Rates and reasons for lack of persistence with anti-osteoporotic drugs: analysis of the Campania region database

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Summary

Subjects with chronic diseases are more likely to be non-persistent to pharmacological treatment. Lack of persistence is common among subjects using oral anti-osteoporotic drugs, and leads to increased risk of fragility fracture. The aim of our retrospective study is to analyze the rates and reasons for discontinuation of anti-osteoporotic drugs in the Campania Region. Subjects aged over 40 years were included if they had received at least one prescription for any anti-osteoporotic drugs. Data were obtained from an administrative database of regional data on outpatient drug prescriptions reimbursed by the National Health Service. Patients were followed until the discontinuation of anti-osteoporotic therapy or until the end of the observation period. A total of 30,048 were incident users of anti-osteoporotic drugs: 28,317 (94.2%) females. The mean age of the cohort was 69.0±10.0 years. Weekly bisphosphonates (51.1%) were the most commonly prescribed drugs. In the overall population, persistence rates were 34.8% after 6 months and 13.4% at one year. A multivariate Cox proportional hazard analysis showed that daily regimen (HR 1.9) treatments remained at higher risk of early discontinuation compared to weekly regimen therapies. Our data showed that the persistence to osteoporosis therapy is significantly worse than reported in literature.

KEY WORDS: osteoporosis; persistence; database; anti-osteoporotic drugs; bisphosphonates.

Introduction

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increased risk of minimal trauma fractures (1). Fragility fractures are underestimated and this is often due to the underdiagnosis of osteoporosis in patients at higher risk, resulting in the undertreatment of this condition and consequently in an additional risk of fractures (2). Osteoporosis treatment involves several therapeutic options, including long-term drug therapy (3). Osteoporotic patients, like those suffering from other chronic disorders, are more likely to be non-adherent and/or non-persistent to pharmacological treatment. In 2008, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group defined compliance or adherence as "the extent to which patients take medication as prescribed by their physicians", whereas persistence is the time from treatment initiation to discontinuation (4). It was demonstrated that in osteoporotic patients, only women with higher persistence (>66%) had a larger increase in bone mineral density (BMD) at lumbar spine and hip (5), while low compliance and low persistence rates for anti-osteoporotic drugs lead to increased rates of fragility fractures (6). A systematic review showed a 46% increase of fracture risk in noncompliant patients to bisphosphonates treatment (7). Our previous data showed that persistence to anti-osteoporotic drugs is significantly worse in Southern Italy population than the one reported in world literature, with the 70% of the subjects that discontinued their treatment 6 months after the initiation, and only the 13.9% of them are still on treatment at 1 year (8). The most common reasons for discontinuation from anti-osteoporotic medication had been identified as side effects, costs, inconvenient dosing, advice from other specialists, socioeconomic conditions, and lack of motivation (9). The relative impact of the factors responsible for the lack of persistence, in particular those drug related, has not been fully investigated. Therefore the aim of our study is to analyze, in a large population of Campania region, the rates and the risk factors for discontinuation of anti-osteoporotic drugs.

Materials and methods

Data sources and patient selection

Data were retrieved from an administrative database of pharmacies-derived regional data regarding medication prescriptions in Campania region, Southern Italy, which has a population of about six million inhabitants. For this study, we used data collected in the years 2009-2011. The database contains all the information con-

Table 1 - Baseline characteristics of the study population (N =30,048).

	Daily BP *n* (%) 134 (0.4%)	Weekly BP *n* (%) 15,354 (51.1%)	Montly BP *n* (%) 5,273 (17.5%)	Raloxifene *n* (%) 198 (0.7%)	S. Ranelate *n* (%) 9,089 (30.2%)	Total
Sex (female) *n* (%)	117 (87.31%)	14,319 (93.26%)	5,000 (94.82%)	194 (97.98%)	8,687 (95.58%)	28,317 (94.2%)
Age (mean ±SD)	69.73±10.16	69.16±10.01	68.28±10.07	63.58±9.81	69.37±9.89	69.0±10.0
Switcher n (%)	29 (21.64%)	639 (4.16%)	359 (6.81%)	8 (4.04%)	497 (5.47%)	1,532 (5.1%)
Calcium – Vitamin D intake n (%)	48 (35.82%)	6,115 (39.83%)	3,217 (61.01%)	65 (32.83%)	4,264 (46.91%)	13,709 (46.2%)

cerning outpatient drug prescriptions reimbursed by the National Health Service (NHS) and dispensed in pharmacies of the entire Campania region.

The database also includes demographic information (i.e. age, gender). To protect the patients' privacy, the patient code was encrypted into an unique alpha-numeric code. The reliability of this strategy as a way of producing epidemiological information has been previously documented (8). The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

The study was designed as a retrospective cohort study. Subjects 40 years of age or older were included if at least one prescription for any anti-osteoporotic drug had been filled in between July 1, 2009 and June 30, 2010. The date of first prescription was considered as the index date. Criteria for patients' selection have been described in a previous paper (8). Patients were followed from the index date until the discontinuation of anti-osteoporotic therapy or until the end of the observation period (June 30, 2011). For each patient, the following characteristics were assessed from the database at baseline: age, gender, co-prescription of calcium/vitamin D and switch.

Patients were stratified into five cohorts based on dosing regimen treatment at the index date. Persistence was defined as the length of time in days from the date of the index prescription to the date of discontinuation therapy. Discontinuation was evaluated by using the gap method. A gap is a period during which no medication is available to the patient. A treatment period was considered discontinued if the gap between two prescriptions exceeded a period covered by drug prescribed > 30 days. Persistence was analyzed according to the type of dosing regimen. To avoid underestimating true persistence, switching of medications was allowed when establishing persistence status for all treatments combined.

Statistical analysis

Baseline characteristics of the study population were analyzed using descriptive statistics. Persistence esteems over time were derived using Kaplan-Meier survival analysis considering treatment discontinuation as failure event and comparing differences using Log-rank test (4 degrees of freedom).

A multivariate Cox proportional hazard analysis was used to identify the association of dosing regimen and other variables with persistence with the initial medication. The patients who initiated with weekly bisphosphonates (BPs) regimen were used as the reference group. Statistical significance was defined at an α level of 0.05 with a hazard ratio higher than 1 indicating a relative increase in the risk of early discontinuation.

All analyses were performed using SPSS software version 17.1 for Windows (SPSS Inc, Chicago, IL, USA).

Sensitivity analyses

Sensitivity analyses were carried out for the measurement of persistence by extending the refill gap from the 30 days baseline analysis to 45 and 60 days. Sensitivity analyses were also performed using two alternative definitions of persistence, excluding or including patients who were switchers.

Results

In the study period, in Campania region, subjects with at least one prescription (of any drug) and aged over 40 years in our database were 1,690,192. Among these subjects, 30,048 (1.78%) were incident users of anti-osteoporotic drugs: 1,731 (5.8%) males and 28,317 (94.2%) females. The mean age (SD) of the cohort was 69.0 (10.0) years. Baseline characteristics of the study population are shown in Table 1. Weekly BPs (51.1%), were the most commonly prescribed drugs, followed by strontium ranelate (SR) (30.2%), monthly BPs (17.5%), raloxifene (R) (0.7%) and daily BPs (0.4%). Co-prescription with calcium and vitamin D was most common for monthly BPs (61%). On the other hand, patients starting with daily BPs and weekly BPs had fewer co-prescriptions of calcium and vitamin D (35.8 and 39.8% respectively). In the overall study cohort, 1,532 (5.1%) were switchers. Switching rates were higher for patients taking daily BPs (21.6%) and lower for patients taking monthly BPs and weekly BPs (6.8 and 4.2% respectively).

Table 2 summarizes cohort data at 90, 180, 270 and 365 days after initiation of treatment. In the overall population, 13.4% of subjects were still on therapy after one year. Persistence was higher when the refill gap period was increased: at 45 or 60 days persistence was 19.8 *vs* 13.4% (≤30 days) and 23.8 *vs* 13.4% (≤30 days), respectively, after 1 year.

Table 3 shows that inclusion or exclusion of switchers had minimal influence on the observed persistence; the rates differ by <3%, independently from any definition of refill gap duration.

Kaplan-Meier analysis showed the details grouped by individual regimen (Figure 1). At 12 months the percentage of patients that remained on treatment was, in decreasing order: 17.2% for monthly BPs; 14.7% for weekly BPs; 8.1% for R; 5.4% for SR; 5.2% for daily BPs.

A multivariate Cox proportional hazard analysis was estimated to identify variables that were significantly associated with non-persistence. The final estimated model is presented in Table 4. Patients receiving daily BPs regimen and SR were at a higher risk of early discontinuation (HR, 1.98, $p<0.001$, 95% CI, 1.63-2.42 and HR, 1.6, $p<0.001$, 95% CI, 1.57-1.66 respectively) compared to patients in treatment with weekly BPs regimen. Moreover, patients treated with monthly BPs regimen had a lower risk of early di-

Table 2 - Persistence over time with oral osteoporosis treatments (switching allowed).

Time point	**Total cohort (*N* =30,048)**	
	Patients on therapy (%)	95% CI
3 months	59.2	58.6 – 59.8
6 months	34.8	34.2 – 35.4
9 months	22.3	21.9 – 22.7
1 year	13.4	13.0 – 13.8

Table 3 - Sensitivity analysis on 1 year persistence with regard to prescription gap and treatment switch.

Prescription refill gap	Total cohort (*N* =30,048)	
	Switchers* defined as non-persistent, n (%)	Switchers defined as persistent, n (%)
30 days	3,667 (12.2%)	4,025 (13.4%)
45 days	5,396 (18.0%)	5,960 (19.8%)
60 days	6,455 (21.5%)	7,156 (23.8%)

*Switching of oral dosing regimen
Switching of individual drugs within the same regimen (changers) was not considered as non-persistence

Table 4 - Determinants of non-persistence (multivariate Cox hazard model).

Covariates	HR	p value	95% CI	
Sex				
Female	0.890	<0.001	0.844	0.937
Dosing regimen				
Daily BPs dosing regimen	1.983	<0.001	1.626	2.420
Montly dosing regimen	0.929	<0.001	0.896	0.963
Strontium Ranelate	1.614	<0.001	1.568	1.660
Raloxifene	1.289	0.001	1.110	1.497
Calcium – Vitamin D intake				
yes	0.717	<0.001	0.699	0.736

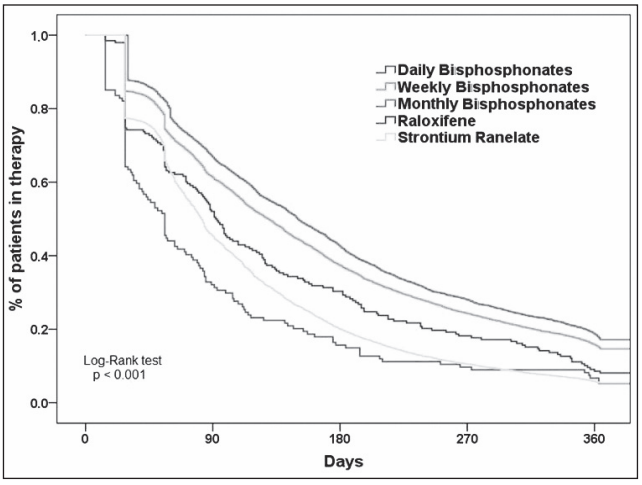

Figure 1 - One year persistent (%) with antiosteoporotic drugs.

scontinuation (HR, 0.9, p<0.001 95% CI, 0.90-0.96) compared to patients in treatment with weekly BPs regimen. In our cohort, male gender was associated with a 11% higher risk of discontinuation compared to female gender (HR, 0.89, p<0.001, 95% CI, 0.84-0.94). Patients who started treatment with a co-prescription with calcium and vitamin D had a lower risk of early discontinuation (HR, 0.72, p<0.001 95% CI, 0.70-0.74).

Discussion

Campania is a region of Southern Italy which has a total population of 5,834,056 (9), of which 1,690,192 (29%) are those aged over 40 years who are taking at least one drug, according to drug prescription database that includes all outpatient drug prescriptions reimbursed by the NHS, and 1.78% of these is taking an anti-osteoporotic drug. In this cohort of patients, our data showed that the persistence to osteoporosis therapy is significantly worse than that reported in literature (10), but similar to a previous paper that considered a smaller population of the same region (not including population referring to the first Local Health District of Naples ASLNA1) in the year 2009 (8). Although anti-osteoporotic drugs demonstrated to be effective, in clinical practice, anti-fracture effectiveness is significantly reduced by the high rate of discontinuation (11). Siris et al. emphasized the importance of good treatment compliance and persistence with osteoporosis therapies in order to achieve a significant therapeutic benefit in terms of reduced rates of fragility fractures (12). Gallagher et al., analysing the United Kingdom General Practice Research Database, reported that only 41.7% of patients were still on treatment at one year, resulting in a reduction of hip fractures rate (-22%) (13). In particular, in our cohort, only 34.8% and 13.4% of the patients continued anti-osteoporotic treatment at 6 months and at one year respectively, after initiation of therapy, and this being a demonstration of a doubling of discontinuation rates compared to previous studies (11). The most important risk factors of the lack of persistence to treatment seem to be the type of drug and the dose regimen. In 2007, a meta-analysis suggested that both compliance and persistence to drug therapy for osteoporosis were enhanced with weekly dosing compared with daily dosing regimen (14). In our study, we reported a lower persistence rate in subjects treated with daily BPs or SR (5% in 1 year) than in subjects treated with monthly BPs (21.6%), that showed, in our cohort, the best persistence at 1 year. The most common circumstances when patients and/or physicians consider changing medication are side effects and safety concerns, uncomfortable dosing, perception of ineffectiveness, and cost of drugs (15). In our study, switching rates were higher for patients taking daily BPs or SR and lower for patients taking weekly BPs, highlighting the prominent role of side effects and inconvenient dosing regimens. In our cohort, male gender was associated with a higher risk of discontinuation compared to female gender (HR 0.89), that is much less than that reported in a previous study in Italian hip fracture patients (16). Although there is little persistence with calcium and vitamin D supplementation alone, when it is combined with other anti-osteoporotic drugs, it positively influences the persistence rate (17). Our study confirms that patients who received a co-prescription with calcium and vitamin D had a lower risk of early discontinuation (HR 0.72). The limitation of our study is due to the use of administrative database, which does not allow us to analyze potential clinical factors that negatively affect the persistence rates, including side effects, no perceived benefits, misinformation given by the physician, and lack of motivation. Our findings suggest that the prescription of drugs with less frequent dosing regimen represents the keystone of the therapeutic strategy to obtain an optimal persistence to anti-osteoporotic drugs. This could be related to the relative less frequent side effects. This conclusion might be extended to any long-term treatment and therefore the dosing regimen should be always considered by doctors before any prescription. In particular, osteoporotic patients, who have usually several comorbidities and take several drugs, might perceive a less frequent dosing regimen as a facilitator enhancing their motivation.

Conflict of interest

All Authors have no conflicts of interest.

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