PATIENT COMPLIANCE WITH DRUG THERAPY FOR POSTMENOPAUSAL OSTEOPOROSIS

ALI AHMAD, MOHAMMAD YOUNUS KHAN
Department of Orthopaedics, Hamdard College of Medicine & Dentistry, Karachi

ABSTRACT
Objective: *To determine compliance and factors affecting compliance to antiresorptive drugs in osteoporosis, and to compare compliant and non compliant groups in a tertiary care setting.*
Design & Duration: *Cross sectional study from May 2004 to April 2007.*
Setting: *Hamdard University Hospital, Karachi.*
Patients: *A total of 800 patients with postmenopausal osteoporosis were included in the study.*
Methodology: *The demographic and reproductive characteristics of all the patients were recorded. Type of antiresorptive drugs prescribed, degree of compliance, time and reasons for discontinuation were studied and analyzed.*
Results: *The mean age of the patients was 64 (±9) years and their mean duration of follow-up 18 (±5) months. The prevalence of risk factors for osteoporosis were evenly distributed among treatment groups; 73% patients had a co-morbidity besides osteoporosis while 27% were osteoporotic alone. One or more previous vertebral fractures due to osteoporosis was reported by 14.5% of patients, whereas 35.5% had at least one non-vertebral fracture in their medical history.*

Out of the total patients 21.5% discontinued the prescribed drug before attending the bone mass re-evaluations, more than half of these within first six months of starting the drugs. The medication that was most frequently discontinued within one year was calcium and vitamin-D (33.7%, $p<0.01$) while the least discontinued medication was Alendronate (5.9%, $p < 0.01$) which is taken once a week.
Conclusion: *In this study the most important determinant of compliance was the type of drug prescribed and its dose frequency, with a definite preference for Alendronate once a week. Treatment compliance was particularly poor for calcium and vitamin-D regimen, thereby emphasizing the need to find new ways of administering supplements, particularly for vitamin-D.*

KEY WORDS: *Osteoporosis, Compliance, Antiresorptive Therapy, Vitamin-D*

INTRODUCTION

Poor therapeutic adherence among patients suffering from chronic asymptomatic disease is a major issue facing physicians today[1]. It has been observed that up to 50% of patients with chronic diseases such as hypertension, depression and asthma discontinue medication, with the rate rising in different therapeutic areas; upto 70% of patients prescribed preventive asthma medication stop treatment. In USA 51% of the patients continue with their anti-hypertensive drugs as compared to 26% in the Seychells. Poor adherence is considered to be the primary reason for the suboptimal clinical benefit of therapy[2].

Since the primary objective of the treatment is not met, patient may experience complications. Furthermore, patients may experience reduced quality of life, which in turn leads to greater health care costs. Therefore, addressing the problem of poor adherence could potentially benefit both the patients and society[2].

There is an increasing evidence to demonstrate that a substantial proportion of patients abandon their current

Correspondence:
Dr. Ali Ahmad, Asstt. Prof. Orthopaedics,
Hamdard University Hospital,
M. A. Jinnah Road, Karachi.
Phones: 0333-2165441.
E-mail: aliahmad57@gmail.com

osteoporosis treatment within just 6-7 months of treatment initiation[3-5] and that the probability of continuing osteoporosis treatment decreases over time[6]. The proportion of patients with uninterrupted therapy after one year was found to be close to only 20% for any type of antiresorptive therapy[7].

Compliance to prescribed dosing that generally shows how well a patient follows a physician's instruction during a specific period of time, is also often inadequate[8]. It has been recognized that the full benefits of medications for osteoporosis can not be reached if the compliance is low.

Poorly compliant patients have a smaller bone mineral density (BMD) gains, a weaker suppression of the bone turnover and ultimately a greater risk for fractures, as compared to patients who adhere to their prescribed therapy[1,9]. The causes of discontinuation and low compliance to medical therapy for osteoporosis in patients treated in clinical practice are complex and poorly defined.

PATIENTS & METHODS

This study was conducted by the Department of Orthopaedics, Hamdard University Hospital, Karachi from May 2004 to April 2007 on 800 patients, either as outpatient or inpatient basis. The study population included all postmenopausal women of ages 50 years and above presenting with symptoms consistent with osteoporosis.

After obtaining an informed consent, the patients were asked to complete a questionnaire. The data was then entered on a specific data collection form. The patient's demographic and reproductive characteristics recorded included age, weight, height, education level, residence (urban/rural), age at menopause and the type of menopause (natural/surgical). In addition, details about the clinical and lifestyle risk factors were collected like history of fragility after the age of 40 years, history of fragility hip fractures in mother, problems with sense organs (sight, hearing), regular exercise and mobility status. The presence of concurrent diseases that may increase the risk of the osteoporosis or falls were also recorded.

Table I. Characteristics of the patients

Character	No.	%
Urban	752	94.0
Rural	48	6.0
Literate	696	87.0
Illiterate	104	13.0
Dependent	420	52.5
Non-dependent	380	47.5
On medical cover	224	28.0
Not on medical cover	576	72.0

The following information was obtained on osteoporosis treatment prescribed at the first visit. The type of drug used (Calcium & Vitamin-D, Raloxifene, Disodium pamidronate, Alendronate sodium 100mg daily, Alendronate sodium 70mg weekly, Risendronate 5mg daily), degree of compliance, time and reasons for discontinuation were recorded. In the non-compliant group of patients, major factors responsible like cost, side effects, drug availability, forgetfulness, education, deliberate missing and lack of counseling by physician were recorded.

The degree of compliance was also noted. Those who missed >12 doses in the preceeding six months were regarded as severely non-compliant, those who missed 6-12 doses were regarded as moderately non-compliant and those who missed <6 doses were considered as mildly non-compliant. Given the nature of the study, the data on treatment adherence was exclusively self reported.

Bone mineral density (BMD) measurement included dual energy X-ray absorptiometry (DEXA) at the level of lumbosacral spine and hip joint or quantitative ultrasound (QUS) evaluation at the calcaneous bone. Rest of the patients were diagnosed as osteoporotic on X-ray of lumbosacral spine.

The data was analyzed on SPSS (Statistical Package for Social Sciences, vesion-12). Results were presented as means with standard deviations for continuous variables and percentages for categorical variables. In univariate analysis, Chi-Square test was used to assess differences in proportions between the compliant and non-compliant groups.

RESULTS

The study population consisted of 800 postmenopausal women, mean age 64±9 years (Table I), who were followed-up for to atleast 15 months and have been prescribed one of the antiresorptive drugs at random. The prevalence of risk factors for osteoporosis were evenly distributed among the treatment groups. These included reduced physical activity (<30 minutes / day spent on walking - 44%), low body weight (<57Kg - 34%), and

Factors	Compliant group 78.5% (n=628)	Non-Compliant group 21.5% (n=172)	P-Values
Mean age	65.4 years	62.4 years	0.08
Literate	85.1% (388)	89.5% (308)	0.05
Medical Coverage	29.8% (136)	25.6% (88)	0.50
Dependence	59.8% (272)	43.0% (148)	0.02

Table II. Comparison of Compliant and Non-Compliant group

early menopause (before 45 years of age-22%).

Among the literate patients 9.1% were postgraduates, 12.5% were graduates, 21.2% were matriculate, 24.7% were educated upto middle level and 32.5% upto primary level. Around 73% patients had a co-morbidity besides osteoporosis, while 27% were osteoporotic alone. The most frequent co-morbidity was hypertension (36%), others being ischaemic heart disease (30%), dyslipidaemia(32%), diabetes mellitus (36%), joint disease (18%), chronic renal failure (3%), lung disease (2.5%) and stroke (1.5%).

The diagnosis of osteoporosis was made by DEXA evaluation in only 8.5% patients, on QUS of calcaneum in 536 (67%) patients and X-ray lumbosacral spine in 24.5% patients. One or more previous vertebral fractures due to osteoporosis was reported by 14.5% of patients and 35.5% had at least one non-vertebral fracture in their medical history.

Comparison of the compliant and non-compliant groups is given in Table II. The literate patients (matriculate or higher) were more in the compliant group than the non-compliant group (42.8 versus 28.12). Table III lists the principal characteristics of the study population according to prescribed treatments. The patients taking bisphosphonates (Pamidronate, Alendronate and Risedronate) were comparable in all parameters, while patients on Raloxifene and Cacium & Viatmin-D were significantly younger and their bone mass values significantly higher than the global mean.

Alendronate, Raloxifene and Risendronate were prescribed in 80% of the women with previous vertebral fractures for the secondary prevention of osteoporotic fractures, while in 75% of the patients with previous hip fractures Alendronate or Risendronate was given.

The timing and rate of discontinuation are listed in Table IV for each t ype of treatment. Overall, 21.5% of the patients discontinued the prescribed drug before attaining the bone mass re-evaluation, more than half of these with in the first six months of starting the drug.

The discontinuation rate was significantly different between treatment groups (Chi Square test). The medication that was most frequently discontinued with in one year was calcium & vitamin-D (33.7%, $p<0.01$ versus any other treatment), while by far the least discontinued medication was Alendronate once a week (5.9%, $p<0.01$ versus any other treatment).

Table III. Distribution of the study population according to the treatment: mean and standard deviations (SD)

Treatment	Age	Age at menopause	BMI (Kg/m^2)	QUS Calcaneus (T-Score)
Calcium & Vitamin-D (n=142)	63 (10)	48 (5)	26.2 (4.5)	-2.0 (1.1)
Raloxifene (n=132)	60 (08)	48 (6)	25.0 (4.0)	-2.4 (1.1)
Disodium pamidronate (n=98)	67 (08)	45 (5)	25.7 (4.3)	-2.8 (1.1)
Alendronate Sodium 100mg daily (n=136)	67 (08)	48 (5)	25.3 (4.0)	-3.4 (1.1)
Alendronate Sodium 70mg weekly (n=168)	66 (09)	48 (5)	25.7 (4.3)	-3.1 (1.1)
Risendronate 5mg daily (n=124)	67 (09)	48 (5)	25.5 (4.2)	-3.0 (0.9)
Total (n=800)	64 (09)	48 (5)	25.5 (4.2)	-2.7 (1.2)

The patients who discontinued treatment had to select one of seven predefined causes of discontinuation (Fig. 1). The most frequent reasons for discontinuation were drug related side effects. The prevalence of the reasons for discontinuation were different among treatments. Lack of the motivation was the most common cause for calcium & vitamin D group and drug related side effects were the most common cause of ceasing Alendronate and Risenedronate treatments.

DISCUSSION

Poor compliance and persistence with therapy are common problems in chronic diseases. Compliance typically ranges from 50%-60%, and is usually lower when the disease is asymptomatic and treatment confers bothersome side effects[7,10]. Therefore it is not surprising that 11% of postmenopausal women in our study were no longer adherent to the therapy after 6 months following initiation of the treatment, and by the end of one year nearly 21.5% were adherence failure. Thus there appears to be a large cohort of patients who discontinue treatment soon after therapy initiation; in those who persist this time point, the failure rate is much lower.

Drug compliance was self reported in the present study and was not verified by objective tools, so this may be a source of over estimation of global adherence. In addition our results are applicable only to patients in whom the osteoporosis treatment was prescribed on the basis of X-ray or densiometric evaluation. In studies carried out from data derived by health insurance or administrative data bases, adherence to treatment has been found comparable ranging from 25%-50%[7,11-14].

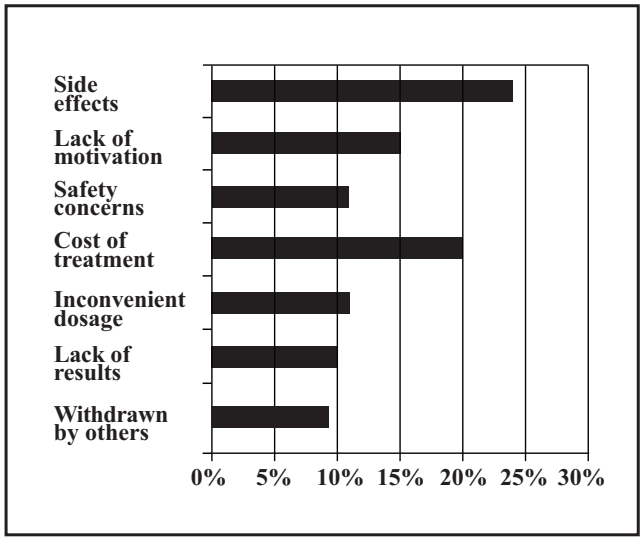

Fig. 1. Reason for drug discontinuation

The discontinuation for different drugs were very similar with the only remarkable exception being Alendronate (once a week), which showed a treatment persistence rate three fold higher than that of any other treatment. It has been shown that treatment adherence improves as number of doses taken each day decreases[15], and with weekly versus daily regimen[14,16-18]. Our results also provide further evidence that in comparison to daily dosing, weekly dosing does improve persistence to treatment not only during controlled clinical trials but also in routine clinical practice.

The most common reasons for treatment discontinuation were the appearance of side effects which accounted for a quarter of all cases. This proportion is considerably

Table IV. Treatment discontinuation

Timing of Discontinuation	Calcium & Vitamin D	Disodium pamidronate	Raloxifene	Alendronate Sodium 10mg daily	Alendronate Sodium 70mg weekly	Risendronate daily	Total
< 6 months	31	11	15	6	6	19	88
	(21.8%)	(11.2%)	(11.3%)	(4.4%)	(3.6%)	(15.3%)	(11%)
6-12 months	10	4	8	13	3	6	44
	(7%)	(4.08%)	(6%)	(9.5%)	(1.8%)	(4.8%)	(5.5%)
> 12 months	7	15	2	11	1	4	40
	(4.9%)	(15.3%)	(1.5%)	(8%)	(0.59%)	(3.2%)	(5%)
Total Discontd.	48	30	25	30	10	29	172
	(33.7%)	(30.5%)	(18.8%)	(21.9%)	(5.9%)	(23.3%)	(21.5%)
Total Patients	142	98	132	136	168	124	800

lower than the 80% reported by Tosteson et al[3]. However our questionnaire provided patients a broader range of possible causes than that of Tosteson et al, including cost, inconvenient dosing, advice from other specialists and these alternatives were frequently chosen by the patients. One should recognise that the causes of inadequate treatment adherence may differ considerably depending on cultural and economic conditions. Lack of motivation may largely depend on the prestige of the prescriber or the clinical relevance attributed to the diseases under different cultural conditions. A similar relationship is also reported by Rossini etal[19]. The use of benzodiazepine and gastroprotective agents was predictor of poor treatment persistence, possibly in relationship with underlying comorbidity.

We also evaluated treatment compliance among patients who did not discontinue therapy. The compliance was rather poor for calcium & vitamin-D supplements, with only two third of the patients taking prescribed doses. While, there is significantly greater treatment compliance for Alendronate (once a week) therapy versus all other bisphosphonates. This indicates that this treatment regimen is associated not only to increased persistence but also to greater compliance.

Treatment compliance was poorer in patients suffering gastrointestinal problems, but was enhanced by the ready availability of bone measurements with values with in the range of osteoporosis. This is in agreement with previous reports that showed that those who understood their bone densiometry results were more likely to follow their prescriptions[3,20,21].

CONCLUSION

The most important determinant of compliance to treatment was the type of drug prescribed, with definite preference for Alendronate (once a week). Treatment compliance was particularly poor for calcium & vitamin-D regimen, thereby emphasizing the need to find new ways of administering supplements, particularly for vitamin-D. The main reasons for the discontinuation were side effects, cost of treatment and lack of motivation, while the best treatment adherence was observed in patients with severe and well documented osteoporosis. The clinical implications of treatment compliance and associated financial consequences require further studies and research.

REFERENCES

1. Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks, et al. The impact of compliance with Osteoporosis therapy on fracture rates in actual practice. Osteoporosis Intl 2004; 15: 1003-8.

2. World Health Organisation. Prevention and management of Osteoporosis. World Health Organ Tech Rep Ser 2003; 921: 1-164.

3. Tosteson AN, Grove MR, Hammond CS, Moncur MM, Ray GT, Herbert GM, Pressman AR, Ettinger B. Early discontinuation of treatment for Osteoporosis. Am J Med 2003; 115: 209-16.

4. Segal E, Tamir A, Ish-Shalom S. Compliance of Osteoporotic patients with different treatment regimens. Isr Med Assoc J 2003; 5: 859-62.

5. Turabi C, Herrero-Beaumont G, Acebes JC, Torrijos A, Grana J, Miguelez R, Sacristan JA, Marin F. Compliance and satisfaction with Raloxifene versus Alendronate for the treatment of postmenopausal Osteoporosis in clinical practice: An open-label, prospective, non-randomized observational study. Clin Therap 2004; 26: 245-56.

6. Lombas C, Hakim C, Zanchetta JR. Compliance with Alendronate treatment in an Osteoporosis clinic. J Bon Miner Res 2001; 15(Suppl-1): 529-33.

7. McCombs JS,Thiebaud P, Mclaughlin-Milley C, Shi J. Compiance with drug therapies for the treatment and prevention of Osteoporosis. Maturitas 2004; 48: 271-87.

8. Hamilton B, McCoy K, Taggart H. Tolerability and compliance with Risedronate in clinical practice. Osteoporosis Intl 2003; 14: 259-62.

9. Yood AR, Emani S, Reed JI, Edelman Lewis B, Charpentier M, Lydick E. Compliance with pharmacologic therapy for Osteoporosis. Osteoporosis Intl 2003; 14: 965-68.

10. Steiner JF, Earnest MA. University of Colorado Health Sciences Center, Lingua Medica: The language of medication-taking. Ann of Intern Med 2000; 132: 926-30.

11. Kayser J, Ettinger B, Pressman A. Postmenopausal hormonal support: Discontinuation of Raloxifene versus estrogen. Menopause 2001; 8: 328-32.

12. Ettinger B, Li DK, Klein R. Alendronate use among 812 women: Prevalence of gastrointestinal complaints, non-compliance with patient instructions and discontinuation. J Manag Care Pharma 1998; 4: 488-92.

13. Kotzan JA, Martin BC, Wade WE. Persistence with estrogen therapy in a postmenopausal medic aid population. Pharmacotherapy 1999; 19: 363-69.

14. Recker RR, Gallagher R, MacCosbe PE. Effects of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. Maj Clin Proc 2005; 80: 856-61.

15. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23: 1296-1310.

16. Simon JA, Lewiecki EM, Smith ME, Petruschke RA, Wang L, Palmisano JJ. Patient preference for once weekly Alendronate 70 mg versus once daily Alendronate 10 mg: A multicenter, randomized, open-label, crossover study. Clin Ther 2002; 24: 1871-86.

17. Kendler D, Kung AWC, Fuleihan GE, et al. Patients with Osteoporosis prefer once weekly to once daily dosing with Alendronate. Maturitas 2004; 48: 243-251.

18. Weiss M, Vered I, Foldes AJ, Cohen YC, Shamir-Elron Y, Ish-Shaloms S. Treatment preference and tolerability with Alendronate once weekly over a 3 months period: An Israeli multicenter study. Aging Clin Exp Res 2005; 17: 143-49.

19. Rossini M, Bianchi G, DMunno O, Giannini S, Minisola S, Sinigaglia L, Adami S. Determinants of adherence to Osteoporosis treatment in clinical practice. Osteoporosis Intl 2006; 17: 914-921.

20. Pressman A, Forsyth B, Ettinger B, Tosteson A. Initiation of Osteoporosis treatment after bone mineral density testing. Osteoporosis Intl 2001; 12: 337-42

21. Pickney CS, Amason JA. Correlation between patient recall of bone densiometry Results and subsequent treatment adherence. Osteoporosis Intl 2005; 16: 1156-60.