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A New Active Vitamin D Analog, ED-71, Causes Increase in Bone Mass with Preferential Effects on Bone in Osteoporotic Patients

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Abstract As a candidate for active vitamin D analogs that have selective effects on bone, 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D3 (ED-71) has been synthesized and is currently under clinical trials. In ovariectomized rat model for osteoporosis, ED-71 caused an increase bone mass at the lumbar vertebra to a greater extent than 1α-hydroxyvitamin D3 (alfacalcidol), while enhancing calcium absorption and decreasing serum parathyroid hormone levels to the same degree as alfacalcidol. ED-71 lowered the biochemical and histological parameters of bone resorption more potently than alfacalcidol, while maintaining bone formation markers.An early phase II clinical trial was conducted with 109 primary osteoporotic patients. The results indicate that oral daily administration of ED-71 (0.25, 0.5, 0.75, and 1.0 μg) for 6 months increased lumbar bone mineral density in a dose-dependent manner without causing hypercalcemia and hypercalciuria. ED-71 also exhibited a dose-dependent suppression of urinary deoxypyridinoline with no significant reduction in serum osteocalcin. These results demonstrate that ED-71 has preferential effects on bone with diminished effects on intestinal calcium absorption. ED-71 offers potentially a new modality of therapy for osteoporosis with selective effects on bone. J. Cell. Biochem. 88: 286–289, 2003.

Key words: 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D3; ED-71; 1α-hydroxyvitamin D3; 1α,25-dihydroxyvitamin D3; osteoporosis; alfacalcidol

Various analogs of 1α,25-dihydroxyvitamin D3 [1,25(OH)2D3], a hormonally active sterol of native vitamin D3, have been investigated in attempts to separate differentiation-induction and antiproliferation activities from calcemic activity, with the aim of obtaining useful analogs for the medical treatment of psoriasis, secondary hyperparathyroidism, cancer, etc. [Bouillon et al., 1995]. There is also much interest in obtaining analogs more potent than 1,25(OH)2D3 or 1α-hydroxyvitamin D3 (alfacalcidol), a clinically important prodrug of 1,25(OH)2D3 that can modulate calcium and phosphorous metabolism. Such compounds represent a potential treatment for bone diseases such as osteoporosis [Miyamoto et al., 1993]. 1α,25-Dihydroxy-2β-(3-hydroxypropoxy) vitamin D3 (ED-71) is an analog of 1,25(OH)2D3 bearing a hydroxypropoxy substituent at the 2β-position [Ono et al., 1997] and [Ono et al., 1998] and possesses one eighth the binding affinity to vitamin D receptor (VDR) and 2.7-fold affinity to vitamin D binding protein (DBP) (Fig. 1). The relatively long plasma half-life of ED-71 is believed to be due to its strong affinity to DBP [Okano et al., 1989]. In our initial evaluation of ED-71 using ovariectomized (OVX) rats, orally administered ED-71 showed a dose-dependent increase in bone mass (Fig. 2) [Kobayashi et al., 1993]. Thus, the development of ED-71 as a promising candidate for the treatment of osteoporosis was initiated. In this article, ED-71 and alfacalcidol are compared using OVX rats and early phase II clinical results of ED-71 are disclosed.

COMPARISON EXPERIMENTS WITH ALFACALCIDOL

Although active vitamin D is used in certain countries for the treatment of osteoporosis, the risk of causing hypercalcemia/hypercalciuria

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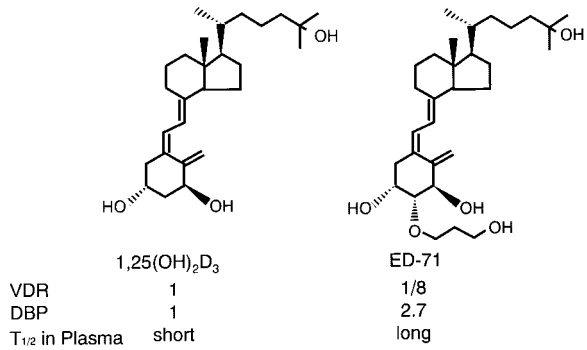

Fig. 1. Structure and basic characteristics of 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D3 (ED-71) compared to 1,25(OH)2D3.

means that there is only a narrow therapeutic window which has precluded worldwide approval. The results of our previous animal studies suggested that the therapeutic effect of active vitamin D on bone loss after estrogen deficiency can be dissociated, in part, from the effect of enhancing intestinal calcium absorption and suppressing parathyroid hormone (PTH) secretion [Shira-Ishi et al., 1999, 2000]. To further test this, we compared the effects of ED-71 with orally administered alfacalcidol, on bone mineral density (BMD) and the bone remodeling process as a function of their effects on calcium metabolism and PTH in an OVX model of osteoporosis. ED-71 increased bone mass at the lumbar vertebra to a greater extent than

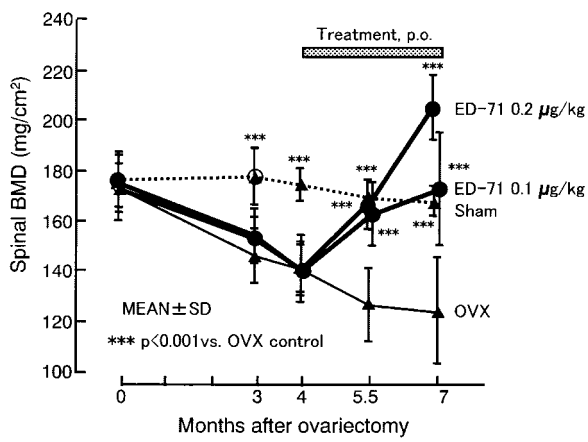

Fig. 2. The effects of ED-71 on bone mass in ovariectomized (OVX) rats. Eight-month-old Wister-Imamichi rats were ovariectomized, sufficient bone loss was confirmed after 4-month and then twice-weekly administration of ED-71 (0, 0.1, or 0.2 μg/kg) was carried out for 3 months. Each value represents the mean + SE. ***$P < 0.001$ (vs. OVX, Dunnett's multiple comparison test).

alfacalcidol (Fig. 3A) while enhancing calcium absorption indicated by urinary calcium excretion. Serum PTH levels decreased to the same degree as alfacalcidol (data not shown). ED-71 lowered the biochemical and histological parameters of bone resorption more potently than alfacalcidol (Fig. 3B), while maintaining bone formation markers (Fig. 3C). Theses results suggest that ED-71 exerts an anti-osteoporotic effect by inhibiting osteoclastic bone resorption while maintaining osteoblastic function, and that these anti-catabolic/anabolic effects of ED-71 take place independently of its effects on calcium absorption and PTH [Uchiyama et al., 2002].

EARLY PHASE II CLINICAL TRIAL

In an early phase II clinical trial, a randomized controlled study with ED-71 in 109 osteoporotic subjects (102 females and 7 males), 49 to 81 years of age (mean 65.0 years) was conducted. The patients were randomly assigned to either 0.25, 0.5, 0.75, or 1.0 μg/day of ED-71 administered orally. Patients were treated for 6 months, and BMD and bone markers were evaluated. ED-71 treatment increased the BMD at L2-4 in a dose-dependent manner (0.34 ± 0.73, 0.50 ± 0.91, 3.00 ± 0.65, and 2.66 ± 0.71% in the 0.25, 0.5, 0.75, and 1.0 μg groups, respectively, mean ± SE). The percentages of patients that showed an increase in the L2-4 BMD over 3% after 6 months also increased dose-dependently (21.7, 26.1, 54.2, and 45.5% in the 0.25, 0.5, 0.75, and 1.0 μg groups, respectively). Although 24 patients (23.3%) showed serum 25(OH)D levels below 20 ng/ml, the effect of ED-71 on the L2-4 BMD was not affected by the serum 25(OH)D level. ED-71 also exhibited a dose-dependent suppression of urinary deoxypyridinoline and Crosslaps excretion as well as serum bone-type alkaline phosphatase, whereas serum osteocalcin was not suppressed, suggesting a maintenance of bone formation with a suppression of bone resorption. ED-71 was well tolerated without causing hypercalcemia, and no patient exhibited sustained postprandial hypercalciuria over 0.4 mg/dL GF. Although the detailed results of the present study will be reported elsewhere in due course, the results warrant further long-term clinical studies to examine the effects of ED-71 on bone fracture in osteoporotic patients [Matsumoto and Kubodera, 2000].

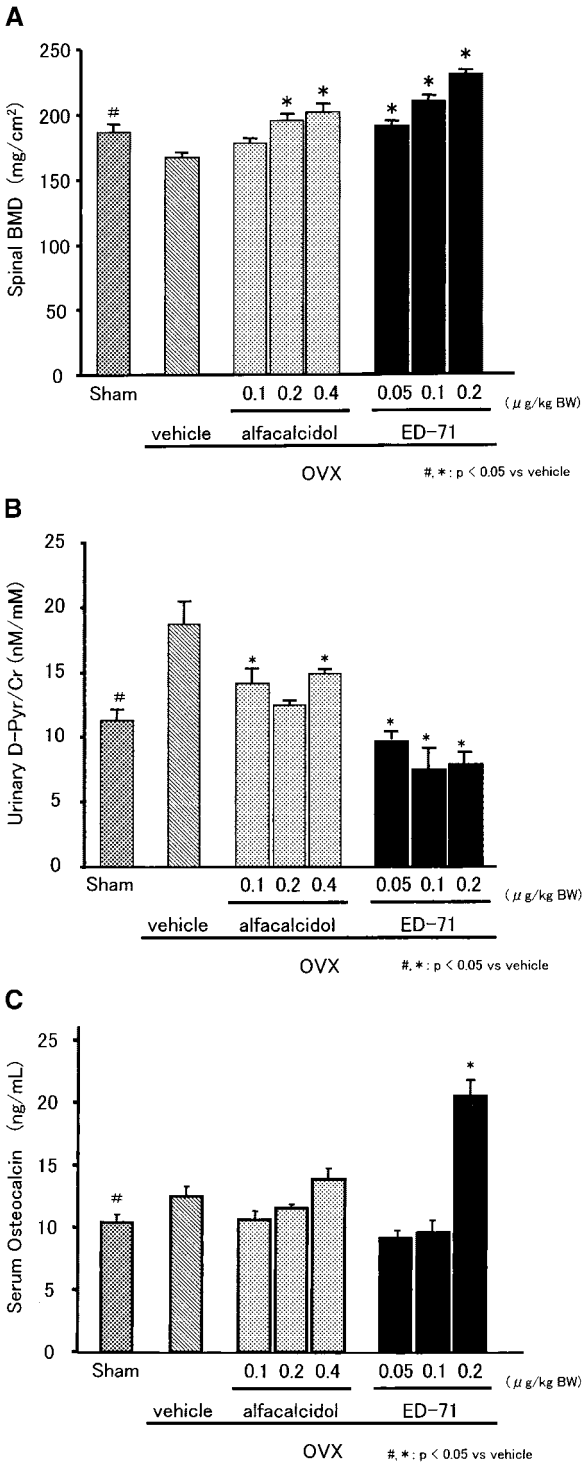

Fig. 3. Comparison of ED-71 with alfacalcidol in OVX rats. Eight-month-old OVX Wister-Imamichi rats were treated orally with indicated doses (μg/kg BW) of ED-71 or alfacalcidol, twice or thrice per week, respectively, for 3 months. Bone mineral density (BMD) at the lumbar vertebrae (**A**) was measured by dual-energy X-ray absorptiometry. Urinary deoxypyridinoline (D-Pyr) (**B**) was measured using a Pyrilinks-D assay kit. Serum osteocalcin (**C**) was measured using rat osteocalcin radioimmunoassay (RIA) reagents.

LATE PHASE II CLINICAL TRIAL

Based on the promising results of early phase II trials with ED-71, further clinical studies as late phase II are currently underway using the following protocol:

- Subjects: primary osteoporosis 200 patients.
- Design: randomized double-blinded study.
- Doses: 0, 0.5, 0.75, and 1.0 μg/day.
- Treatment: once a day for a successive 48-week treatment.
- 400 or 200 IU vitamin D3 is added depending on initial 25(OH)D levels.
- End points at 48 weeks: lumber (L2-4) spine BMD and bone markers.

CONCLUSION

1. ED-71 showed more potent inhibition of bone resorption than alfacalcidol in an estrogen-deficient rat model.
2. ED-71 increased bone mass without causing hypercalcemia and hypercalciuria possibly via its preferential effects on bone in osteoporotic patients.
3. These results suggest that ED-71 represents a promising new treatment modality and therapuetic candidate for treatment of osteoporosis.

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