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Type of Article: Brief Report

ABSTRACT

Objective: Long-term treatment of osteoporosis is required for optimal efficacy, but adherence to therapy is suboptimal with daily and weekly oral bisphosphonates. The aim of this study was to assess real-world persistence (long-term adherence) with weekly alendronate.

Patients and methods: Persistence data were collected according to World Health Organization criteria for the prior month and year for 102 consecutive patients with osteoporosis at three outpatient clinics in Croatia. Persistence was assessed using medication possession ratios (MPR). Adequate persistence was defined as sufficient medication supply to ensure antifracture efficacy (MPR ≥80 %). Self-reported persistence data were compared with resupply prescription data from primary care physicians (PCPs). The effect of patient age, co-therapy, co-morbidity, and time since osteoporosis was diagnosed were evaluated.

Results: A diagnosis of osteoporosis was established 3.21±1.83 years prior for the 96 women and 6 men enrolled (mean age 66.92 ± 8.05 years). During the previous year, 86.3 % patients reported not missing any tablets. Age correlated with the number of missed tablets, with older patients missing more tablets (p=0.038). Patients with co-therapy (p=0.042) missed more tablets. PCPs reported that 65.7 % of the patients were issued prescriptions for 52 tablets. A total of 68.7% had MPR ≥80%. Patients with rheumatoid arthritis did not impact MPR (p=0.936). Previous fractures or number of fractures were not associated with persistence (p>0.05).

Conclusions: In Croatia, persistence was superior with weekly administered alendronate than has been reported elsewhere, perhaps due to socio-cultural factors. Larger, longitudinal studies are needed to confirm these results.

Key words: adherence, alendronate, bisphosphonate, osteoporosis, persistence, weekly therapy

Short Title: Weekly Alendronate Therapy in Croatia

Introduction

Osteoporosis is “clinically silent“ because the patient is typically unaware of bone density loss or the change in bone architecture prior to the time a fracture occurs. Because osteoporosis has no symptoms, many patients do not accept long-term therapy as a necessity. This is a major obstacle to treatment, because osteoporosis medication must be taken as instructed over a long period in order to achieve the full benefit.

Adherence rates reported in clinical trials are likely to differ from that in clinical practice. Suboptimal therapeutic adherence is a widespread issue in clinical practice. In chronic diseases, the rate of patient non-adherence varies from 20% in asthma to 71% in arthritis.[1] Consistent with other chronic, largely asymptomatic conditions, long-term compliance with medication in osteoporosis is generally poor.[2] We observed anecdotally that patients in Croatia appear to adhere to their once-a week alendronate therapy better than published studies might suggest. This pilot study was conducted to evaluate the persistence, defined as long-term adherence, of patients in Croatia receiving alendronate on the basis of densitometric evaluation to weekly administered alendronate (ALN/70).

Patients and methods

Data on persistence (missed tablets of ALN 70 mg/week) for the previous month and year were collected for 102 consecutive patients with osteoporosis at three outpatient rheumatology clinics according to World Health Organization (WHO) criteria. Medication possession ratios (MPR = days of supply/365 days) were used to assess medication persistence. Adequate persistence was defined as sufficient medication supply to ensure antifracture efficacy (MPR ≥ 80%). Resupply prescription data were obtained from patients' primary care physicians. The effect of patient age, co-therapy, co-morbidity, and time since osteoporosis was diagnosed were also evaluated.

Descriptive statistics, Chi-square test, T-test, Spearman's test and Cramer's V test were used to analyze the results. The SPSS ver. 13.0 statistical program was used for all statistical analyses.

Results

Data were collected for 6 men and 96 women, mean age 66.9 ± 8.05 years, who presented at three outpatient rheumatology clinics. The diagnosis of osteoporosis was established a mean of 3.21 ± 1.83 years ago in this population. Hypertension (38/102) and rheumatoid arthritis (36/102) were the most common co-morbidities. Eighty-one patients (79.4%) were receiving concomitant therapy. Study patients were taking a mean of 2.58 ± 2.18 additional drugs daily, with each patient receiving from 1-7 different drugs, not including alendronate.

Only two patients reported missing 1 or 2 tablets of ALN 70 in the previous month. During the previous year, 86.3 % patients reported that they did not miss any tablets. The one-year persistence details are presented in Table 1. Age correlated with number of missed tablets, with older patients missing more tablets (Spearman's test p=0.038). Resupply prescription data from primary care physicians showed that 65.7% of patients were issued prescriptions for all 52 tablets in the previous year. According to self-reported persistence data, patients receiving co-therapy had more missed tablets (Mann-Whitney test p=0.042), although the number of co-therapies did not reach significance (Spearman's Correlation test p=0.192). Using the more objective criterion of issued prescription co-therapies, and including cut-off groups of two versus three or more drugs, or no co-therapy versus two or more drugs, did not affect the targeted MPR (Chi square test p=0.632, Chi square test p=0.787, t-test p=0.279). While rheumatoid arthritis was one of the most common comorbidities, having rheumatoid arthritis did not affect MPR (Cramer's V test p=0.936).

A negative correlation was found between the time of diagnosis and the start of antiresorptive therapy with the number of purchased tablets (Spearman's test p=0.004)

so that, as expected, the longer the patient were diagnosed to have had osteoporosis and the longer they used antiresorptive therapy, the fewer tablets they received.

Thirteen patients had radiological vertebral fractures, 11 had clinical vertebral fractures, 3 had hip fractures, and 11 had any other fracture. Neither the occurrence of previous fractures nor number of fractures (spine, hip, or other) was associated with persistence ($p>0.05$ in all cases).

Discussion

Suboptimal adherence (<80%) is associated with suboptimal outcomes. Patients with osteoporosis and poor adherence tend to have smaller decreases in rate of bone turnover,[3] lower bone mineral density,[3-5] and significantly higher risk of fractures.[6] In two large surveys of osteoporosis, the mean rate of discontinuation was 19% over 7 and 14 months, respectively.[7,8] Paid claims data from real-world treatment settings showed that one-year compliance rates were <25% for different osteoporosis therapies, including bisphosphonates, raloxifene, estrogen, and estrogen plus progestin.[9]

In our study, 86% of patients reported that they had not missed any tablets, and 65% were issued prescriptions for all 52 tablets. These percentages are higher than in the study by Recker et al. where adherence for weekly regimens was 55%, or in another study, based on administrative claims from 30 health plans in the U.S., which reported 44.2% persistence.[11, 12] Even lower adherence was reported in a study based on prescription data from U.S. pharmacies over one year, where only 30% of women new to weekly oral bisphosphonate therapy had prescriptions filled covering about three-quarters of the year (271 days); 68.7% had MPR $\geq$80%.[13] Cramer et al. found MPR of 69.2% for once-weekly bisphosphonates users, with dosing frequency the strongest predictor of discontinuation time.[12] In our study, those with longer-standing antiresorptive treatment purchased fewer tablets, but co-therapy and co-morbidity did not affect the targeted MPR $\geq$80%.

One could presume that patients with previous fracture would be more aware of the importance of consistently taking the prescribed therapy. It is interesting that neither

previous fracture occurrence nor number of fractures were associated with persistence in our study. This result may be due to the small number of patients with fractures. Patient non-compliance and non-persistence with chronic therapy are costly. Compliant patients use fewer physician services, hospital outpatient services, and hospital care.[9] The prescribed number of doses per day is inversely related to compliance, i.e. less frequent dosing regimens result in better compliance across a variety of therapeutic classes.[10] This is true with antiresorptive therapy, too. Patients taking weekly administered bisphophonates have significantly better compliance and adherence than those taking more frequent, daily doses, but it is still suboptimal.[11, 12] The cost of antiresorptive therapy was reimbursed to all patients with established osteoporosis by the public health care system in Croatia; cost should therefore not have influenced the results. Strong support, and awareness for osteoporosis through activities of professional association and non-profitable patients' associations might have played the role in relatively better persistence of antiresorptive treatment in Croatia . Moreover, although we found no study that specifically look into it, we feel that there is considerable amount of trust in doctors and treatment they offer to their patients in Croatia, partly due to traditionally rather high and in general equally distributed level of health standard.

In conclusion, we conducted a study on persistence of weekly-administered alendronate in a small cohort of consecutive patients with osteoporosis who were treated in three outpatient clinics for rheumatology. In Croatia, the patients' persistence with weekly administered alendronate is better than the persistence recorded in other countries. Socio-cultural factors could play a role in the results. Larger, longitudinal studies are needed to confirm or contradict these results.

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Table 1. Number of missed tablets of alendronate 70 mg in the previous year (n=102).

No. of missed tablets	No. of patients	% of patients	Cumulative % of patients
0 tablets	88	86.3	86.3
1 tablets	2	2.0	88.2
2 tablets	5	4.9	93.1
3 tablets	3	2.9	96.1
4 tablets	2	2.0	98.0
12 tablets	1	1.0	99.0
15 tablets	1	1.0	100.0
Total	102	100.0	