Eldecalcitol for the treatment of osteoporosis

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Abstract: Eldecalcitol (1α, 25-dihydroxy-2β-[3-hydroxypropyloxy] vitamin D3; ED-71) is a new analog of the active form of vitamin D. Eldecalcitol has recently been approved for the treatment of osteoporosis in Japan. In addition to regulation of calcium metabolism carried out by conventional vitamin D analogs, eldecalcitol possesses a strong inhibitory effect on bone resorption and causes a significant increase in bone mineral density. A Phase III clinical trial on osteoporosis showed that eldecalcitol reduced the incidence of new vertebral fractures over 3 years by 26% compared with alfacalcidol. Although the overall risk of nonvertebral fractures was not reduced by eldecalcitol, the risk of wrist fracture was decreased significantly in the eldecalcitol group (71%) compared with the alfacalcidol group. The serum level of 25-hydroxyvitamin D (25(OH)D) was normalized by supplementation of native vitamin D in this trial, so the desirable effects on bone by eldecalcitol were considered to be derived from its distinctive pharmacological action. Increased blood calcium was observed in 21% of patients treated with eldecalcitol, and hypercalcemia (>11.5 mg/dL) occurred in 0.4% of eldecalcitol recipients, so serum calcium concentration should be monitored after starting eldecalcitol treatment. Eldecalcitol has dual effects on the metabolism of bone and calcium and is useful for the treatment of osteoporosis, especially for elderly patients (who frequently suffer from vitamin D deficiency). This article reviews the clinical efficacy and safety of eldecalcitol in the treatment of osteoporosis.

Keywords: vitamin D, osteoporosis, bone mineral density, nonvertebral fracture

Introduction

Osteoporosis is a systemic skeletal disease associated with low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture risk.1 Osteoporosis-related fractures occur commonly in the spine, hip and distal radius. These fractures impact negatively on quality of life and increase morbidity and mortality.2,3 Treatment of osteoporosis is important for preventing osteoporotic fractures and reducing the health care burden.

Vitamin D is a crucial factor for the intestinal absorption of calcium to maintain bone strength. A deficiency in vitamin D causes impaired absorption of calcium and bone mineralization, leading to rickets in children and osteomalacia in adults.4–6 The elderly are at risk of a deficiency and an insufficiency of vitamin D because of their reduced mobility and consequent decreased exposure to sunshine, a low food intake, and decline in renal function.4,7 Vitamin D insufficiency causes greater secretion of parathyroid hormone (PTH) due to the low serum levels of calcium and active vitamin D, resulting in high bone turnover and increased bone resorption. Vitamin D insufficiency is also associated with muscle weakness, leading to an increased risk of falling.8,9
These detrimental effects may contribute to osteoporosis and increased fracture risk in patients with a deficiency and an insufficiency of vitamin D.\textsuperscript{10}

Clinical trials have suggested that the active form of vitamin D reduces the risk of fractures and falls.\textsuperscript{11–13} A new analog of vitamin D, eldecalcitol, has recently been approved for the treatment of osteoporosis in Japan. Eldecalcitol has strong effects on the reduction of bone resorption and increase in bone mineral density (BMD) in addition to the effects on calcium metabolism retained by conventional vitamin D analogs.\textsuperscript{14,15}

**Vitamin D**

**Metabolism and action**

Vitamin D is one of the lipid-soluble hormones produced in the skin through ultraviolet irradiation of 7-dehydrocholesterol. Vitamin D is also obtained from animal-based (vitamin D\textsubscript{3}) or plant-based (vitamin D\textsubscript{2}) foods.\textsuperscript{10,16} In the human body, vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25[OH]D) and subsequently in the kidney to its biologically active form: 1,25-dihydroxyvitamin D (1,25[OH]\textsubscript{2}D) (Figure 1).\textsuperscript{16,17} In the circulation, these vitamin D metabolites (25[OH]D and 1,25[OH]\textsubscript{2}D) are bound to vitamin D-binding protein (DBP). The active metabolite 1,25(OH)\textsubscript{2}D enters the cell and binds to the vitamin D receptor (VDR), which belongs to the nuclear receptor superfamily. This ligand-bound VDR forms a heterodimer with the retinoid X receptor (RXR). The VDR/RXR complex binds to the vitamin D-responsive element on a target gene to regulate its transcription. Vitamin D regulates serum concentrations of calcium and phosphate by increasing intestinal absorption of calcium and phosphate, promoting renal reabsorption of calcium, and stimulating bone resorption.\textsuperscript{16,18}

**Vitamin D deficiency and osteoporosis**

The serum level of 25(OH)D is the best indicator of vitamin D status.\textsuperscript{19,20} Vitamin D deficiency is defined as a 25(OH)D level < 20 ng/mL (50 nmol/L) and vitamin D insufficiency as a 25(OH)D level of 21–29 ng/mL (52.5–72.5 nmol/L).\textsuperscript{19,20} Deficiency/insufficiency of vitamin D is very common in elderly people due to their low intake of vitamin D, decreased exposure to sunlight, and impaired renal function. More than one-half of postmenopausal women have a 25(OH)D level < 30 ng/mL.\textsuperscript{21,22}

Severe vitamin D deficiency can cause rickets in children and osteomalacia in adults, characterized by impaired bone mineralization.\textsuperscript{9,10} Conversely, deficiency/insufficiency of vitamin D causes a decrease in the serum concentration of calcium due to a reduction in intestinal absorption of calcium. This hypocalcemia stimulates PTH secretion (secondary hyperparathyroidism), resulting in an increase in bone resorption and decrease of BMD. This may contribute to the

![Figure 1](https://www.dovepress.com/)

Figure 1 Chemical structures of native vitamin D\textsubscript{3} and active vitamin D\textsubscript{3} analogs.
pathogenesis of osteoporosis. Vitamin D deficiency is also associated with muscle weakness, leading to an increased risk of falling and fractures. A significant correlation between the serum concentration of 25(OH)D and falls in elderly people has been reported.

Active form of vitamin D for the treatment of osteoporosis

The active form of vitamin D (1α,25-dihydroxyvitamin D₃, calcitriol) and its prodrug (1α-hydroxyvitamin D₃, alfacalcidol) have been approved for the treatment of osteoporosis in Japan (Figure 1). Both calcitriol and alfacalcidol showed a modest increase in BMD and reduced the risk of vertebral and nonvertebral fractures. The number of falls were also reduced by treatment with active vitamin D analogs.

Meta-analyses suggest that the vitamin D analogs (alfacalcidol and calcitriol) are more effective in preventing bone loss, fractures, and falls compared with native vitamin D.

Eldecalcitol

Eldecalcitol: a new, active vitamin D analog

Eldecalcitol (1α, 25-dihydroxy-2β-[3-hydroxypropyloxy] vitamin D₃, ED-71) has a hydroxypropyloxy group at the 2β-position of 1,25(OH)₂D₃, which has been isolated from >900 vitamin D analogs, based on the activity that stimulated BMD in vivo. Compared with 1,25(OH)₂D₃, eldecalcitol has a higher affinity for serum DBP, binds more weakly to VDR, and shows lower potency in suppression of serum PTH (Table 1). The plasma half-life of eldecalcitol is longer than that of 1,25(OH)₂D₃, probably due to the higher affinity for DBP.

Preclinical studies

In ovariectomized (OVX) animal models of osteoporosis, eldecalcitol suppressed osteoclastic bone resorption and increased BMD to a greater extent than alfacalcidol. There was no significant difference in calcium absorption and serum PTH suppression between eldecalcitol and alfacalcidol, so the effect of increasing BMD by eldecalcitol seems to be independent of calcium metabolism. Eldecalcitol also prevented glucocorticoid-induced alterations in bone metabolism by increasing intestinal absorption of calcium, reducing osteoclastic bone resorption, and enhancing mineralization in OVX rats. Histological and histomorphological analyses revealed that eldecalcitol and alfacalcidol reduced osteoclast numbers and diminished osteoclastic activity/function without promoting osteoclast apoptosis in OVX rats. It has been shown that administration of eldecalcitol preferentially suppressed the expression of receptor activator of nuclear factor kappa B ligand (RANKL) in osteoblast-lineage cells around the trabecular bone compared with 1,25(OH)₂D₃. Eldecalcitol and alfacalcidol dose-dependently stimulated focal bone formation that started without prior bone resorption (bone mimimodeling). Reduction of bone resorption and stimulation of focal bone formation were more clearly observed in eldecalcitol-treated rats than in 1,25(OH)₂D₃-treated rats.

Combination treatment of eldecalcitol with alendronate or raloxifene in OVX rats

In OVX rats, the combination of alendronate and eldecalcitol improved the mechanical properties of the lumbar spine and mid-shaft femur by additive suppression of bone resorption while maintaining bone formation, which was more beneficial than monotherapy with alendronate or eldecalcitol. The combination of alendronate and eldecalcitol had a more beneficial antiosteoporotic effect by inhibiting osteoclastic bone resorption and maintaining osteoblastic function, compared with combination treatment with alendronate and alfacalcidol. Combination treatment with eldecalcitol and raloxifene improved bone mechanical strength in OVX rats more than either type of monotherapy by increasing BMD and suppressing bone turnover.

Clinical studies

Pharmacokinetics and pharmacology

A single dose of eldecalcitol (0.75 µg) was administered to 32 healthy men while fasting. The vitamin D analog was absorbed rapidly and eliminated gradually from serum, with a mean time to maximum drug concentration (Tₘₐₓ) of ~3.4 hours and a mean half-life (t₁/₂) of ~53 hours. The time courses of serum eldecalcitol concentrations with administration while fasting and after a meal were similar. With multiple dosing, the serum eldecalcitol concentration reached steady state by
13 days after the first dose. The pharmacokinetics of eldecalcitrol were linear in the dose range 0.1–1.0 µg.\textsuperscript{45}

To compare the effects of eldecalcitrol and alfacalcidol on the metabolism of bone and calcium, a randomized open-label clinical trial was conducted in 59 post-menopausal women. Eldecalcitrol could effectively inhibit bone resorption more strongly than alfacalcidol with a similar effect on bone formation and a comparable effect on urinary excretion of calcium.\textsuperscript{46}

**Phase II studies**

In an early Phase II clinical trial, a randomized controlled study with eldecalcitrol was conducted with 109 osteoporotic subjects. The patients were assigned randomly to 0.25, 0.5, 0.75, or 1.0 µg/day of eldecalcitrol administered via the oral route for 6 months. Eldecalcitrol increased lumbar BMD in a dose-dependent manner without causing hypercalcemia or hypercalcuria. Eldecalcitrol also exhibited a dose-dependent suppression of a bone resorption marker (urinary deoxypyridinoline) without a significant reduction in osteocalcin.\textsuperscript{47,48}

Many patients have serum 25(OH)D levels <20 ng/mL. Hence, the effect of eldecalcitrol on bone mass might be influenced by vitamin D insufficiency and could merely reflect a nutritional supplementary effect of vitamin D insufficiency. To solve this problem, a randomized, double-blind, placebo-controlled clinical trial was conducted with 219 osteoporotic patients under vitamin D supplementation (200 or 400 IU/day). Subjects were assigned randomly to receive 0.5, 0.75, or 1.0 µg/day of eldecalcitrol for 12 months. After treatment with eldecalcitrol for 12 months, lumbar spine BMD increased from baseline by 2.2%, 2.6%, and 3.1% in the 0.5, 0.75, and 1.0 µg eldecalcitrol groups, respectively; whereas, lumbar spine BMD decreased by 0.7% in the placebo group. Total hip BMD also increased with 0.75 and 1.0 µg eldecalcitrol from baseline by 0.6% and 0.9%, respectively. Conversely, in the placebo and 0.5 µg eldecalcitrol group, total hip BMD decreased slightly from baseline (−0.9% and −0.8%). Markers of bone formation and resorption were suppressed by ≥20% after 12 months of treatment with 0.75 and 1.0 µg eldecalcitrol. Transient increase in serum calcium level >10.4 mg/dL (>2.6 mmol/L) occurred in 7%, 5%, and 23% of subjects in the 0.5, 0.75, and 1.0 µg eldecalcitrol groups, respectively; but none of them developed sustained hypercalcaemia.\textsuperscript{49} Post hoc analyses of the trial revealed that eldecalcitrol could increase lumbar and hip BMD in osteoporotic patients, regardless of their vitamin D status.\textsuperscript{50,51} These results suggest that eldecalcitrol can exert its effect on bone independently of the nutritional supplementation with native vitamin D.

**Phase III studies**

Based on the results of Phase II clinical studies, a 3-year, randomized, double-blind, active comparator, superiority trial was carried out to compare the effect of eldecalcitrol (0.75 µg/day) with that of alfacalcidol (1 µg/day) in preventing fractures in patients with osteoporosis.\textsuperscript{52} A total of 1,054 patients aged 46–92 years (mean, 72.1 years) were assigned randomly to receive eldecalcitrol (n = 528) or alfacalcidol (n = 526). Patients with low serum levels of 25(OH)D (<20 ng/mL) were supplemented with 400 IU/day of vitamin D. Compared with the alfacalcidol group, the incidence of vertebral fractures was lower in the eldecalcitrol group after 36 months of treatment (13.4% versus 17.5%) with a relative risk reduction of 26% (P = 0.092; hazard ratio [HR] 0.74; 90% confidence interval [CI]: 0.56–0.97) (Figure 2). The incidence of new vertebral fractures was not different between the two groups during the first year, but was significantly lower in the eldecalcitrol group during the third year (3.9% versus 7.0%, odds ratio [OR] 0.51, P = 0.037; 95% CI 0.27–0.97). With regard to the total number of nonvertebral fractures at 36 months, no significant difference was observed between the eldecalcitrol and alfacalcidol groups (8.0% versus 9.5%, HR 0.85, 95% CI 0.55–1.31). However, eldecalcitrol reduced the incidence of three major nonvertebral fractures (humerus, wrist, hip) compared with alfacalcidol (2.5% versus 4.9%, HR 0.51, 95% CI 0.25–1.03), which was due, in particular, to a marked decrease in the incidence of wrist fractures (1.1%)}
Eldecalcitol increased lumbar and hip BMD more strongly than alfacalcidol (Figures 4A and B). Levels of bone turnover markers (bone-specific alkaline phosphatase [BSAP] and urinary crosslinked N-telopeptide of type-I bone collagen [NTX]) were significantly lower with eldecalcitol than with alfacalcidol (Figures 4C and D). The decrease from baseline in bone turnover markers after the eldecalcitol treatment exceeded the minimum significant change, authorized by the Japan Osteoporosis Society. These results suggest that eldecalcitol is more efficacious than alfacalcidol in preventing vertebral and wrist fractures in osteoporotic patients.

Among the adverse events, the prevalence of an increase in serum and urinary levels of calcium was higher in the eldecalcitol group compared with the alfacalcidol group (Table 2). Increased serum calcium was observed in 21.0% of eldecalcitol recipients and 13.5% of alfacalcidol recipients, while hypercalcemia developed in two patients (0.4%) in the eldecalcitol group but none in the alfacalcidol group. There was no significant difference in the prevalence of urolithiasis and in the estimated glomerular filtration rate between the two groups.

Post hoc analyses of the Phase III study revealed that the incidence of vertebral fracture at the lower spine was lower in the eldecalcitol group than in the alfacalcidol group (P = 0.029). The incidence of severe vertebral fractures (grade III) was lower in the eldecalcitol group than in the alfacalcidol group (3.8% versus 6.7%; HR, 0.53; 95% CI, 0.29–0.96; P = 0.036). Eldecalcitol and alfacalcidol improved health-related quality of life (HRQoL) scores, but overall improvement from the baseline of HRQoL scores was observed clearly in the eldecalcitol group.

Eldecalcitol reduced the incidence of osteoporotic fractures, as defined by the World Health Organization, more than alfacalcidol (18.6% versus 25.2%; HR, 0.70; 90% CI, 0.54–0.93; P = 0.013) and decreased the risk of major osteoporotic fractures included in the Fracture Risk Assessment Tool (FRAX) (11.1% versus 16.3%; HR, 0.66; 95% CI, 0.46–0.94; P = 0.020). A significant decrease in the incidence of nonvertebral fractures was also observed in the eldecalcitol group.

To ascertain if eldecalcitol can cause severely suppressed bone turnover, post hoc analyses of the Phase III trial about the changes in bone turnover markers after eldecalcitol
Eldecalcitol reduced markers of bone turnover rapidly and kept them within the normal range. In patients whose baseline values for bone turnover markers were low, eldecalcitol treatment did not reduce the bone turnover markers further during a 3-year treatment period.

The effects of eldecalcitol on bone geometry and the biomechanical properties of the proximal femur were investigated by computed tomography in a subgroup of the Phase III study (n = 193). Longitudinal analyses of hip geometry revealed the advantages of eldecalcitol over alfacalcidol in: increased cortical cross-sectional area; volumetric BMD of the neck and shaft of the femur; bone mass; and maintenance of cortical thickness (probably through mitigating endocortical bone resorption). By improving the biomechanical properties of the proximal femur, eldecalcitol could reduce the risk of hip fracture.

The vitamin D analogs alfacalcidol and calcitriol have been used for the treatment of osteoporosis in Japan. However, these drugs are not used as first-line therapy for osteoporosis, because they have weaker inhibitory effects on fractures than bisphosphonates, selective estrogen receptor modulators, or teriparatide. The new active form of vitamin D, eldecalcitol,
Eldecalcitol has stronger effects on the inhibition of bone resorption, increases BMD, and prevents osteoporotic fractures compared with alfacalcidol. It has been reported that native and active vitamin D increased lower osteoclast number and decreased bone resorption. The increased macrophage number and the decreased osteoclast number in the bone marrow of eldecalcitol-treated rats were also observed. Recent histological analyses in OVX rats revealed that the preosteoblastic layer, with which osteoclastic precursors interact for mutual differentiation, was poorly developed in eldecalcitol-treated rats. Eldecalcitol also promoted focal bone formation, known as bone minimodeling, which is independent of bone resorption. The increased macrophage number and the decreased osteoclast number in the bone marrow of eldecalcitol-treated rats were also observed. It has also been reported that RANKL was expressed preferentially by immature osteoblasts, and the expression level decreased during bone formation, known as bone minimodeling, which is independent of bone resorption. The increased macrophage number and the decreased osteoclast number in the bone marrow of eldecalcitol-treated rats were also observed.
A recent study revealed that the active form of vitamin D, including eldecalcitol, significantly suppressed the expression of bone tropic S1PR2 in circulating osteoclast precursor monocytes. As a result, mobilization of the osteoclast precursor monocytes from the bone to the blood was enhanced, causing a suppression of bone resorption.

**Conclusion**

Eldecalcitol possesses a strong inhibitory effect on bone resorption and causes a significant increase in BMD. Phase III clinical trials revealed that the incidence of vertebral and wrist fractures was significantly reduced in the eldecalcitol group compared with the alfacalcidol group. To date, eldecalcitol is not available outside of Japan. Therefore, all clinical trials have been conducted in Japan. This unique vitamin D analog is thought to be useful, especially for patients with osteoporosis and vitamin D deficiency. Approval of the drug for osteoporosis treatment in other countries is expected. Increases in blood and urinary levels of calcium were the most frequent adverse events in the treatment with eldecalcitol, though hypercalcemia was observed in only a few patients. Blood and urinary calcium should be monitored during eldecalcitol treatment. Large-scale clinical trials that compare the effects of eldecalcitol with other drugs for osteoporosis, as well as evaluation of combination therapy, should be carried out.

**Disclosure**

The authors report no conflicts of interest in this work.

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