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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Introduction

In postmenopausal women, osteoporosis is a common disease which may lead to increased incidence of spine and hip fractures and several agents are currently available for osteoporosis prevention and treatment.[1]

In osteoporosis, because of excessive bone resorption, an imbalance between bone resorption and bone formation occurs, resulting in reduced bone mass.[2] Multiple antiresorptive therapeutic agents are now approved for prevention and treatment of postmenopasal osteoporosis.[3] In clinical trials, the antifracture efficacy of these agents are shown to correlate with their therapeutic effects on BMD and bone turnover markers[4]

Both selective estrogen modulator(SERM), RLX and biphosphanate ALN have been shown to treat osteoporosis and can prevent new vertebral fractures, this causing a reduction in bone remodelling, an increase in bone mineral density (BMD) and a decrease in biochemical markers of bone turnover5. ALN decreases the number and activity of osteoclasts and inhibits bone resorption by binding hydroxyapatite. Similar to RLX, ALN prevents new vertebral fractures in postmenopausal women, but not been hip fractures or other non-vertebral fractures. RLX binds estrogen receptors and isoforms leading to inhibition of bone resorption, and decreases the markers of bone turnover and lipid metabolism. Previous studies showed that RLX does not increase endometrial thickness or breast density demonstrating estrogen antagonist effects of these tissues.[6,7]

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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 postmenopausal 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, Indianopolis, 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

	Placebo (n=95)	RLX (n=95)	ALN(n=95)	P
Age (yr)	62.1± 5.3	62.4± 6.3	62.7± 6.1	0.97
BMI (kg/m^2)	24.8± 3.8	24.3± 3.9	24.7± 3.7	0.70
Years after menopause	16.5± 7.1	17.6± 8.1	15.6± 7.2	0.42
Dietary calcium intake (mg/dl)	770± 415	830± 480	740± 485	0.18
Lumbar Spine BMD (g/cm^2)	0.77± 0.12	0.77± 0.11	0.79± 0.12	0.58
Femoral Neck BMD(g/cm^2)	0.63± 0.08	0.61± 0.08	0.62± 0.09	0.38
BSALP (µg/liter)	14.5± 6.4	14.6 ± 6.3	14.5± 6.0	0.75
u DHOP	12.6± 6	12.9± 5	12.5± 6	0.62

Values are mean±SD. BMI, Body mass index

lumbar spine BMD with ALN was significantly different from the 2% increase in RLX group (P<0.001) (Table 2). The 2.6 % increase in femoral neck BMD with ALN was different from the 1.8% increase in the RLX group (P=0.03).

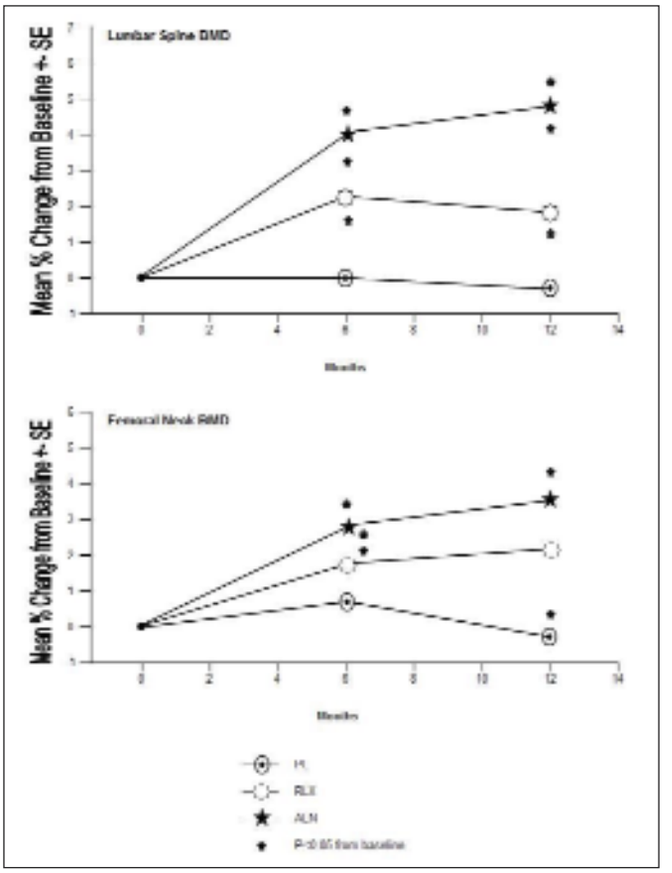

Figure 1: Mean percentage changes± SD in lumbar spine and femoral neck after 6 and 12 months

Table 2: Percantage changes in BMD and bone turnover markers from baseline to 1 yr.

	Placebo	RLX	ALN
Lumbar Spine BMD	-0.005± 2	2.3 ± 0.3	4.2± 0.4
Femoral Neck BMD	0.2± 0.5	1.5± 0.3	2.8± 0.3
BSALP(µg/liter)	-10.3	-34.5	-57.1
u DHOP	-11.2	-35.8	-58

BMD values are mean percentage change ±SD. Bone turnover markers are median percentage change.

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).

Table 3: Adverse effects during treatment period

	Placebo	RLX	ALN	P
Substernal chest pain	2.1%	4.5%	6.9%	0.48
Nausea	2.4%	1.2%	2.4%	0.52
Bone pain	4.9%	4.9%	4.8%	1.00
Headache	6.1%	7.3%	10.8%	0.60
Urticaria	4.9%	8.5%	9.6%	0.62

P value among treatment groups as calculated by Pearson's x^2 test

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 reduction8. Previous clinical trials in humans and preclinical animal models showed that greater reductions in fracture risk are associated with the larger increases in BMD[9,10]. 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.[11,12] Several studies have proved the efficacy of biphosphonates in postmenopausal.[13,14,15] 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.[16,17] Estrogen-agonist effects of RLX are increases in BMD and decreases in bone turnover markers and lipid metabolism.[18,19,20] 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

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.[21]

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.[22]

An excess risk of gastroduodenal ulcers and esophagus 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.[23] 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.[24]

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.

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

AMAÇ: Bu çalışmanın amacı haftalık Alendronat (ALN) ve günlük Raloksifen (RLX) kullanımının kemik mineral dansite ve kemik turnover markerları üzerine etkilerini karşılaştırmak.

GEREÇ VE YÖNTEM: Çalışmaya osteoporozu olan (femoral boyun BMD T- score -2.5'in altında) 343 postmenopozal hasta alındı ancak 286 (%83. 4) hasta çalışmayı 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 kalça ve omurga BMD ve kemik spesifik alkalen fosfataz (BSAP) ve idrar dehidroksiprolin (D-OHP) değerlerinin tedavinin başında, 6. ve 12. ayında değerlendirilmesi ile yapıldı.

BULGULAR: Tedavinin başında ve 12. ayında plasebo ve aktif tedavi gruplarının BMD ve kemik turnover markerlarında değişiklikler tespit edildi (P<0.05). ALN grubunda, 1. yılda BMD değerlerindeki artış RLX grubuna göre belirgin olarak yüksek bulundu. ALN grubunda bel omurga BMD değerlerinde %4. 5 artış, RLX grubundaki %2 lik artışa göre farklı tespit edildi (P<0.001). ALN grubunda femur boyun BMD değerinde %2. 6 artış, RLX grubunda %1. 8 lik artışa göre farklı tespit edildi (P=0.03).

Her iki tedavinin 1. yılında kemik turnover biyokimyasal markerlarından D- OHP ve BSAP plasebo gruba 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 belirgi olarak daha fazla bulundu (P<0.001).

SONUÇ: Tedavinin 1. yılında, haftalık 70 mg ALN tedavisinin RLX tedavisine göre anlamlı olarak omurgada, anlamlı olmadan kalça BMD değerlerini yükseltirken, kemik turnover markerlarında anlamlı düşme tespit edildi. Hem ALN hem de RLX tedavilerinde benzer güvenlik ve tolerabilite profili izlendi.

Anahtar Kelimeler: Alendronat, Raloksifen, BMD, Kemik turnover marker, Tolerabilite, Osteoporoz

References

1. Cummings SR. Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761-67.
2. Garrett- Connor E. Bone strength and its determinants. Osteoporos Int 2003;14:13-18.
3. Hochberg MC. Greenspan S. Warnich RD. et al. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab 2002;87:1586- 92.
4. Sambrook PN. Geusens P. Ribot C. et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT. J Int Medicine 2004;255:503-11.
5. Turbi C. Herrero-Beaumont G. Acebes JC. et al. Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: An open- label, prospective, nonrandomized, observational study. Clin Therap 2004;2:245-56.
6. Prestwood KM. Gunness M. Muchmore DB. et al. A comparison of the effects of raloxifene and estrogen on bone

in postmenopausal women. J Clin Endocrinol Metab 2000;85:2197-202.

7. Luckey M. Kagan R. Greenspan S. et al. Once- weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause 2004; 11:405-15.
8. Amman P. Rizzoli R. Bone strength and its determinants. Osteoporos Int 2003;14:13-18.
9. Balena R. Toolan BC. Shea M. et al. The effects of 2- year treatment with the aminobisphonate alendronate on bone metabolism, bone histomorphometry, and bone strength in ovariectomized non- human primates. J Clin Invest 1993; 92:2577-86.
10. Li Z. Meredith MP. Hoseyni MS. A method to asses the proportion of treatment effect explained by a surrogate endpoint. Stat Med 2001;20:3175-88.
11. Cranney A. Wells G. Willan A. et al. Osteoporosis methodology group and the osteoporosis research advisory group. Meta- analyses of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23: 508-16.
12. Papapoulos SE. Quandt SA. Liberman UA. et al. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int 2005;16:468-74.
13. Sarioglu M. Tuzun C. Unlu Z. et al. Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers in postmenopausal osteoporosis. Rheumatol Int 2006;26:195-200.
14. Reid DM. Hosking ., Kendler D. et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis. Clin Drug Invest 2006;26:63-74.
15. Rosen CJ. Hochberg MC. Bonnick SL. et al. treatment with once weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: A randomized double- blind study. J Bone Miner Res 2005;20:141-51
16. Jonston Jr CC. Bjarnason NH. Cohen FJ. et al. Long term effects of raloxifene on bone mineral density, bone turnover, and serum lipids in early postmenopausal women: three- year data from two double- blind, randomized placebo- controlled trials. Arch Intern Med 2000; 160:3444-50.
17. Goldstein SR, Scheele WH, Rajagopalan SK, Wilkie JL, Walsh BW, Parsons AK. A 12- month comparative study of raloxifene, estrogen and placebo on the postmenopausal endometrium. Obstet Gynecol 2001;95:95- 103.
18. Fugere P. Scheele WH. Shah A. et al. Uterine effects of raloxifene in comparison with continous- combined hormone replacement theraoy in postmenopausal women. Am J Obstet Gynecol 2000;182:568- 74.
19. Oktem M. Esinler I. Eroglu D. et al. The effects of once-weekly alendronate 70 mg, risedronate 35 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis in Turkish population. Gynecol Obstet Reprod Med 2007;13:52- 57.
20. Luckey M. Kagan R. Greenspan S. et al. Once- weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause 2004; 11:405-15.
21. Michalska D. Stepan JJ. Basson BR. et al. The effect of raloxifene after discontinuation of long- term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2006;91:870-77.

In our study,

22. Jonell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002; 87:985-92.
23. Vestergaard P. Schwartz K. Pinholt EM. et al. Gastric and esophagus events before and during treatment of osteoporosis. Calcif Tissue Int 2010;86:110-5.
24. Vestergaard P. Schwartz K. Pinholt EM. et al. Use of bisphosphonates and raloxifene and risk of deep venous thromboembolism and pulmonary embolism. Osteoporos Int 2009 PMID: 19859641