Gynecology; and Gynecological Oncology

Effects of Alendronate and Raloxifene on Bone Density and Bone Turnover Markers in Postmenopausal Women

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OBJECTIVE: The aim of this study was to compare the effects of once weekly alendronate sodium (ALN) and daily raloxifene hydrochloride (RLX) treatment on bone mineral density (BMD) and bone turnover markers in postmenopausal osteoporotic women.

STUDY DESIGN: We included 343 postmenopausal women with osteoporosis (femoral neck BMD T-score, less than -2.5), but 286 (83.4%) completed the study. Women (aged ≤75 yr; ≥2 yr since their last menstrual period) randomly classified into three groups. Group 1 (n=96) received ALN (70mg/week) and group 2 (n=95) received RLX (60 mg/day) and group 3 (n=95) received placebo. The efficacy of treatment was evaluated by BMD measurements at spine and hip, as well as by the measurement of bone turnover markers such as bone specific alkaline phosphatase (BSAP) and urine dehydroxyproline (D-OHP) at baseline, 6th and 12th months.

RESULTS: The evaluation of the changes in BMD and bone markers at 12 months were different between the placebo and each of the active treatment groups (P<0.05). The increase in BMD at 1 yr in ALN group was significantly greater than RLX group. The 4.5% increase in lumbar spine BMD with ALN was different from the 2% increase in RLX group (P<0.001). The 2.6% increase in femoral neck BMD with ALN was different from the 1.8% increase in the RLX group (P=0.03).

The biochemical markers of bone turnover D-OHP and BSAP in both treatment groups decreased from baseline and were different from placebo at 1 year. The decreases in D-OHP and BSAP were approximately 2.1 fold greater in the ALN group. The decreases were significantly greater in ALN group than in RLX group (P<0.001).

CONCLUSION: ALN 70 mg once- weekly significantly produced greater increases in spine and greater but not significantly increases in hip BMD and significantly greater reductions in markers of bone turnover than RLX in 1 yr treatment period. Both ALN and RLX treatment groups have similar safety and tolerability profiles.

Key Words: Alendronate, Raloxifene, BMD, Bone turnover markers, Tolerability, Osteoporosis

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In this study, we aimed to evaluate BMD and biochemical markers of bone turnover for ALN and RLX, compared with placebo in postmenopausal women at risk for osteoporotic fractures during a 12-month period.

**Material and Method**

**Patients:** The study participants were ambulatory post-menopausal women aged up to 75 yr, with their last menstrual period at least 6 months before the study entry and had low bone density (defined as a BMD measurement which had a T score less than -2.5, by dual-energy x-ray absorptiometry at lumbar spine or proximal femur). Patients were able to accept either treatment and were preffered to be in good general health and patients who agreed to participate and provide written informed consent were enrolled in the clinical study. Investigators obtained local Institutional Review Board approval.

Subjects were excluded from the study for any of the following reasons: bilateral hip replacement, hypertriglyceridaemia, malignant diseases, severe chronic diseases, uterine and ovarian abnormalities, esophageal stricture or achalasia, use of antiresorptive treatment (except for calcium and vitamin D) within the 3 months before the study, active venous thromboembolic disease.

**Study Design:** This prospective double-blind study was conducted at Zekai Tahir Burak Women Health Teaching and Research Hospital, Ankara. A total of 248 women were randomly assigned to receive either ALN (Fosamax, Merck & Co., Inc., White-house station, NJ, USA) 70 mg once weekly or RLX (Evista,Eli, Lilly, Indianapolis, IN, USA) 60mg daily. All women received a supplement containing approximately 500 mg/d elemental calcium and vitamin D 400-600 IU/d. Patients were inducted to take the once weekly tablet with a large glass of water and no food or drink was to taken for 30 min afterward. The daily tablet could be taken at any time of the day.

**Measurements:**

Lumbar spine and femoral neck BMD and biochemical markers of bone turnover were performed at baseline, 6th and 12th months in all patients using the Hologic QDR (Hologic, Inc., Waltham, MA) densitometer. Efficacy measurements were set as T scores of lumbar spine and femoral neck. The markers included serum bone-specific alkaline phosphatase (BSAP) (Ostase IRMA, Hybritech, San Diego, CA) and urine dehydroxyproline (D-OHP). During the treatment period, adverse effects and fractures were recorded.

**Statistical Methods:**

SPSS version 11.5 was used for statistical analysis. Data are represented as means±SD (SD). Normally distributed parametric variables were tested by analysis of variance (ANOVA) using Bonferroni test for hoc analysis. Differences between pre-and post-treatment values in the same group were analyzed by Friedman test and Wilcoxon signed rank test was performed for their post-hoc analyses. Mann-Whitney U-test was used to analyze the differences between the groups at baseline, 6th and 12th months. P values <0.05 were considered to be significant.

**Results**

The baseline characteristics of women randomly assigned to treatment were not statistically different between the groups (Table 1). In all groups, age, menopause age, body mass index and daily calcium intake were similar. Also, baseline BMD at lumbar spine and hip sites and bone turnover markers were similar between the treatment groups. The most common background medical conditions reported by the patients were hyperlipidemy (38%), hypertension (31.4%) and cardiac diseases (7.8%) of the 343 patients enrolled, 286 (83.4%) completed the study.

Femoral neck and lumbar spine BMD in treatment groups at 1 yr significantly increased from baseline and also were significantly greater than placebo (Fig 1). The 4.5% increase in

**Table 1: The characteristics of study patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=95)</th>
<th>RLX (n=95)</th>
<th>ALN(n=95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.1± 5.3</td>
<td>62.4± 6.3</td>
<td>62.7± 6.1</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8± 3.8</td>
<td>24.3± 3.9</td>
<td>24.7± 3.7</td>
<td>0.70</td>
</tr>
<tr>
<td>Years after menopause</td>
<td>16.5± 7.1</td>
<td>17.6± 8.1</td>
<td>15.6± 7.2</td>
<td>0.42</td>
</tr>
<tr>
<td>Dietary calcium intake (mg/dl)</td>
<td>770± 415</td>
<td>830± 480</td>
<td>740± 485</td>
<td>0.18</td>
</tr>
<tr>
<td>Lumbar Spine BMD (g/cm²)</td>
<td>0.77± 0.12</td>
<td>0.77± 0.11</td>
<td>0.79± 0.12</td>
<td>0.58</td>
</tr>
<tr>
<td>Femoral Neck BMD (g/cm²)</td>
<td>0.63± 0.08</td>
<td>0.61± 0.08</td>
<td>0.62± 0.09</td>
<td>0.38</td>
</tr>
<tr>
<td>BSALP (µg/liter)</td>
<td>14.5± 6.4</td>
<td>14.6 ± 6.3</td>
<td>14.5± 6.0</td>
<td>0.75</td>
</tr>
<tr>
<td>u DHOP</td>
<td>12.6± 6</td>
<td>12.9± 5</td>
<td>12.5± 6</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI, Body mass index
The biochemical markers of bone turnover, D-OHP and BSAP in both treatment groups decreased from baseline and were different from the placebo at 1 yr. The decreases in D-OHP and BSAP were approximately 2.1 fold greater in the ALN group. The decreases were significantly greater in ALN group than RLX group (P<0.001). Both ALN and RLX have similar safety and tolerability profiles (Table 3).

Discussion

This study demonstrated 1 yr treatment with RLX and ALN decreased bone turnover, as estimated by BMD and biochemical markers of bone turnover. When compared with baseline and placebo in healthy postmenopausal women with osteoporosis, the effects of ALN on all BMD and bone turnover marker were significantly greater than those with RLX.

BMD and biochemical markers are considered to be the best indicators of clinical efficiency and also have been proposed as appropriate surrogate markers for fracture risk reduction. Previous clinical trials in humans and preclinical animal models showed that greater reductions in fracture risk are associated with the larger increases in BMD. Currently, BMD is the best predictor of fracture risk and the most important determinant of bone strength.

In double blind, placebo controlled studies, ALN 10 mg once daily treatment was conducted in postmenopausal women with osteoporosis and these studies showed significant increases in BMD measured at lumbar spine and hip sites compared to baseline and placebo. Several studies have proved the efficacy of biphosphonates in postmenopausal. But there are limited data about their comparative effects with RLX in postmenopausal osteoporosis. In this study, we wanted to compare the efficacy of ALN and RLX since both of the drugs are antiresorptive agents which work by decreasing bone turnover on different molecular targets.

In postmenopausal osteoporosis, another drug choice is a SERM, RLX. On bone tissue it acts like an estrogen and in clinical trials, tissue specific actions of RLX have been documented. Estrogen-agonist effects of RLX are increases in BMD and decreases in bone turnover markers and lipid metabolism. In our study, effects of RLX on BMD and bone turnover markers were weaker than ALN but there were significant increases in BMD when it was compared to placebo. But, if patients have a family history of breast cancer or have high plasma lipid levels, RLX has more advantages than ALN. However major disadvantages of RLX treatment are increased risk of venous thromboembolism and hot flushes. Side effects

Table 3: Adverse effects during treatment period

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RLX</th>
<th>ALN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substernal chest pain</td>
<td>2.1%</td>
<td>4.5%</td>
<td>6.9%</td>
<td>0.48</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.4%</td>
<td>1.2%</td>
<td>2.4%</td>
<td>0.52</td>
</tr>
<tr>
<td>Bone pain</td>
<td>4.9%</td>
<td>4.9%</td>
<td>4.8%</td>
<td>1.00</td>
</tr>
<tr>
<td>Headache</td>
<td>6.1%</td>
<td>7.3%</td>
<td>10.8%</td>
<td>0.60</td>
</tr>
<tr>
<td>Urticaria</td>
<td>4.9%</td>
<td>8.5%</td>
<td>9.6%</td>
<td>0.62</td>
</tr>
</tbody>
</table>

P value among treatment groups as calculated by Pearson’s χ² test
of ALN were found lower than the previous studies in our study. But especially side effects following the ingestion of RLX was found better than ALN.

Michalska and his friends compared BMD and bone turnover markers in patients receiving long-term ALN therapy who continued ALN, were switched to RLX, or discontinued antiresorptive therapy. BMD preservation and increase were most pronounced in patients continuing ALN. RLX, compared with placebo, demonstrated beneficial effects on BMD and bone turnover after discontinuation of long-term ALN.

Also Johnell et al reported that, although the increases in lumbar spine BMD and changes in bone turnover markers with ALN alone and in combination therapy were similar and greater than that observed with RLX alone, the effects of combined RLX and ALN on BMD were independent and additive.

An excess risk of gastroduodenal ulcers and esophageal perforations with the use of bisphosphonates has been indicated by Vestergaard et al. However, little is known about the contribution of comorbid conditions and concomitant drug use on this risk. According to our findings, both ALN and RLX have similar safety and tolerability profiles. Several drugs against osteoporosis are associated with an increased risk of esophagitis, esophageal ulcers, esophageal perforation, and gastroduodenal ulcers. However, the increase might already be present before initiation of the drug for several types of drugs against osteoporosis. Patients with osteoporosis might have comorbid conditions and drugs, such as nonsteroidal anti-inflammatory drugs and corticosteroids. Also, in another study of Vestergaard et al., ALN seems to be associated with an increased risk of deep venous embolism and pulmonary embolism when compared with RLX.

In conclusion, this study demonstrated that in healthy postmenopausal women with osteoporosis, ALN and RLX increased lumbar spine and femoral neck BMD and decreased bone turnover markers compared with placebo and baseline and also ALN has significantly greater effects than did RLX on lumbar spine BMD and bone turnover, with similar tolerability.

References


Postmenopozal Kadınlarda Alendronat ve Raloksifenin Kemik Mineral Dansite ve Kemik Turnover Markerleri Üzerine Etkileri

AMAÇ: Bu çalışmanın amacıhaftalık Alendronat (ALN) ve günlük Raloksifen (RLX) kullanımının kemik mineral dansite ve kemik turnover markerleri üzerine etkilerini karşılaştırmaktır.

GEREÇ VE YöNTEM: Çalışmaya osteoporozu olan (femoral boyun BMD T-score -2.5’in altında) 343 postmenopozal hasta alındı ancak 286 (%83.4) hasta çalışmaya tamamlayabildi. Hastalar (75 yaş altı; son adetin üzerinden en az 2 yıl geçmiş olan) randomize edilerek 3 gruba ayrıldı. Grup 1 (96 kişi) ALN (70mg/hafta), Grup 2 (95 kişi) RLX (60 mg/gün) ve Grup 3 (95 kişi) plasebo tedavilerini aldı. Tedavinin etkinliği kaleva ve omur-ga BMD ve kemik spesifik alkalen fosfataz (BSAP) ve idrar de-hidrokspilron (D-OHP) değerlerinin tedavinin başında, 6. ve 12. yılında değerlendirilmesi ile yapıldı.

BULGULAR: Tedavinin başına ve 12. aynda plasebo ve aktif tedavi gruplarının BMD ve kemik turnover markerlerinde değişiklikler tespit edildi (P<0.05). ALN grubunda, 1. yılda BMD değerlerinde artış RLX grubuna göre belirgin olarak yüksek bulundu. ALN grubunda bel omurga BMD değerlerinde %4.5 artış, RLX grubundaki %2 artışa göre farklı tespit edildi (P<0.001). ALN grubunda femur boyun BMD değerinde %2.6 artış, RLX grubunda %1.8 artışa göre farklı tespit edildi (P=0.03).

Her iki tedavinin 1. yılında kemik turnover biyokimyasal mar-kерlerinden D-OHP ve BSAP plasebo grubu göre daha düşük tespit edildi. ALN grubundaki D-OHP ve BSAP düzeylerindeki düşüş 2.1 kat daha fazla bulundu. RLX grubuna göre ALN grubundaki bu düşüş belirgin olarak daha fazla bulundu (P<0.001).

SONUÇ: Tedavinin 1. yılında,haftalık 70 mg ALN tedavisinin RLX tedavisiine göre anlamlı olarak omurgada, anlamlı olma-daın kalça BMD değerlerini yükseltirken, kemik turnover markerlerinde anlamlı düşme tespit edildi. Hem ALN hem de RLX tedavilerinde benzer güvenirlik ve tolerabilite profili izlendi.

Anahtar Kelimeler: Alendronat, Raloksifen, BMD, Kemik turn-over marker, Tolerabilite, Osteoporoz

References


In our study,

