Additive effects of eldecalcitol in poorly responding long-term bisphosphonate treatment for osteoporosis

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ABSTRACT

Objectives: We examined whether eldecalcitol (ELD) provided additive bone mineral density (BMD) and bone turnover marker gains in patients undergoing long-term bisphosphonate (BP) usage, especially in osteoporotic individuals exhibiting a poor response to BPs.

Methods: Forty-two post-menopausal patients with primary osteoporosis and low lumbar BMD (L-BMD) and/or bilateral total hip BMD (H-BMD) values receiving long-term BP treatment were prospectively enrolled. Serum bone alkaline phosphatase (BAP) was measured as a bone formation marker and urinary N-terminal telopeptide of type I collagen (NTX) was assessed as a bone resorption marker. L-BMD, H-BMD, and femoral neck BMD (N-BMD) were recorded before, at the commencement of, and during ELD administration.

Results: BAP and urinary NTX were significantly decreased by BP therapy prior to ELD. ELD addition further significantly decreased the bone turnover markers (both \( p < 0.01 \)). The mean L-BMD increase rate was 0.2% \( (p = 0.81) \) from 2 to 1 years before ELD administration, −0.7% \( (p = 0.30) \) during the year before ELD, and 2.9% \( (p < 0.01) \) during 1 year of ELD. Similar findings were observed for the mean increase rate of H-BMD, with values of 0.2% \( (p = 0.55) \), −0.7% \( (p < 0.01) \), and 1.2% \( (p < 0.01) \), respectively. The mean N-BMD increase rate was significantly increased after ELD administration \( (1.1\% \), \( p = 0.03) \) despite no gains by BP therapy alone.

Conclusions: This study suggests that ELD addition may be useful for osteoporotic patients exhibiting a diminished long-term BP therapy response.

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1. Introduction

Osteoporosis (OP) is a widespread skeletal disorder requiring long-term management to prevent fractures, maintain activities of daily living, and ultimately reduce mortality. Bisphosphonates (BPs) are the most common drugs for OP. With their bone anti-resorptive properties, BPs improve bone turnover, increase bone mineral density (BMD), and decrease fracture incidence [1,2]. Nitrogen-containing BPs inhibit farnesyl pyrophosphate synthetase in the mevalonate pathway in osteoclasts, [3] thereby suppressing their function and modulating osteoclast activity.

Vitamin D is essential for maintaining bone and calcium (Ca) metabolism. While circulating serum 25-hydroxyvitamin D3 (25 \( [\text{OH}]D_3 \)) is the major and main storage form of vitamin D in the human body, active vitamin D \( (1,25(\text{OH})_2\text{D}_3) \) regulates bone and Ca metabolism. As a vitamin D analog, 1,25-dihydroxycholecalciferol \( (1,25(\text{OH})_2\text{D}_3) \) has been approved for OP treatment in Japan [4] and is frequently employed in disease management to modulate serum \( 1,25(\text{OH})_2\text{D}_3 \) and parathyroid hormone levels without affecting bone turnover markers [5]. Combination therapy of bone antiresorptive drugs and

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ALF exhibited additive antosteoporotic effects when compared with anti-resorptive drug monotherapy in postmenopausal women [5,6]. Recently, 1α,25(OH)₂-2β-(3-hydroxypropyloxy)D₃ (eld-ecalcitol; ELD) has been introduced in OP treatment as a newly developed analog of active vitamin D [7,8] that inhibits bone resorption through the disruption of osteoclast formation. In a trial of Japanese patients with OP, ELD increased BMD and decreased the incidence of vertebral fractures more effectively than did ALF [5]. Moreover, a combination of bone antiresorptive drugs and ELD produced enhanced antosteoporotic effects over non-ELD monotherapy in postmenopausal women [9].

The BMD gains imparted by BPs in OP are especially prominent during the first few years of treatment. However, drug effectiveness can diminish over longer treatment periods [10], and BMD plateaus and even decreases have been encountered regardless of the BP usage. We previously reported that in BP poor-response patients, many of whom receiving therapy for over 5 years, BMD decreased significantly over time [11]. In such cases, alternative treatment is required.

We earlier described that BP therapy combined with ELD was more effective for OP treatment than when combined with ALF since ELD subsequent to ALF significantly suppressed bone turnover and increased lumbar BMD (L-BMD), [12] suggesting a superiority of combination BP therapy with ELD even in BP poor-response patients. To our knowledge, no reports have addressed the additive effects of ELD on poor responders to long-term BPs until the current investigation.

2. Patients and methods

2.1. Patient recruitment and diagnosis of OP

Patient demographic data are summarized in Table 1. Only postmenopausal female patients were enrolled in this prospective study. During the period from November 2014 to August 2017, we recruited 46 BP response-poor patients with primary OP and low L-BMD and/or total hip BMD (H-BMD) values undergoing long-term BP therapy. A total of 42 subjects were enrolled after 4 patients were excluded due to insufficient data collection during observation. We defined poor BP responders as individuals in whom L-BMD or H-BMD did not apparently increase with chronic BP administration over a 2-year period. In 21 of 42 patients, bone turnover markers were measured before and after ELD addition. The diagnosis of primary OP in this study was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research [13].

2.2. Inclusion and exclusion criteria for this study

The inclusion criteria for this study were postmenopausal Japanese women with primary OP. The exclusion criteria were the presence of obvious complications, such as chronic renal failure, bone metabolic disorders, liver dysfunction, and diabetes mellitus, all of which might affect OP. Serum renal and hepatic enzymes were within normal ranges before BP administration in all patients.

2.3. Drug selection

Alendronate, risedronate, and minodronate were adopted in various regimens during the long-term BP pretreatment. We did not examine the effects of individual BPs since they were often switched for patients exhibiting poor responsiveness. All participants took daily oral ELD of 0.75 μg/day after breakfast during the study period. All patients received BPs without Ca or vitamin D supplementation before and during ELD administration.

2.4. Measurement of bone turnover markers

Serum bone alkaline phosphatase (BAP) (Beckman Coulter, Inc., Tokyo, Japan) was measured as a bone formation marker using a chemiluminescent enzyme immunoassay with inter- and intra-assay coefficients of variation (CVs) of 3.0% and 2.5%, respectively. Urinary N-terminal telopeptide (NTX) of type I collagen (Osteomark; Osteos International, Seattle, WA, USA) was assessed as a marker of bone resorption using an enzyme-linked immunosorbent assay with inter- and intra-assay CVs of 11.5% and 12.7%, respectively. Each marker was measured before BP administration, just prior to ELD addition, and at 4 months of ELD administration. After overnight fasting, serum and first-void urine samples were collected between 8:30 a.m. and 10:00 a.m. Immunoassays were performed by SRL, Inc. (Tokyo, Japan).

2.5. Measurement of BMD

BMD was measured using a dual-energy X-ray absorption fan-beam bone densitometer (Lunar Prodigy; GE Healthcare Bio-Sciences Corp., Little Chalfont, UK) at the lumbar 1–4 level of the posteroanterior spine and at the bilateral hips as the mean of the right and left sides. Fracture sites were avoided for BMD evaluation. The CVs of BMD measurement at the lumbar spine, total hip, and femoral neck were 0.8%, 0.7%, and 1.2%, respectively. The respective least significant changes of these measurements were 2.3%, 1.8%, and 3.3% [14,15].

2.6. Statistical analysis

For statistical analysis, comparisons of markers and BMD at each measurement point were conducted using paired t-tests with Bonferroni correction. Results were expressed as the mean±standard deviation. Annual BMD change rates were analyzed using oneproduct t-tests. Statistical analyses were performed using the statistical package R, version 3.5.1 (available at http://www.r-project.org). A P-value of <0.05 was considered statistically significant.

2.7. Ethical approval

This investigation was performed in accordance with the ethical tenets set forth in the revised 2014 Declaration of Helsinki. The study was approved by the Institutional Ethics Committee of Shinshu University School of Medicine (Protocol No. 2014-22). Written informed consent was obtained from all patients.

3. Results

The cohort’s demographic characteristics are presented in Table 1. Figs. 1 and 2 summarizes the changes in bone turnover markers. Figs. 3 and 4 respectively show the values and percent
Prior to BP treatment, mean serum BAP was 19.5 ± 9.6 U/L, which had decreased significantly to 11.5 ± 3.6 U/L prior to ELD addition (P < 0.01). Afterwards, BAP further decreased significantly to 9.6 U/L, which had decreased significantly to 25.0 ± 10.6 nmol BCE/mmol Cr prior to ELD addition (P < 0.01) (Fig. 1). With ELD, BAP became further significantly decreased to 2.2 U/L (P < 0.01). With ELD, BAP further decreased significantly to 11.5 ± 2.2 U/L (P < 0.05). After 1 year of ELD treatment, L-BMD was 0.871 ± 0.078 g/cm², which was a significant increase compared with values at any point before ELD addition (P < 0.01) (Fig. 3). With respect to percent increases, these were 0.2% (95% confidence interval [95% CI] –1.1% to 1.4%, P = 0.81) from 2 to 1 years before ELD, –0.7% (95% CI, –2.0% to 0.7%, P = 0.30) during the year before ELD, and 2.9% (95% CI, 1.9% to 4.0%, P < 0.01) during 1 year after ELD commencement. L-BMD increased significantly after starting ELD despite no observable gains beforehand (Fig. 4).

H-BMD also tended to decrease before ELD commencement. At 1 year of ELD addition, H-BMD was 0.754 ± 0.094 g/cm² and significantly higher than that prior to ELD (P < 0.01). Femoral neck BMD (N-BMD) had similar a tendency to decrease prior to ELD. N-BMD was significantly decreased just before ELD treatment compared with at 1 year beforehand. At 1 year of ELD addition, N-BMD was 0.684 ± 0.076 g/cm², which was not significantly higher than that prior to ELD. Values are presented as the mean ± standard deviation (n = 42).

3.3. BMD results

L-BMD tended to decrease prior to ELD. After 1 year of ELD treatment, L-BMD was 0.871 ± 0.078 g/cm², which was a significant increase compared with values at any point before ELD addition (P < 0.01) (Fig. 3). With respect to percent increases, these were 0.2% (95% confidence interval [95% CI] –1.1% to 1.4%, P = 0.81) from 2 to 1 years before ELD, –0.7% (95% CI, –2.0% to 0.7%, P = 0.30) during the year before ELD, and 2.9% (95% CI, 1.9% to 4.0%, P < 0.01) during 1 year after ELD commencement. L-BMD increased significantly after starting ELD despite no observable gains beforehand (Fig. 4).

H-BMD also tended to decrease before ELD commencement. At 1 year of ELD addition, H-BMD was 0.754 ± 0.094 g/cm² and significantly higher than that prior to ELD (P < 0.01) (Fig. 3). Respective percent increases were 0.2% (95% CI, –0.5% to 0.9%, P = 0.55), –0.7% (95% CI, –1.2% to –0.2%, P < 0.01), and 1.2% (95% CI, 0.5% to 1.9%, P < 0.01) for the time periods of 2 to 1 years before, the year before, and during 1 year of ELD administration. H-BMD increased significantly after ELD administration with no prior gains (Fig. 4).

Femoral neck BMD (N-BMD) had similar a tendency to decrease prior to ELD. N-BMD was significantly decreased just before ELD treatment compared with at 1 year beforehand. At 1 year of ELD addition, N-BMD was 0.684 ± 0.076 g/cm², which was not significantly higher than that prior to ELD (P < 0.01) during the year before ELD, and 1.1% (95% CI, 0.1% to 2.2%, P = 0.03) during 1 year of ELD administration. N-BMD increased significantly after ELD commencement despite no improvement beforehand (Fig. 4).

No adverse effects, such as fractures or hypercalcemia, were observed during the study period.

4. Discussion

In the present study of patients with primary OP, bone turnover markers were significantly decreased by BP administration and became further significantly suppressed by ELD addition. Although L-BMD, H-BMD, and N-BMD were no longer increased by chronic
ELD, L-BMD values increased significantly after a regimen change of ELD to BP therapy. The addition of ELD in poorly responding patients apart from stronger inhibitory effects on bone resorption is unclear.

In osteoporotic patients exhibiting a poor response to long-term BP therapy, ELD addition may further decrease bone turnover markers and increase L-BMD and H-BMD to represent a good treatment option.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported. **ORCID.** Mikio Kamimura: 0000-0003-1519-3047. Shota Ikekami: 0000-0001-6404-5249. Keijiro Mukaiyama: 0000-0002-8861-1679. Hidefumi Koiwai: 0000-0002-5358-7736. Yukio Ikegami: 0000-0001-6404-5249.

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**Fig. 4.** Percent changes in lumbar bone mineral density (L-BMD), total hip BMD (H-BMD), and femoral neck BMD (N-BMD) from 2 to 1 years before eldecalcitol (ELD), during the year before ELD, and during 1 year of ELD. For L-BMD, percent increases were 0.2% (95% confidence interval [95% CI] –1.1% to 1.4%, P = 0.81) from 2 to 1 years before ELD, –0.7% (95% CI, –2.0% to 0.7%, P = 0.30) during the year before ELD, and 2.9% (95% CI, 1.9% to 4.0%, P = 0.01) during 1 year of ELD administration. Regarding H-BMD, the respective percent increases were 0.2% (95% CI, –0.5% to 0.9%, P = 0.55), –0.7% (95% CI, –1.2% to –0.2%, P = 0.01), and 1.2% (95% CI, 0.5% to 1.9%, P = 0.01) for the time periods of 2 to 1 years before the year before, and during 1 year of ELD administration. For N-BMD, percent increases were 0.3% (95% CI, –0.8% to 1.3%, P = 0.59) from 2 to 1 years before ELD, –1.1% (95% CI, –2.0% to –0.3%, P = 0.01) during the year before ELD, and 1.1% (95% CI, 0.1% to 2.2%, P = 0.03) during 1 year of ELD administration.
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