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Original article

# Two-year effectiveness of zoledronic acid with or without eldecalcitol in Japanese patients with osteoporosis: A randomized prospective study

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ABSTRACT

*Objectives:* This study aims to examine the 2-year outcomes of zoledronic acid (ZOL) with or without eldecalcitol (ELD) on bone mineral density (BMD) and fracture in Japanese patients with osteoporosis.
*Methods:* The subjects were 98 patients who were randomly (1:1) assigned to treatment with ZOL combined with ELD (ZOL + ELD group; n = 51) and ZOL alone (ZOL group; n = 47). Treatment efficacy was examined based on a comparison of changes in BMD from baseline (ΔBMD) in the lumbar spine, total hip, and femoral neck in the 2 groups.
*Results:* The percent change from baseline in BMD values for the lumbar spine, total hip, and femoral neck at 24 months were 10.8% ± 6.1%, 6.0% ± 6.6%, and 5.1% ± 5.1%, respectively, in the ZOL + ELD group, and 7.7% ± 6.2%, 5.1% ± 5.6%, and 2.9% ± 8.3%, respectively, in the ZOL group. The percent change from baseline BMD for the lumbar spine at 24 months differed significantly between the 2 groups.
*Conclusions:* The effect of a combination of ZOL + ELD on BMD for 24 months was more favorable than that of ZOL alone. This drug combination is promising for the treatment of drug-naïve Japanese patients with primary osteoporosis.


## 1. Introduction

Osteoporosis is a systemic bone disease, in which low bone mass and poor bone quality can result in fragility fractures of the vertebrae and hip, which are further associated with higher mortality [1–6]. Osteoporosis is commonly treated with bisphosphonates (BPs), including zoledronic acid (ZOL), which is administered at a dose of 5 mg once yearly. ZOL can reduce bone turnover, increase bone mineral density (BMD) in the lumbar spine and hip, and reduce the risk of vertebral and hip fractures [7–14]. Eldecalcitol (ELD), an analog of 1α, 25-dihydroxyvitamin D3, is also often used to treat osteoporosis in Japanese patients and has similar effects to those of ZOL [15–19]. However, treatment of osteoporosis using a BP with ELD in combination is controversial [20–24], and the effects of combination of ZOL and ELD on BMD and osteoporotic fractures are uncertain.

Previously, we evaluated the safety and efficacy of ZOL treatment with and without ELD for 12 months in patients with osteoporosis [25], and the results suggested that % changes in BMD of the lumbar spine (LS-BMD), total hip (TH-BMD), and femoral neck (FN-BMD) did not differ significantly between the ELD and non-ELD groups. However, long-term results are essential in the assessment of osteoporosis treatment goals [26]. Therefore, further investigation on the effectiveness of this treatment is needed. With the aforementioned findings, this study aims to compare the efficacy of ZOL with or without ELD for 2 years in Japanese patients with osteoporosis.

## 2. Methods

### 2.1. Patients and treatment

A randomized, open-label clinical trial was performed in 98 patients without a history of treatment for osteoporosis. The

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inclusion criteria were a young adult mean (YAM) ≤ 70% for the lumbar spine or total hip on dual energy X-ray absorptiometry (DXA), or a history of fragility fracture of the lumbar spine or proximal femur and YAM <80%. The exclusion criteria were a history of treatment for osteoporosis and secondary osteoporosis. The clinical trial center at our institution randomly assigned the patients in a 1:1 ratio to groups treated with ZOL (5 mg infusion) and ELD (0.5–0.75 μg daily) (ZOL + ELD group) and ZOL (5 mg infusion) alone (ZOL group). Patients with kidney dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 $m^2$) received ELD at 0.5 μg. This study was approved by the institutional ethical review board (TGE00841-064) and followed the Declaration of Helsinki. All patients agreed to participate in the study and provided written informed consent.

### 2.2. Assessment of clinical effects

BMDs of the LS-BMD, TH-BMD, and FN-BMD were measured at baseline and 3, 6, 12, 18, and 24 months using DXA (Prodigy System; GE Healthcare, Madison, WI, USA). The LS-BMD was measured from L1 to L4 vertebrae. Vertebral fractures were evaluated at baseline and 24 months using plain X-ray from the T8 vertebra to the lumbar spine. A semiquantitative grading scale was used to identify a new vertebral fracture, using a criterion of ≥1 increase in score ≥1, while worsening of a current fracture was defined as a ≥ 20% loss of vertebral height [13]. Procollagen type I N-terminal propeptide (P1NP) and tartrate-resistant acid phosphatase-5b (TRACP-5b) were measured at baseline and 3, 6, 12, 18 and 24 months as markers of bone turnover.

### 2.3. Statistical analysis

Patients who made at least 1 visit after ZOL infusion were included in the analysis. The demographics of the ZOL + ELD and ZOL groups were compared by analysis of variance, Mann–Whitney *U* test, and Fisher's exact test. The % changes in BMD and bone turnover markers at 3, 6, 12, 18, and 24 months from baseline were evaluated by paired *t* test. $P < 0.05$ was considered significant in all analyses. The effects of ELD were also examined using an observed case analysis. The minimum sample size was 28 patients in both groups using effect size of 0.5, α level of 0.05, and power of 0.8. The result of power analysis was 0.95 using an effect size of 0.5 and α level of 0.05 in this study.

## 3. Results

The demographics and clinical characteristics at baseline did not differ significantly between the ZOL + ELD and ZOL groups (Table 1). The persistence rates in the two groups were 82.4% and 89.4%, respectively, at 12 months, and 66.7% and 61.7%, respectively, at 24 months (Fig. 1).

### 3.1. Changes in BMD

The percent change from baseline in BMD values at 3, 6, 12, 18, and 24 months in the ZOL + ELD group were 4.8% ± 5.1%, 6.9% ± 5.2%, 8.3% ± 4.8%, 10.6% ± 5.3%, and 10.8% ± 6.1% for the lumbar spine; 1.8% ± 3.4%, 2.8% ± 3.3%, 4.5% ± 6.3%, 6.1% ± 8.8%, and 6.0% ± 6.6% for the total hip; and 1.2% ± 6.6%, 2.1% ± 7.2%, 3.0% ± 4.8%, 5.5% ± 4.8%, and 5.1% ± 5.1% for the femoral neck, respectively (Fig. 2); with a significant increase in LS-, TH-, and FN-BMD in the ZOL + ELD group at each time point. Similarly, the percent change from baseline in BMD values at 3, 6, 12, 18, and 24 months in the ZOL group were 3.8% ± 3.3%, 5.7% ± 4.6%, 6.7% ± 5.7%, 7.7% ± 6.2%, and 7.3% ± 5.0% for the lumbar spine; 2.6% ± 4.1%, 2.3% ± 4.1%, 4.0% ± 3.8%, 4.6% ± 5.2%, and 5.1% ± 5.6% for the total hip; and 1.9% ± 7.6%, 1.8% ± 7.0%, 2.7% ± 6.6%, 3.1% ± 9.1%, and 2.9% ± 8.3% for the femoral neck, respectively (Fig. 2); and there was also a significant increase in LS-, TH-, and FN-BMD in the ZOL group at each time point. The percent change from baseline in BMD for the lumbar spine at 24 months differed significantly between the ZOL + ELD and ZOL groups, but the percent change from baseline in BMD for the total hip and femoral neck did not show significant differences at any time point.

### 3.2. Changes in bone turnover markers

The % changes from baseline in bone turnover markers at 3, 6, 12, 18, and 24 months were −61.9% ± 21.8%, −67.0% ± 20.4%, −65.2% ± 18.3%, −65.6% ± 30.8%, and −63.5% ± 22.8%, respectively, for P1NP; and −64.0% ± 11.5%, −62.1% ± 12.1%, −60.6% ± 13.4%, −64.1% ± 15.8%, and −61.0% ± 15.0%, respectively, for TRACP-5b in the ZOL + ELD group; and −61.3% ± 29.0%, −63.1% ± 20.2%, −51.3% ± 31.8%, −55.2% ± 35.0%, and −48.3% ± 43.1%, respectively, for P1NP; and −55.7% ± 18.7%, −53.6% ± 16.5%, −48.0% ± 21.4%, −48.5% ± 31.0%, and −46.6% ± 37.4%, respectively, for TRACP-5b in the ZOL group. The % changes from baseline in P1NP and TRACP-5b showed significant decreases at all time points in both groups. There were significant differences between the groups for the % changes from baseline in P1NP at 12 ($p = 0.008$) and 24 ($p = 0.040$) months, and the % changes from baseline in TRACP-5b at 3 ($P = 0.015$), 6 ($P = 0.005$), 12 ($P = 0.003$), and 18 ($P = 0.004$) months.

### 3.3. New vertebral and non-vertebral fractures

New vertebral fractures occurred in 3 patients in the ZOL + ELD group and 5 patients in the ZOL group from 0 to 12 months, and in 1

**Table 1**
Demographic characteristics at baseline of the zoledronic acid + eldecalcitol and zoledronic acid groups; univariate analysis.

| Variables, median (Q1, Q3) | ZOL + ELD group (n = 51) | ZOL group (n = 47) | P-value |
|---|---|---|---|
| Age, yr | 75 (72, 81) | 75 (70, 82) | 0.550 |
| Female, n (%) | 48 (92.3) | 44 (93.6) | 1.000 |
| Body mass index, kg/$m^2$ | 22.4 (19.9, 24.5) | 21.9 (20.4, 23.7) | 0.784 |
| Cr-eGFR, mL/min/1.73$m^2$ | 68.5 (59.8, 77.0) | 68.2 (59.6, 76.7) | 0.862 |
| Value of serum calcium, mg/dL | 9.5 (9.3, 9.8) | 9.6 (9.3, 9.8) | 0.839 |
| Presence of vertebral fractures, n (%) | 25 (49.0) | 25 (53.2) | 0.692 |
| Lumbar spine T-score | −2.6 (−3.3, −1.8) | −2.5 (−3.0, −1.8) | 0.370 |
| Total hip T-score | −2.3 (−2.9, −2.0) | −2.5 (−2.9, −2.1) | 0.722 |
| Femoral neck T-score | −2.8 (−3.3, −1.8) | −2.8 (−3.3, −2.3) | 0.709 |
| P1NP, ng/mL | 68.3 (53.4, 86.0) | 69.0 (48.6, 80.7) | 0.768 |
| TRACP-5b, mU/dL | 573 (445, 667) | 511 (416, 678) | 0.211 |

ZOL, zoledronic acid; ELD, eldecalcitol; Q1, 25th percentile; Q3, 75th percentile; Cr-eGFR, estimated glomerular filtration rate calculated by creatinine; P1NP, N-terminal propeptide of type I procollagen; TRACP-5b, tartrate-resistant acid phosphatase-5b.

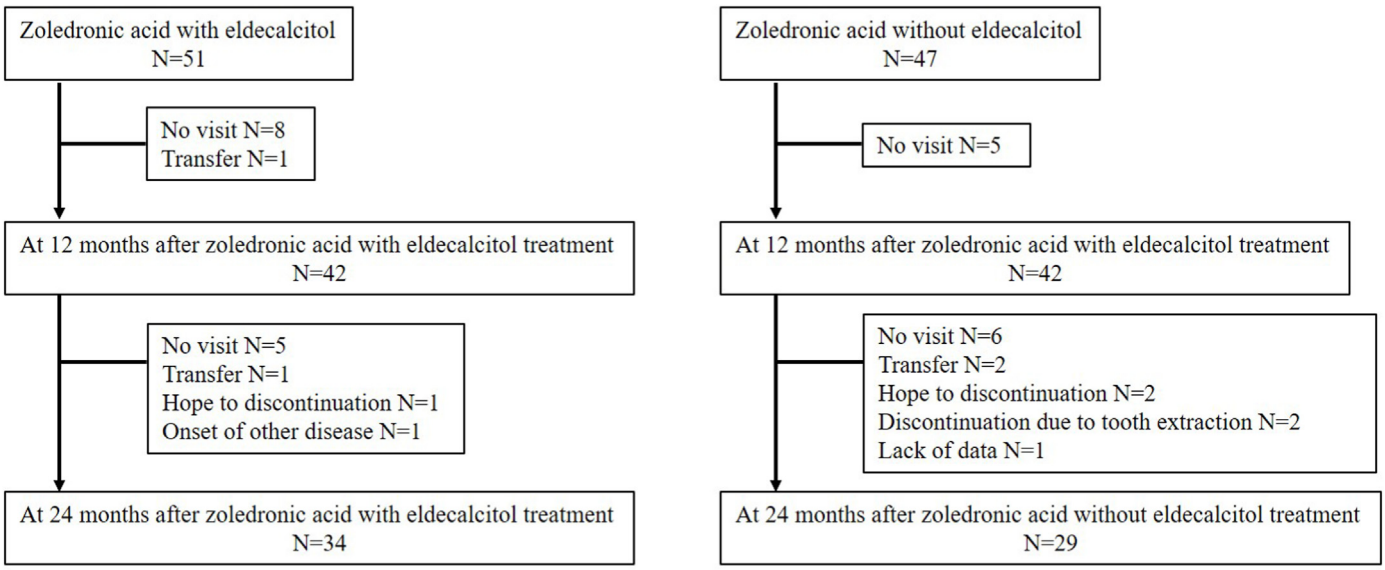


**Fig. 1.** Flow chart of the disposition of patients in the study.

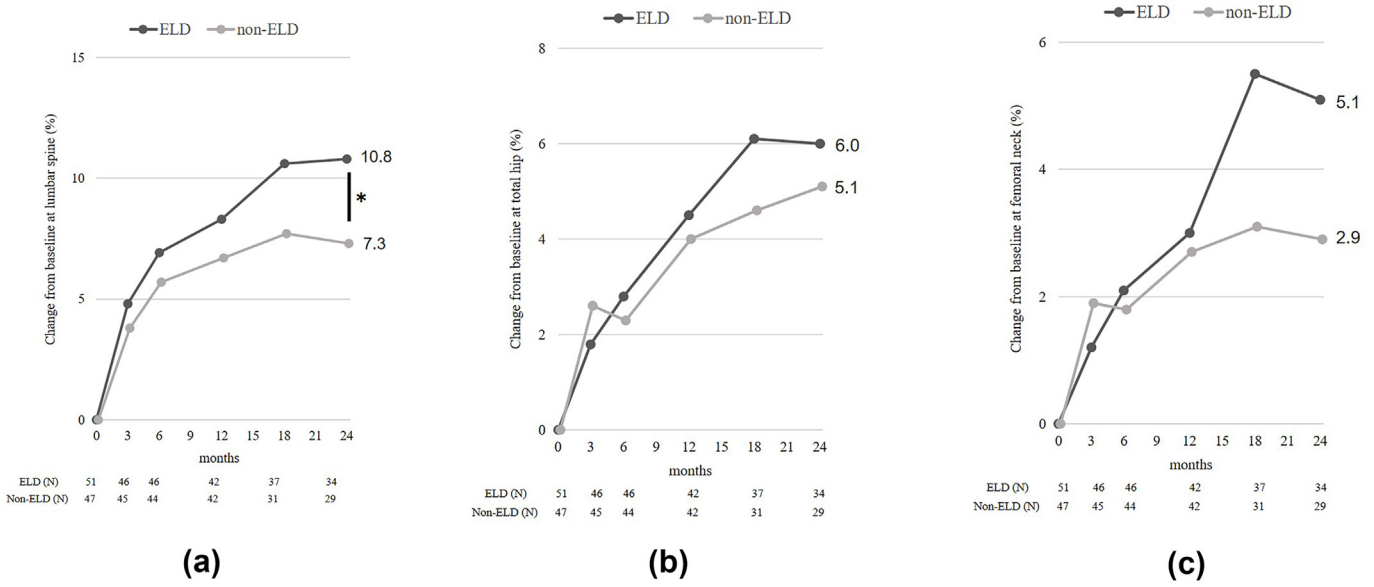


**Fig. 2.** Percentage changes from baseline in the bone mineral densities of the (a) lumbar spine, (b) total hip, and (c) femoral neck.

patient in each group from 12 to 24 months. Among the patients with new vertebral fractures, the worsening in already-existing vertebral fractures during the 2 years occurred in 1 patient in the ZOL + ELD group and 3 patients in the ZOL group. There were also 3 non-vertebral fractures in the 24-month study period, including in 1 patient in the ZOL + ELD group and 2 patients in the ZOL group.

### 3.4. Acute phase reactions at the first and second infusions

Acute phase reactions (APRs) occurred in 35 patients (35.7%) at the first ZOL infusion, and 32 of these patients received a second ZOL infusion. APRs occurred in 1 patient following the second ZOL infusion.

## 4. Discussion

In this study, treatment with ZOL significantly increased LS-BMD, TH-BMD, and FN-BMD at 24 months. This is consistent with the findings in the ZONE study showing that treatment increased BMD by 8.1%, 3.3%, and 3.6% in the lumbar spine, total hip, and femoral neck at 24 months in Japanese patients [13]. In the ZONE study, all patients received 400 IU of vitamin D daily, whereas those in the ZOL + ELD group in the current study received an active vitamin D analog, ELD. A comparison of the efficacy of denosumab, a monoclonal antibody used to treat osteoporosis, combined with ELD or native vitamin D showed significantly greater improvement of FN-BMD with ELD compared to that with native vitamin D [27]. Similarly, alendronate (ALD) with ELD has been shown to increase

FN-BMD significantly compared to ALD with native vitamin D + Ca [20]. The present study results showing a greater increase in BMD with ZOL + ELD are consistent with these findings.

Following ELD treatment for osteoporosis, LS-BMD has been found to increase by 2.3–4.0% and 3.5% and TH-BMD by 0.6–1.4% and 0.4% at 12 and 36 months, respectively [16–18]. Combination treatment with a BP and ELD has previously been shown to increase BMD more effectively than with a BP alone: minodronate, a third-generation BP used in Japan, combined with ELD increased LS-, TH- and FN-BMD by 3.6%, 2.8%, and 3.5%, respectively, after 12 months compared to minodronate alone [21], and ibandronate combined with ELD was 2.2% more effective than ibandronate alone for LS-BMD at 12 months [24]. In the current study, LS-, TH-, and FN-BMD were 1.6%, 0.5%, and 0.3% higher, respectively, after 12 months, and 3.5%, 0.9%, and 2.2% higher, respectively, after 24 months with ZOL + ELD compared to ZOL alone. These results indicate that the ZOL + ELD combination may be especially effective for increasing LS-BMD over 24 months.

ELD alone has been shown to reduce bone turnover markers by 30%–60% [15,20,28,29], and this effect is further enhanced when ELD is used in combination with a BP [20–22], which is in agreement with the findings in this study. ELD and BPs affect different pharmacological pathways, but the mechanism of action of ELD is poorly characterized. ELD has been shown to control migration of osteoclast precursors and restrict osteoclastic bone resorption [30], and to suppress nuclear factor kappa-B ligand expression in trabecular bone [31]. These effects may explain the increased BMD of ELD with ZOL in combination in the current study.

APRs, including pyrexia, arthralgia, fatigue, appetite loss, myalgia, and headache, occurred in 35.7% of patients after the first ZOL infusion, but decreased markedly after the second ZOL infusion. A phase III study reported APR rates of 51.2% and 12.3% after the first and second ZOL infusions, respectively [32]. The current and previous results suggest that the frequency of APRs is reduced in the second ZOL infusion, even in patients with APRs after the first ZOL infusion.

This study has several limitations. First, 25(OH)D levels were not evaluated at baseline. However, ELD appears to affect bone independently from vitamin D supplementation [33], and thus, vitamin D insufficiency is likely to have had negligible effects on the outcomes of the study. Second, the study period was relatively short. ΔBMD for the lumbar spine at 24 months differed significantly between the ZOL and ZOL + ELD groups, but LS-, TH- and FN-BMD have been shown to increase further with continued ZOL treatment for 3 years [7]. Thus, our results may have differed had we continued ZOL treatment for a longer period. Within these limitations, we believe that the study provides important insights into the effects of ZOL and ELD in combination, and that the results will provide a basis for future studies.

## 5. Conclusions

ZOL + ELD for 24 months increased BMD and reduced bone turnover markers more effectively than ZOL alone in patients with osteoporosis. These results suggest that ZOL + ELD combination treatment is a promising therapeutic option for drug-naïve Japanese patients with primary osteoporosis.

## CRediT author statement

**Takeshi Mochizuki**: Conceptualization, Investigation, Data Curation, Writing-Original draft. **Koichiro Yano**: Formal analysis. **Katsunori Ikari**: Conceptualization, Writing-Review & editing. **Ken Okazaki**: Writing-Review & editing.

## Conflicts of interest

Takeshi Mochizuki received honoraria for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Mochida, Pfizer, Takeda, and Tanabe-Mitsubishi. Koichiro Yano received honoraria for lectures from AbbVie, Astellas, AYUMI, Bristol-Meyers, Eisai, Hisamitsu, Mochida, and Takeda. Katsunori Ikari received honoraria for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Eisai, Eli Lilly, Janssen, Takeda, Tanabe-Mitsubishi, and UCB. The other authors declare that they have no conflicts of interest. The sponsors were not involved in the study design; collection, analysis, and interpretation of data; writing of the article; and/or decision to submit the results for publication.

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