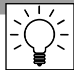

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Alendronate 70 therapy in elderly women with post-menopausal osteoporosis: the problem of compliance

Stopień przestrzegania zaleceń długotrwałej terapii alendronianem 70 przez pacjentki leczone z powodu osteoporozy

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Abstract

Introduction: More than half of those with chronic diseases, including osteoporosis, discontinue treatment during the first year of its administration. This problem increases over the course of continued follow-up. Additionally, it has been observed that 13% of women, prescribed oral daily alendronate, do not even start the treatment, while 20% of patients discontinue the therapy during the first four months. On the other hand, those patients who are compliant achieve increased bone mass density with a simultaneous decrease of fracture risk. The aim of our study was to assess the adherence to the recommended alendronate 70 administration protocol over the course of 12 months by women with post-menopausal osteoporosis.
Material and methods: Adherence (compliance plus persistence) to alendronate 70 therapy was assessed in a prospective study of 153 post-menopausal women, followed up for one year with monitoring every two months.
Results: Adherence to therapy of all the study participants was high during the entire study period, the patients remaining compliant after a year in 95.08 ± 1.39% (mean ± SEM) of cases, and the mean persistence with medication was 347.05 ± 5.07 days. In the group of patients who interrupted treatment, the mean persistence was 212.44 days. One of the study participants did not start the treatment, and another two discontinued the therapy within 30–60 days of the study onset (between the first two visits). Facilitated contacts with the doctor, continuous access to prescribed treatment and frequent visits significantly improved patient compliance. The common reason for discontinuation was side effects, while age (but not education) affected the rate of compliance with therapy. The worst results were obtained in the group of patients with osteoporosis diagnosed more than five years before the study, particularly in the subgroup where alendronate was being used for the first time or where treatment resumed after a substantial break.
Conclusions: The obtained results indicate that better adherence to alendronate 70 therapy, administered once a week, depends on more frequent monitoring of treated patients. **(Pol J Endocrinol 2011; 62 (1): 24–29)**

Key words: *osteoporosis, compliance, persistence, alendronate 70, reasons for therapy discontinuation*

Streszczenie

Wstęp: Wykazano, że ponad 50% pacjentów leczonych z powodu chorób przewlekłych, w tym osteoporozy, przerywa terapię w ciągu pierwszego roku jej stosowania. Problem ten narasta z czasem trwania obserwacji. Stwierdzono, że 13% pacjentów z osteoporozą w ogóle nie rozpoczyna leczenia, a ponad 20% przerywa terapię w ciągu pierwszych 4 miesięcy trwania choroby. Wykazano, że przestrzeganie przez pacjentów wprowadzonej terapii osteoporozy poprawia gęstość mineralną kości i zmniejsza ryzyko złamań.
Celem pracy była ocena, w rocznym badaniu prospektywnym, stopnia przestrzegania zaleceń długotrwałej terapii preparatem alendronian 70 przez pacjentki leczone z powodu osteoporozy.
Materiał i metody: Ocenie poddano 153 pacjentki w wieku 48–89 lat z rozpoznaną osteoporozą leczone alendronianem 70 mg, jeden raz w tygodniu, przez okres roku. Pacjentki monitorowano co 2 miesiące. Wzięto pod uwagę czas trwania choroby, ciągłość i systematyczność przyjmowania leków oraz przyczynę przerwania stosowanego leczenia.
Wyniki: Podczas trwania badania stopień przestrzegania zasad terapii u wszystkich uczestniczek badania był wysoki i łącznie systematyczność po roku utrzymało 95,08 ± 1,39% (średnia ± SEM), a średnia długość przyjmowania leków wyniosła 347,05 ± 5,07 dni. W grupie pacjentek, które przerwały leczenie średni okres stosowania się do zaleceń wyniósł 212,44 dnia. Z całej grupy jedna pacjentka w ogóle nie

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podjęła leczenia, 2 przerwały w okresie 30–60 dni stosowania, czyli między 2 kolejnymi wizytami. Ułatwienie pacjentowi kontaktu z lekarzem, stały dostęp do leku oraz częste wizyty w znaczny sposób poprawiają stosowanie się pacjentów do zaleceń. Najczęstszą przyczyną przerwania leczenia były działania niepożądane stosowanego preparatu. Wiek, lecz nie wykształcenie, miały wpływ na przestrzeganie terapii. Najgorsze wyniki uzyskano w grupie pacjentek z rozpoznaniem osteoporozy dłuższym niż 5 lat, szczególnie w podgrupie, u której włączono alendronian 70 pierwszy raz lub podjęto leczenie po przerwie.
Uzyskane wyniki wskazują na fakt lepszego przestrzegania zaleceń lekarskich przez pacjentów leczonych z powodu osteoporozy w trakcie dobrego monitorowania terapii preparatem cotygodniowym. Krytycznymi momentami decydującymi o przerwaniu leczenia były objawy niepożądane związane z terapią.
Wnioski: W przeprowadzonym badaniu wykazano, że częstsze monitorowanie w znaczący sposób poprawia przestrzeganie zasad terapii alendronianem stosowanym w dawkach cotygodniowych. **(Endokrynol Pol 2011; 62 (1): 24–29)**

Słowa kluczowe: *osteoporoza, systematyczność, ciągłość, alendronian 70, przyczyny przerwania terapii*

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PRACE ORYGINALNE

Introduction

Osteoporosis is a major public health problem in many countries, including Poland [1]. Currently available treatment options serve to increase bone mineral density (BMD) and decrease fracture risk [2–7]. In order to obtain the benefits of medication, treated patients should maintain optimal compliance and persistence with their osteoporosis therapy [8–10], since, in the words of C. Everett Koop, the former US Surgeon General: “Drugs don’t work in patients who don’t take them.” There are some negative consequences of poor adherence (compliance + persistence) to oral osteoporosis treatment [11–15].

It has been shown that more than 50% of people with chronic diseases, especially in their subclinical stages, including osteoporosis, hypertension and hypercholesterolaemia, discontinue treatment during the first year of its administration [16]. Many patients take drugs incorrectly, infrequently, or do not take them at all. This problem increases over the course of continued follow-up. It has been found that 13% of women prescribed daily oral alendronate did not even start the treatment and 20% of patients discontinued the therapy during the first four months [17, 18].

Longitudinal, retrospective analyses of large databases indicate that adherence to recommended osteoporosis therapies is less than optimal. Persistence on daily bisphosphonate therapy has been observed in 25–35% of patients during the first year of its administration. The persistence with weekly bisphosphonate treatment has been better, ranging between 35% and 45% [12].

The problem does not depend on the form of treatment [12]. Boguzzi et al. [19] presented the results of a study involving a cohort of 10,566 women, showing that their adherence during the first year was higher with two bisphosphonates: daily alendronate (60.7%) and daily risedronate (58.4%), while lower with raloxifene (53.9%). The persistence rate was, however, poor for all the agents (daily alendronate 23%, daily risedronate 19.4%, and raloxifene 16.2%). A somewhat higher persistence level during the first 12 months has been presented in other papers [20]. In three examined countries, the compliance was as follows: United States 32%, UK 40%, and France 44%. Women on daily alendronate persisted with treatment for 185 days in the United States, 208 in the United Kingdom and 155 in France [20]. The persistence curves for osteoporosis medications showed a rapid decrease within the first three months of therapy [17–19]. Similarly, a retrospective study of post-menopausal women, who used daily alendronate, calcitonin, HRT, raloxifene or risedronate, showed their compliance below 66% over a 60-day period [21]. Adherence to medication recommendations in cases of osteoporosis is very important because rates of compliance with recommended therapy below 66% result in suboptimal outcomes regarding bone mineral density [22].

In our previous study, compliance to daily alendronate therapy was assessed for six or 18 months in clinical practice of post-menopausal osteoporosis [15]. Using a retrospective study of medical records at our university hospital’s Outpatient Clinic, as well as telephone interviews with patients, compliance of post-menopausal patients with daily alendronate regimen was assessed. After 18 months of observation, 20.4% of patients, and after 6 months 8.5%, of patients, discontinued their treatment as a result of intolerance especially side effects from the gastrointestinal tract (47.8% of those discontinuing), health problems unrelated to osteoporosis (8.7%), finding the daily regimen inconvenient (13.1%), the costs of therapy (4.3%) and a less than expected improvement in clinical condition (26.1%). It is worth mentioning that in both periods of observation (18 months and six months), almost the same percentage of patients stopped their consultations at our Outpatient Clinic (15.6% and 14.4%, respectively). Telephone interviews with the patients who stopped attending the Outpatient Clinic at the Regional Centre of Menopause and Osteoporosis revealed that more than 50% of them discontinued the treatment.

Table I. *Compliance and persistence in different age groups. Significance: ***p < 0.05 compared to group aged 70–79*

Tabela I. *Systematyczność i ciągłość terapii w grupach wiekowych. Znamienność: ***p < 0,05 w porównaniu z grupą wiekową 70–79 lat*

Age group	Number of patients	Compliance in % (mean ± SEM)	Persistence (days of treatment during one year) (mean ± SEM)
< 59	25	94.25 ± 3.04	344 ± 11.1
60–69	41	99.6 ± 0.28***	363.54 ± 1.02***
70–79	66	92.73 ± 2.64	338.45 ± 9.63
80–89	21	94.66 ± 4.43	345.52 ± 16.16
Total	153	95.08 ± 1.39	347.05 ± 5.08

The aim of this study was to assess the adherence rate to weekly alendronate therapy, administered for 12 months to women with post-menopausal osteoporosis, by monitoring them every two months.

Material and methods

Based on a prospective study of 153 post-menopausal women aged between 48 and 89, the compliance and persistence to alendronate 70 therapy was assessed during one year follow-up, with monitoring of all the patients every two months. Of the participating women, 61 were either antiresorptive drug-naïve or had had at least a one year break in therapy before the study onset. All of them were informed about osteoporosis and signed a consent form to participate in the study. Bone mineral density ≤ –2.5 SD in hip or spine and/or osteoporotic fracture(s), diagnosed or in history, were the inclusion criteria.

Single factor variance analysis was applied with the NIR Fisher Test for the patient's age, education and the time of diagnosis. Student-t test was used for the other parameters.

Results

After one year of the study period, the compliance rate of all the study participants was high, amounting to 95.08%. The mean persistence with medication was 347.05 ± 5.08 days (Table I). The grouping of patients by age is shown in Figure 1. In the group of patients who interrupted treatment, the mean persistence was 212.44 days. The patients aged 60–69 (Table I) demonstrated better compliance than any other age group, but statistically significant difference between 60–69 and 70–79 was observed. The lowest compliance and persistence (although not statistically significant) were observed in the group of patients who had reached vocational education (Table II). The lowest compliance and persistence were also found in the group of patients with osteoporosis diagnosed more than five years before the study (Table III), especially in the subgroup where alendronate 70 was either introduced for the first time or re-administered after discontinuation (Table IV). In assessing very good compliance and persistence, it was found that doctors from regional centres were more effective than those at the Outpatient Clinic of the Medical University (Table V).

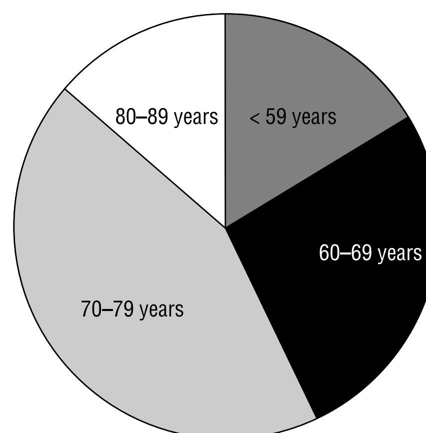

Figure 1. *Age ranges of the study participants (%)*

Rycina 1. *Podział pacjentek na grupy wiekowe (%)*

Facilitation of patient contacts with the doctor, continuous access to prescribed medication and frequent visits considerably improved the patients' adherence to prescribed recommendations. The commonest reasons for discontinuation of treatment were adverse effects of an applied agent and hospitalisation (Table VI).

Discussion

Osteoporosis is a chronic disease, demanding long-term clinical observations and strict adherence to medication regimens.

Table II. *Compliance and persistence of patients depending on their educational level*

Tabela II. *Systematyczność i ciągłość terapii w zależności od poziomu wykształcenia*

Educational level	Number of patients	Compliance % (mean ± SEM)	Persistence (days of treatment during one year) (mean ± SEM)
Primary	36	97.34 ± 1.94	355.31 ± 7.07
Vocational	40	92.73 ± 3.14	338.47 ± 11.46
Secondary	47	93.99 ± 3.16	343.06 ± 11.52
University	30	97.21 ± 1.77	354.83 ± 6.48
Total	153	95.08 ± 1.39	347.05 ± 5.08

Table III. *Compliance and persistence of patients after one year of observation, depending on time since the diagnosis of osteoporosis. Significance: ***p < 0.05 compared to Group 3*

Tabela III. *Systematyczność i ciągłość terapii po roku leczenia w zależności od czasu rozpoznania osteoporozy. Znamienność: ***p < 0,05 w porównaniu z grupą 3*

Time since the diagnosis of osteoporosis	Number of patients	Compliance in % (mean ± SEM)	Persistence (days of treatment during one year) (mean ± SEM)
1. One month	27	95.33 ± 3.06	347.96 ± 11.15
2. One year	21	97.98 ± 1.66	357.62 ± 6.05
3. More than one year, but less than five years	72	97.03 ± 1.62	354.15 ± 5.86
4. ≥ 5 years	33	88.79 ± 4.60***	324.10 ± 16.79***
Total	153	95.08 ± 1.39	347.05 ± 5.08

Table IV. *Compliance and persistence of patients after one year of therapy, including the first time alendronate 70 (ALE 70) users and the participants taking the drug again after at least a one year break. Significance: ***p < 0.05 compared to group of patients continuing therapy with ALE 70*

Tabela IV. *Systematyczność i ciągłość po roku terapii z podziałem na pacjentki w trakcie stosowania leku lub pacjentki stosujące ALE70 pierwszy raz lub po co najmniej 1 rocznej przerwie. Znamienność: ***p < 0,05 w porównaniu z grupą pacjentek kontynuującą terapię alendronianu 70*

Patient type	Number of patients	Compliance in % (mean ± SEM)	Persistence (days of treatment during one year) (mean ± SEM)
Patients continuing therapy with ALE 70	92	95.68 ± 1.51	349.22 ± 5.51
First time ALE 70 users and participants taking the drug after a break	61	94.19 ± 2.66	343.79 ± 9.7***

Table V. *Compliance and persistence of patients, treated by physicians at the Outpatient Clinic of the Medical University and at regional centres. Significance: ***p < 0.05*

Tabela V. *Systematyczność i ciągłość terapii z podziałem na lekarzy pracujących w Poradni Uniwersyteckiej lub Poradni Regionalnej. Znamienność: ***p < 0,05*

Venue	Number of patients	Number of first time ALE 70 users	Compliance in % (mean ± SEM)	Persistence (days of treatment during one year) (mean ± SEM)
Medical University	77	32	91.55 ± 2.59	334.14 ± 9.46
Regional centres	76	29	98.67 ± 0.81***	360.13 ± 2.96***

Table VI. *Reasons for non-compliance (%)*
Tabela VI. *Przyczyny przerwania terapii (%)*

Reasons for non-compliance	Number of patients	%
Side effects	11	61.10
Infection/hospitalisation	3	16.67
Fractures	1	5.56
Failure to start treatment	1	5.56
Other	2	11.11
Total	18	100

Unexpectedly, in the reported study, the compliance with alendronate 70 therapy, administered every week in the clinical practice of osteoporosis, was very good. An analysis of seven visits during one year demonstrated 95.08% of patients with osteoporosis, who had been treated before and after our initial consultation, continued their treatment. The main reasons for therapy discontinuation were side effects (61.10%) and infections or hospitalisations (16.67%). Data from our previous retrospective study showed that, after 18 months of observation, 20.4% of patients and, after six months, 8.5% of patients, discontinued their treatment [15]. It is worth mentioning that in both periods of observation, almost the same percentage of patients stopped attending our Outpatient Clinic (15.6% and 14.4%, respectively). Telephone interviews with those patients revealed that more than 50% of them had discontinued the treatment.

The results of our paper can be compared to the work of a Canadian group [23]. The Canadian Database of Osteoporosis and Osteopenia (CANDOO), a prospective observational database designed to capture clinical data, was searched for patients who started therapy, with 1,196 initiating etidronate, 477 alendronate therapy for women and men and 294 hormone replacement therapy for women. After one year, 90.3% of those patients were still taking etidronate, compared to 77.6% on daily alendronate and 80.1% of patients on HRT, which decreased to 44.5% after six years. Reginster and Lecart [24] suggest that the persistence rates in the CANDOO study may be artificially high. The study took place in a clinic, where the patients initially signed a consent form and were given verbal encouragement to continue treatment. Our observations were similar to the prospective CANDOO study.

In several reports, persistence scores are far from encouraging. For example, medication persistence was demonstrated in only 39.0% of the patients receiving daily alendronate therapy at month 12 of one study period [25]. In a questionnaire study of 219 women with osteoporosis and on daily risedronate, one in four did not comply correctly with dosing instructions, despite counselling [26]. Using a telephone interview survey in a subsequent study, it was reported that within 13 months of observation of 812 women with osteoporosis, treated with daily alendronate, 56% of the patients were non-compliant [27].

Good adherence to osteoporosis treatment is very important for the effectiveness of administered medications. Among 999 responding patients with osteoporosis, effectiveness was ranked as by far the most important determinant of preference (79%), followed by the time on the market (14%), dosing procedure (4%) and dosing frequency (3%). An incorporation of patient preferences into the medication decision-making process could enhance patient compliance and clinical outcomes [28]. This is very important, as it has been shown that compliance rates below 66% in drug treatment result in sub-optimal improvement in bone density [22]. On the other hand, better compliance in the actual practice may significantly decrease osteoporosis-related fracture risks (16% over two years) [29]. It has been observed that the anti-fracture effectiveness associated with high adherence to oral bisphosphonates, varies substantially by age and fracture type [30]. Caro et al. [31] showed that poorly compliant patients were significantly more often hospitalised (53.4%) compared to compliant ones (42.6%), leading to a 14% increase in the costs of medical services.

In our analysis, the main reason for discontinuation of weekly alendronate treatment were side effects, especially from the gastrointestinal tract (61.10%), infections (16.67%), and fracture (5.56%). One person did not start therapy (5.56%) and other causes were 11.11%, these results being similar to those of other authors [22, 32].

Among patients completing another study (4,231), the percentages of high compliance patients were: 80% (raloxifene), 79% (daily alendronate), 65% (weekly alendronate) and 76% (risedronate). Discontinuation, due to side effects, was highest for weekly alendronate (7.0%), followed by daily alendronate (6.4%), raloxifene (3.8%) and risedronate (3.4%). The discontinuation rate was higher for patients with a history of surgical menopause, advanced age, and a lack of knowledge about the medical prevention of osteoporosis [33].

Claxton et al. [34] has suggested that the prescribed number of doses per day is inversely related to compliance. In other words, less frequent dosing regimens result in better compliance across a variety of therapeutic classes. This is reflected in osteoporosis therapy. Post-menopausal women, prescribed a weekly regimen of bisphosphonates, demonstrated significantly higher compliance rates than daily regimen patients, and they also persisted longer with treatment. However, compliance and persistence rates were suboptimal for both regimens [20, 35].

Osteoporosis is a chronic disease which needs long-term clinical monitoring and strict adherence to therapeutic recommendations.

Analysing our observations and the results of others, we suggest that the main reasons for discontinuation of treatment are not only digestive incidents but also problems with obtaining prescriptions within the first three months of treatment, dissatisfaction with therapy results, and poor monitoring.

In our opinion, effective communication and more frequent follow-up visits would greatly improve the adherence to osteoporosis treatment modalities.

Our study showed that monitoring, performed every two months, was very helpful both for compliance and persistence scores. Variations in adherence to the medical treatment of osteoporosis may also depend on other factors: an individual patient's convictions, a patient's social and economic conditions, physical predispositions or health problems, age, and the time elapsed since the diagnosis of osteoporosis, which was presented in our study. Compliance could be improved by patients choosing their treatment regimen. It is of utmost importance that patients are informed about diagnosis results and their long-term treatment plan, highlighting the role of persistence with therapy and compliance with dosing recommendations [36]. Adherence to drug administration regimens in the therapy of osteoporosis improves BMD, reduces femoral neck and spine fracture risks, while also decreasing the costs of inpatient therapy. Some data suggests that psychobehavioural interventions may help improve patient motivation [8].

Conclusions

Good adherence to medical recommendations by patients treated for osteoporosis with alendronate 70 depends on fairly frequent monitoring visits. The critical points, decisive for treatment discontinuation, include therapy-induced adverse effects.

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