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Comparison of Denosumab and Zoledronic Acid in Postmenopausal Women With Osteoporosis: Bone Mineral Density (BMD) and Trabecular Bone Score (TBS)

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ABSTRACT

Background: Denosumab (DEN) and zoledronic acid (ZOL) currently represent the most potent antiresorptive agents for the treatment of osteoporosis. Despite similar effects on bone resorption, these agents have distinct mechanisms of action. The objective of this study was to compare the effect of DEN and ZOL after two-year administration on bone mineral density (BMD), trabecular bone score (TBS), bone turnover markers, and persistence.
Methods: A total of 585 postmenopausal women with osteoporosis who did not use osteoporosis medications were retrospectively reviewed. 290 patients were administered 60 mg DEN subcutaneously every 6 months from 2017 to 2018, and 295 patients were treated with 5 mg ZOL intravenously yearly from 2015 to 2017. BMD, TBS, and C-terminal cross-linking telopeptide of type 1 collagen (CTX) measurements were obtained at baseline and two-year after DEN injection or ZOL infusion.
Results: After two-year follow-up, 188 patients in the DEN group and 183 patients in the ZOL group were compared. BMD change from baseline at two years was significantly greater in the DEN group compared with the ZOL group ($P < 0.001$). The changes of TBS in the DEN group were statistically significant compared with baseline ($P < 0.001$) and the ZOL group ($P < 0.001$). The DEN group led to significantly greater reduction of CTX compared with ZOL group ($P = 0.041$).
Conclusion: In postmenopausal women with osteoporosis, DEN was associated with greater BMD increase at all measured skeletal sites, greater increase of TBS, and greater inhibition of bone remodeling compared with ZOL.

Keywords: Osteoporosis; Denosumab; Zoledronic Acid

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and deteriorated bone structure, resulting in decreased bone strength and increased risk of fractures.[1] The purpose of osteoporosis treatment is to increase bone mass by changing the balance of osteoblast and osteoclast in bone remodeling. Antiresorptive agents are the main treatment options for the prevention and treatment of osteoporosis. Denosumab (DEN)

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Park SY. Data curation: Kang T, Lee SH. Formal analysis: Park SY. Investigation: Kang T, Lee SH. Methodology: Kang T, Park JH. Project administration: Suh SW, Park JH. Supervision: Park JH, Suh SW. Validation: Lee SH, Park SY. Visualization: Park SY. Writing - original draft: Kang T. Writing - review & editing: Kang T, Park SY.

and zoledronic acid (ZOL) currently represent the most potent antiresorptive agents, and these agents have proven to be effective treatments for osteoporosis.[2,3] Thus, these agents significantly reduce bone turnover markers (BTMs), increase BMD, and reduce risk for fracture.[2-6] Despite similar effects on bone resorption, the agents have distinct mechanisms of action.[7]

ZOL, a third-generation aminobisphosphonate drug, is administered intravenously at a dosage of 5 mg every 12 months and is the strongest of clinically available bisphosphonates. ZOL has a high binding affinity for bone mineral and effects its antiresorptive action by inhibition of farnesyl pyrophosphate synthase enzyme.[8] ZOL treatment has been shown to increase BMD and reduce the risk of fractures at all skeletal sites.[2]

DEN is a fully human monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL), a major mediator of osteoclast differentiation, activation, and survival. DEN inhibits osteoclast formation and survival by interfering with the binding of RANKL.[9] DEN is administered subcutaneously at a dosage of 60 mg every 6 months. DEN inhibited bone resorption and remodeling as measured by reducing BTMs, increasing BMD in all measured skeletal sites, and reducing the risk of fractures.[3,10]

Although BMD is informative and useful, BMD does not reflect bone microarchitecture which is also an important factor in fragility fractures.[11] The trabecular bone score (TBS) is a new gray-level texture measurement. TBS uses two-dimensional scans obtained during routine dual-energy X-ray absorptiometry (DXA) and variograms to characterize the three-dimensional rate of gray-level amplitude variations in the bone.[12-15] Higher scores reflect more robust and fracture-resistant microarchitecture, while lower scores indicate weaker bone more susceptible to fracture.[12,15] TBS has been shown to be highly related to the direct measurement of bone microarchitecture and predicts current and future fragility fractures in postmenopausal women with osteoporosis.[12,13,16,17] Furthermore, the TBS was changed in response to therapeutic effects on antiresorptive drugs.[18,19]

Persistence is important for improving outcomes for patients with osteoporosis. It is widely recognized that persistence is critical for optimal outcomes.[20-23] Several studies have shown low persistence with osteoporosis treatment, and poor persistence has been reported as significantly increasing the risk of fracture, morbidity, and mortality.[24-27] Long dosing intervals and injectable medications may contribute to better persistence possibly improving clinical outcomes.[20,21,27,28]

To best of our knowledge, no study has directly compared the effect of DEN and ZOL treatment in naïve postmenopausal women with osteoporosis in terms of BMD, TBS, BTMs, and persistence. The primary outcome of our study was to compare the effect after two-year administration of DEN and ZOL on BMD and TBS in postmenopausal women with osteoporosis. Secondary outcomes were to compare their effect on BTMs and persistence.

MATERIALS AND METHODS

Study design

We hypothesized DEN had greater effect than ZOL on BMD at all skeletal sites, TBS, as well as effecting rapid reduction in bone turnover.

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A total of 585 postmenopausal women with osteoporosis who did not use osteoporosis medications were retrospectively analyzed. All patients during the study period were treated with either DEN or ZOL. During this period, no patients were treated with other medications. Patients who had taken drugs that could affect bone metabolism such as systemic glucocorticoid or hormone replacement were excluded.

As the DEN group, 290 patients were reviewed from March 2017 to December 2018 and were administered 60 mg subcutaneously every 6 months. We reviewed 295 patients from January 2015 to February 2017 as the ZOL group. These patients were treated with 5 mg ZOL intravenously once yearly (**Fig. 1**). As DEN was first introduced in March 2017 in our country, all naïve osteoporotic patients were treated with DEN after March 2017. From 2015 to February 2017, all naïve osteoporotic patients were treated with ZOL. These patients were followed up for 2 years, we included administration for a period of 1 month before and after the exact period.

BMD, TBS, osteocalcin, and C-terminal cross-linking telopeptide of type 1 collagen (CTX) measurements were obtained at baseline, one, and two years after DEN injection or ZOL infusion and were compared. Endpoints and analyses included the percentages of patients who persisted with DEN and ZOL at two years; the changes in BMD, TBS, osteocalcin, and CTX in persisted patients; and the incidence of adverse events and fractures.

BMD was measured by Hologic DXA bone densitometers. BMD measurements were recorded at the lumbar spine for L1 through L4, femoral neck, and total hip. TBS measurement was performed using software (TBS iNsight Software, Version 2.2; Med-Imaps, Pessac, France) on lumbar spine DXA scans. TBS was calculated as the average of individual measurements for the L1–L4 vertebrae, excluding the vertebrae not included in the BMD assessments due

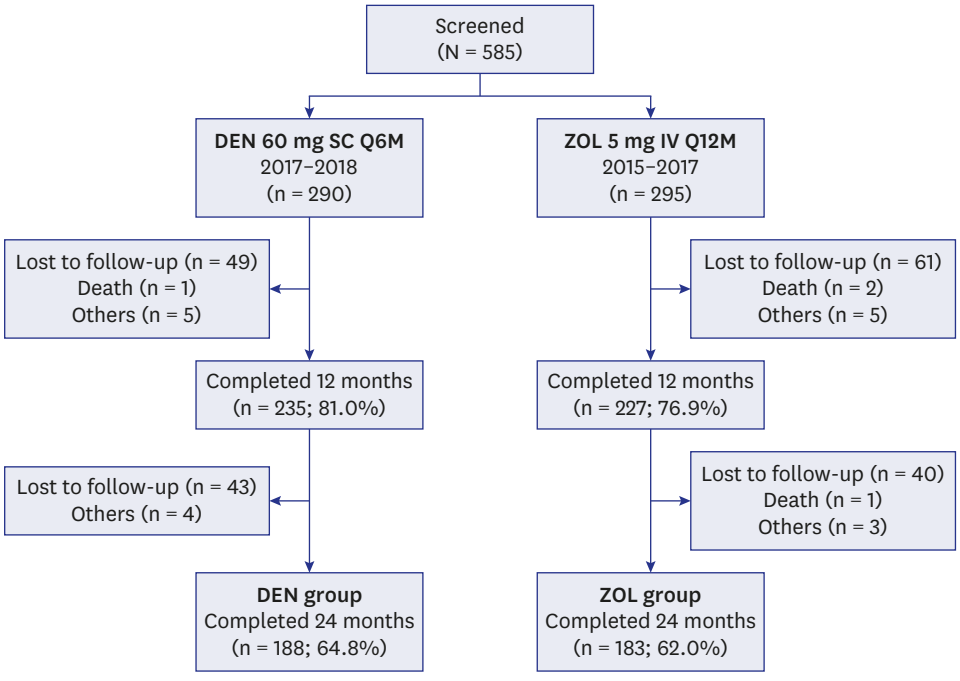

Fig. 1. Trial profile. Among 290 patients of DEN group and 295 patients of ZOL group, a total of 188 patients in DEN group and 183 patients in ZOL group were analyzed after two-year follow-up.
DEN = denosumab, ZOL = zoledronic acid, SC = subcutaneous, IV = intravenous, Q6M = every 6 months, Q12M = every 12 months.

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to fracture or artifact. The coefficient of variance (CV) of BMD and lumbar spine TBS was 1% and 1.1%, respectively.

For biochemical markers, osteocalcin and CTX levels were evaluated. The samples were obtained in overnight fasting status during the morning to minimize diurnal variations. Osteocalcin level was measured by automated immunoassay (Elecsys β-CrossLaps; Roche Diagnostics, Mannheim, Germany; intraassay CV < 4.0%, interassay CV < 6.5%). CTX level was measured by automated immunoassay (Elecsys β-CrossLaps; Roche Diagnostics; intraassay CV < 3.5%, interassay CV < 8.4%).

Persistence was measured at 12 and 24 months after the initial date and was defined as remaining for each subsequent period.

Statistical analysis

Data for continuous variables are expressed as mean ± standard error of the mean. For categorical variables, a χ^2 test was used for between group comparisons. Independent *t*-test and Mann-Whitney *U* test were used to test the difference between groups for continuous variables. The change of BMD and TBS from the baseline was calculated as the absolute change and was divided by the baseline value for expression as percentages. The level of significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS Statistics software Version 20.0 (IBM, Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Review Board of Korea University Anam Hospital (2020AN0179), and informed consent was waived because this study reviewed pre-existing data.

RESULTS

Baseline data

Age, body mass index (BMI), smoking history and comorbidity using American Society of Anesthesiologists (ASA) classification were not significantly different between the two groups (**Table 1**). The mean age of the DEN group was 71.5 ± 8.93 years and that of the ZOL group was 73.9 ± 8.39 years. The mean BMI of the DEN group was 23.7 ± 4.3 kg/m^2 and that of the ZOL group was 23.9 ± 3.8 kg/m^2. BMI remained essentially unchanged throughout the study in both groups. Seven patients in the DEN group and 10 patients in the ZOL group had a history of smoking.

The mean BMD of the DEN group was −2.53 ± 1.15 in the lumbar spine and −3.03 ± 0.66 in the total hip; those of the ZOL group were not significantly different, −2.56 ± 1.17 in the lumbar spine and −3.02 ± 0.72 in the total hip. The mean TBS level was not significantly different between the two groups (1.27 ± 0.08 vs. 1.25 ± 0.10 ng/mL). The serum osteocalcin level was not significantly different between the two groups (49.2 ± 20.5 vs. 47.6 ± 29.9 ng/mL). The serum CTX level was not significantly different between the two groups (0.629 ± 0.214 vs. 0.611 ± 0.229 ng/mL). The serum vitamin D level was not significantly different between the two groups (22.8 ± 3.2 vs. 23.8 ± 3.7 ng/mL). The serum creatinine level was not significantly different between the two groups (0.79 ± 0.21 vs. 0.83 ± 0.22 mg/dL). The serum parathyroid hormone level was not significantly different between the two groups (38.4 ± 2.5 vs. 36.6 ± 2.7 ng/mL). The serum calcium level was not significantly different between the two groups (9.84 ± 0.81 vs. 9.63 ± 0.76 mg/dL).

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Table 1. Demographic data

Characteristics	DEN (n = 188)	ZOL (n = 183)	*P* value
Age, yr	71.5 ± 8.93	73.9 ± 8.39	0.464
BMI, kg/m^2	23.7 ± 4.3	23.9 ± 3.8	0.246
Smoking	7	10	0.588
ASA classification (1-2-3)	109-60-19	103-62-17	0.437
BMD (t-score)			0.224
Spine	−2.53 ± 1.15	−2.56 ± 1.17	
Hip	−3.03 ± 0.66	−3.02 ± 0.72	
Femoral neck	−2.87 ± 0.72	−2.83 ± 0.77	
TBS	1.27 ± 0.08	1.25 ± 0.10	0.299
CTX, ng/mL	0.629	0.611	0.126
Osteocalcin, ng/mL	49.2	47.6	0.228
Calcium, mg/dL	9.84 ± 0.81	9.63 ± 0.76	0.386
Vitamin D, ng/mL	22.8 ± 3.2	23.8 ± 3.7	0.284
PTH, ng/mL	38.3 ± 2.4	36.6 ± 2.7	0.275
Creatinine, mg/dL	0.79 ± 0.21	0.83 ± 0.22	0.311
Previous fracture	12	13	0.201

DEN = denosumab, ZOL = zoledronic acid, BMI = body mass index, ASA = American Society of Anesthesiologists, BMD = bone mineral density, TBS = trabecular bone score, CTX = C-terminal cross-linking telopeptide of type 1 collagen, PTH = parathyroid hormone.

Clinical data

Clinical data at two-year follow-up is shown in **Table 2**.

BMD increased progressively from baseline at one- and two-year follow-up in both groups. BMD change from baseline at one year was significantly greater in the DEN group compared with the ZOL group at the lumbar spine (4.45 ± 0.9% vs. 3.41 ± 0.6%; $P < 0.001$), total hip (2.56 ± 0.7% vs. 2.04 ± 0.5%; $P < 0.001$), and femoral neck (3.12 ± 0.7% vs. 2.17 ± 0.4%; $P < 0.001$). BMD change from baseline at two years was also significantly greater in the DEN group compared with the ZOL group at the lumbar spine (9.74 ± 1.1% vs. 6.05 ± 0.9%; $P < 0.001$), total hip (3.85 ± 0.9% vs. 3.14 ± 0.4%; $P < 0.001$), and femoral neck (5.22 ± 0.8% vs. 3.86 ± 0.5%; $P < 0.001$) (**Fig. 2**).

In the DEN group, progressive increases from baseline at one- and two-year follow-up were observed for TBS (mean increases of 1.47 ± 0.6% and 2.51 ± 0.5%, respectively). In the ZOL group, TBS changes from baseline at one- and two-year follow-up were as shown (mean increases of −0.54 ± 0.2% and 0.12 ± 0.2%, respectively) (**Fig. 2**). The changes in TBS in the DEN group were statistically significant compared with baseline ($P < 0.001$) and the ZOL group ($P < 0.001$).

Table 2. Clinical outcomes after 2 years follow-up

Characteristics	DEN (n = 188)	ZOL (n = 183)	*P* value
BMD (t-score)			
Spine (% change)	−2.11 ± 1.15 (9.74 ± 1.1)	−2.33 ± 1.22 (6.05 ± 0.9)	
Hip (% change)	−2.88 ± 0.64 (3.85 ± 0.9)	−2.89 ± 0.78 (3.14 ± 0.4)	
Femoral neck (% change)	−2.67 ± 0.66 (5.22 ± 0.8)	−2.70 ± 0.71 (3.86 ± 0.5)	
TBS	1.28 ± 0.07	1.25 ± 0.07	0.182
CTX, ng/mL	0.193	0.251	0.041
Osteocalcin, ng/mL	22.1	25.2	0.002
Fracture	2	2	0.421
Adverse events	1	2	0.344

DEN = denosumab, ZOL = zoledronic acid, BMD = bone mineral density, TBS = trabecular bone score, CTX = C-terminal cross-linking telopeptide of type 1 collagen.

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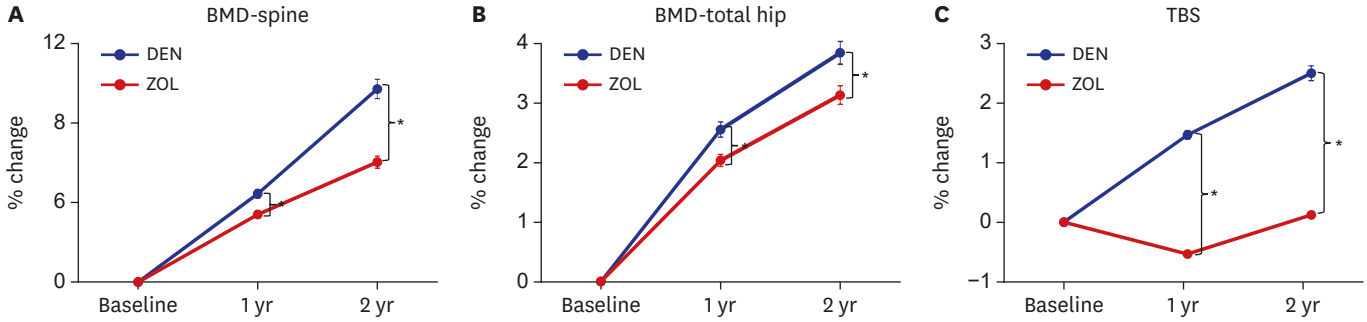

Fig. 2. Mean percentage change from baseline at one- and two-year follow-up in BMD at the (**A**) lumbar spine, (**B**) total hip, (**C**) femoral neck, and (**D**) TBS.
BMD = bone mineral density, TBS = trabecular bone score, DEN = denosumab, ZOL = zoledronic acid.
*$P < 0.001$.

CTX was reduced in both the DEN and ZOL groups. In the DEN group, CTX decreased to 0.178 ng/mL and 0.193 ng/mL at one- and two-year follow-up, respectively. In the ZOL group, CTX decreased to 0.225 ng/mL and 0.251 ng/mL at one- and two-year follow-up, respectively. The DEN group had a significantly greater reduction of CTX compared with the ZOL group ($P = 0.041$). The changes of CTX in both groups were statistically significant from baseline ($P < 0.001$).

There was no statistically significant difference between the two groups in terms of fracture risk and adverse events. Two patients in each group developed new osteoporotic fractures within the two-year follow-up period. One patient in the DEN group reported transient erythema in the injection site. Two patients in the ZOL group experienced an acute phase flu-like symptom. There was no serious adverse effect in either group.

Twenty-four-month persistence

The patients receiving DEN (every 6 months dosing frequency) had higher rates of persistence than the patients receiving ZOL (yearly dosing frequency). One-year persistence was 81.0% (235/290) in the DEN group and 76.9% (227/295) in the ZOL group. Two-year persistence was 64.8% (188/290) in the DEN group and 62.0% (183/295) in the ZOL group. There was no statistically significant difference between the two groups in terms of persistence. There was no significant difference in clinical characteristics between the patients who completed and not completed 2 years follow-up.

DISCUSSION

The purpose of this study was to compare the effect after two-year administration of DEN and ZOL on BMD, TBS, BTMs, and persistence. DEN and ZOL increased BMD by reducing osteoclastic bone resorption, but the mechanism of action and pharmacodynamic profiles of these agents are different. In postmenopausal women with osteoporosis, DEN was associated with greater BMD increase at all measured skeletal sites, greater increase of TBS, greater inhibition of bone remodeling, and higher persistence compared with ZOL after two-year administration.

TBS is a novel tool for assessing fracture risk in postmenopausal women.[29] TBS which is derived from lumbar spine DXA scans, provides information about bone microarchitecture and future fracture risk, helping physicians identify patients at risk of fracture.[29] TBS has also been shown to reflect the effects on the treatment of osteoporosis and may help monitor treatment effectiveness.[18,19] Changes in TBS appear to be affected by the type of osteoporosis

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treatment. TBS may be considered useful as an additional tool in routine clinical practice for noninvasively evaluating bone microarchitecture.[30]

In this study, DEN showed a more marked improvement in TBS than ZOL at each annual assessment. Our results were consistent with previous studies which have evaluated DEN and ZOL individually. McClung et al.[30] have reported that DEN showed significant progressive improvement of TBS independently of BMD (mean increase of 1.4%, 1.9%, and 2.4% in each of three consecutive years). Popp et al.[19] have reported the changes of TBS with yearly administrated ZOL (0.03%, 1.11%, and 1.41% in each of three consecutive years). Changes in TBS were significantly greater as of month 24 (P = 0.049). Sato et al. reported a significant increase of TBS in alendronate (1.4%), DEN (2.8%), and teriparatide (3.6%) treated groups after 24 months. Senn et al.[31] have reported greater improvement in TBS with teriparatide compared with ibandronate.

In this study, DEN showed a significant improvement in BMD than ZOL. The BMD results of our study are consistent with other studies which have evaluated DEN and ZOL individually. While an increase in spine BMD of 9.2% at 3 years was shown in patients taking DEN, an increase in spine BMD of 6.7% at 3 years was found in patients taking ZOL.[2,3]

The result of this study was consistent with two recently published meta-analyses compared the efficacy and safety of DEN and bisphosphonates in patient with osteoporosis.[32,33] There were only two studies comparing DEN and ZOL directly, and even these studies were conducted in patients who had previously been treated.[34,35]

Differences in the changes of BMD, TBS, and CTX in both groups may reflect the distinct mechanisms of action of these agents in inhibiting bone resorption. The superiority of DEN in comparison to ZOL can be explained by a greater antiresorptive effect. The osteoclast inhibition of bisphosphonate requires binding to bone minerals, but DEN works by directly binding to RANKL. As DEN binds to RANKL, DEN distinctively inhibits osteoclast formation, function, and survival.[7] Unlike bisphosphonates, DEN is a circulating antibody and is expected to reach all sites in the bone including intracortical and trabecular bones. The strong affinity of bisphosphonates to hydroxyapatite and their incorporation into the bone matrix may limit their even distribution throughout the bone, especially deep inside the bone.[7,36]

In our study, two-year persistence of DEN and ZOL were 64.8% and 62.0%, respectively. The persistence of oral osteoporosis medications is generally low; injectable medications are associated with a higher rate of persistence.[37] Longer dosing intervals are also likely to improve persistence. Since DEN is administered once every 6 months and ZOL is taken once a year, patients' persistence with these agents may be increased. Injectable medications including teriparatide, DEN, and ZOL had significantly higher persistence compared with oral medications such as raloxifene and oral bisphosphonates.[38] Injectable medications can overcome some of the disadvantages of oral medications such as cumbersome administration instructions and gastrointestinal side effects.[39-41] Tremblay et al.'s population-based study reported persistence rates of DEN and ZOL were 63.3% and 74.8%, respectively, after two years.[42] Rates of persistence with DEN for one year have ranged between 63% and 82%, and rate of persistence for ZOL was 68% at one year.[28,43]

This study had several limitations. First, a retrospective medical record analysis was performed. Due to retrospective nature of this study, effects of comorbidities that might

affect bone metabolism such as diabetes mellitus, neoplasms, hyperparathyroidism, and rheumatoid arthritis could not be evaluated. In addition, it was not possible to evaluate the reason for discontinuation of medication. Second, a small number of patients were included in the study. However, there was no previous study that compared the effect of DEN and ZOL in naïve postmenopausal osteoporotic patients in terms of BMD, TBS, BTMs, and persistence after two-year administration of these drugs. There were not enough new osteoporotic fracture patients, so it was not meaningful to compare the effects of the two agents preventing new fractures. However, DEN significantly increased TBS reflecting microarchitecture as well as BMD compared to ZOL. In the future, it is necessary to conduct a large-scale randomized comparative study comparing the BMD, TBS, and fracture preventing effects of these two agents.

In conclusion, in postmenopausal women with osteoporosis, two-year treatment with DEN was superior to treatment with ZOL in BMD at all measured skeletal sites, microarchitecture assessed by TBS, and inhibition of bone remodeling.

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