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Observational Study of Compliance and Continuance Rates of Raloxifene in the Prevention and Treatment of Osteoporosis

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ABSTRACT

Background: Medical practitioners face the challenge of noncompliance with prescriptions, particularly in chronic, asymptomatic, diseases such as osteoporosis.

Objective: The aim of this study was to assess the raloxifene compliance and continuance rates and adverse effects over 24 months in clinical practice.

Methods: Using a retrospective study of clinical histories obtained from a database at the Metabolic Research Institute, University of El Salvador School of Medicine, Buenos Aires, Argentina, as well as telephone interviews, we assessed compliance and continuance with raloxifene therapy in postmenopausal patients who had received prescriptions for raloxifene to prevent or treat osteoporosis. Patients were contacted by telephone 24 months after they had received a prescription for raloxifene. Compliance and continuance rates were calculated based on the data provided by the patients.

Results: Data from 419 patients (mean [SD] age, 61.4 [7.4] years [range, 42–90 years]) were included in the study. At the time of the telephone interview, 225 (53.7%) were still receiving raloxifene, 105 (25.1%) had stopped treatment at their own discretion, 59 (14.1%) had not started treatment, and 30 (7.2%) had discontinued treatment as a result of advice from a physician. The reasons for not starting treatment were fear of thrombolytic events (21 patients [35.6%]); lack of interest in starting treatment (12 [20.3%]); other physician's advice (11 [18.6%]); family problems (3 [5.1%]); dissatisfaction with the prescribing physician, treatment cost, health problems unrelated to osteoporosis, and mistrust in the prescription (each, 2 [3.4%]); and advice from family/friends, fear of breast cancer, belief that raloxifene is hormonal, and that the patient was already polymedicated (each, 1 [1.7%]). Eleven of the 59 patients (18.6%) who had not started therapy were advised by a physician other than the prescribing physician not to start treatment and were excluded from the compliance analysis. Thus, the compliance analysis included 408 patients. The 2 most common reasons for discontinuing treatment at the patient's own discretion were health problems unrelated to osteoporosis

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(25 [23.8%]) and digestive problems not considered treatment related (16 [15.2%]). The compliance rates were 75.0%, 71.1%, 65.0%, 57.1%, and 52.0% at 3, 6, 12, 18, and 24 months, respectively. In patients who started raloxifene treatment, the continuance rates were 85.0%, 80.6%, 73.6%, 64.7%, and 58.9% at 3, 6, 12, 18, and 24 months, respectively. Sixty-two of the 135 patients who discontinued treatment did so within 3 months of receiving the prescription, accounting for 45.9% of all discontinuations.

Conclusions: In the present study of raloxifene compliance and continuance in clinical practice, the compliance rate appeared to be relatively high compared with those of hormone-replacement therapy (HRT) and other non-HRT treatments. Almost half of patients who discontinued treatment did so in the first 3 months. (*Curr Ther Res Clin Exp.* 2004;65:470–480)

Key words: compliance, adherence, raloxifene.

INTRODUCTION

In patients with chronic, asymptomatic diseases, the rate of compliance with therapy is ~50%.[1] In 1979, Haynes et al[2] defined *compliance* as the degree to which a patient's behavior coincides with the physician's prescription or advice. Forgetfulness and the medication being perceived as unnecessary are the most frequent reasons for noncompliance.[3] In these cases, patients refuse to buy the medication, forget to take it regularly, or discontinue it completely.

Osteoporosis is a chronic and often asymptomatic disease; therefore, ensuring compliance can be difficult. *Continuance,* defined as receiving medication for a duration long enough to achieve the desired effect,[4] should also be addressed. In osteoporosis, the chronic nature of the disease necessitates years rather than months of therapy. Consequently, treatment compliance and continuance are essential for successful treatment.

Osteoporosis has been managed with hormone-replacement therapy (HRT). However, encouraging compliant behavior is difficult with HRT due to adverse effects (AEs) and fear of a potential increase in cancer risk. Raloxifene, a selective estrogen receptor modulator, has been approved for the prevention and treatment of postmenopausal osteoporosis. Clinical trials[5,6] have shown it to be effective in maintaining bone mass and reducing the incidence of vertebral fractures. However, in the clinical trial setting, the high adherence rate (>80%)[5] to the raloxifene treatment regimen is not necessarily reflective of the situation in clinical practice.

The aim of this study was to assess the rates of compliance and continuance over 24 months after the prescription of raloxifene for the prevention or treatment of osteoporosis.

PATIENTS AND METHODS

We retrospectively reviewed the database at the Metabolic Research Institute, University of El Salvador School of Medicine, Buenos Aires, Argentina, to identify all postmenopausal patients prescribed raloxifene from March 1998 through October 2000. From among these patients, we included those who could be contacted by telephone. All of the patients included had undergone bone mineral density measurement, had received a prescription for raloxifene 60 mg/d for the prevention or treatment of osteoporosis, and were enrolled in a health insurance plan.

The script used in the telephone interviews was approved by the institutional review board at the Metabolic Research Institute, and patients were required to provide verbal informed consent for the interview.

Two people conducted the telephone interviews, which consisted of 2 sections—open and closed questions—to assess compliance, continuance, and AEs associated with raloxifene treatment. Closed questions included multiple-choice and yes/no questions (eg, "Did you experience any adverse events after starting treatment with raloxifene?"). If a patient found it difficult to remember certain data, she was asked, "Do you remember having hot flashes after starting treatment with raloxifene?"

Following data collection, patient behavior was classified according to compliance. Patients were considered compliant if they met any of the following criteria: (1) they were still taking raloxifene at the time of the interview; (2) they had discontinued raloxifene treatment as a result of advice from the physician who prescribed raloxifene or another physician; (3) they had temporarily interrupted treatment as a result of advice from a physician due to a transitory condition (eg, prolonged rest); or (4) they had not started treatment as a result of receiving an alternative prescription from the prescribing physician or as a result of advice from another physician. In addition, patients who had temporarily interrupted raloxifene treatment for <5% of the total time of treatment were considered partially compliant and were included in the compliant group. Noncompliant patients were those who, at their own discretion, had not started treatment or had discontinued it. The rate of continuance was calculated as the number of compliant patients among those who had started therapy. Compliance and continuance were assessed at 3, 6, 12, 18, and 24 months after the prescription was given.

Statistical Analysis

Time to discontinuation was analyzed using the Kaplan-Meier method of survival analysis. To determine a relationship between some of the variables and compliance, we attempted to perform an analysis of logistic regression. Statistical analysis was performed using Statistix version 7.0 (Analytical Software, Tallahassee, Florida).

RESULTS

The database identified 455 eligible postmenopausal patients who had been prescribed raloxifene. Of these, 419 patients could be contacted by telephone and were included in the analysis (mean [SD] age, 61.4 [7.4] years [range, 42–90 years]). The baseline characteristics of the study patients are shown in **Table I**.

Of the 419 patients included in the analysis, 360 (85.9%) had started treatment at the time of the telephone interview. Two hundred twenty-five patients (53.7%) were still taking raloxifene (24 months after prescription) at the time of the interview, 105 (25.1%) had discontinued therapy at their own discretion, and 30 (7.2%) had discontinued treatment due to a physician's advice. The 59 remaining patients (14.1%) had not started therapy, the reasons for which are shown in **Table II**. Eleven of these 59 patients (18.6%) were considered compliant because they had followed the advice of another

Table I. Baseline demographic and clinical characteristics of the study patients (N = 419).

Characteristic	Value
Age, y	
Mean (SD)	61.4 (7.4)
Range	42–90
Age group, y, no. (%)	
<50	17 (4.1)
50–<60	190 (45.3)
60–<70	168 (40.1)
70–<80	39 (9.3)
≥80	5 (1.2)
Years since menopause	
Mean (SD)	14 (7.8)
Range	1–42
Concomitant medications, mean (range)	2.91 (0–11)
BMD classification,*† no. (%)	
Normal	14 (3.3)
Mild osteopenia	26 (6.2)
Moderate osteopenia	52 (12.4)
Severe osteopenia	119 (28.4)
Osteoporosis	208 (49.6)

BMD = bone mineral density.
*Measured by T-score (the number of SDs above or below the average BMD value for young, healthy, white women). Scale: ≥–1.0 = normal; <–1.0 to >–1.5 = mild osteopenia; ≤–1.5 to >–2.0 = moderate osteopenia; ≤–2.0 to >–2.5 = severe osteopenia; ≤–2.5 = osteoporosis.
†Percentages do not total 100 due to rounding.

Table II. Reasons for not starting raloxifene treatment (n = 59).

Reason	No. (%)
Fear of thrombolytic events after reading the package insert	21 (35.6)
Lack of interest in starting treatment	12 (20.3)
Advice from a physician other than the prescribing physician*	11 (18.6)
Family problems	3 (5.1)
Dissatisfaction with prescribing physician	2 (3.4)
Treatment cost	2 (3.4)
Health problems unrelated to osteoporosis	2 (3.4)
Mistrust in the prescription	2 (3.4)
Advice from family/friends	1 (1.7)
Fear of breast cancer	1 (1.7)
Belief that raloxifene is a hormonal treatment	1 (1.7)
Patient was already polymedicated	1 (1.7)

*These patients were considered to be compliant.

physician (general practitioner [6 patients], cardiologist [2], gynecologist [2], and hematologist [1]). The reasons these physicians advised the patients against raloxifene therapy were not recorded.

Of 30 patients who discontinued treatment as a result of advice from a physician (compliant patients), the physician who initially prescribed raloxifene subsequently prescribed another drug due to lack of raloxifene efficacy (12 patients), or a physician (mainly gynecologists) other than the prescribing physician advised the patient to discontinue raloxifene, believing that there were better drugs for the prevention and treatment of osteoporosis (18). In the 105 patients who discontinued treatment at their own discretion (noncompliant patients), the 2 most common reasons were health problems unrelated to osteoporosis (25 [23.8%]) and digestive problems not considered treatment related (16 [15.2%]) (**Table III**). The 25 patients who discontinued treatment due to health problems unrelated to osteoporosis reported that they considered their other health problems more serious or troubling than osteoporosis. These health conditions included arthralgia (12), cardiac problems (12), and tiredness (1).

Of the 135 discontinuers, 62 discontinued within 3 months of receiving the prescription, accounting for 45.9% of all discontinuers. Of these, 52 patients (38.5%) did so at their own discretion, and 10 (7.4%) as a result of advice from a physician. An additional 42 patients (31.1%) discontinued treatment within 12 months of receiving the prescription, 30 (22.2%) at their own discretion, and 12 (8.9%) as a result of advice from a physician. Twenty-seven more patients (20.0%) discontinued treatment within 24 months of receiving the prescription, 20 (14.8%) at their own discretion, and 7 (5.2%) as a result of advice from a physician.

Table III. Reasons for discontinuing raloxifene treatment (n = 105).*

Reason	No. (%)
Health problems unrelated to osteoporosis	25 (23.8)
Digestive problems not considered treatment related	16 (15.2)
Lack of interest in starting treatment	12 (11.4)
Treatment cost	12 (11.4)
Vasodilation	12 (11.4)
Fear of thrombolytic events after reading the package insert	7 (6.7)
Lower limb discomfort	5 (4.8)
Patient was already polymedicated	5 (4.8)
Leg cramps	4 (3.8)
Family problems	3 (2.9)
Lower limb edema	3 (2.9)
Belief that raloxifene is not necessary	1 (1.0)

*Percentages do not total 100 due to rounding.

The discontinuation rates among patients who started treatment (n = 360) were 17.2% (62 patients), 11.7% (42), and 7.5% (27) at 3, 12, and 24 months, respectively. Among all 419 patients, this overall rate was 105 (25.1%).

Eleven of 419 patients analyzed (2.6%) were advised by a physician other than the prescribing physician not to start treatment and were excluded from the compliance analysis. The compliance rate in the remaining 408 patients was 75.0% (306 patients) at 3 months, 71.1% (290) at 6 months, 65.0% (265) at 12 months, 57.1% (233) at 18 months, and 52.0% (212) at 24 months. Once patients had started treatment (360 patients), the rates of continuance were 85.0%, 80.6%, 73.6%, 64.7%, and 58.9% at 3, 6, 12, 18, and 24 months, respectively (**Figure**).

The logistic regression analysis showed that compliance did not seem to be affected by age, number of concomitant medications, lumbar T-score, femoral neck T-score, or knowledge of the presence of vertebral and nonvertebral fractures.

DISCUSSION

Well-designed clinical trials[5,7] demonstrated that the efficacy of the various osteoporosis therapies in increasing bone mass or reducing fracture risk is pivotal for clinical success. However, the success of a treatment is also heavily dependent on a patient's compliance with that treatment. In other words, it is the combination of efficacy and compliance that determines the effectiveness

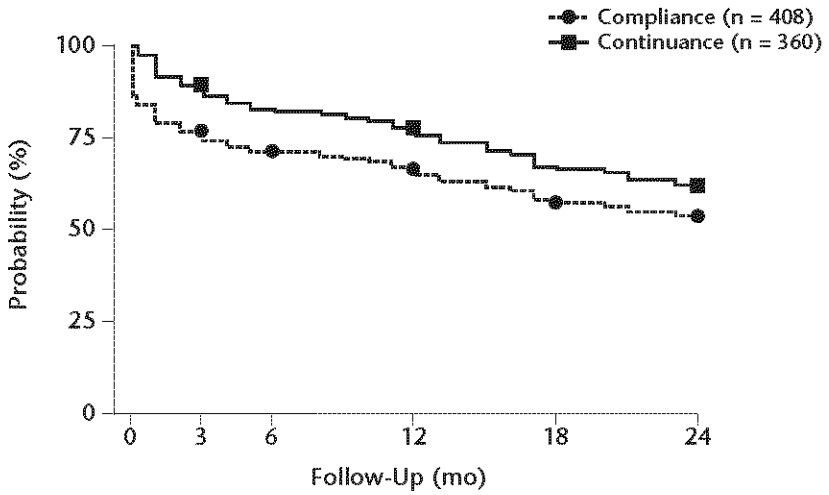

Figure. Compliance and continuance rates over time (analysis excludes 11 patients who were advised by a physician other than the prescribing physician not to start treatment).

of treatment in the clinical setting. Studies designed to assess compliance with HRT have reported low rates of compliance.[8–10] For example, one study found that nearly half of women who started HRT were reported to have discontinued therapy after a mean of 9 months.[11] The investigators suggested this could have been due in part to the fear of the risk for breast and/or endometrial cancer associated with HRT.[11] Thus, despite the extraskeletal benefits of HRT (eg, improved lipid levels and vasomotor symptoms), many women are reluctant to accept this therapeutic option. Vaginal bleeding is another common reason that women discontinue HRT.[12] Using results from population-based studies and clinical trials, Hammond[13] assessed patients' compliance with HRT. He determined that <20% of postmenopausal women in the United States have been prescribed treatment with HRT on at least 1 occasion, and of those who started treatment, <40% continued it after 1 year. Another study by Ettinger et al[12] showed differences in the reasons for starting and abandoning HRT in younger women (aged 50–55 years) and older women (aged ≥65 years): older women started HRT to treat osteoporosis, whereas the younger women did so to ease vasomotor symptoms. The HRT discontinuation rate was higher in the older group than in the younger group.

In a third, retrospective study, Ettinger et al[14] assessed compliance with alendronate therapy using telephone interviews with 812 women (mean age, 68.7 years). Overall, 28.5% of women reported discontinuation of alendronate within 8 months of initiating therapy. Based on a review of prescription data, 34.9% of these women had discontinued by 6 months, most often because of gastrointestinal AEs. Another study designed to determine compliance with

alendronate reported that some patients did not necessarily follow dosing instructions (eg, patients reported lying down or eating within 30 minutes of receiving alendronate).[15]

Kayser et al[16] reported differences in compliance between women receiving raloxifene and those receiving estrogen-containing therapies. Both groups were similar in age (mean age, 69 years), but raloxifene was more commonly prescribed by internists than by gynecologists. Overall, 19% of patients receiving raloxifene and 31% receiving estrogen-containing therapy did not have the prescription refilled. At 12 and 24 months, discontinuation was reported in 50% and 56%, respectively, of patients receiving raloxifene therapy compared with 63% and 72%, respectively, of those receiving estrogen-containing therapy. Women of a similar age receiving raloxifene were 25% less likely to discontinue medication than those receiving estrogen-containing therapy.

In the present study, the most common reason for not starting raloxifene therapy was the fear of thrombolytic events after reading the package insert, which lists it as a possible AE. In contrast, 2 large survey studies[17,18] reported that up to 20% of patients did not have their prescriptions filled, most frequently because they believed they did not need the medication prescribed. Another study found that among patients who did have the prescription filled, the 2 most frequent reasons for noncompliance were dose omission and drug ingestion at an incorrect time point.[19] These noncompliant behaviors are also common in patients with other chronic conditions, such as hypertension, hypercholesterolemia, and epilepsy.[20–23]

Rudd et al[18] introduced the term *partial compliance* to refer to the behavior of patients who do not discontinue their medication entirely but interrupt it for a period of time. In the elderly, this type of noncompliance is often unintentional.[3]

An important finding in the present study was the lack of short-term compliance: 45.9% of the discontinuations occurred in the first 3 months, 83.9% of which were at patients' own discretion. Drug discontinuation was mainly associated with personal circumstances or choices. For example, 4.8% of discontinuers considered it inconvenient to add another drug to their usual regimen (polymedicated), and family problems prevented 2.9% of discontinuers from taking care of their own health. The recognized AEs of raloxifene (eg, vasodilation, leg cramps) were not associated with increased discontinuation, which supports the safety and tolerability of the drug. No cases of deep venous thrombosis or pulmonary thromboembolism were reported.

In the present study, patients who discontinued treatment at the recommendation of a physician were considered compliant. In these patients, interruption of treatment was recommended either by the physician who initially wrote the prescription for raloxifene and then prescribed another drug due to lack of efficacy, or by another physician who advised the patient to stop

treatment, with no further explanation from the physician. In the latter group, the patients did not know the reason for the regimen change. It is possible that conflicting advice from prescribers may contribute to confusion among patients. Another possibility may be ineffective provider communication (eg, insufficient information provided by the physician, inadequate response to a patient's individual needs).

Noncompliance as a consequence of drug cost may also be a significant problem. In the present study, 3.3% (14/419) of patients stated they could not afford the medication. In a survey of elderly patients,[3] cost was given as the reason for noncompliance by 10% of patients. Clinical experience suggests that elderly patients with fixed incomes sometimes make strategic decisions about which medications they can afford.[23]

Regarding the logistic regression analysis, given the small sample size, there was not sufficient power to draw a conclusion.

Most of the patients who come to the Metabolic Research Institute are enrolled in privately owned health insurance plans that allow them to visit physicians who specialize in osteoporosis without being referred by a primary care physician. This could represent a potential selection bias. Another limitation of the study concerned the sensitivity of the survey instruments, which may not have been accurate in verifying that a participant actually received raloxifene as reported. We measured adherence to raloxifene treatment through patient reports by telephone and review of clinical histories. Both of these measures are indirect and thus have some limitations. Telephone interviews may have led to significant recall bias. Moreover, it is not clear whether the results of the present study can be applied to other clinics, and further studies would be required to clarify this.

Our research provides a basis for the study of raloxifene compliance and can be used to develop ways of promoting it. The results suggest a need for a collaborative physician-patient relationship and for tailoring care to individual patients, with attention to their social context (eg, social norms and health risks in older [age, >65 years] patients). Many older patients are unable to understand their diseases and treatment goals, and insufficient information provided by the physician or inadequate attention to an individual patient's needs may lead to poor compliance. Some patients, particularly older ones, may remember only part or none of the dosing instructions. A physician's enthusiasm and use of several methods of communication (eg, charts, instructions written in large letters) can help patients remember the instructions. Physicians should also highlight the benefits of compliance and explain the risks of noncompliance (ie, fractures). One study showed that spending 15 minutes counseling older adults about their medications increased their understanding of the need for treatment compliance.[24] Finally, the high discontinuation rate during the first 3 months could have been the result of routine clinical practice at our center: the first medication follow-up visit is scheduled for 6 months after the prescrib-

ing visit. We suggest that more frequent follow-up visits (eg, at the first and third months following prescription of the drug) also could help improve adherence.

CONCLUSIONS

In the present study of raloxifene compliance and continuance in postmenopausal patients, the compliance rate appeared to be relatively high compared with those of HRT and other non-HRT treatments. Almost half of patients who discontinued treatment did so in the first 3 months. We suggest attention to individual patients' needs, effective communication, and more frequent follow-up visits would improve adherence with osteoporosis treatment modalities.

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