

# Compliance of Osteoporotic Patients with Different Treatment Regimens

Elena Segal MD<sup>1</sup>, Ada Tamir PhD<sup>2,3</sup> and Sophia Ish-Shalom MD<sup>1,2</sup>

<sup>1</sup>Metabolic Bone Diseases Unit, Rambam Medical Center, Haifa, Israel

<sup>2</sup>Technion Faculty of Medicine, Haifa, Israel

<sup>3</sup>Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel

**Key words:** osteoporosis, treatment, compliance, alendronate, raloxifene

## Abstract

**Background:** The treatment of osteoporosis among postmenopausal women represents a major public health challenge since long-term therapy is needed to prevent fractures and chronic disability.

**Objectives:** To assess compliance with osteoporosis drug therapy among Israeli postmenopausal women treated with either a bisphosphonate (alendronate) or a selective estrogen receptor modulator (raloxifene); to identify factors affecting compliance among these patients; and to compare adherence to the treatment in these two groups.

**Methods:** Our study included 178 consecutive patients aged  $67.41 \pm 8.52$  years who were treated for osteoporosis with alendronate or raloxifene in the Metabolic Bone Diseases Unit. All the patients received supplementation with calcium carbonate 1,500 mg and 600 IU vitamin D daily. Compliance was assessed at a clinic visit 6 months after starting therapy.

**Results:** The dropout rate was 23% (41 patients): 20 patients (31%) in the raloxifene group and 21 (18%) in the alendronate group ( $P = 0.0041$ ). The main reasons for dropout were side effects and/or non-compliance, 16 and 24 patients (39% and 58.53%) respectively. The most frequent side effect was abdominal pain in 9 patients (42.8%) who discontinued alendronate use. The reasons for non-compliance were a fear of side effects and high drug price in 6 (30%) and 4 (20%) patients respectively in the raloxifene group, and inconvenience caused by medication use in 3 patients (14.3%) in the alendronate group. Logistic regression analysis of factors that may influence compliance included age, previous fractures, family history of osteoporosis, bone density T-score less than -2.5, and presence and number of concomitant diseases. Age was the only statistically significant parameter in this model:  $67.8 \pm 8.8$  in non-compliant versus  $64.11 \pm 7.4$  in compliant patients ( $P = 0.029$ ).

**Conclusion:** At least 20% of the patients discontinued chronic treatment for osteoporosis during the initial 6 months of therapy. The main reasons were gastrointestinal side effects in the alendronate group and fear of side effects and high drug price in the raloxifene group. Older age was the only statistically significant factor influencing compliance.

*IMAJ 2003;5:859-862*

Osteoporosis is a major public health problem. Accurate measurements of bone mineral density allow us to identify women with osteoporosis well before they begin to suffer its devastating consequences [1]. Implementing osteoporosis prevention strategies, such as lifestyle modification, dietary changes and pharmacologic treatment, will reduce morbidity and mortality as well as diminish the cost to the healthcare system [2]. The pharmacologic agents most frequently used for osteoporosis prevention and

treatment are selective estrogen receptor modulators (raloxifene) and bisphosphonates (alendronate). Effective medical therapy is readily available, yet, as in other chronic conditions, patient compliance is a key factor for treatment success [3].

To the best of our knowledge no study has been conducted in Israel on compliance with osteoporosis treatment in a "real life setting," i.e., not in the context of a controlled clinical trial. In the current study we assessed compliance with osteoporosis treatment among Israeli postmenopausal women and attempted to identify the factors that may affect patient compliance.

## Patients and Methods

The analysis included 178 consecutive women attending the Metabolic Bone Diseases Clinic, who were at least 1 year postmenopausal and diagnosed as osteoporotic or osteopenic according to bone density measurements using criteria established by the World Health Organization. The women's mean age was  $67.41 \pm 8.52$ , median 68.5 years.

## Bone density measurements

BMD measurements of the lumbar spine (L2-L4), total hip and femoral neck were performed using dual energy X-ray absorptiometer (Lunar DPX scanner, Madison, WI, USA).

## Drug therapy

Treatment with alendronate 10 mg/day was prescribed to 115 patients (64.6%), and with raloxifene 60 mg/day to 63 (35.4%). All patients received daily supplementation with calcium carbonate 1,500 mg and vitamin D 600 IU.

## Compliance assessment

Compliance was assessed by self-reported medication use at the clinic visit 6 months after treatment initiation.

## Statistical analysis

Compliance was the study outcome variable; all other variables were considered as explanatory variables. Descriptive analysis included frequencies and distributions of all study variables. The pattern of adverse events was analyzed according to treatment, and the correlation between adverse events and treatment compliance was examined. Pearson's correlation test was used to compare the

BMD = bone mineral density

**Table 1.** Reasons for non-compliance with two treatment regimens

Reasons	Alendronate	Raloxifene	Total
Fear of side effects	2 (9.5%)	6 (30%)	8 (19.5%)
High price	0	4 (20%)	4 (9.8%)
Inconvenience	3 (14.3%)	0	3 (7.3%)
Good general health	2 (9.5%)	2 (10%)	4 (9.8%)
Poor general health	2 (9.5%)	0	2 (4.9%)
Denied any treatment	1 (4.8%)	0	1 (2.4%)
Family physician recommendation	1 (4.8%)	0	1 (2.4%)
No clinical effect	0	1 (5%)	1 (2.4%)
Total	11 (52.3%)	13 (65%)	24 (58.5%)

variables between the groups. Logistic regression analysis was performed to detect factors influencing compliance.

## Results

Forty-one of the 178 patients stopped taking the prescribed drug or changed it to another treatment (dropout rate 23%): 21 patients in the alendronate group (18%) and 20 in the raloxifene group (31%) ( $P = 0.0041$ ). The reasons for treatment discontinuation were: a) non-compliance in the absence of side effects in 24 (58.53%): 11 (52.3%) in the alendronate group and 13 (65%) in the raloxifene group; b) side effects in 16 (39%) patients: 10 (47.6%) and 6 (30%), respectively. One patient (2.4%) was lost to follow up. Major reasons for non-compliance were: fear of side effects in 8 patients (19.5%), high drug price in 4 (9.8%), and inconvenience due to drug use in 3 (7.3%) [Table 1]. The side effects observed during the follow-up are presented in Table 2.

**Table 2.** Side effects observed with the two treatment regimens

Side effect	Alendronate	Raloxifene	Total
Upper gastrointestinal tract complaints	9 (42.8%)	0	9(21.6%)
Muscular pain	1 (4.8%)	0	1 (2.4%)
Thromboembolic events	0	2 (10%)	2 (4.8%)
Neuro-emotional events*	0	4 (20%)	4 (9.6%)

\* Such as nervousness, insomnia, emotional instability.

**Table 3.** Concomitant diseases in study patients

Disease	Concomitant diseases in the compliant group			Concomitant diseases in the non-compliant group		
	Alendronate group	Raloxifene group	Total	Alendronate group	Raloxifene group	Total
Gastrointestinal	6 (5.2%)	8 (12.7%)	14 (7.9%)	2 (9.5%)	3 (15%)	5 (12.2%)
Cardiovascular	42 (36.5%)	16 (25.4%)	58 (31.9%)	6 (28.8%)	5 (25%)	11 (26.8%)
Endocrine	19 (16.5%)	12 (19%)	31 (17.4%)	4 (19%)	1 (5%)	5 (12.2%)
Ophthalmologic	4 (3.5%)	3 (4.8%)	7 (3.9%)	2 (9.5%)	1 (5%)	3 (7.3%)
Urological and urogenital	2 (1.7%)	0	2 (1.1%)	0	0	0
Skeletal	4 (3.5%)	1 (1.6%)	5 (2.8%)	0	0	0
Respiratory	4 (3.5%)	1 (1.6%)	5 (2.8%)	1 (4.8%)	2 (10%)	3 (7.3%)
Neoplastic	10 (8.6%)	3 (4.8%)	13 (7.3%)	5 (23.8%)	1 (5%)	6 (14.6%)

One of the factors considered to influence patient compliance was family, history of osteoporosis. Of 137 patients continuing the treatment 83 had a family history of osteoporosis: 60 in the alendronate group (43.8% of the compliant group, 63% of all patients prescribed alendronate), and 23 patients in the raloxifene group (16.8% of the compliant group, 53.5% of all patients prescribed raloxifene). The difference between the groups was not statistically significant.

Another possible influencing factor is the history of previous osteoporotic fractures. Previous osteoporotic fractures occurred in 52 patients (55.3%) in the alendronate-compliant group and 14 (32.6%) in the raloxifene-compliant group ( $P = 0.013$ ). Among the patients who discontinued the treatment, previous fractures were reported in 14 of the alendronate group (66.7%) and 6 of the raloxifene group (30%) ( $P = 0.019$ ). The discontinuation rate in the patients with fractures was 21.2% in the former (14 patients) and 30% in the latter group (6 patients). The difference was not statistically significant.

The effect of BMD results on compliance was also assessed. Osteoporosis was diagnosed in 71 (75%) of the alendronate-compliant patients and 16 (37.2%) of the raloxifene-compliant patients. Osteopenia was diagnosed in 23 (24.5%) and 27 (62.8%) of compliant patients respectively. Among non-compliant patients in the alendronate group 6 (28%) had osteopenia and 15 (71%) had osteoporosis. In the raloxifene group 14 (72%) were osteopenic and 6 (28%) were osteoporotic. The difference between the groups was not statistically significant. Concomitant diseases were also considered a factor influencing compliance [Table 3].

The difference between compliant and non-compliant groups was not statistically significant due to the small number of patients in each group. Logistic regression analysis included age, previous fractures, family history of osteoporosis, BMD T-scores less than -2.5, and the presence and number of concomitant diseases. Age was found to be the only statistically significant factor influencing patient compliance:  $67.8 \pm 8.8$  years in non-compliant versus  $64.11 \pm 7.4$  in compliant patients ( $P = 0.029$ ).

We analyzed the current treatment of patients who discontinued the initially prescribed treatment [Table 4]. One-third of patients who discontinued daily alendronate treatment successfully continued with the weekly formulation of the drug. Seventeen (41.5%) patients who discontinued the initially prescribed treatment

regimen remained with the calcium and vitamin D supplementation only. Six patients (14.6%) had not received treatment for osteoporosis at the time of the survey.

## Discussion

Compliance is the extent to which the patient's behavior coincides with medical or health advice [3]. An important barrier in trans-

**Table 4.** Treatment after discontinuation of the initially prescribed therapy

Current treatment	Alendronate	Raloxifene	Total
HRT	0	3 (15%)	3 (7.3%)
Caltrate + D	7 (33.3%)	10 (50%)	17 (41.5%)
Raloxifene	4 (19.6%)	1 (5%)	5 (12.5%)
Alendronate 70 mg/week	6 (28.6%)	2 (10%)	8 (19.5%)
Nasal calcitonin	1 (4.8%)	0	1 (2.4%)
Not known	0	1 (5%)	1 (2.4%)
No treatment	3 (14.3%)	3 (15%)	6 (14.6%)
Total	21 (100%)	20 (100%)	41 (100%)

forming scientific progress to improvement in clinical outcomes is compliance (adherence to physicians' prescriptions). Hundreds of studies found that only 50–60% of patients take their medications for chronic disease as prescribed [3]. The decision to comply with therapeutic recommendation is multifactorial and includes the following components: probable beneficial effect (e.g., reducing the risk for hip fractures), probable risks (e.g., esophagitis, abdominal pain), certain inconveniences (e.g., disrupting the daily routine, feeling of dependency), and economic burden. Each of these components has a different impact on the final decision of each woman. The health-belief model suggests that patients are more likely to comply with doctors' orders when they feel susceptibility to illness, believe that the illness has potential serious consequences for health or daily functioning, and do not anticipate major obstacles such as side effects or costs [4]. Studies have found that non-compliance tends to be higher under certain conditions: a) when medical regimens are more complex [5], b) when the disorder is asymptomatic, c) when the treatment period lasts for longer periods, d) and when there are several troublesome drug-related side effects [3]. Interestingly, there seem to be few consistent relationships between non-compliance and such factors as social class, age, gender, education, and marital status [5].

To the best of our knowledge no studies have been undertaken on compliance with treatment for osteoporosis in a "real life setting" in Israel, that is, not in the context of a controlled clinical trial. Although this retrospective study may have been influenced by probable recall bias, our current observations represent a "sneak preview" of the compliance patterns with osteoporosis treatment among Israeli postmenopausal women. Further large-scale studies are required.

Compliance with chronic therapy is known to be problematic, especially in relatively young and asymptomatic patients, such as osteopenic and some osteoporotic patients. It was found [6] that acceptance of recommended treatments was relatively higher following bone mass measurement. Of course, the treatment decision should be based on each patient's medical history and personal preferences [2]. Raloxifene was viewed as an ideal agent, targeted to bone and acting as an anti-estrogen in the breast and uterus [7,8]. With the introduction of SERMs to the pharmacologic market, women who are afraid of the side effects of hormone

replacement therapy can effectively prevent and treat osteoporosis by using these new agents, which produce the beneficial estrogen-like effects of SERMs on bone while antagonizing estrogen in reproductive tissue [9]. In the study by Karakoc and Erenus [10] the discontinuation rate of HRT use was 28.7%, which is comparable to the discontinuation rate of raloxifene in our study. It is likely that some women accepted SERM as a kind of HRT; however, Kayser et al. [11] report a 25% higher compliance with raloxifene versus estrogen. In this study the discontinuation rate of HRT was 72% during 2 years, as compared to 56% of raloxifene users. All our patients received a detailed explanation about the mechanism of action of the drugs and the possible side effects. The substantial number of discontinuations due to fear of side effects in the raloxifene group was probably due to the influence of friends, media and misinterpretation of current events, such as transient leg pain that was considered a sign of thrombosis. Comparing the therapeutic effects of alendronate 10 mg daily and alendronate 70 mg weekly, Schnitzer and colleagues [12] concluded that a less frequent weekly dosing regimen will provide patients with a more convenient therapeutic alternative and may enhance compliance in long-term treatment. Our data support this statement: six patients (28%) who discontinued alendronate 10 mg/day continued with a once weekly form of the same drug.

The major reason for non-compliance with alendronate was adverse gastrointestinal experience. According to Ettinger et al. [13], alendronate users were 1.6 times more likely to have acid-related upper gastrointestinal disorders. Another study [14] found that the incidence of upper gastrointestinal symptoms and therapy discontinuation after re-challenge with alendronate or placebo was similar and comprised about 30%, perhaps reflecting a high background incidence of upper gastrointestinal symptoms in osteoporotic patients. The increased incidence of upper gastrointestinal symptoms can be attributed to age above 70 years, concurrent use of non-steroidal anti-inflammatory drugs, use of glucocorticoids, or non-compliance with patient safety instructions [13].

Rosini and co-workers [15] promote intermittent alendronate therapy as an option for patients with low compliance to continuous therapy. Another important consideration should be the durability of the therapeutic effect after treatment discontinuation. Bisphosphonates accumulate in bone for years [16] and decreased bone turnover – one of the major factors in fracture rate reduction – persists for at least 1 year after treatment discontinuation [17]. The effect of raloxifene is not sustained after discontinuation of therapy. Thus, treatment that has a sustained effect may be administered on an intermittent basis with greater effect in terms of fracture reduction, even when compliance is suboptimal. This issue warrants further investigation in larger scale studies.

## Conclusion

Twenty-three percent of the women in our study discontinued their osteoporosis treatment during the initial 6 months. There was no

significant difference in the discontinuation rates between the two treatment groups (alendronate and raloxifene). Apart from side effects, older age was the only statistically significant factor influencing compliance. Forty percent of the patients who stopped the prescribed treatment continued with calcium and vitamin D supplements only. About one-third of the patients who discontinued daily alendronate regimen continued with the weekly formulation of the drug.

---

## References

1. Masi L, Bilezikian JP. Osteoporosis: new hope for the future. *Int J Fertil Womens Med* 1997;42:245–54.
2. Mc Garry KA, Kiel DP. Postmenopausal osteoporosis. Strategies for preventing bone loss, avoiding fracture. *Postgrad Med* 2000;108:79–82, 85–88, 91.
3. Sackett DL, Snow JC. Magnitude of compliance and non-compliance. In: Haynes RB, Taylor DW, Sackett DL, eds. *Compliance in Health Care*. Baltimore: Johns Hopkins University Press, 1981:11–23.
4. Conrad P. The meaning of medications: another look at compliance. *Soc Sci Med* 1985;20:29–37.
5. Hingson R, Scotch NA, Sorenson J, Swazey JP. In *Sickness and in Health: Social Dimension of Medical Care*. St. Louis: CV Mosby, 1981.
6. Cole RP, Palushock S, Haboubi A. Osteoporosis management: physicians' recommendations and women's compliance following osteoporosis testing. *Women Health* 1999;29:101–15.
7. Pfeilschifter J. Hormone replacement and selective estrogen receptor modulators (SERMS) in the prevention and treatment of postmenopausal osteoporosis. *Orthopade* 2001;30:462–72.
8. Hochner-Celnikier D. Pharmacokinetics of raloxifene and its clinical application. *Eur J Obstet Gynaecol Reprod Biol* 1999;85:23–9.
9. Bryant HU, Dere WH. Selective estrogen receptor modulators: an alternative to hormone replacement therapy. *Proc Soc Exp Biol Med* 1998;217:45–52.
10. Karakoc B, Erenus M. Compliance considerations with hormone replacement therapy. *Menopause* 1998;5:102–6.
11. Kayser J, Ettinger B, Pressman A. Postmenopausal hormonal support: discontinuation of raloxifene versus estrogen. *Menopause* 2001;8:328–32.
12. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging* 2000;12:1–12.
13. Ettinger B, Pressman A, Schein J. Clinic visits and hospital admissions for care of acid-related upper gastrointestinal disorders in women using alendronate for osteoporosis. *Am J Manag Care* 1998;4:1377–82.
14. Miller PD, Woodson G, Licata AA, et al. Rechallenge of patients who had discontinued alendronate therapy because of upper gastrointestinal symptoms. *Clin Ther* 2000;22:1433–42.
15. Rossini M, Gatti D, Girardello S, Braga V, James G, Adami S. Effects of two intermittent alendronate regimens in the prevention or treatment of postmenopausal osteoporosis. *Bone* 2000;27:119–22.
16. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. *Bone* 1999;25:97–106.
17. Emkey R, Reid I, Mulloy A, et al. Ten-year efficacy and safety of alendronate in the treatment of osteoporosis in postmenopausal women. *J Bone Miner Res* 2002;17(Suppl 1):S139.

---

**Correspondence:** Dr. S. Ish-Shalom, Metabolic Bone Diseases Unit, Rambam Medical Center, P.O. Box 9602, Haifa 31096, Israel.  
Phone: (972-4) 854-2584  
Fax: (972-4) 854-3416  
email: s\_ish\_shalom@rambam.health.gov.il