Comparison of the effects of eldecalcitol with either raloxifene or bisphosphonate on serum tartrate resistant acid phosphatase-5b, a bone resorption marker, in postmenopausal osteoporosis

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Summary

Objective. This study analyzes whether concomitant raloxifene (RLX) or bisphosphonates (BP) plus eldecalcitol (ELD) has excessive suppressive effects on a bone resorption marker during the first 6 months of treatment in postmenopausal women in real-world setting.

Methods. 285 postmenopausal osteoporotic patients who had been treated with RLX or BP plus ELD were evaluated the bone resorption marker, serum tartrate resistant acid phosphatase-5b (TRACP-5b), during the first 6 months of treatment.

Results. In drug-naive group (not received osteoporosis medications before the administration, n=70), the concomitant RLX or BP with ELD significantly decreased levels of TRACP-5b without severe suppression. In vitamin D switch group [RLX or BP plus alfacalcidol (ALF) and then switched to RLX or BP plus ELD, n=215], the replacing ALF with ELD further and significantly decreased TRACP-5b and tertile analyses based on baseline values were significantly decreased far more in the highest, compared with the lowest tertile in the ELD+RLX and ELD+BP groups.

Conclusion. ELD combined with RLX or BP administered for 6 months to postmenopausal women with osteoporosis who were drug-naive or who had switched medications significantly reduced and maintained TRACP-5b values within the reference range.

Key words: trtarate resistant acid phosphatase-5b (TRACP-5b); bone metabolic marker; eldecalcitol; raloxifene; bisphosphonate.

Introduction

Eldecalcitol (ELD) is a novel active vitamin D3 analogue with a hydroxypropyloxy group at the 2β-position of 1α, 25-dihydroxyvitamin D3. It significantly increases bone mineral density (BMD) at the lumbar spine and total hip (1), and decreases bone resorption markers and the incidence of both vertebral and non-vertebral (wrist) fractures compared with alfacalcidol (ALF) (2, 3). A previous study demonstrated that the inhibitory effect of ELD on bone resorption which mechanisms differ from those of other antiresorptive drugs such as raloxifene (RLX) and bisphosphonates (BP) (4, 5). Based on these findings, ELD has been approved for treating osteoporosis in Japan.

First-line treatment for osteoporosis typically comprises RLX and BP; however, serum vitamin D status affects the increase in BMD at the lumbar spine in osteoporotic women (6). Patients in most randomized clinical trials of the effects of antiresorptive drugs were treated with supplemental calcium and vitamin D (7-10) because a vitamin D deficiency seems a common health issue among elderly individuals, especially among those with osteoporosis (11).

Based on the above evidence, the concomitant use of antiresorptive drugs with active vitamin D is a popular strategy for treating osteoporosis in Japan (12) because active, not native, vitamin D is covered for this purpose by Japanese health insurance. However, the suppressive effects of antiresorptive drugs plus ELD on bone resorption might sometimes require clinical evaluation. The present study retrospectively analyzes whether concomitant RLX or BP plus ELD has excessive suppressive effects on a bone metabolic marker during the first 6 months of treatment in postmenopausal women in real-world setting.

Materials and methods

Study design and patients

We retrospectively analyzed 285 postmenopausal patients who had been given ELD (0.75μg/day) with RLX (60mg/day) or BP [alendronate (ALN); 35mg/week, risedronate (RIS); 17.5mg/week, minodronate (MIN); 50mg/month] at least 6 months with medication possession ratio over 80% at five centers in Japan.

All patients were diagnosed according to the Japanese criteria for primary osteoporosis (13). These criteria included low BMD (T score < -2.5) or presence of osteoporotic fractures. All patients had no secondary causes of osteoporosis, no history of treatment with glucocorticoids or drugs affecting bone metabolism, no fractures for 6 months before starting treatment and no new fractures arising during treatment. Serum Ca, P, and ALP in all patients represented within normal range.

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We compared data from patients assigned to either a group that had not received osteoporosis medications before the administration of either RLX or BP plus ELD (Drug-naïve group, ELD+RLX; 18 cases, ELD+ALN; 25 cases, ELD+RIS; 4 cases, ELD+MIN; 23 cases) or a vitamin D switch group (VD-Switch group, ELD+RLX; 139 cases, ELD+ALN; 38 cases, ELD+RIS; 19 cases, ELD+MIN; 19 cases) who had been treated with RLX or BP plus ALF more than 6 months and then switched to RLX or BP plus ELD (Tables 1, 2).

**Bone metabolic marker**

We measured levels of the bone resorption marker, serum tartrate resistant acid phosphatase-5b (TRACP-5b), at the start of RLX or BP plus ELD treatment and within 6 months thereafter. We measured TRACP-5b because the prevalence of chronic kidney disease (CKD) has recently increased among elderly patients, particularly women (14) who have coexistent osteoporosis. Therefore, when bone metabolic status is estimated using a marker dependent on renal function, data interpretation should consider the possible effect of renal dysfunction independently of such status. The guidelines for the use of bone metabolic markers in the diagnosis and treatment of osteoporosis published by the Japan Osteoporosis Society state that CKD (≥ stage 3) does not affect both osteoporosis and its treatment in elderly patients. Among these nine patients, four, four, and one patient had TRACP-5b values of 100-120, 80-100, and 79 mU/dL, respectively. Such suppression was not apparently severe because only four, four, and one patient had TRACP-5b values of 100-120, 80-100, and 79 mU/dL, respectively.

Statistical analyses

Baseline data are shown as means ± standard deviations (SD). The ratios (%) of differences from baseline were regarded as statistically significant when the 95% confidence interval (CI) did not include zero. Data were statistically analyzed using Student’s t-test, Fisher’s exact probability test, the chi-square test and ANOVA, and values were considered statistically significant at P < 0.05 in all tests.

**Results**

Data from both the drug-naive and the VD-switch groups are shown in Figures 1 and 2. No significant differences were observed between groups in age or baseline TRACP-5b values.

**(1) Drug-naïve group (Table 1, Figure 1)**

Mean and median per cent changes of TRACP-5b in both the RLX+ELD and BP+ELD groups significantly decreased during the first 6 months by 34.8 and 54.1%, respectively, and 39.7% and 61.0% (p = 0.002), respectively, which is consistent with BP being a more potent antiresorptive drug than RLX. The rates of patients with TRACP-5b decreasing beyond MSC did not significantly differ between the RLX+ELD and BP+ELD groups (77.8% vs 94.2%, p = 0.067). Values of TRACP-5b decreased below the reference value (120 mU/dL) in 9 (17.3%) of 52 patients in the BP+ELD group, but not in those in the RLX+ELD group (p = 0.057). Among these nine patients, four, four, and one had TRACP-5b levels of 100-120, 80-100, and 79 mU/dL, respectively.

**(2) VD-switch group (Table 2, Figures 2, 3)**

Mean and median per cent changes of TRACP-5b in both treatment groups significantly decreased during the first 6 months. The mean and median per cent changes in the RLX+ELD and BP+ELD were -21.1 and -13.0%, respectively, and -24.5 and -21.9%, respectively, with no significant differences (p = 0.532). The rates of patients with TRACP-5b values that decreased below the MSC in the RLX+ELD and BP+ELD groups were 70.5% vs 60.5% (p = 0.137). Five (3.6%) of 139 and three (3.9%) of 76 patients in the RLX+ELD and BP+ELD groups, respectively, had TRACP-5b values that decreased below the reference range (p = 0.897).

Stratification of the baseline values significantly differed among the highest, middle, and lowest tertiles of patients in the RLX+ELD group (-30.3, -21.1 and -11.6%, respectively; p < 0.001 for trend). The highest and lowest tertiles significantly differed (p < 0.001). The tendency was the same in the ELD+BP group (-30.4, -15.7 and 7.7%, respectively; p < 0.001 for trend), and the highest and lowest tertiles also significantly differed (p < 0.001) (Figure 3).

**Discussion**

ELD is more effective than ALF in preventing osteoporotic fractures with a significant suppression of bone resorption markers in postmenopausal women with osteoporosis (2, 3). Here, we showed that concomitant RLX or BP with ELD significantly decreased levels of the bone resorption marker TRACP-5b in the drug-naive group. ELD decreases bone resorption markers via a different mechanism from RLX and BP (4), but RLX or BP combined with ELD during the first 6 months of treatment did not severely suppress bone resorption markers in the drug-naive group. Nine (17.3%) of the patients administered with BP+ELD had TRACP-5b values that decreased below the reference range. Such suppression was not apparently severe because only four, four, and one patient had TRACP-5b values of 100-120, 80-100 and 79 mU/dL, respectively.

We also showed that replacing ALF with ELD further and significantly inhibited TRACP-5b, even in patients who had been previously treated with a combination of ALF and RLX or BP. To our knowledge, this is the first clinical comparison of postmenopausal women with osteoporosis who were switched from RLX or BP plus ALF to RLX or BP with ELD. The reasons why the replacing ALF with ELD further and significantly inhibited TRACP-5b were not clearly understood. However, a previous study demonstrated that the inhibitory effect of ELD on bone resorption in vivo is elicited via the suppression of receptor activator of NF-κB ligand (RANKL) expression in osteoblasts (4). Another study showed that ELD reduces the number and activities of osteoclasts by decreasing the number of preosteoblastic cells that interact with osteoclast precursors (5). These mechanisms differ from those of other antiresorptive drugs such as RLX and BP. We thus speculated that ELD would have an additional inhibitory effect on bone resorption in the VD-switch group. Tertile analyses based on baseline values revealed a significant trend in both the RLX+ELD and BP+ELD groups. Levels of TRACP-5b were obviously decreased far more in the highest, compared with the lowest tertile, indicating that ELD can further, but not excessively, suppress bone resorption markers, even in patients who had previously taken ALF combined with RLX or BP.

Several limitations are associated with this study. First, Japanese health insurance allows bone resorption markers to be measured only once within the first 6 months of administration. Thus, other bone markers such as CTX and NTX were not assessed and more frequent measurements were required.
Eldecalcitol with RLX or BP on TRACP-5b

Table 1 - Baseline characteristics in treatment naïve group.

<table>
<thead>
<tr>
<th></th>
<th>RLX + ELD</th>
<th>BP + ELD</th>
<th>P value group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18 cases</td>
<td>52 cases</td>
<td></td>
</tr>
<tr>
<td>age (mean ± SD)</td>
<td>70.7 ± 7.96</td>
<td>71.6 ± 8.68</td>
<td>0.629</td>
</tr>
<tr>
<td>TRACP-5b Baseline (mU/dL)</td>
<td>433.3 ± 175.8</td>
<td>450.0 ± 177.2</td>
<td>0.751</td>
</tr>
<tr>
<td>%change Mean (95% CI)</td>
<td>-38.4% (-47.8, -21.8)</td>
<td>-54.1% (-59.6, -48.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>MSC 14 cases, 77.4%</td>
<td>14 cases, 77.4%</td>
<td>49 cases, 94.2%</td>
<td>0.067</td>
</tr>
<tr>
<td>Under reference range 0 cases, 0.0%</td>
<td>9 cases, 17.3%</td>
<td>9.0%</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Table 2 - Baseline characteristics in VD-switch group.

<table>
<thead>
<tr>
<th></th>
<th>RLX + ELD</th>
<th>BP + ELD</th>
<th>P value group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>139 cases</td>
<td>76 cases</td>
<td></td>
</tr>
<tr>
<td>age (mean ± SD)</td>
<td>66.1 ± 7.62</td>
<td>72.5 ± 6.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TRACP-5b Baseline (mU/dL)</td>
<td>333.9 ± 115.2</td>
<td>324.5 ± 117.6</td>
<td>0.618</td>
</tr>
<tr>
<td>%change Mean (95% CI)</td>
<td>-21.5% (-24.9, -17.2)</td>
<td>-10.0% (-21.7, -4.4)</td>
<td>0.032</td>
</tr>
<tr>
<td>MSC 98 cases, 70.5%</td>
<td>98 cases, 70.5%</td>
<td>46 cases, 60.5%</td>
<td>0.137</td>
</tr>
<tr>
<td>Under reference range 5 cases, 3.6%</td>
<td>3 cases, 3.9%</td>
<td>0.897</td>
<td></td>
</tr>
</tbody>
</table>

ELD: eldecalcitol (0.75μg/day); RLX: raloxifene (60mg/day); 18 cases; BP: bisphosphonate; ALN: alendronate (35mg/week); 25 cases; RIS: risedronate (17.5 mg/week); 4 cases; MIN: minodronate (50mg/month); 23 cases; SD: standard deviations; TRACP-5b: tartrate resistant acid phosphatase-5b; CI: confidence interval; MSC: minimum significant changes, 12.4%; Reference range: 120-420 mU/dL.

Conclusion

ELD combined with RLX or BP administered for 6 months to postmenopausal women with osteoporosis who were drug-naïve or who had switched medications significantly not able in this study. However, no significant changes after 6 months administrated treatment in each medication (RLX, BP, ELD) were described before, so that there might not be no further significant change after 6 months in combination therapy. Second, serum vitamin D and PTH were not assessed in this study, because Japanese health insurance does not allow measuring in osteoporosis patients. Third, from an ethical viewpoint, this study lacked a placebo group. Fourth, the number of patients was insufficient to evaluate the relationship between TRACP-5b levels and fracture incidence. Fifth, BP is more powerful than RLX in terms of decreasing bone resorption markers, and BP+ELD included several types of BP (alendronate, risedronate, minodronate).
reduced and maintained TRACP-5b values within the refer-
ence range.

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