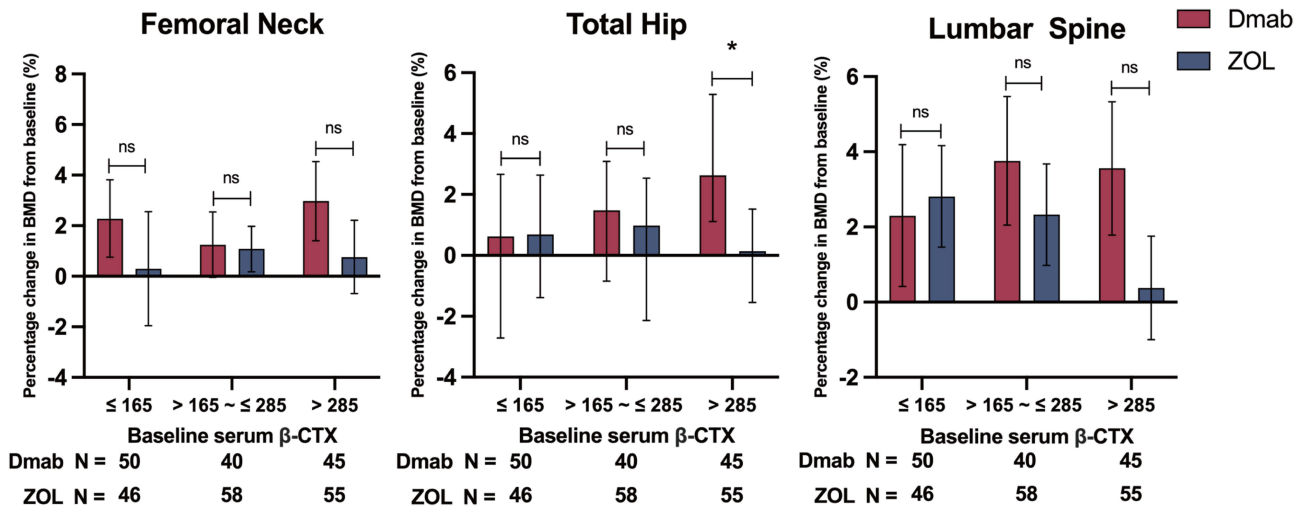


Figure 4 The percentage change in BMD from baseline to month 12 by baseline β-CTX. Mean percentage change in BMD based on an analysis of linear regression adjusted for age at baseline, duration of prior oral ALN treatment, baseline BMD value and baseline 25(OH)D. N = number of subjects with data. *indicates that the raw p and FDR-adjusted p < 0.05. The raw p value was 0.001 (FDR-adjusted p: 0.006) at total Hip in the highest tertiles of baseline β-CTX, respectively. ns means not significant.

β-CTX, compared with the ZOL group, BMD improved more in the Dmab group at total hip (raw $p < 0.001$; FDR-adjusted $p = 0.006$). Although, prior to FDR adjustment, the Dmab group demonstrated greater improvement in femoral neck and L1-L4 BMD than the ZOL group within the highest tertile of baseline β-CTX (raw p value = 0.029 and 0.038, respectively), this difference no longer attained statistical significance following FDR adjustment (FDR-adjusted p value = 0.087 and 0.201, respectively). In the lowest and middle tertiles of baseline β-CTX, the percentage change in BMD did not significantly differ between the two groups (Figure 4). The raw and FDR-adjusted p values are provided in Supplementary Table 2.

Relationship Between New-Onset Fractures and Changes in the Serum β-CTX Level

The potential risk factors of new-onset fractures were further explored. In the ZOL group, the incidence of new-onset fractures showed a trend of negative correlation with the percentage change in serum β-CTX level at month 12 ($r = -0.135$, $p = 0.089$). Nevertheless, no significant correlation was found between percentage change in serum OC from baseline to month 12 and the occurrence of fractures ($r = -0.104$, $p = 0.191$).

BMD and BTMs at Month 24

In this study, 111 subjects (46 in the Dmab group and 65 in the ZOL group) finished 24 months of treatment and completion of BMD and BTMs follow-up examination. The detailed baseline information of these 111 patients is summarized in Supplementary Table 6.

At month 24, the Dmab group's BMD at the femoral neck rose by 3.93% (95% CI = 2.11–5.75%) while the ZOL group's rose by 1.56% (95% CI = 0.52–2.61%) (raw $p = 0.031$; FDR-adjusted $p = 0.047$). The Dmab group's BMD at the total hip rose by 2.94% (95% CI = 1.58–4.31%) while the ZOL group's rose by 0.51% (95% CI = −0.39–1.40%) (raw $p = 0.002$; FDR-adjusted $p = 0.018$). At L1-L4, the Dmab group's BMD rose by 5.86% (95% CI = 4.17–7.56%) from baseline, while the ZOL group's rose by 3.50% (95% CI = 2.09–4.90%) (raw $p = 0.025$; FDR-adjusted $p = 0.045$) (Figure 5A).

At month 18, both groups presented a reduction in β-CTX levels from baseline, with values of −43.09% (−62.29%, −8.54%) in the Dmab group and −37.25% (−61.88%, −5.31%) in the ZOL group (raw $p = 0.881$; FDR-adjusted $p = 0.881$). At month 24, the Dmab group had a significantly greater reduction from baseline than did the ZOL group: −43.24% (−69.69%, 3.01%) and −17.45% (−47.72%, 29.61%) (raw $p = 0.018$; FDR-adjusted $p = 0.027$). The median percentage change in serum OC from baseline was substantially higher with Dmab than with ZOL at month 18 (raw $p = 0.028$; FDR-adjusted $p = 0.037$) and 24 (raw $p < 0.001$; FDR-adjusted $p = 0.002$) (Figure 5B–C).

Additionally, the Dmab group's percentage change in BMD at total hip was substantially larger than the ZOL group's in the highest tertiles of baseline β-CTX (Dmab: 5.18% vs ZOL: 1.30%, raw $p = 0.002$; FDR-adjusted $p = 0.006$) (Supplementary Figure 2). Although, prior to FDR adjustment, the Dmab group demonstrated greater improvement in femoral neck than the ZOL group within the lowest tertile of baseline β-CTX (raw p value = 0.021), this difference no longer attained statistical significance following FDR adjustment (FDR-adjusted p value = 0.087). The raw and FDR-adjusted p values are provided in Supplementary Table 2.

Adverse Event

The adverse events monitored in this study included hypocalcemia, osteonecrosis of the jaw and atypical fractures. No patients experienced these adverse events by the end of the study.

Discussion

The first-line medication for treating primary osteoporosis is oral ALN. However, the therapeutic benefit is impacted due to the low adherence to oral ALN.[15,16] In addition, Erik A. Imel reported that, despite BP adherence, 35% of patients experienced new-onset fractures or a decline in BMD, and 7% of patients experienced incident osteoporotic fractures during treatment. For better osteoporosis therapy, alternate therapy is a feasible approach for patients.[17] ZOL and Dmab, as antiresorptive drugs, are important choices for transitioned treatment after oral BPs.

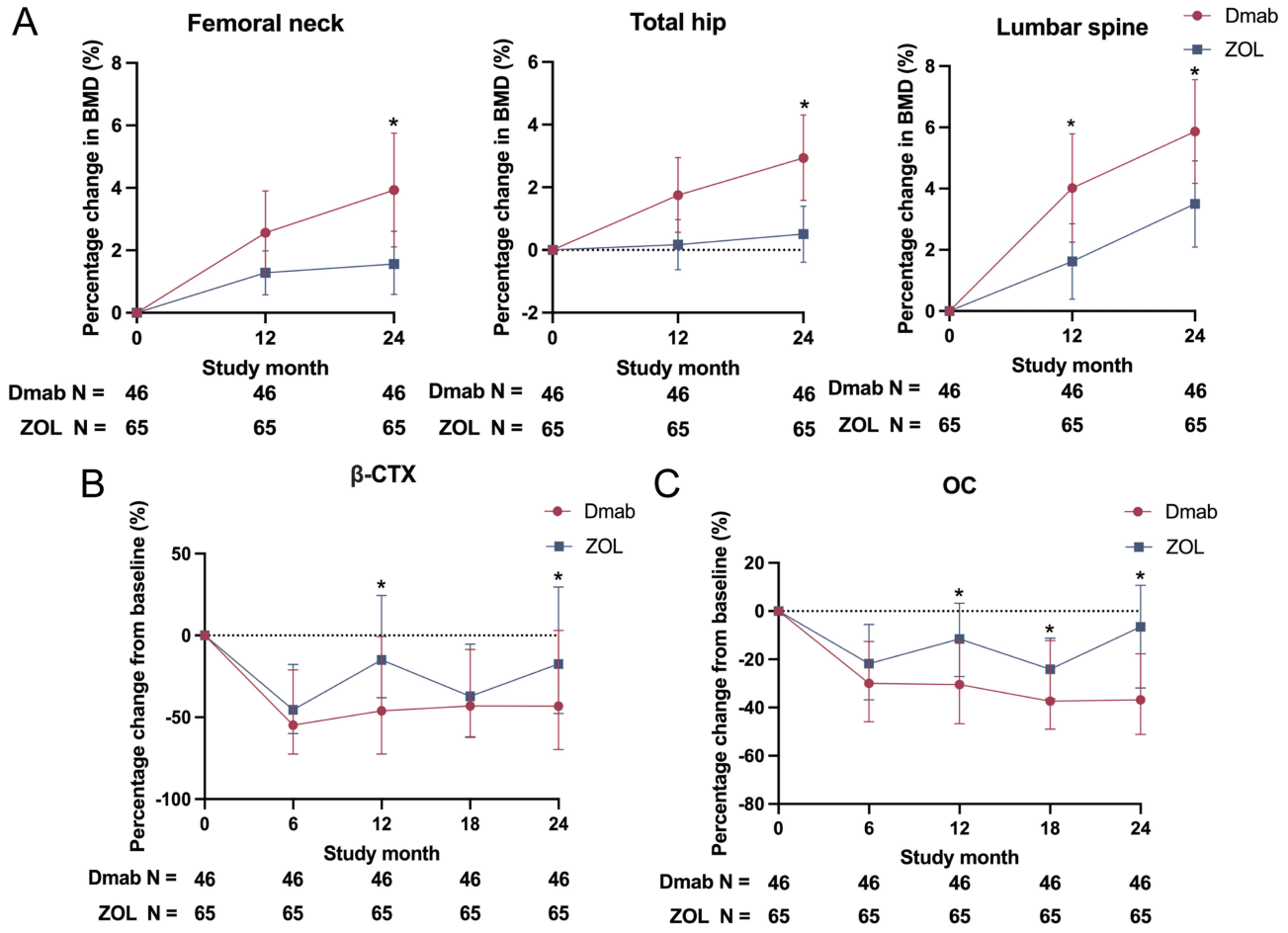


Figure 5 The percentage change in BMD and BTMs from baseline to month 24. (**A**) Mean percentage change in BMD based on an analysis of multiple linear regression adjusted for age at baseline, duration of prior oral ALN treatment, baseline BMD value and baseline 25(OH)D, * means raw p and FDR-adjusted p < 0.05. The raw p value of percentage change in femoral neck and total Hip from baseline to month 24 were 0.031 (FDR-adjusted p value: 0.047) and 0.002 (FDR-adjusted p values: 0.018), respectively. The raw p value of percentage change in L1-L4 from baseline to month 12 and to 24 were 0.009 (FDR-adjusted p values: 0.033) and 0.025 (FDR-adjusted p values: 0.045), respectively. (**B** and **C**) Percentage change in serum β-CTX and OC levels shown as medians and IQRs; *means raw p and FDR-adjusted p < 0.05. The raw p values and FDR-adjusted p values of percentage change in β-CTX from baseline to month 12 and to month 24 were 0.001 (FDR-adjusted p: 0.002) and 0.018 (FDR-adjusted p: 0.027). The raw p values and FDR-adjusted p values of percentage change in OC from baseline to month 12, to month 18 and to month 24 were 0.001 (FDR-adjusted p: 0.002), 0.028 (FDR-adjusted p: 0.037) and 0.001 (FDR-adjusted p: 0.002).

The effectiveness and adverse consequences of Dmab and BPs in PMOP women who had prior oral ALN have been compared in a number of trials.[9,10,14,18,19] Compared with other BPs treatments, one year of Dmab treatment resulted in a larger rise in BMD and more BTM inhibition. However, none of these studies included a formal assessment of osteoporotic fractures, which may have resulted in a lower fracture incidence. Our research demonstrated that switching from oral ALN to Dmab is linked to a decreased incidence of new-onset fractures, greater skeletal benefits, and decreased BTMs, irrespective of how long the previous ALN treatment lasted. Compared to the ZOL group, the Dmab group experienced fewer new-onset fractures (Dmab: 3.79% vs ZOL: 10.39%). Furthermore, the Dmab group experienced fewer vertebral fractures than the ZOL group (Dmab: 1.52% vs ZOL: 8.44%). Two subjects who received ZOL treatment suffered femoral neck fractures and were treated surgically; however, no subjects in the Dmab group experienced hip fractures. Table 4 shows the comparison of our study and previous studies.

BMD changes are crucial for estimating the risk of fracture.[20,21] Anti-osteoporosis treatment can improve BMD and decrease fracture risk.[22,23] In our study, the BMD percentage changes in the Dmab group had a greater increase during treatment than in the ZOL group. Additionally, the Dmab group experienced fewer new-onset fractures than the ZOL group, particularly in the vertebral spine. This could suggest that higher BMD is linked to fewer new-onset fractures.

Table 4 Studies of Efficacy of Bisphosphonate or Denosumab Previously Treated with Oral Alendronate

	Study Design	Anti-Resorptive Drugs	Primary Endpoint	Observed Duration	Results for Primary Endpoint
David L Kendler et al[18]	RCT	ALN vs Dmab	Change in total hip BMD from baseline to month 12	1Y	BMD in total hip in Dmab and continued ALN increased by 1.9% and 1.05% ($p < 0.0001$)
Chris Recknor et al[19]	Open-label study	Ibandronate vs Dmab	Change in BMD from baseline to month 12 for total hip	1Y	BMD in total hip in Dmab and ibandronate increased by 2.3% and 1.1% ($p < 0.0001$)
C. Roux et al[14]	Open-label study	Risedronate vs Dmab	Change from baseline in total hip BMD	1Y	BMD in total hip in Dmab and risedronate increased by 2.0% and 0.5% ($p < 0.0001$)
P D Miller et al[9]	RCT	ZOL vs Dmab	Change from baseline in lumbar spine	1Y	BMD in total hip in denosumab and zoledronic acid increased by 3.2% and 1.1% ($p < 0.0001$)
P D Miller et al[10]	Pooled study	Dmab vs bisphosphonate	Change from baseline in all skeletal sites	1Y	BMD had a better increase in all skeletal sites in Dmab
Current study	Real-world study	ZOL vs Dmab	Newly-onset fractures	2Y	Incidences of newly-onset fractures in denosumab and ZOL were 3.79% and 10.39% (raw $p = 0.028$; FDR-adjusted $p = 0.028$)

Abbreviations: ALN, alendronate; Dmab, denosumab; ZOL, zoledronate.

β-CTX and OC are two bone turnover indicators that reflect bone remodelling and the therapeutic effect of anti-osteoporosis treatment. Michael McClung et al reported that the levels of BTMs increased after ALN treatment followed by ZOL, which means that ZOL cannot inhibit bone remodelling.[24] Several studies indicated a correlation between elevated serum β-CTX levels and an increased likelihood of fractures.[25–27] In the SABRE study, Bauer DC et al reported that the reduction of fracture risk is strongly predicted by both the baseline BTM and the change in BTM.[28,29] In our study, the percentage change (from baseline to month 12) of serum β-CTX had a negative trend to the occurrence of new-onset fracture. This finding implied that a higher prevalence of new-onset fractures might be linked to elevated BTMs.

In this study, the Dmab group showed more significant improvement of BMD during treatment. We further assessed BMD variations stratified by baseline β-CTX levels. Baseline β-CTX levels were divided into tertiles. In the highest tertile of β-CTX, the Dmab group showed greater increases of BMD at all skeletal sites than the ZOL group at month 12 and a greater improvement at total hip in Dmab group at month 24. Shengli Zhao et al found that declining serum BTMs are linked to the increase BMD in lumbar spine in postmenopausal women.[30] As a bone resorption marker, a significant change in β-CTX level after treatment for osteoporosis reflects effectiveness of treatment.[31,32] Some studies showed that Dmab effectively suppresses β-CTX and bone remodeling regardless of whether it is used sequentially with antiresorptive agents, sequentially with teriparatide, or treatment naive.[10,33] Therefore, we suggest that when transitioning from oral ALN to either Dmab or ZOL, the choice of agents can be guided by baseline β-CTX levels.

Our research had several obvious advantages. First, this is the first retrospective cohort study in China to compare the efficacy of Dmab or ZOL in PMOP patients previously who have previously received oral ALN. Preventing osteoporotic fractures is the aim of osteoporosis treatment. Few trials, nevertheless, have evaluated the overall efficacy of switching anti-osteoporosis medications in reducing the incidence of new-onset fractures. In this study, we analysed the incidence of new-onset fractures after two different transition treatments and reported that oral ALN followed by Dmab was an effective treatment strategy for PMOP. Second, in order to ascertain the long-term effectiveness of ZOL and Dmab, this study also examined the changes in BMD and BTMs during prolonged treatment.

Like all studies, this study has several limitations. Although our retrospective cohort study suggested that patients who transitioned from ALN to Dmab experienced fewer new-onset fractures than those who switched to ZOL, this study is a small sample single-center retrospective study, and the duration of oral ALN treatment, the age and the serum level of 25(OH)D at baseline were not balanced between two groups, it is essential to confirm in large-sample prospective cohort studies. Future studies could focus on different study populations to improve the generalizability of the findings.

Conclusion

According to this retrospective cohort study, patients with PMOP may derive greater benefit from switching from oral ALN to DMab than to ZOL. This is attributed to the fact that Dmab not only increases BMD but also reduces the risk of new-onset fractures. Dmab may represent a preferential strategy for optimizing clinical outcomes in sequential anti-osteoporosis treatment protocols for PMOP patients.

Ethical Approval

This study was approved by the Ethics Committee of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (2023-KY-093).

Acknowledgments

We thank all the participants of this study and the staff of the laboratory and information department of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine for their technical assistance and information service.

Funding

This work was supported by the National Key R&D Program of China (2021YFC2501705), the National Natural Science Foundation of China (NFSC) (82070903) to C. Wang and the National Natural Science Foundation of China (NFSC) (82270933) to JM, Gu.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med*. 1993;94(6):646–650. doi:10.1016/0002-9343(93)90218-e
2. Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy N. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785–795. doi:10.1001/jama.285.6.785
3. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. *Mayo Clin Proc*. 2005;80(7):856–861. doi:10.4065/80.7.856
4. Doshi KB, Khan LZ. Should bone turnover markers be used routinely to monitor oral bisphosphonate osteoporosis therapy? Yes: measuring adherence and effectiveness of therapy benefits patients. *Am Fam Physician*. 2023;108(5):442–443.
5. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809–1822. doi:10.1056/NEJMoa067312
6. Räkel A, Boucher A, Ste-Marie LG. Role of zoledronic acid in the prevention and treatment of osteoporosis. *Clin Interv Aging*. 2011;6:89–99. doi:10.2147/cia.S7282
7. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756–765. doi:10.1056/NEJMoa0809493
8. Diab DL, Watts NB. Denosumab in osteoporosis. *Expert Opin Drug Saf*. 2014;13(2):247–253. doi:10.1517/14740338.2014.860133
9. Miller PD, Pannacciulli N, Brown JP, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J Clin Endocrinol Metab*. 2016;101(8):3163–3170. doi:10.1210/jc.2016-1801
10. Miller PD, Pannacciulli N, Malouf-Sierra J, et al. Efficacy and safety of denosumab vs. bisphosphonates in postmenopausal women previously treated with oral bisphosphonates. *Osteoporos Int*. 2020;31(1):181–191. doi:10.1007/s00198-019-05233-x
11. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8(9):1137–1148. doi:10.1002/jbmr.5650080915
12. Parker M, Johansen A. Hip fracture. *BMJ*. 2006;333(7557):27–30. doi:10.1136/bmj.333.7557.27
13. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for bone and mineral research. *J Bone Miner Res*. 2014;29(1):1–23. doi:10.1002/jbmr.1998
14. Roux C, Hofbauer LC, Ho PR, et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. *Bone*. 2014;58:48–54. doi:10.1016/j.bone.2013.10.006
15. Narayanasamy M, Bishop S, Sahota O, Paskins Z, Gittoes N, Langley T. Acceptability and engagement amongst patients on oral and intravenous bisphosphonates for the treatment of osteoporosis in older adults. *Age Ageing*. 2022;51(11). doi:10.1093/ageing/afac255
16. Rabenda V, Vanoverloop J, Fabri V, et al. Low incidence of anti-osteoporosis treatment after Hip fracture. *J Bone Joint Surg Am*. 2008;90(10):2142–2148. doi:10.2106/jbjs.G.00864
17. Imel EA, Eckert G, Modi A, et al. Proportion of osteoporotic women remaining at risk for fracture despite adherence to oral bisphosphonates. *Bone*. 2016;83:267–275. doi:10.1016/j.bone.2015.11.021
18. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res*. 2010;25(1):72–81. doi:10.1359/jbmr.090716
19. Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol*. 2013;121(6):1291–1299. doi:10.1097/AOG.0b013e318291718c
20. Berger C, Langsetmo L, Joseph L, et al. Association between change in BMD and fragility fracture in women and men. *J Bone Miner Res*. 2009;24(2):361–370. doi:10.1359/jbmr.081004
21. Nguyen TV, Center JR, Eisman JA. Femoral neck bone loss predicts fracture risk independent of baseline BMD. *J Bone Miner Res*. 2005;20(7):1195–1201. doi:10.1359/jbmr.050215
22. Cummings SR. How drugs decrease fracture risk: lessons from trials. *J Musculoskelet Neuronal Interact*. 2002;2(3):198–200.
23. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417–1427. doi:10.1056/NEJMoa1708322
24. McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*. 2007;41(1):122–128. doi:10.1016/j.bone.2007.03.011
25. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. *J Bone Miner Res*. 2000;15(8):1526–1536. doi:10.1359/jbmr.2000.15.8.1526
26. Vasikaran S, Eastell R, Bruyère O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int*. 2011;22(2):391–420. doi:10.1007/s00198-010-1501-1
27. Gerdhem P, Ivaska KK, Alatalo SL, et al. Biochemical markers of bone metabolism and prediction of fracture in elderly women. *J Bone Miner Res*. 2004;19(3):386–393. doi:10.1359/jbmr.0301244
28. Bauer DC, Black DM, Bouxsein ML, et al. Treatment-related changes in bone turnover and fracture risk reduction in clinical trials of anti-resorptive drugs: a meta-regression. *J Bone Miner Res*. 2018;33(4):634–642. doi:10.1002/jbmr.3355
29. Black DM, Bauer DC, Vittinghoff E, et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. *Lancet Diabetes Endocrinol*. 2020;8(8):672–682. doi:10.1016/s2213-8587(20)30159-5
30. Zhao S, Mo X, Wen Z, et al. Declining serum bone turnover markers are associated with the short-term positive change of lumbar spine bone mineral density in postmenopausal women. *Menopause*. 2022;29(3):335–343. doi:10.1097/gme.0000000000001920
31. Eastell R, Pigott T, Gossiel F, Naylor KE, Walsh JS, Peel NFA. DIAGNOSIS OF ENDOCRINE DISEASE: bone turnover markers: are they clinically useful? *Eur J Endocrinol*. 2018;178(1):R19–r31. doi:10.1530/eje-17-0585

32. Lorentzon M, Branco J, Brandi ML, et al. Algorithm for the use of biochemical markers of bone turnover in the diagnosis, assessment and follow-up of treatment for osteoporosis. *Adv Ther*. 2019;36(10):2811–2824. doi:10.1007/s12325-019-01063-9
33. Tsourdi E, Makras P, Rachner TD, et al. Denosumab effects on bone density and turnover in postmenopausal women with low bone mass with or without previous treatment. *Bone*. 2019;120:44–49. doi:10.1016/j.bone.2018.10.001