A new active vitamin D₃ analog, eldecalcitol, prevents the risk of osteoporotic fractures — A randomized, active comparator, double-blind study ☆

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ABSTRACT

Background: Eldecalcitol is an analog of 1,25-dihydroxyvitamin D₃ that improves bone mineral density; however, the effect of eldecalcitol on the risk of fractures is unclear. The objective of this study is to examine whether eldecalcitol is superior to alfacalcidol in preventing osteoporotic fractures. This trial is registered with ClinicalTrials.gov, number NCT00144456.
Methods and results: This 3 year randomized, double-blind, active comparator, superiority trial tested the efficacy of daily oral 0.75 µg eldecalcitol versus 1.0 µg alfacalcidol for prevention of osteoporotic fractures. 1054 osteoporotic patients 46 to 92 years old were randomly assigned 1:1 to receive eldecalcitol (n = 528) or alfacalcidol (n = 526). Patients were stratified by study site and serum 25-hydroxyvitamin D level. Patients with low serum 25-hydroxyvitamin D levels (<50 nmol/L) were supplemented with 400 IU/day vitamin D₃. Primary end point was incident vertebral fractures. Secondary end points included any non-vertebral fractures and change in bone mineral density and bone turnover markers. Compared with the alfacalcidol group, the incidence of vertebral fractures was lower in eldecalcitol group after 36 months of treatment (13.4 vs. 17.5%; hazard ratio, 0.74; predefined 90% confidence interval [CI], 0.56–0.97). Eldecalcitol reduced turnover markers and increased bone mineral density more strongly than alfacalcidol. Eldecalcitol reduced the incidence of three major non-vertebral fractures, which was due to a marked reduction in wrist fractures by a post-hoc analysis (1.1 vs. 3.6%; hazard ratio, 0.29; 95% CI, 0.11–0.77). Among the adverse events, the incidence of increase in serum and urinary calcium was higher in the eldecalcitol group, without any difference in glomerular filtration rate between the two groups.
Conclusions: Eldecalcitol is more efficacious than alfacalcidol in preventing vertebral and wrist fractures in osteoporotic patients with vitamin D sufficiency, with a safety profile similar to alfacalcidol.

Introduction

Eldecalcitol (ED-71) is an analog of 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] [1] that increases bone mass and bone strength in rodents [2,3]. An open-label, controlled clinical trial in osteoporotic patients demonstrated that, compared with baseline values, treatment with 0.25 to 1.0 µg/day eldecalcitol for 6 months increased lumbar spine bone mineral density (BMD) in a dose-dependent manner without causing sustained hypercalcemia or hypercalciuria [4,5]. A double-blind, placebo-controlled clinical trial for 12 months with vitamin D supplementation revealed that eldecalcitol increased lumbar spine and total hip BMD in a dose-dependent manner, with a lower incidence of hypercalcemia in the 0.75 µg/day eldecalcitol group than in the highest dose (1.0 µg/day) group [6]. The effect of eldecalcitol on the lumbar spine and total hip BMD was independent of serum 25-hydroxyvitamin D levels (25(OH)D) [7], suggesting that eldecalcitol can increase BMD regardless of the state of vitamin D sufficiency.

A number of studies have examined the effect of alfacalcidol on the incidence of fractures in osteoporotic patients. Although most of those

studies involved only a small number of subjects, some studies demonstrated that alfacalcidol treatment resulted in a significant reduction [8,9], while others did not show a significant reduction [10,11], in vertebral fracture incidence compared with a placebo. However, the effect of eldecalcitol has not been compared head-to-head with that of alfacalcidol.

An open-label clinical trial to compare the effect of eldecalcitol with that of alfacalcidol on bone turnover and calcium (Ca) metabolism showed that 0.5 to 1.0 µg/day eldecalcitol inhibits bone resorption more than alfacalcidol, while their effects on bone formation markers and urinary Ca excretion were similar [12]. The present study was conducted to compare the effect of eldecalcitol with that of alfacalcidol in preventing vertebral fractures in men and women with osteoporosis.

Subjects and methods

Study design and patients

This was a randomized, active comparator, double-blind, superiority trial of the effect of eldecalcitol versus alfacalcidol for reduction in incidence of vertebral fractures. A total of 1054 patients (1030 females and 24 males, all Japanese) aged from 46 to 92 years (mean 72.1 years) from 52 centers in Japan were enrolled between September 2004 and August 2005, and randomly assigned to receive identical capsules of either 0.75 µg eldecalcitol or 1.0 µg alfacalcidol once a day for 36 months. Adherence to the medications was monitored by counting the remaining capsules at each visit, and was more than 95% in average throughout the study period (96.5% in eldecalcitol and 95.7% in alfacalcidol groups, respectively). Serum 25(OH)D measured by Nichols Allegro Lite (Nichols Institute, San Clemente, CA) was below 50 nmol/L in 39.3% of the patients at enrollment (208 in eldecalcitol and 206 in alfacalcidol group). These patients were given 400 IU/day vitamin D_3 throughout the study period.

Patients without vertebral fractures were enrolled if their lumbar spine or total hip BMD T-score was below −2.6 and they were 70 years or older, or if their T-score was below −3.4 and they were younger than 70 years. Patients with lumbar spine or total hip BMD T-score of below −1.7 were enrolled if they had between one and five vertebral fractures. Prevalent vertebral fractures at enrollment were assessed by lateral spine X-ray examination of the thoracic and lumbar vertebrae, and were diagnosed quantitatively according to the criteria of the Japanese Society for Bone and Mineral Research [13,14]. Women were at least 3 years after menopause or older than 60 years. Patients were excluded if they had primary hyperparathyroidism, Cushing's syndrome, premature menopause due to hypothalamic, pituitary or gonadal insufficiency, poorly controlled diabetes mellitus (HbA1c over 9%) or other causes of secondary osteoporosis, or had a history of urolithiasis. Patients were also excluded if they had taken any oral bisphosphonates within 6 months before entry or for more than 2 weeks during the period 6 to 12 months before entry, or intravenous bisphosphonates at any time; had taken glucocorticoids, calcitonin, vitamin K, active vitamin D compounds, raloxifene, or hormone replacement therapy within the previous 2 months; had serum Ca levels of above 10.4 mg/dL (2.6 mmol/L) or urinary Ca excretion of over 0.4 mg/dL glomerular filtrate (GF) (0.1 mmol/L GF); had serum creatinine above 1.3 mg/dL (115 µmol/L); or had clinically significant hepatic or cardiac disorders. The protocol was approved by the internal human studies review board at each center, and informed consent was obtained from each patient.

Randomization and masking

Patients who satisfied all eligibility criteria were randomly assigned in a 1:1 ratio to receive eldecalcitol or alfacalcidol. Treatment was assigned by use of dynamic allocation, via a central enrollment center. The randomization sequence was created by the person responsible for investigational product randomization. Randomization was stratified by study site with minimization for 25(OH)D level (<50 nmol/L, ≥50 nmol/L) at provisional enrollment. Both patients and investigators were masked to treatment assignment throughout the study follow-up.

Procedures

The primary end point was incident vertebral fractures. Secondary end points included any non-vertebral fractures, changes in bone mineral density of the total hip and lumbar spine, and changes in bone turnover markers. All investigators who performed end point evaluations were unaware of the study-group assignments of patients.

Lateral radiographs of the thoracic and lumbar spine were taken at baseline and at 6, 12, 24, and 36 months or at termination. Three expert investigators independently evaluated vertebrae from T4 to L4. Prevalent fractures were assessed semiquantitatively as grades 0 to 3 [15]. Incident vertebral fractures were diagnosed quantitatively if the anterior, posterior, or middle vertebral height had decreased by at least 15% and by ≥4 mm in a vertebra that was assessed at baseline as grade 0, 1, or 2 [16]. If the investigators' assessments disagreed, the final assessment was made after conference by all the investigators. Seven subgroups due to age, serum 25(OH)D, the presence or absence, the number, and the semi-quantitative grade of prevalent vertebral fractures, lumbar spine BMD, and total hip BMD were predefined to test for interaction.

All non-vertebral fractures were identified symptomatically as clinical fractures. Suspected non-vertebral fractures without excessive trauma assessed centrally were confirmed radiographically. Subgroup analyses were predefined at major six non-vertebral sites (clavicle, humerus, wrist, pelvis, hip and leg) and major three non-vertebral sites (humerus, wrist and hip).

Dual-energy X-ray absorptiometry (DXA) measurements of the lumbar spine BMD (posteroanterior projection) and the total hip were made at baseline and at 6, 12, 24, and 36 months. T-score was calculated based upon the database from nationwide survey [13]. A central facility performed quality assurance of the longitudinal adjustment, by calibrating each machine with standardized phantoms. All DXA measurements were analyzed at a central site by a radiologist blinded to treatment group assignment.

Serum and postprandial urine samples were collected at baseline, 0.5, 1, and 2 months, and every second month thereafter until 36 months for routine analyses, including Ca concentrations. At baseline, 6, 12, 24, and 36 months, we determined serum bone-specific alkaline phosphatase (BSAP) (Metra-BAP EIA; Quidel, San Diego, CA; reference range 7.9 to 29.0 U/L) and urinary type I collagen N-telopeptide (NTX) (Osteomark; Inverness Medical Innovations, Waltham, MA; reference range 9.3 to 54.3 nmol BCE/mol Cr) as bone turnover markers, and 25(OH)D (HPLC-competitive protein binding assay), 1,25$(OH)_2$D (HPLC radioreceptor assay) and intact parathyroid hormone (PTH) (Eclusys PTH, Roche Diagnostics, Penzberg, Germany) as calcium-regulating hormones. Nichols Allegro Lite was used for the measurement of 25(OH)D only at enrollment, because manufacturing of the kit was discontinued thereafter. Regression analysis between the two measurements revealed that there was a linear relationship between the 25(OH)D values from HPLC-competitive binding assay (y) and Nichols Allegro Lite assay (x): $y = 1.016x + 4.555$.

If increase in serum Ca over 11.0 mg/dL (2.75 mmol/L) developed, or if increase in serum Ca over 10.4 mg/dL (2.6 mmol/L) along with urinary Ca over 0.4 mg/dL GF (0.1 mmol/L GF) developed, treatment was discontinued. If serum Ca in these patients subsequently decreased to below 10.4 mg/dL (2.6 mmol/L) and urinary Ca decreased to below 0.4 mg/dL GF (0.1 mmol/L GF), treatment was resumed with reduced doses (0.5 µg eldecalcitol and alfacalcidol). Fifteen patients in eldecalcitol group, and 12 patients in alfacalcidol group discontinued treatment. Among them, all 15 patients in eldecalcitol group and 9 patients in alfacalcidol group resumed treatment with reduced doses. Compliance

with the study treatment was assessed with the use of medication diaries and counts of residual medication supplies.

All patients were questioned about adverse events at each visit, and all adverse events were analyzed regardless of the investigators' assessments of causality. The Medical Dictionary for Regulatory Activities (MedDRA, Version 8) was used to categorize reported adverse events.

Statistical analysis

All randomized patients who took any dose of a study drug were included in the safety analysis, and all randomized patients with drug administration who had a baseline assessment and at least one post-randomization assessment were included in the efficacy analysis (Fig. 1).

Analysis of vertebral fracture incidence included patients who underwent radiography at baseline and at least once during the study period. The incidence of new vertebral fractures was analyzed by a log-rank test stratified by the number of prevalent vertebral fractures at baseline. Kaplan–Meier estimates of new vertebral fracture incidence were calculated at times when radiography was performed. A stratified proportional hazard model was used to estimate relative risks and 95% confidence intervals. Reported P values are defined by a two-sided alpha of 0.05, except for the primary endpoint in which significance was defined by a two-sided alpha of 0.10 with 90% confidence intervals.

This study examining the superiority of eldecalcitol over alfacalcidol in vertebral fracture prevention had a power of 90% to detect a 35% reduction in risk of morphometric vertebral fractures by eldecalcitol, assuming a 3-year incidence of 22.5% in the alfacalcidol group with 421 patients. Serum 25(OH)D at baseline was added as a stratification factor when primary analyses were conducted. Two-sided Student's t-tests were used to determine the intergroup differences in changes of BMD and bone turnover markers. No adjustments were made for multiple comparisons of all endpoints. No methods of imputation were used for missing data. The incidence of adverse events was compared by risk ratio. Results on spinal radiographs, BMD, biochemical markers, and other variables were collected centrally and transferred to the sponsor for statistical analyses. Seven pre-specified subgroups were analyzed with a stratified proportional hazard model to evaluate the interactions between treatments and subgroups with respect to the risk of incident vertebral fractures. We report the results of all these analyses. P values were calculated by log likelihood test. Statistical analyses were performed by statisticians from the sponsor, and the analyses were confirmed by an outside institution. The authors had access to all the data and take responsibility for the veracity of the analyses.

Results

There were no statistically significant differences in baseline characteristics between the eldecalcitol and the alfacalcidol groups (Table 1). Incident vertebral fractures occurred in 64 eldecalcitol-treated and 80 alfacalcidol-treated patients during the 36-month treatment period. Kaplan–Meier estimates of risk after 36 months were 13.4% in the eldecalcitol group and 17.5% in the alfacalcidol group,
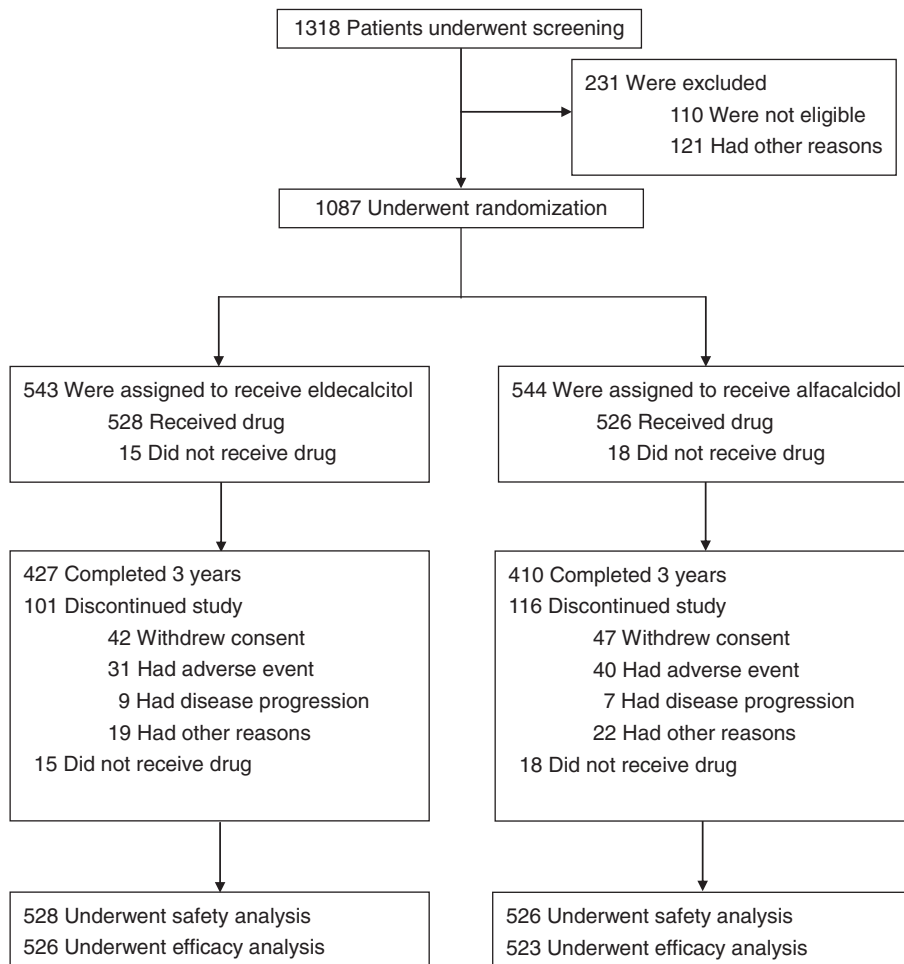

Fig. 1. Enrollment and outcomes. The 33 patients in both groups who did not receive a study drug at baseline were excluded from the safety analysis; 5 patients in the safety analysis who were ineligible for inclusion at baseline or did not have any efficacy data were excluded from the efficacy analysis.

Table 1
Baseline characteristics of enrolled patients.

	Eldecalcitol (n = 528)	Alfacalcidol (n = 526)
Age (years)	72.2 (6.60)	72.1 (6.64)
Height (cm)	149 (5.76)	149 (6.04)
Male patients	9 (1.70%)	15 (2.85%)
Body mass index (kg/m^2)	22.2 (3.19)	22.3 (3.20)
Time since menopause (years)	22.5 (7.78)	22.7 (7.69)
Number of prevalent vertebral fractures	1.18 (1.28)	1.25 (1.36)
0	199 (37.7%)	194 (36.9%)
1	156 (29.5%)	160 (30.4%)
≥ 2	173 (32.8%)	172 (32.7%)
Lumbar bone mineral density T-score	−2.71 (0.94)	−2.71 (0.91)
	(n = 527)	(n = 526)
Total hip bone mineral density T-score	−2.26 (0.82)	−2.27 (0.79)
	(n = 486)	(n = 485)
Serum bone-specific alkaline phosphatase (U/L)	33.3 (14.4)	33.8 (12.6)
Urinary type I collagen N-telopeptide (nmol BCE/mol Cr)	58.1 (58.6)	56.9 (32.7)
Ca intake (mg/day)	714 (343)	734 (337)
Serum 25(OH)D (HPLC-CPBA, nmol/L)	68.9 (22.3)	67.8 (22.0)
Serum 1,25(OH)$_2$D (pmol/L)	123.8 (35.3)	123.9 (37.9)
Serum intact PTH (pg/mL)	37.6 (15.1)	38.6 (14.3)

Data are means (SD) or number (%).

with a relative risk reduction of 26% by eldecalcitol ($P = 0.092$; 90% CI, 0.56–0.97) (Fig. 2A). The incidence of new vertebral fracture was not different between the two groups during the first 12 months; however, it was significantly lower in the eldecalcitol group during the third year (odds ratio 0.51; $P = 0.037$; 95% CI, 0.27–0.97) (Fig. 2B).

Eldecalcitol increased lumbar spine BMD by 2.3 percentage points at 12 months ($P < 0.001$) and 3.3 percentage points at 36 months compared with alfacalcidol ($P < 0.001$) (Fig. 3A). Eldecalcitol also increased total hip BMD by 1.4 percentage points at 12 months ($P < 0.001$) and 2.7 percentage points at 36 months ($P < 0.001$) compared with alfacalcidol (Fig. 3B).

Compared with alfacalcidol, eldecalcitol decreased serum BSAP by 17 percentage points at 12 months ($P < 0.001$) and 18 percentage points at 36 months ($P < 0.001$) (Fig. 3C). Urinary NTX was also significantly lower with eldecalcitol than with alfacalcidol by 29 percentage points at 12 months ($P < 0.001$) and by 23 percentage points at 36 months ($P < 0.001$) (Fig. 3D).

Serum 25(OH)D levels were elevated from baseline to 83.0 (SE 1.0) and 86.2 (1.0) nmol/L in eldecalcitol and alfacalcidol groups, respectively, at 6 months and remained at similar levels throughout the study (Fig. 4A). As a result, serum 25(OH)D levels were over 50 nmol/L in more than 92% of the patients during the study period. Serum 1,25(OH)$_2$D was suppressed sharply to 65.7 (SE 1.5) pmol/L in eldecalcitol group, whereas it was modestly elevated to 138 (1.6) in alfacalcidol group at 6 months, and remained almost stable during the study in both groups (Fig. 4B). Serum intact PTH levels were suppressed at 6 months in both groups, but the suppression was less in eldecalcitol group than in alfacalcidol group (Fig. 4C), as reported previously [7,12].

No significant difference was observed between the eldecalcitol and alfacalcidol groups in the incidence of total non-vertebral fractures at 36 months (8.0 and 9.5%, respectively; hazard ratio, 0.85; 95% CI, 0.55–1.31). Analysis of the two pre-defined subgroups revealed that the incidence of non-vertebral fractures tended to be lower at the major three sites (2.5 and 4.9%, respectively; hazard ratio, 0.51; 95% CI, 0.25–1.03). Post-hoc analysis of the fracture incidence in each of the three sites (humerus, wrist and hip) revealed that the incidence of only wrist fracture was significantly lower in the eldecalcitol group than in the alfacalcidol group at 36 months (1.1 and 3.6%, respectively; hazard ratio, 0.29; 95% CI, 0.11–0.77; $P = 0.009$) (Fig. 5). No significant difference between the two groups was observed in the fracture incidence of any other non-vertebral sites.
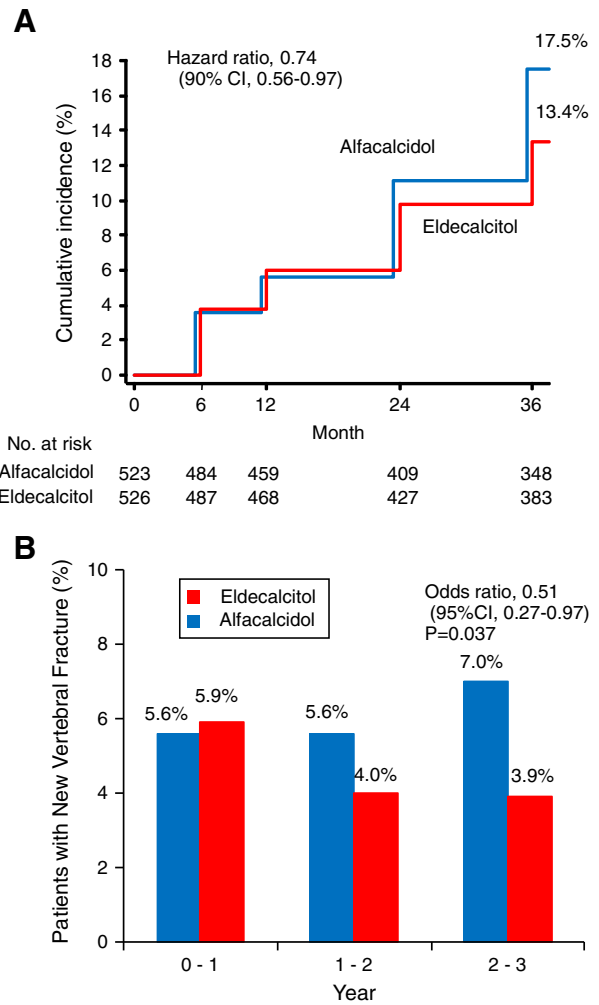

Fig. 2. Incidence of new vertebral fractures during the 3-year study period. Kaplan–Meier estimates of the incidence of new vertebral fractures (Panel A), the annual incidence of new vertebral fractures (Panel B) are shown for both study groups.

Adverse events with more than 5% incidence in either of the two groups are listed in Table 2. Urinary Ca excretion increased in both the eldecalcitol and alfacalcidol groups; mean postprandial urinary Ca levels at 36 months were 0.242 and 0.209 mg/dL GF (0.061 and 0.052 mmol/L GF), respectively. The increase in urinary Ca was not associated with a decrease in estimated glomerular filtration rate (eGFR) throughout the study period (69.0 ± 13.6 and 68.4 ± 14.5 at baseline, and 65.8 ± 14.4 and 66.7 ± 14.3 at 36 months with eldecalcitol and alfacalcidol, respectively; means ± SD). Increase in serum Ca over 10.4 mg/dL was observed at least once in the study in 111 and 71 patients, in eldecalcitol and alfacalcidol groups, respectively. Patients with hypercalcemia over 11.5 mg/dL (2.875 mmol/L) at least once during the study numbered 2 and 0 in the eldecalcitol and alfacalcidol groups, respectively. Serum and urinary Ca returned to baseline levels within 1 month after the study period (Supplement 1). The incidence of constipation and exanthem was lower in eldecalcitol than in alfacalcidol group (Table 2). There was no significant difference in the incidence of any other adverse events between the eldecalcitol and alfacalcidol groups.

Analyses of the seven pre-specified subgroups revealed that there were no significant interactions between treatment effect and any baseline clinical findings. Among patients with two or more prevalent vertebral fractures, the hazard ratio for incident vertebral fractures was 0.61 (95% CI, 0.40–0.93) in favor of eldecalcitol over alfacalcidol. The hazard ratio for incident vertebral fractures among patients with a total
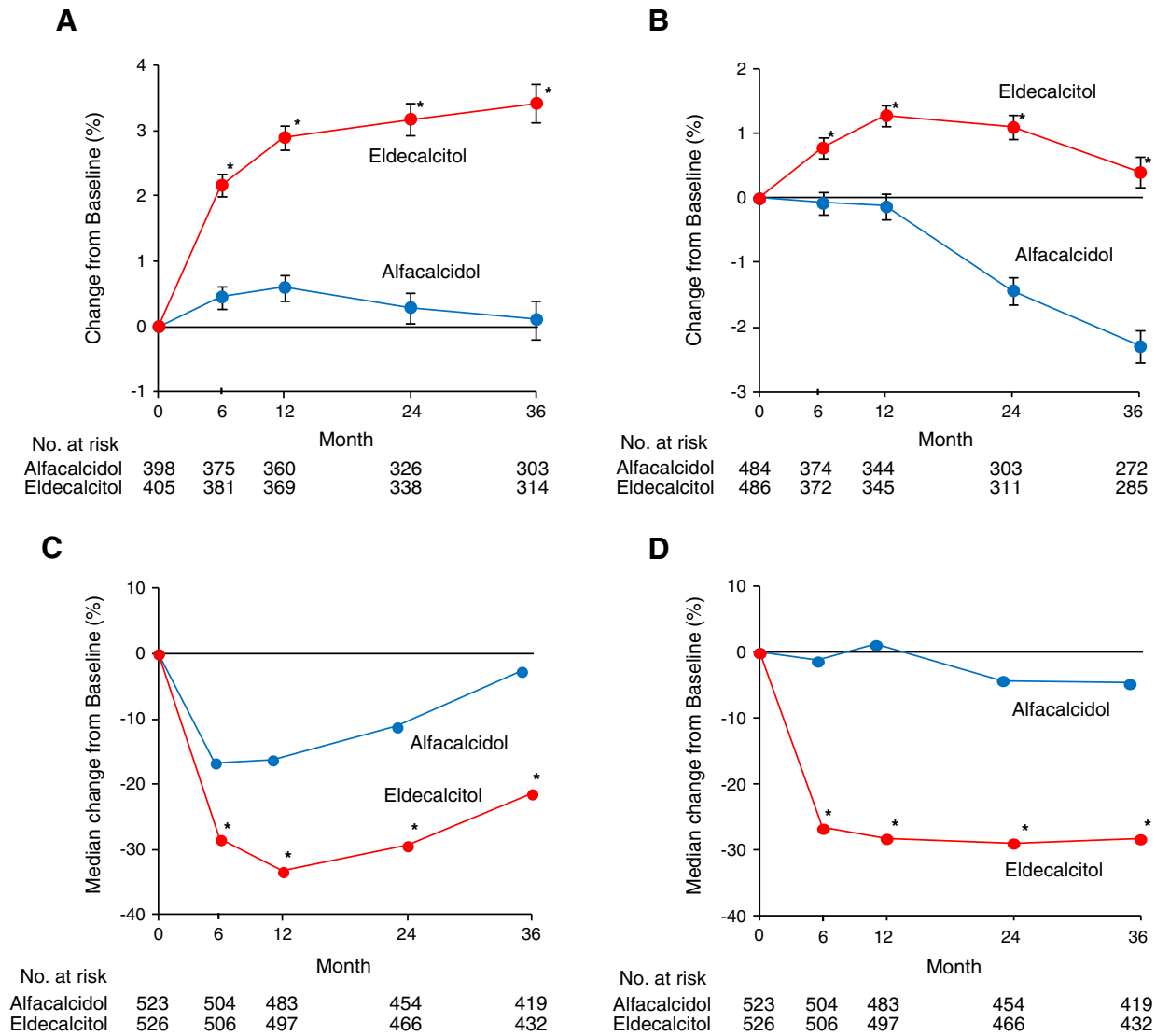
Fig. 3. Bone mineral density (BMD), and bone turnover markers during the 3-year study period. BMD of the lumbar spine (Panel A) and total hip (Panel B), and biochemical markers of bone turnover including serum bone-specific alkaline phosphatase (BSAP) (Panel C) and urinary N-terminal propeptide of type I collagen (NTX) (Panel D) are shown for both study groups. Data are means $\pm$ SE for lumbar spine and hip BMD, and medians for bone turnover markers. $*P<0.001$ in comparison with alfacalcidol.

hip BMD T-score of less than -2.5 was 0.56 (95% CI, 0.34–0.90), indicating the superior effect of eldecalcitol among patients with low total hip BMD (Fig. 6).

Discussion

This 3-year trial demonstrated that eldecalcitol decreased the risk of vertebral fractures more than did alfacalcidol. Subgroup analyses suggested that the effect of eldecalcitol on reducing risk of vertebral fractures is greater in patients with more severe osteoporosis, indicated by total hip BMD T-scores of less than -2.5 or multiple fractures.

The effect of alfacalcidol on vertebral fracture incidence has been examined. Some studies reported positive results [8,9], while others did not show a significant reduction in vertebral fractures with alfacalcidol [10,11]. A previous meta-analysis reported that active and native vitamin D_3 reduced the risk of vertebral fracture [17]. However, that analysis did not have the power to distinguish the effect of alfacalcidol and $1,25(OH)_2D_3$ from that of native vitamin D_3, and the effect of active vitamin D_3 was influenced by one large study using $1,25(OH)_2D_3$ [18]. Thus, controversy remained as to the anti-fracture effect of active vitamin D_3. In the present study, patients with serum 25(OH)D below 50 nmol/L were supplemented with 400 IU vitamin D_3 daily, and serum

25(OH)D was over 50 nmol/L in more than 92% of the patients. Because the anti-fracture effect of eldecalcitol was observed among vitamin D-sufficient osteoporotic patients, the effects of eldecalcitol on fractures, as well as on BMD [6], were unlikely to be the effect of supplementing for vitamin D insufficiency.

Eldecalcitol reduced vertebral fracture incidence with a suppression of urinary NTX as a bone resorption marker. As to the mechanism of the suppression of bone resorption, eldecalcitol was shown to reduce the number of preosteoblastic cells which interact with osteoclast precursors, resulting in a reduction in the number and activity of osteoclasts on the bone surface [19]. In agreement with these observations, in vivo administration of eldecalcitol to mice reduced perimeter of receptor activator of NF-kB ligand-positive cell surface around the trabecular bone (Saito H, et al. personal communication). These results are consistent with the notion that eldecalcitol suppresses the formation and activation of osteoclasts mainly via its effect on preosteoblastic cells.

In addition to preventing vertebral fractures, eldecalcitol reduced the incidence of wrist fracture, but had no significant effect on other non-vertebral fractures. There are two possibilities to explain at least a part of the effect on wrist fracture. First, we recently reported using clinical CT that eldecalcitol improved hip geometry better than alfacalcidol by increasing cross-sectional area, volumetric BMD, and cortical thickness
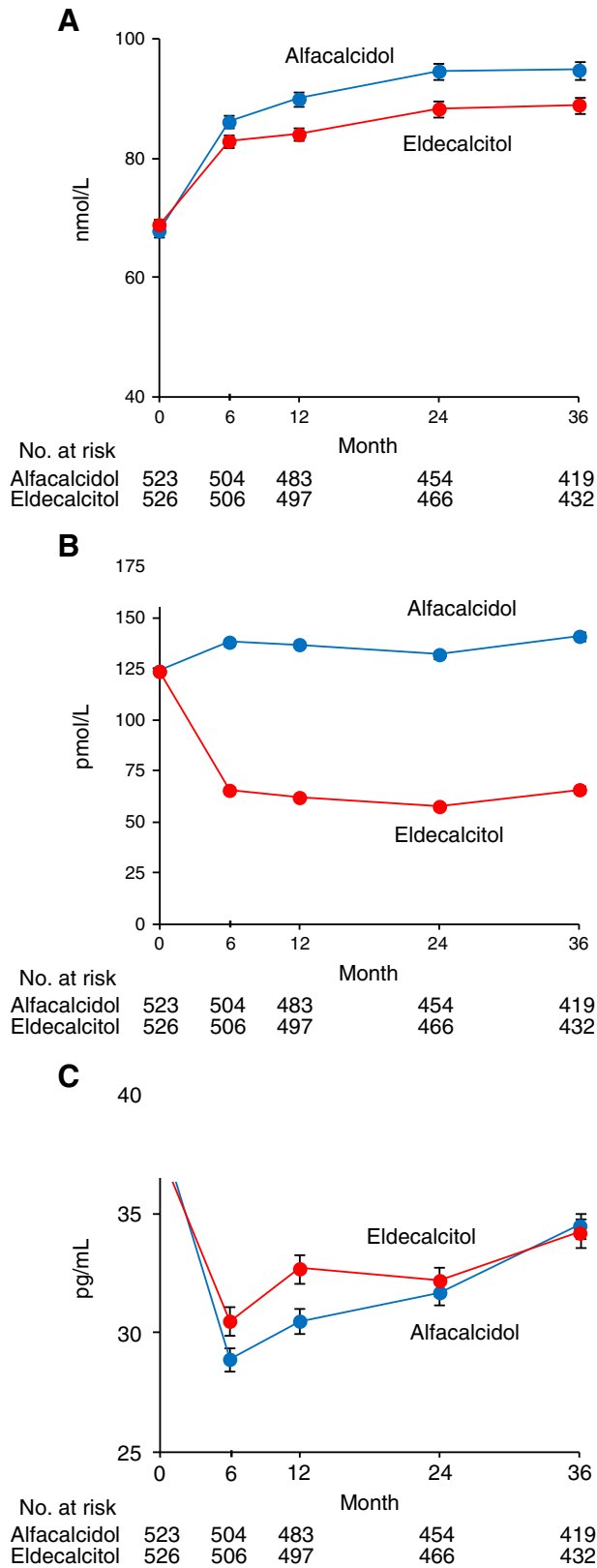
A

No. at risk

Alfacalcidol	523	504	483	454	419
Eldecalcitol	526	506	497	466	432

B

No. at risk

Alfacalcidol	523	504	483	454	419
Eldecalcitol	526	506	497	466	432

C

No. at risk

Alfacalcidol	523	504	483	454	419
Eldecalcitol	526	506	497	466	432

Fig. 4. Calcium-regulating hormones during the 3-year study period. Serum 25(OH)D (Panel A), serum 1,25(OH)$_2$D (Panel B), and serum intact PTH (Panel C) are shown for both study groups. Data are means ± SE.

by mitigating endocortical bone resorption [20]. Therefore, eldecalcitol may have a better effect in improving biomechanical properties of long bones. However, direct assessment of the effect of eldecalcitol on radial

No. at risk

Alfacalcidol	523	498	474	439	399
Eldecalcitol	526	504	491	455	425
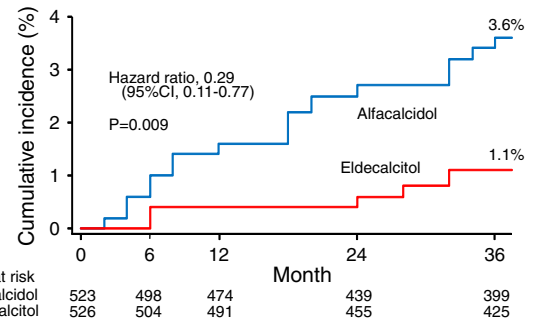
Fig. 5. Incidence of wrist fracture. Kaplan–Meier estimates of the incidence of wrist fractures in eldecalcitol and alfacalcidol groups are shown over a 3-year period.

geometry is required to clarify this issue. Second, although the incidence of falls was not monitored in the present study, there have been reports demonstrating the effect of vitamin D supplementation or active vitamin D treatment in reducing the risk of falls [21,22], and the effect was mediated by an improvement of postural and dynamic balance [23]. In addition, higher serum 1,25(OH)$_2$D$_3$ concentrations were associated with lower fall rates [24]. Because vitamin D receptor-deficient mice exhibit vestibular dysfunction with poor balance/posture control [25], and because Bsm1 polymorphism of vitamin D receptor gene is associated with the risk of falls [26], the effect of vitamin D on vestibular function and falls appears to be mediated via vitamin D receptor. Thus, there is a possibility that eldecalcitol may have a stronger effect than

Table 2
Incidence of adverse events.

Event[a]	Eldecalcitol (N = 528)	Alfacalcidol (N = 526)	Risk ratio	95% CI
	No. of patients[b]			
General				
Any adverse events	520 (98.5%)	518 (98.5%)	1.00	0.99–1.02
Nasopharyngitis	332 (62.9%)	312 (59.3%)	1.06	0.96–1.17
Contusion	119 (22.5%)	118 (22.4%)	1.00	0.80–1.26
Urine calcium increased	135 (25.6%)	82 (15.6%)	1.64	1.28–2.10
Blood calcium increased	111 (21.0%)	71 (13.5%)	1.56	1.19–2.04
Back pain	72 (13.6%)	81 (15.4%)	0.89	0.66–1.19
Osteoarthritis	82 (15.5%)	70 (13.3%)	1.17	0.87–1.57
Arthralgia	54 (10.2%)	52 (9.9%)	1.03	0.72–1.48
Eczema	54 (10.2%)	50 (9.5%)	1.08	0.75–1.55
Constipation	39 (7.4%)	58 (11.0%)	0.67	0.45–0.99
Headache	51 (9.7%)	39 (7.4%)	1.30	0.87–1.94
Diarrhea	50 (9.5%)	38 (7.2%)	1.31	0.88–1.96
Gastroenteritis	46 (8.7%)	41 (7.8%)	1.12	0.75–1.67
Periarthritis	45 (8.5%)	41 (7.8%)	1.09	0.73–1.64
Spinal fracture	38 (7.2%)	46 (8.7%)	0.82	0.54–1.24
Cystitis	36 (6.8%)	44 (8.4%)	0.82	0.53–1.24
Hypertension	41 (7.8%)	36 (6.8%)	1.13	0.74–1.75
Gastritis	34 (6.4%)	40 (7.6%)	0.85	0.54–1.32
Pain in extremity	31 (5.9%)	40 (7.6%)	0.77	0.49–1.21
Stomatitis	37 (7.0%)	32 (6.1%)	1.15	0.73–1.82
Dermatitis contact	38 (7.2%)	28 (5.3%)	1.35	0.84–2.17
Insomnia	34 (6.4%)	32 (6.1%)	1.06	0.66–1.69
Dizziness	29 (5.5%)	32 (6.1%)	0.90	0.55–1.47
Cataract	32 (6.1%)	27 (5.1%)	1.18	0.72–1.94
Joint sprain	29 (5.5%)	28 (5.3%)	1.03	0.62–1.71
Spinal osteoarthritis	23 (4.4%)	34 (6.5%)	0.67	0.40–1.13
Stomach discomfort	27 (5.1%)	25 (4.8%)	1.08	0.63–1.83
Exanthem	15 (2.8%)	33 (6.3%)	0.45	0.25–0.82
Serious adverse events	110 (20.8%)	134 (25.5%)	0.82	0.66–1.02
Death	4 (0.8%)	6 (1.1%)	0.66	0.19–2.34
Cancer	11 (2.1%)	16 (3.0%)	0.68	0.32–1.46
Discontinued due to adverse events	31 (5.9%)	40 (7.6%)	0.77	0.49–1.21
Calcium-related adverse events				
Urolithiasis	7 (1.3%)	5 (1.0%)	1.39	0.45–4.37

[a] Data are compiled using ICH Medical Terminology MedDRA Ver 8.0.
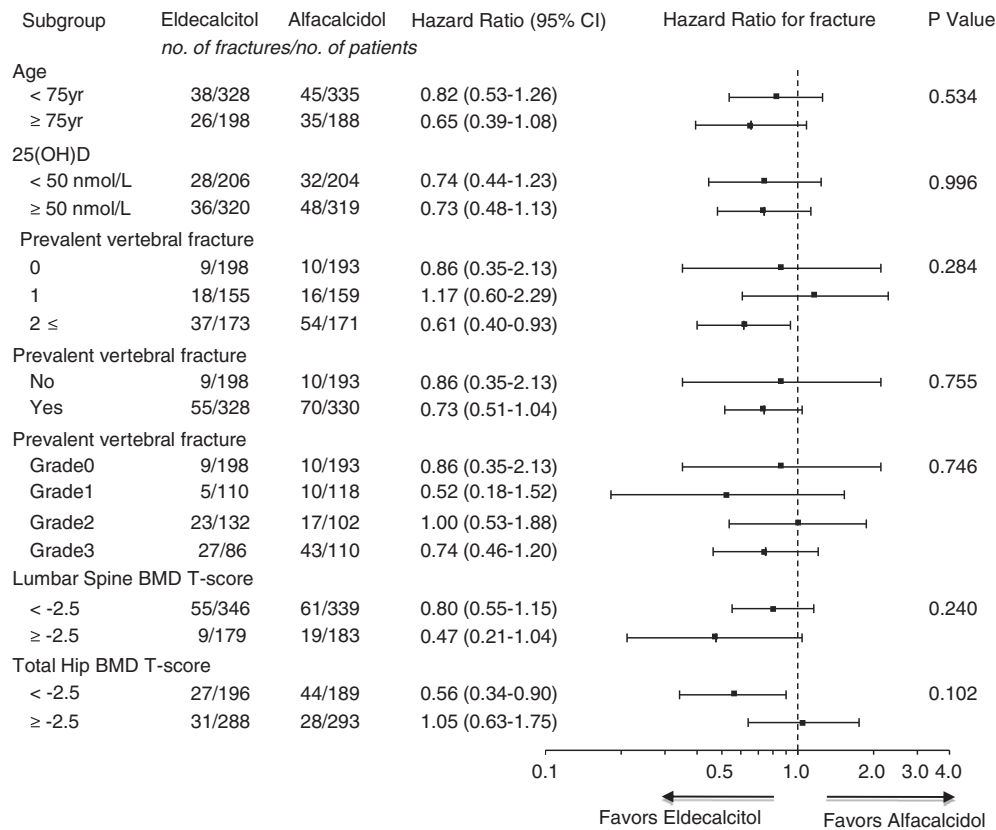[b] All data are reported as number of patients (%).

Subgroup	Eldecalcitol	Alfacalcidol	Hazard Ratio (95% CI)	Hazard Ratio for fracture	P Value
	no. of fractures/no. of patients				
Age					
< 75yr	38/328	45/335	0.82 (0.53-1.26)		0.534
≥ 75yr	26/198	35/188	0.65 (0.39-1.08)		
25(OH)D					
< 50 nmol/L	28/206	32/204	0.74 (0.44-1.23)		0.996
≥ 50 nmol/L	36/320	48/319	0.73 (0.48-1.13)		
Prevalent vertebral fracture					
0	9/198	10/193	0.86 (0.35-2.13)		0.284
1	18/155	16/159	1.17 (0.60-2.29)		
2 ≤	37/173	54/171	0.61 (0.40-0.93)		
Prevalent vertebral fracture					
No	9/198	10/193	0.86 (0.35-2.13)		0.755
Yes	55/328	70/330	0.73 (0.51-1.04)		
Prevalent vertebral fracture					
Grade0	9/198	10/193	0.86 (0.35-2.13)		0.746
Grade1	5/110	10/118	0.52 (0.18-1.52)		
Grade2	23/132	17/102	1.00 (0.53-1.88)		
Grade3	27/86	43/110	0.74 (0.46-1.20)		
Lumbar Spine BMD T-score					
< -2.5	55/346	61/339	0.80 (0.55-1.15)		0.240
≥ -2.5	9/179	19/183	0.47 (0.21-1.04)		
Total Hip BMD T-score					
< -2.5	27/196	44/189	0.56 (0.34-0.90)		0.102
≥ -2.5	31/288	28/293	1.05 (0.63-1.75)		

0.1   0.5   1.0   2.0 3.0 4.0

← Favors Eldecalcitol   Favors Alfacalcidol →

Fig. 6. Analysis for heterogeneity of treatment effect according to baseline characteristics. Subgroup analysis of the effect of eldecalcitol in comparison with alfacalcidol on vertebral fractures is shown according to seven pre-specified baseline characteristics.

alfacalcidol in preventing falls. Further studies to compare the effect of eldecalcitol with that of alfacalcidol on the risk of falls can clarify these issues, as well as the reasons why eldecalcitol treatment reduced the incidence of wrist fractures.

Serum $1,25(OH)_2D$ was suppressed by about 50% in eldecalcitol group, probably due to the suppressive effect of eldecalcitol on 25 (OH)D-1α-hydroxylase, while the suppression of serum intact PTH by eldecalcitol was less than that by alfacalcidol as reported previously [6,12]. Therefore, the stronger suppression of bone turnover by eldecalcitol cannot be explained by a suppression of PTH levels. Previous studies in animals revealed that eldecalcitol showed a stronger effect than alfacalcidol on bone compared with that on serum or urinary Ca [3,5]. Taken together, it is plausible to assume that eldecalcitol exerts a stronger suppression of bone turnover and a larger increase in BMD than alfacalcidol with similar effect on serum and urinary Ca, resulting in the superior effect in preventing vertebral and possibly wrist fractures.

It should be noted that the suppression of serum intact PTH and BSAP levels was maximum after 6 months of treatment by both eldecalcitol and alfacalcidol, and both of these levels tended to rise after 6 months. This was not due to changes in vitamin D or Ca metabolism, because serum 25 (OH)D and $1,25(OH)_2D$ were stable after 6 months of treatment, and serum and urinary Ca levels remained almost unchanged throughout the study period (Supplement 1). Thus, the reason for the dissipation of the suppressive effect of both eldecalcitol and alfacalcidol on intact PTH and BSAP levels after 6 months of treatment remains unclear.

The present study included 24 male patients; 9 of them were in eldecalcitol group and 15 of them were in alfacalcidol group. Incident vertebral fracture occurred in one out of 9 males and 2 out of 15 males in eldecalcitol and alfacalcidol groups, respectively. Mean changes in lumbar BMD were 10.9 and − 0.24 percentage points after 36 months of treatment with eldecalcitol and alfacalcidol, respectively. Mean changes in total hip BMD were 1.8 and − 0.61 percentage points after 36 months of treatment with eldecalcitol and alfacalcidol, respectively. From these results, the effect of eldecalcitol may be superior among males as well. However, the number of subjects was too small to draw any conclusions, and larger studies are needed to clarify this issue.

There was no significant difference in the incidence of any adverse events, and the number of serious adverse events was smaller in the eldecalcitol-treated group. Although the incidence of urinary Ca increase over 0.4 mg/dL GF was higher in the eldecalcitol group, the incidence of urolithiasis was the same and no significant difference in eGFR was observed between the two groups. In addition, the incidence of hypercalcemia of greater than 11.5 mg/dL was low in both groups (2 and 0 in the eldecalcitol and alfacalcidol groups, respectively). These results demonstrate that eldecalcitol is safe for at least 3 years.

The present study has limitations. First, the present study lacked a placebo group. Second, as a limitation relating to the size of the study as an active comparator study, the statistical significance of the primary endpoint was predefined as a two-sided alpha of 0.10 with 90% confidence interval. Finally, although there was no statistical difference in the incidence of hypercalcemia over 11.5 mg/dL or urolithiasis between the eldecalcitol and alfacalcidol groups, the incidence of increase in serum and urinary Ca was significantly higher in the eldecalcitol group. Therefore, the long-term safety of eldecalcitol needs to be studied.

In conclusion, in vitamin D-sufficient patients with osteoporosis, daily treatment with 0.75 μg eldecalcitol for 3 years is associated with a lower risk of vertebral and wrist fractures, greater improvements in lumbar spine BMD, and greater decreases in bone turnover than daily treatment with 1.0 μg alfacalcidol. The long-term efficacy and safety remains to be studied.

References

[1] Miyamoto K, Murayama E, Ochi K, Watanabe H, Kubodera N. Synthetic studies of vitamin D analogues. XIV. Synthesis and calcium regulating activity of vitamin D3 analogues bearing a hydroxyalkoxy group at the 2 beta-position. Chem Pharm Bull (Tokyo) 1993;41:1111–3.
[2] Tsurukami H, Nakamura T, Suzuki K, Sato K, Higuchi Y, Nishii Y. A novel synthetic vitamin D analogue, 2 beta-(3-hydroxypropoxy)1 alpha, 25-dihydroxyvitamin D3 (ED-71), increases bone mass by stimulating the bone formation in normal and ovariectomized rats. Calcif Tissue Int 1994;54:142–9.
[3] Uchiyama Y, Higuchi Y, Takeda S, Masaki T, Shira-ishi A, Sato K, et al. ED-71, a vitamin D analog, is a more potent inhibitor of bone resorption than alfacalcidol in an estrogen-deficient rat model of osteoporosis. Bone 2002;30:582–8.
[4] Matsumoto T, Kubodera N, Group TE-S. 1alpha,25-Dihydroxy-2beta-(3-hydroxypropoxy) vitamin D3 (ED-71): a promising candidate for the treatment of osteoporosis. University of California, Riverside: Vitamin D Workshop, Inc.; 2000. p. 985–92.
[5] Kubodera N, Tsuji N, Uchiyama Y, Endo K. A new active vitamin D analog, ED-71, causes increase in bone mass with preferential effects on bone in osteoporotic patients. J Cell Biochem 2003;88:286–9.
[6] Matsumoto T, Miki T, Hagino H, Sugimoto T, Okamoto S, Hirota T, et al. A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab 2005;90:5031–6.
[7] Matsumoto T, Kubodera N. ED-71, a new active vitamin D3, increases bone mineral density regardless of serum 25(OH)D levels in osteoporotic subjects. J Steroid Biochem Mol Biol 2007;103:584–6.
[8] Hayashi Y, Fujita T, Inoue T. Decrease of vertebral fracture in osteoporotics by administration of 1alpha-hydroxy-vitamin D3. J Bone Miner Metab 1992;10:184–8.
[9] Orimo H, Shiraki M, Hayashi S, Hoshino T, Onaya T, Miyazaki S, et al. Effects of 1 alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. Calcif Tissue Int 1994;54:370–6.
[10] Shiraki M, Kushida K, Yamazaki K, Nagai T, Inoue T, Orimo H. Effects of 2 years' treatment of osteoporosis with 1 alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. Endocr J 1996;43:211–20.
[11] Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: the Yamaguchi Osteoporosis Prevention Study. Am J Med 2004;117:549–55.
[12] Matsumoto T, Takano T, Yamakido S, Takahashi F, Tsuji N. Comparison of the effects of eldecalcitol and alfacalcidol on bone and calcium metabolism. J Steroid Biochem Mol Biol 2010;121:261–4.
[13] Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I, et al. Diagnostic criteria of primary osteoporosis. J Bone Miner Metab 1998;16:139–50.
[14] Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, et al. Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 2001;19:331–7.
[15] Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137–48.
[16] Fukunaga M, Nakamura T, Shiraki M, Kuroda T, Ohta H, Hosoi T, et al. Absolute height reduction and percent height ratio of the vertebral body in incident fracture in Japanese women. J Bone Miner Metab 2004;22:104–10.
[17] Papadimitropoulos E, Wells G, Shea B, Gillespie W, Weaver B, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmeno-pausal women. Endocr Rev 2002;23:560–9.
[18] Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992;326:357–62.
[19] de Freitas PH, Hasegawa T, Takeda S, Sasaki M, Tabata C, Oda K, et al. Eldecalcitol, a second-generation vitamin D analog, drives bone minimodeling and reduces osteoclastic number in the trabecular bone of ovariectomized rats. Bone 2011;49:335–42.
[20] Ito M, Nakamura T, Fukunaga M, Shiraki M, Matsumoto T. Effect of eldecalcitol, an active vitamin D analog, on hip structure and biomechanical properties: 3D assessment by clinical CT. Bone 2011;49:328–34.
[21] Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA 2004;291:1999–2006.
[22] Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
[23] Bischoff-Ferrari HA, Conzelmann M, Stahelin HB, Dick W, Carpenter MG, Adkin AL, et al. Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? Osteoporos Int 2006;17:656–63.
[24] Faulkner KA, Cauley JA, Zmuda JM, Landsittel DP, Newman AB, Studenski SA, et al. Higher 1,25-dihydroxyvitamin D3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporos Int 2006;17:1318–28.
[25] Minasyan A, Keisala T, Zou J, Zhang Y, Toppila E, Syvala H, et al. Vestibular dysfunction in vitamin D receptor mutant mice. J Steroid Biochem Mol Biol 2009;114:161–6.
[26] Barr R, Macdonald H, Stewart A, McGuigan F, Rogers A, Eastell R, et al. Association between vitamin D receptor gene polymorphisms, falls, balance and muscle power: results from two independent studies (APOSS and OPUS). Osteoporos Int 2010;21:457–66.