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¶

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OBJECTIVE: We aimed to compare the efficacy and tolerability of once-weekly alendronate 70 mg/weekly, risedronate 35 mg/weekly and raloxifene 60 mg/daily in the treatment of postmenopausal osteoporosis.

STUDY DESIGN: Retrospective case-control study. 216 aged matched postmenopausal women with osteoporosis who received alendronate (n=70), risedronate (n=74), or raloxifene (n=72) for 24 months were retrospectively evaluated. Additionally, all patients received 600 mg Calcium+ 400 IU Vit D daily. Bone mineral density (BMD) was measured by dual X-ray absorptiometry. T scores at baseline and 24 months were evaluated in the lumbar spine, total hip, femur neck, and trochanter.

RESULTS: Baseline T scores of each region were not significantly different among three groups. T scores increased in the lumbar spine ($p<0.01$), femur neck ($p<0.05$), trochanter ($p<0.01$) and total hip ($p<0.05$) following 24 months of alendronate treatment. In the risedronate group, there was a significant increase in the lumbar spine only ($p<0.01$). Raloxifene treatment did not change T scores of any regions. There was only one case (1.4%) with fracture of forearm in the alendronate group. However, in the risedronate group, 5 cases (6.7%) with fracture (one case of elbow, two cases of finger, one case of hip and one cases of vertebral fractures) were seen during the treatment period. In the raloxifene group, 5 cases (6.9%) of bone fracture (including, three cases of fracture of forearm and one case of hip and one case of vertebral fracture) were seen. The rates of fracture and adverse effects in three groups were comparable.

CONCLUSİONS: Alendronate 70 mg/weekly was well tolerated and produced significantly greater increases in BMD than other drugs with low fracture incidence.

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Key Words: Osteoporosis, Alendronate, Risedronate, Raloxifene, Postmenopausal women

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture which can result in substantial morbidity and mortality[1]. In osteoporosis, excessive bone resorption leads to an imbalance between bone resorption and bone formation, resulting in reduced bone mass[2]. Optimal management of osteoporosis includes the detection of low bone mass, then, initiation of efficient antiresorptive therapy. Both bisphosphonates and selective oestrogen receptor modulators (SERMs) are used to treat osteoporosis because of their ability to decrease bone resorption, increase bone mineral density (BMD) and decrease risk of fractures[3]. Each antiresorptive therapy achieves its therapeutic effects on bone through different modes of action. Bisphosphonates bind to hydroxyapatite and inhibit bone resorption by decreasing the number and activity of osteoclasts[4]. Although the mechanisms of action of SERMs are yet to be elucidated, some factors that contribute to the tissue specific actions of SERMs include binding to estrogen receptor and isoform, binding of the SERM-estrogen receptor complex to target genes, and modification of gene expression by cellular proteins[5].

Effects of bisphosphonates and raloxifene on T scores of spine or hip and fraction rates were evaluated by several studies[6,7]. However, to our knowledge, comparison of three different drug regimens such as risedronate, raloxifene and, alendronate has not been studied yet, even retrospectively.

In this study, we aimed to compare the efficiency and tolerability of alendronate 70 mg/week, risedronate 35 mg/week and raloxifene 60 mg/day treatments in postmenopausal osteoporosis for 24 months.

Materials and Methods

Two hundred sixteen women diagnosed as osteoporosis in gynecologic outpatient clinic of Baskent University were ret-

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rospectively recruited. Osteoporosis was defined as bone mineral density (BMD) of the lumbar spine that was below -2.5 SD from the mean value of premenopausal Turkish women. Amenorrhea longer than last 12 months or serum FSH levels above the 40 mIU/ml was accepted as diagnostic criteria for menopause. We excluded women with known causes of osteoporosis (or other disorders of bone and mineral metabolism), such as treatment with glucocorticoids, vitamin D deficiency, rheumatoid arthritis, and clinical hyperparathyroidism. Patients with a history of the following conditions were also excluded: active peptic ulcer disease; abnormal renal function; abnormal hepatic function; abnormalities of the lumbar spine precluding the assessment of BMD; a history of hip fracture, and cancer within the past 10 years. Moreover, patients who had any prior treatment with one of bisphosphonates, estrogen, progestin, calcitonin, fluoride, or anabolic steroid were excluded.

The patients were divided into three different groups. Group I was composed of 70 patients who received alendronate 70 mg weekly (Fosamax, Merck-Sharp&Dohme, Istanbul, Turkey), Group II was consisted of 74 women who received risedronate 35 mg weekly (Actonel, Aventis Pharma, Istanbul, Turkey) and remained 72 women who were consisted of Group III took raloxifene 60 mg daily (Evista, Lilly, Istanbul, Turkey). Additionally, all patients received 600 mg Calcium+400 IU Vitamin D daily (Cal-D-VitA, Bayer, Istanbul, Turkey) and were continued to the treatment for 24 months.

Bone mineral density (BMD) of the spine (L1–L4) and hip were measured by dual X-ray absorptiometry (DEXA) (Hologic 010-0667, Bedford Maryland, USA) at baseline and 24 months of treatment in all patients. Efficacy measurements were set as T scores of the lumbar spine, total hip, neck, and trochanter at baseline and 24 months. During the treatment period, adverse effects and fractures were recorded. Drugs were usually given at physicians' choice with no prejudice of a drug's superiority over others.

Statistical analysis was performed by SPSS 11.5 software (Statistical Package for Social Sciences). Data are represented as means ± SD unless otherwise stated. Normally distributed parametric variables were tested by analysis of variance (ANOVA) using Bonferroni test for post hoc analysis. To evaluate the treatment effect on bone indices of each drug group, paired t test was used. The Chi-Square test and Fisher's exact test were used to analyze nominal variables in form of frequency tables. P value less than 0.05 was accepted as statistically significant.

Results

The baseline characteristics of three groups were shown in Table 1. Baseline and post-treatment T scores of each group were shown in Table 2.

Table 1. Baseline characteristics of three groups

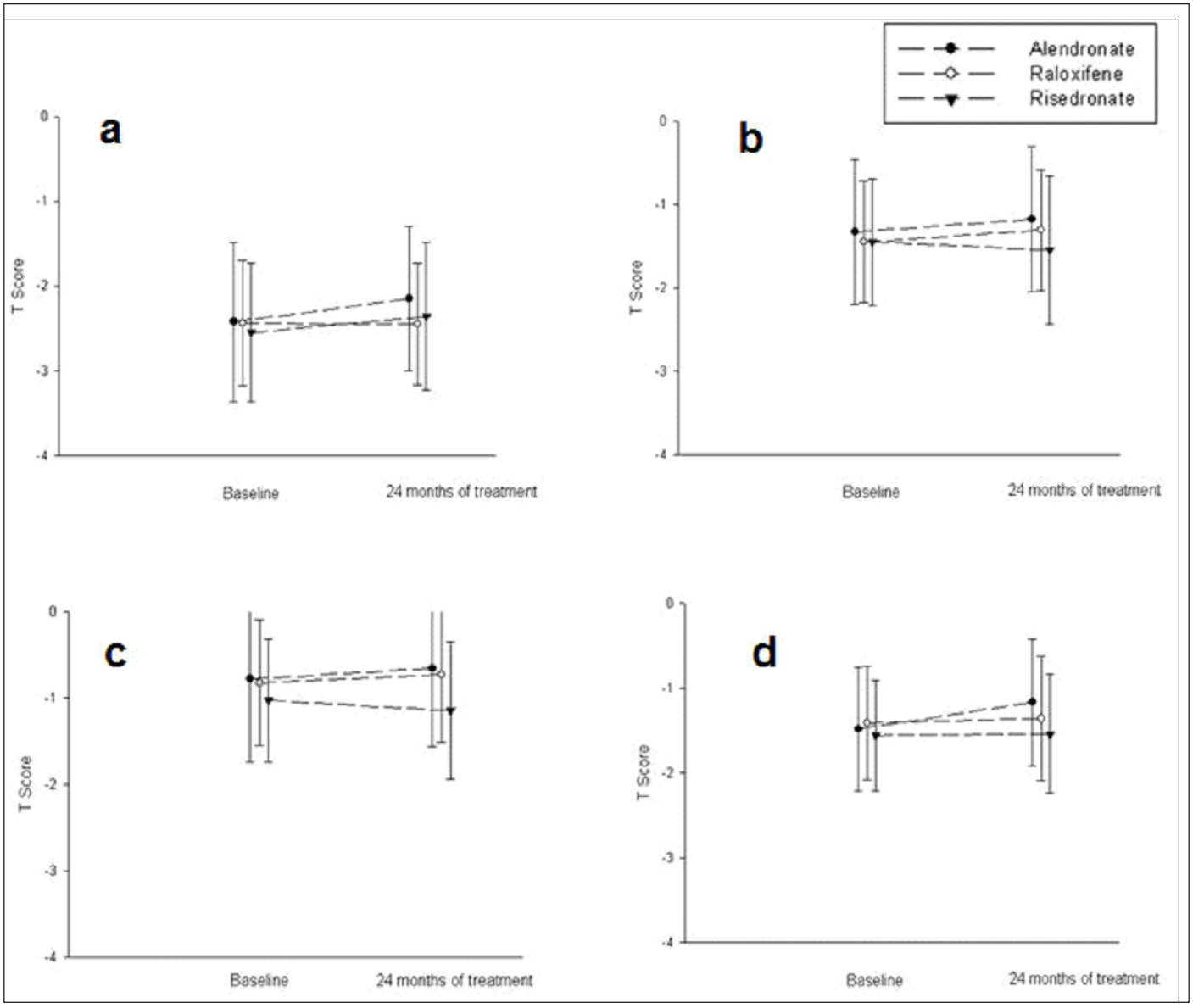
	Group I Alendronate 70mg/week	Group II Raloxifene 10 mg/day	Group III Risedronate 35 mg/week	P values
Age (y)	58.94±7.31	60.10±7.01	58.91±7.97	NS
Age of menopause (y)	46.70±4.61	46.43±4.97	46.76±5.09	NS
Duration of menopause (y)	12.11±7.64	13.69±7.96	12.09±7.38	NS
Parity	2.06±1.42	1.97±1.08	2.03±1.36	NS
Body Mass Index (kg/m^2)	26.77±3.74	26.16±3.14	26.26±3.16	NS
NS=Non Significant				

Table 2: Baseline and post-treatment T scores of lumbar spine, femur neck, trochanter and total hip in three groups

	Group I Alendronate 70mg/week		**Group II Raloxifene 10 mg/day**		**Group III Risedronate 35 mg/week**		*P Value[a]*	*P Value[b]*	*P Value[c]*	*P Value[d]*	*P Value[e]*
T Scores	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*					
Lumbar spine	-2.42±0.94	-2.15±0.85	-2.44±0.74	-2.45±0.72	-2.55±0.82	-2.36±0.87	NS	<0.01	NS	<0.01	NS
Femur neck	-1.33±0.87	-1.18±0.87	-1.45±0.73	-1.31±0.72	-1.45±0.76	-1.55±0.89	NS	<0.05	0.07	NS	<0.05
Trochanter	-1.48±0.73	-1.17±0.75	-1.41±0.67	-1.36±0.73	-1.56±0.65	-1.54±0.70	NS	<0.01	NS	NS	<0.05
Total hip	-0.78±0.96	-0.66±0.90	-0.82±0.82	-0.73±0.79	-1.03±0.71	-1.15±0.79	NS	<0.05	NS	0.08	<0.01

[a]Comparison of pre-treatment T scores in three groups.
[b]Comparison of pre-treatment and post-treatment T scores in Group I.
[c]Comparison of pre-treatment and post-treatment T scores in Group II.
[d]Comparison of pre-treatment and post-treatment T scores in Group III.
[e]Comparison of post-treatment T scores in three groups.

Figure 1. Baseline and post-treatment T scores (mean±SD) in lumbar spine (a), femur neck (b), total hip (c) and, trochanter (d)



Baseline T scores of each region were not significantly different among three groups. T scores increased in the lumbar spine ($p<0.01$), femur neck ($p<0.05$), trochanter ($p<0.01$) and total hip ($p<0.05$) following 24 months of alendronate treatment. In the risedronate group, there was a significant increase in the lumbar spine only ($p<0.01$). Raloxifene treatment did not change T scores of any regions. Baseline and post-treatment T scores (mean±SD) in lumbar spine (a), femur neck (b), total hip (c) and, trochanter (d) were shown in Figure 1.

There was only one case (1.4%) with fracture of forearm in the alendronate group. However, in the risedronate group, 5 cases (6.7%) with fracture (one case of elbow, two cases of finger, one case of hip and one cases of vertebral fractures) were seen during the treatment period. In the raloxifene group, 5 cases (6.9%) of bone fracture (including, three cases of fracture of forearm and one case of hip and one case of vertebral fracture) were seen. The rates of fracture in three groups were comparable.

Adverse effects, which had been detected during the treatment period, were shown in Table 3. There was no adverse

effect, which caused to cessation of the treatment. Raloxifene group had significantly lower adverse effects than the other groups ($p<0.05$).

Table 3: Adverse effects during treatment period

Adverse effects	**Group I Alendronate 70mg/week**	**Group II Raloxifene 10 mg/day**	**Group III Risedronate 35 mg/week**
No. of patients	70	72	74
Headache	1	0	2
Nausea	2	0	2
Dizziness	1	0	2
Dyspeptic complaints	1	0	2
Pruritus	0	0	2
Bone pain	0	0	1
Urticaria	0	2	0
Elevated liver enzymes	1	0	0
Gastrointestinal bleeding	1	0	0
Muscle stiffness	1	0	0
Total (n, %)	8 (11.4)	2 (2.7)[a]	11 (14.8)

[a] Statistically different from Group I and III, $p<0.05$

Discussion

In this study, we noted that alendronate 70 mg once weekly significantly increased the T scores in lumbar spine, femur neck, and trochanter and total hip. However, risedronate 35 mg once weekly increased T scores of lumbar spine only. Risedronate did not change T scores of other regions. Raloxifene 60 mg/day treatment did not change T scores of any regions. Drug tolerability of raloxifene was better than alendronate and risedronate.

Although fracture prevention is considered the major concern for determining the efficiency of therapy, the BMD and biochemical markers are considered as indicators of clinical efficiency. In general, BMD is an important predictor of bone strength and the prevention of bone loss is an important mechanism of fracture prevention8. Both preclinical animal models, as well as clinical trials in humans, indicate that larger increases in BMD are associated with greater reductions in fracture risk[9,10.]

The efficacy of alendronate 10 mg once daily in increasing bone mass was tested in double blind, placebo controlled clinical studies conducted in postmenopausal women with osteoporosis[11-14.] In these studies, significant increases in BMD relative to baseline and placebo were observed at each measurement site; total body BMD also increased significantly. Two-year extension studies showed continued increases in BMD measured at the lumbar spine and trochanter, plus maintenance of BMD at the femoral neck, forearm, and total body[11-14.] For patients who met the criteria of osteoporosis, as defined by the World Health Organization (WHO), the overall risk reduction was 55% (95% CI 29% to 72%, P=0.0008) [15].

Another bisphosphonate, risedronate has been shown to reduce risk of vertebral, non-vertebral and hip fractures in postmenopausal women[16-18]. Daily risedronate yielded increases in BMD at the spine, hip, and wrist compared with placebo. An additional study demonstrated the therapeutic equivalence of risedronate 35 mg once weekly in increasing BMD over 1 year [16-18]. However, in our study we noted that, risedronate 35 mg once weekly increased T scores of lumbar spine only. It did not change T scores of other regions.

A recent well-accepted drug choice is a selective estrogen receptor modulator "raloxifene". It acts like an estrogen on bone tissue. In the MORE study, raloxifene 60 mg/daily reduced the risk of new vertebral fracture by 39% (95% CI, 0.43-0.88), which was not significantly different from the relative risk in the first 3 years of the study, but again, there was no significant reduction in the rate of non-vertebral fractures[19]. In addition, effects on T scores and bone remodeling markers (Urinary N-Telopeptide) are weaker than bisphosphonates. However, the major advantage of raloxifene is better tolerability than bisphosphonates. Raloxifene is especially beneficial when patients have high plasma lipid levels or a family history of breast cancer. However, raloxifene treatment has been associated with an increased risk of hot flushes and venous thromboembolism[20,21].

In postmenopausal women with low bone mineral density, improvements in BMD and markers of bone turnover were substantially greater during treatment with alendronate compared to raloxifene[6]. These results were also supported by several prospective randomized studies[7].

Treatment linked to BMD increase is well-known feature of bisphosphonates. The impact of bisphosphonates on BMD is greater than raloxifene and BMD changes do not indicate objective reduction of vertebral fracture risk. In fact, one study with raloxifene has demonstrated that the change (suppression) of markers is a better predictor of fracture prevention than a change (increase) in BMD. However, an effect on non-vertebral fracture risk of raloxifene is another controversial issue[22].

The major drawback to raloxifene is the potential to aggravate hot flashes in some women and the slight but statistically significant increase in venous thromboembolism of similar magnitude to estrogen[23].

Compliance of anti-resorptive agents is often low. Despite of lower side effect rate, raloxifene had lower duration of continuous therapy than bisphosphonates[24]. Drug tolerability and side effects following the ingestion of raloxifene is better than bisphosphonate as shown in this study. The side effects, which may lead to patient giving up on the bisphosphonate treat-

ment, are lower than previous studies[25].

In conclusion, as a member of bisphosphonates family, alendronate has better effect on BMD than risedronate and raloxifene. In addition, side effects, which caused to cessation therapy, were lower than previously reported articles. However effects of alendronate, risedronate and, raloxifene on fracture prevention was not determined properly due to short follow-up period.

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