

Original Research Article

Relationship between the effect of eldecalcitol and serum 25(OH)D level[☆]Toshiyuki Takano^a, Satoshi Kondo^a, Hitoshi Saito^a, Toshio Matsumoto^{b,*}, The Eldecalcitol Study Group^a Chugai Pharmaceutical Co., Ltd., Tokyo 103-8324, Japan^b Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Health Biosciences, Tokushima 770-8503, Japan

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ABSTRACT

In previous studies, we demonstrated that 12-month treatment with 0.75 µg/day eldecalcitol increased bone mineral density in osteoporotic patients regardless of serum 25-hydroxyvitamin D (25(OH)D) level, and in a 3-year randomized double-blind clinical trial, eldecalcitol significantly reduced the incidences of vertebral and wrist fractures compared to alfacalcidol. However, it remains unclear whether the fracture risk reduction by eldecalcitol is affected by serum 25(OH)D. In the fracture prevention trial, patients with low 25(OH)D level at baseline were supplemented with 400 IU/day native vitamin D₃. In the current study, patients from that trial were divided according to the tertiles of serum 25(OH)D level at 6 months after treatment initiation. The increases in lumbar and hip BMD by eldecalcitol were significantly higher in all tertiles than those by alfacalcidol. The incidences of vertebral and osteoporotic fractures tended to be lower in each tertile of the eldecalcitol-treated group than in the corresponding tertile of the alfacalcidol-treated group, with the exception of vertebral fractures in the low tertile. We also investigated whether eldecalcitol treatment affected levels of serum 25(OH)D, serum 1,25(OH)₂D, and parathyroid hormone in patients without vitamin D supplementation. With eldecalcitol treatment, serum 1,25(OH)₂D concentration was reduced by approximately 50%, whereas serum levels of parathyroid hormone and 25(OH)D were not affected. The major findings of the present study were that eldecalcitol did not affect serum 25(OH)D levels, and that it reduced the incidence of osteoporotic fractures and increased BMD in comparison with alfacalcidol regardless of serum 25(OH)D level within the range of serum 25(OH)D concentrations at or higher than 20 ng/mL. Whether eldecalcitol is similarly effective at vitamin D deficient serum 25(OH)D levels remains to be clarified.

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1. Introduction

Active vitamin D₃ (calcitriol; 1,25-dihydroxyvitamin D₃; 1,25(OH)₂D₃) is a key regulator of metabolism in the bone, intestine, keratinocytes, pancreatic cells, and immune cells [1]. A meta-analysis of the effect of vitamin D compounds indicated that administration of vitamin D compounds reduces the risk of vertebral fractures by 37% in patients with postmenopausal osteoporosis [2].

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Eldecalcitol is a new calcitriol analog that bears a hydroxypropyloxy substituent at the 2β position of calcitriol. In a fracture prevention trial comparing alfacalcidol and eldecalcitol, eldecalcitol significantly increased lumbar and total hip BMD and reduced the incidences of vertebral and wrist fractures [3]. The effect of eldecalcitol on vertebral fractures was not affected by 25(OH)D value at baseline. However, because patients with low levels of 25(OH)D (below 20 ng/mL) at baseline were supplemented with 400 IU of native vitamin D₃, it was not known whether 25(OH)D concentration during the study period affected the treatment effect of eldecalcitol. And although eldecalcitol strongly induces CYP24A1 from the data of the animal study [4], it remains unknown whether eldecalcitol has a possibility to influence the concentration of serum 25(OH)D. The present study is a post hoc analysis of the fracture prevention trial to investigate the relation between 25(OH)D concentration during the study period and the efficacy of eldecalcitol. We also investigated the influence of eldecalcitol on serum 25(OH)D concentration.

Table 1

Baseline characteristics of enrolled patients divided according to each tertile of serum 25(OH)D level at 6 months. The tertile boundaries are following; low (<29.5 ng/mL), middle (≥ 29.5 to <37.3 ng/mL), and high (≥ 37.3 ng/mL).

	Eldecalcitol			Alfacalcidol		
	Low (n = 180)	Middle (n = 174)	High (n = 152)	Low (n = 152)	Middle (n = 166)	High (n = 186)
Age (years)	72.1	72.1	72.4	71.8	72.2	72.1
BMI (kg/m ²)	22.3	22.4	22.1	22.4	22.5	22.2
No. of prevalent vertebral fractures						
0 (%)	68(38)	66(38)	56(37)	58(38)	62(37)	66(35)
1 (%)	50(28)	54(31)	46(30)	43(28)	54(33)	58(31)
≥ 2 (%)	62(34)	54(31)	50(33)	51(34)	50(30)	62(33)
Lumbar BMD T-score	−2.66	−2.77	−2.66	−2.69	−2.81	−2.66
Total hip BMD T-score	−2.23	−2.23	−2.33	−2.37	−2.22	−2.23
25(OH)D (ng/mL)	23.3	22.2	21.8	23.8	23.0	20.7
Intact PTH (pg/mL)	36.5	37.0	38.8	36.5	38.3	40.3
1,25(OH) ₂ D (pg/mL)	46.9	50.6	51.5	48.2	49.1	51.2
No. of vitamin D suppl (%)	17(9)	73(42)	111(73)	9(6)	56(34)	129(69)

2. Subjects and methods

Details of the double-blind fracture prevention clinical study of eldecalcitol have been published previously. Briefly, 1054 patients with primary osteoporosis were divided into two groups: an eldecalcitol group ($n = 528$) and an alfacalcidol group ($n = 526$). They were given either oral eldecalcitol (0.75 μ g) or oral alfacalcidol (1.0 μ g) once a day for 3 years (36 months). Patients with serum 25(OH)D values lower than 20 ng/mL at the time of enrollment were given an oral native vitamin D₃ supplement (400 IU) once a day without calcium supplementation. The primary endpoint of the study was the incidence of new non-traumatic vertebral fractures, and the secondary endpoints were the percent change in lumbar spine BMD and total hip BMD, percent change of bone turnover markers, and incidence of non-vertebral fractures. The incidence of new non-traumatic vertebral fractures was evaluated by using lateral radiographs of the thoracic and lumbar spine obtained at baseline and at 6, 12, 24, and 36 months after initiation of drug administration. Three expert investigators independently evaluated the vertebrae from T4 to L4.

In the current study, serum 25(OH)D was originally measured by Nichols Allegro Lite (Nichols Institute). However, because the assay became unavailable during the study, we re-assessed all the samples by HPLC – competitive protein binding assay (CPBA), in which 25(OH)D was first purified by HPLC and then the amount of 25(OH)D in the 25(OH)D fraction was measured by CPBA. As a result, the baseline serum 25(OH)D became higher than those assayed by Nichols assay. Patients were stratified into tertiles according to their 25(OH)D level at 6 months after treatment initiation (low tertile: <29.5 ng/mL; middle tertile: ≥ 29.5 to <37.3 ng/mL; high tertile: ≥ 37.3 ng/mL). We investigated the change in lumbar and total hip BMD, and the incidence of vertebral fractures, “all osteoporotic fractures”, and “non-vertebral osteoporotic fractures” occurring in each tertile at 6, 12, 24, and 36 months after treatment initiation.

“Osteoporotic fractures” are defined by WHO as fractures whose risk of incidence is associated with low bone mass and whose incidences rise with age after the age of 50 years. Fractures pertinent to these criteria are those of the spine, distal forearm (wrist), humerus, ribs, clavicle/scapula/sternum, pelvis, tibia/fibula, hip, and other femoral fractures. “Non-vertebral osteoporotic fractures” means “osteoporotic fractures” other than fractures of the spine.

The value of 25(OH)D was evaluated at 6, 12, 24, and 36 months after treatment initiation for all patients in each group divided into patients who received or did not receive vitamin D supplementation. The values of 1,25(OH)₂D (as assessed by HPLC–radioreceptor assay) and intact PTH (Eclusys PTH; Roche

Diagnostics, Penzberg, Germany) were evaluated at 6, 12, 24, and 36 months after treatment initiation for all patients in each group divided according to the tertile of 25(OH)D value at 6 months.

3. Results and discussion

There were no marked differences in baseline characteristics regardless of serum 25(OH)D level at 6 months after treatment initiation in any of the groups except for the proportion of patients receiving vitamin D supplementation (Table 1).

Eldecalcitol significantly increased lumbar BMD from baseline by 3.3% in the low tertile, 3.1% in the middle tertile, and 4.0% in the high tertile at 36 months, whereas alfacalcidol changed lumbar BMD by 0.40% in the low tertile, −0.22% in the middle tertile, and 0.17% in the high tertile at 36 months (Fig. 1A). Eldecalcitol also significantly increased total hip BMD from baseline by 0.25% in the low tertile, 0.48% in the middle tertile, and 0.50% in the high tertile at 36 months, whereas alfacalcidol changed total hip BMD by −2.6% in the low tertile, −2.2% in the middle tertile, and −2.1% in the high tertile at 36 months (Fig. 1B). The increase in lumbar and hip BMD by eldecalcitol was significantly higher than that by alfacalcidol in all the tertiles at 36 months.

The incidences of vertebral fractures, “osteoporotic fractures,” and “non-vertebral osteoporotic fractures” are indicated in Fig. 2. In each tertile, the incidence of fractures tended to be lower with eldecalcitol treatment than with alfacalcidol treatment.

Changes in calcium regulating hormones are shown in Fig. 3. In patients receiving vitamin D₃ supplementation, serum 25(OH)D increased in both the eldecalcitol and alfacalcidol treatment groups, whereas in patients without vitamin D₃ supplementation, serum 25(OH)D did not change in either treatment group (Fig. 3A). Serum 1,25(OH)₂D decreased by approximately 50% in all tertiles of the eldecalcitol treatment groups, whereas, 1,25(OH)₂D increased by approximately 20% in all tertiles of the alfacalcidol treatment group (Fig. 3B). Serum PTH levels were slightly suppressed in all tertiles of both the eldecalcitol and alfacalcidol treatment groups (Fig. 3C).

We previously demonstrated that, compared to treatment with 1.0 μ g/day alfacalcidol, treatment with 0.75 μ g/day eldecalcitol increased BMD and reduced the risk of vertebral and wrist fractures in patients with osteoporosis. In this post hoc analysis, we investigated whether the effect of eldecalcitol was affected by serum 25(OH)D concentration during treatment. We found that the effect of eldecalcitol on lumbar and total hip BMD and on vertebral, “osteoporotic,” and “non-vertebral osteoporotic” fractures was similar in all tertiles of serum 25(OH)D concentration at 6 months.

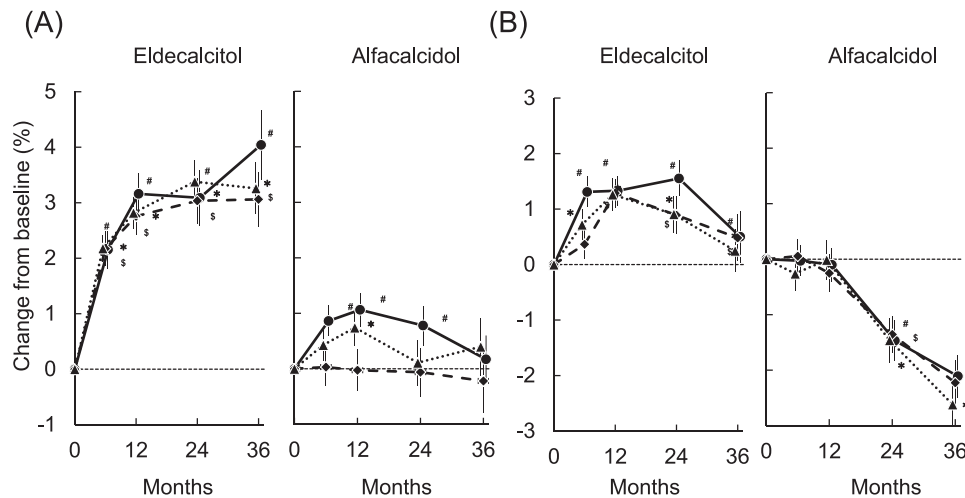


Fig. 1. Change in BMD in eldecalsitol and alfacalcidol treated group. The BMD values in (A) lumbar spine, and (B) total hip for both eldecalsitol- and alfacalcidol-treated groups were described according to serum 25(OH)D level at 6 months. Closed triangles (▲), closed diamonds (◆), and closed circles (●) represent low tertile (<29.5 ng/mL), middle tertile (≥ 29.5 to <37.3 ng/mL), and high tertile (≥ 37.3 ng/mL), respectively. Data represent means $\pm$ SEM. #, *, and \$ $p < 0.05$ by Student's t -test compared with pre-treatment value.

Because a sufficient level of serum 25(OH)D is needed to make osteoporotic drugs work, in most clinical trials of osteoporotic drugs (bisphosphonates, SERMs [selective estrogen receptor modulators], and so on) patients receive supplemental native vitamin D and calcium [5–7]. Ishijima et al. reported that in osteoporotic patients treated with alendronate, the increase in BMD was greater in patients with a serum 25(OH)D concentration of above 25 ng/mL at baseline than in patients whose baseline 25(OH)D concentration was below 25 ng/mL [8]. In contrast, in the case of active vitamin D compound, one may expect to see a greater effect on BMD in subjects with low serum 25(OH)D. However, in the present study, among 15 subjects with serum 25(OH)D below 20 ng/mL, there was a large variation in the change in lumbar BMD by eldecalsitol. Therefore, it is difficult to draw any conclusions about whether the effect of eldecalsitol on BMD is affected by serum 25(OH)D at vitamin D deficient levels.

Among the calcium regulating hormones investigated, 25(OH)D did not change in either the eldecalsitol or alfacalcidol treatment groups without vitamin D supplementation. Serum 1,25(OH)₂D

increased by approximately 20% in the alfacalcidol treatment group but decreased by approximately 50% in the eldecalsitol treatment group, regardless of the value of 25(OH)D at 6 months. In regard to the mechanism whereby eldecalsitol reduces serum 1,25(OH)₂D concentration, eldecalsitol is shown to drastically induce CYP24A1 and suppress CYP27B1 in the kidney [4]. In contrast, because alfacalcidol itself is converted to calcitriol, the net effect is a slight increase in serum 1,25(OH)₂D concentration. On the other hand, the effect of eldecalsitol in suppressing intact PTH tends to be slightly weaker than that of alfacalcidol. Previous basic and clinical studies have shown that the effect of eldecalsitol in suppressing PTH is lower than that of calcitriol or alfacalcidol [9,10]. As a result, we speculate that eldecalsitol decreases serum 1,25(OH)₂D concentration without much changes in serum PTH level.

The present study has limitations. In this study, supplementation with native vitamin D₃ was given if the patient's serum 25(OH)D was below 20 ng/mL. Therefore, serum 25(OH)D at 6 months was relatively high. According to the result of a previous study by eldecalsitol, in which native vitamin D₃ supplementation

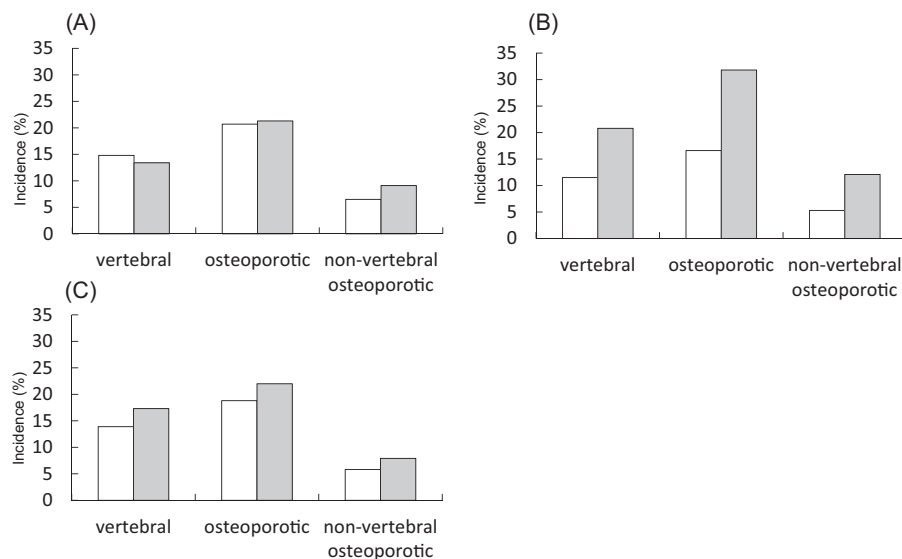


Fig. 2. Incidence of fractures occurring over 3 years according to serum 25(OH)D at 6 month. (A) Low tertile, (B) middle tertile, and (C) high tertile. White bar and gray bar mean eldecalsitol group and alfacalcidol group, respectively.

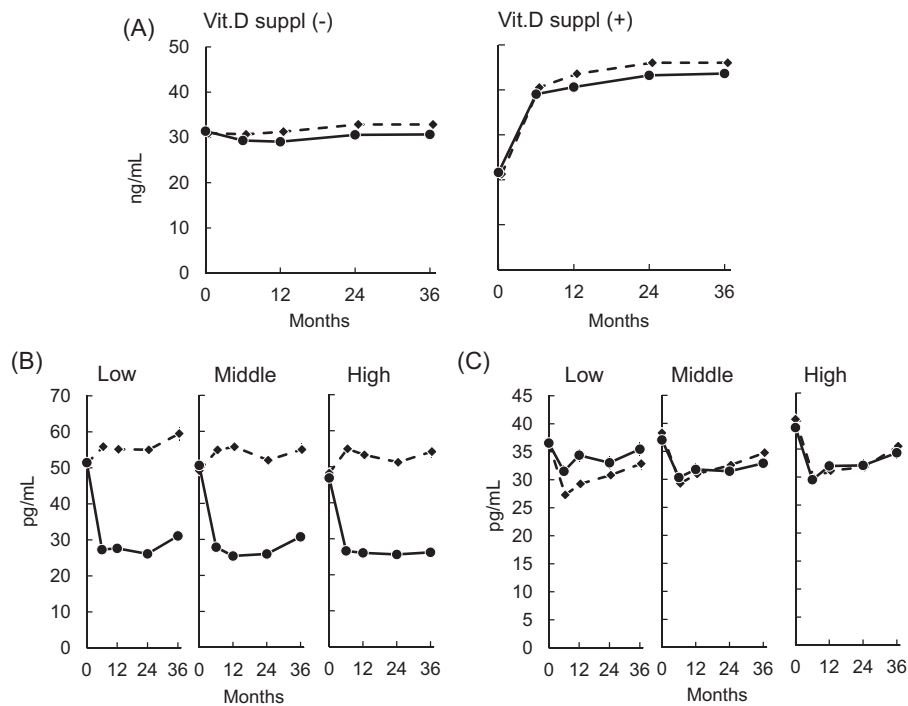


Fig. 3. Change in calcium regulating hormones. (A) Serum 25(OH)D in patients with or without vitamin D supplementation, (B) 1,25(OH)₂D, and (C) intact PTH in patients divided into the tertiles according to serum 25(OH)D level at 6 months. Closed circles (●) and closed diamonds (◆) represent eldecacitol treatment groups and alfalcacitol treatment groups, respectively in all graphs. Data are means ± SEM.

was not given, there was no correlation between serum 25(OH)D concentration and the increase in lumbar BMD [11]. However, because there was a large variation in the change in BMD by eldecacitol among subjects with serum 25(OH)D below 20 ng/mL, prospective studies with and without vitamin D supplementation are necessary to investigate its influence on the efficacy of eldecacitol.

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