Low persistence with oral bisphosphonate treatment in postmenopausal osteoporosis

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ABSTRACT

Background: Osteoporotic fractures are a major cause of morbidity and mortality. It is recognized that persistence with medication is crucial to reach optimal clinical outcomes. We aimed to estimate the persistence level to weekly and monthly oral bisphosphonates (OBP) in women with postmenopausal osteoporosis (PMO) over 24 months from therapy initiation in a population-based setting.

Methods: Prospective observational cohort study of PMO women ≥50 years initiating OBP recruited through community pharmacies. Data were collected at baseline during face-to-face interviews. Follow-up included pharmacy records (refill dates and medication possession; cohort 1) and telephone-surveys for patients who agreed to be interviewed (cohort 2). Patients were classified as persistent if they refilled their prescription within 30 days after exhausting the time covered by their previous supply. Log-rank tests were used to compare Kaplan-Meier curves of time to non-persistence.

Results: Of 427 women recruited with a mean age of 65.0 years, 380 (89%) agreed to be interviewed (cohort 2). Over 24-months of follow-up, 3.4% (95% CI: [2.0%; 5.6%]) of all subjects were persistent to OBP based on pharmacy records. Analysis combining both self-reported information and pharmacy records (cohort 2) showed a persistence estimate of 20.0% (95% CI: [16.1%; 24.2%]). Lower persistence was associated with more frequent OBP dosing and living alone. The most common reason for treatment discontinuation was self-reported adverse events (27.6%).

Conclusions: Results indicate a low level of persistence with OBP. Barriers and reasons leading to discontinuation of anti-PMO therapies should be proactively addressed to promote persistence and improve fracture protection.

Keywords: Postmenopausal osteoporosis; Bisphosphonates; Persistence; Adherence; Discontinuation

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BACKGROUND

Osteoporosis is a growing public health concern affecting over 200 million people worldwide[1]. Considering the ageing demographic trends, these figures are expected to worsen in coming years[1]. Osteoporosis causes more than 8.9 million fractures annually worldwide[2] and represent a major cause of morbidity and mortality in developed countries[3,4].

Hip fractures, which are usually considered a good indicator for osteoporosis epidemiology and quality of clinical care[5], are increasing globally, and Portugal is no exception[6–8]. However, the available evidence indicates that anti-osteoporotic treatment rates in Portugal are low[2,9], especially among women aged 65 years and older[10].

In Portugal as in other European countries, a variety of osteoporosis medications with proven anti-fracture efficacy are available for the prevention and treatment of osteoporosis[11]. OBP are currently the most commonly prescribed post-menopausal osteoporosis (PMO) treatment[2]. Although it is recognized that adherence and persistence with medication is crucial to reach optimal clinical outcomes[2,3,12], it has been consistently shown that real-world persistence and adherence to OBP are low, resulting in a significant increase in the risk of fracture[13,14] and health care costs[15–17].

This study was conducted in Portugal where contrasting with many other countries, pharmacy records are not centralized. Hence, unlike the majority of pub-

lished OBP persistence and adherence studies, which used secondary data (defined as data that were already collected for another purpose, *e.g.* as part of administrative records or patient health care), namely large administrative databases[18], that are known to be often poor in covariates, this study used also primary data [defined as data collected prospectively for a particular study (*de novo* data collection)] that were originally collected for this specific research purpose, thus taking advantage of an increase control over the type and amount of available information, particularly in what concerns to medication-taking behavior and reasons for discontinuation[19,20].

With a variety of health and delivery systems and different real-world drug landscapes across countries, it is acknowledged that country-specific analyses in everyday clinical practice are necessary to understand the levels of persistence with OBP and to determine the factors associated with medication-taking behaviour. Against this background, we estimated persistence and adherence levels with weekly and monthly OBP among a Portuguese treated population of post-menopausal women, over 24 months from therapy initiation. Additionally, we aimed to explore and potentially identify factors associated with non-persistence.

METHODS

STUDY DESIGN, SETTING AND POPULATION

An observational, prospective cohort study of post-menopausal osteoporotic women, recruited by the Portuguese community pharmacies, was conducted between 31 January 2011 and 30 July 2013. Invitation letters were sent to all community pharmacies from the National Association of Pharmacies (ANF) with the required software to participate in this study (n=1068; 37% of Portuguese pharmacies). The pharmacists who agreed to participate were invited to attend a half-day training session. For all those pharmacists who were unable to attend the training sessions, conference calls were arranged. A pilot study was conducted in November 2010 in order to test study feasibility, namely data collection instruments, data management systems, measurement methods and the recruitment strategy.

Subjects were recruited based on pre-defined eligibility criteria. Inclusion criteria included being a woman, aged 50 years or more, initiating a PMO treatment with weekly (alendronate 70 mg, alendronate 70 mg + colecalciferol 2800 or 5600 UI, or risedronate 35 mg) or monthly OBP (ibandronate 150 mg) and consenting to be included in the study. Subjects were excluded if they had done any PMO treatment (self-reported) within 6 months prior to recruitment (with the exception of calcium or vitamin D) or if they depended on others to take medication. For the eligible subjects who did not accept to participate, information regarding the age group, the OPB filled and the medical specialty responsible for subject's prescription were collected through a refusal log form.

After enrolment, subjects were asked to take part in telephone follow-up interviews to confirm the persistence status and to report reasons for non-persistence. Cohort 1 included subjects who accepted to participate in the study but did not consent to telephone follow-up interviews and cohort 2 included subjects who accepted telephone interviews.

Data were collected through three different sources. At baseline, patients had a face-to-face interview with a trained pharmacist to collect demographic (birth date, educational level, city council of residence, employment status, co-residence status and number of people living in subject's household) and self-reported clinical characteristics such as health care habits (physical activity, frequency of medical appointments during the twelve months prior to recruitment), age at osteoporosis diagnosis, awareness and knowledge of bone mineral density test (BMD), menopause and age at menopause, history of fractures (fractured bone, age at fracture and hospitalization), co-morbidities, concomitant therapy and OBP treatment status [posology, medical specialty responsible for subject's prescription and duration, naïve (incident) *vs* re-starter (prevalent) subject and, if applicable, previous bisphosphonates therapy experienced (date of the last bisphosphonates refilling)].

Over the study period, data regarding persistence and adherence (e.g. refill dates and medication possession) were collected by an electronic data capture system developed for electronic transfer of patients' pharmacy records from pharmacy to the Centre for Health Evaluation & Research (CEFAR) from ANF. For cohort 2 participants, confirmation of non-persistence status (e.g. acquisition of OBP in a different pharmacy) and reasons for non-persistence were obtained through structured telephone questionnaires every time subjects were identified as potential non-persistent through the pharmacy records database. Tele-

phone follow-up ceased whenever the non-persistent status was confirmed by the subject. To minimize potential recall bias, a 4-week period was considered to obtain responses, counting from when the patient was identified as non-persistent through the database. Each subject remained under observation during 24 months and was followed prospectively through the pharmacy-records database, regardless their persistence status during the study period.

Since there was no hypothesis being tested, a sample size of 418 patients was determined in order to estimate a 30% persistence rate after 24 months of follow-up[21], for an expected incidence OBP use rate of 1.9% (95% confidence intervals (CI): 1.1; 2.7%) (data obtained from a one week national census survey conducted in 105 pharmacies from a total of 1091 OBP prescriptions), with a 5% absolute error for the half-width of the 95% CI. A 30% lost-to-follow patients was considered.

STUDY DEFINITIONS

Persistence was defined as the accumulation of time from initiation to discontinuation of treatment, based on the number of consecutive days of study medication dispensed to the subject. Persistence was quantified with the Estimated Level of Persistence with Therapy (ELPT) method. This was calculated as the proportion of subjects refilling each subsequent prescription within a grace period of 30-days (after the days' supply from the previous prescription was exhausted). A non-persistent subject was defined as one who missed prescription cycles according to the definition of persistence and was considered non-persistent for the remainder of the study, regardless of whether the subject had collected medication for the subsequent months (according to the definition of non-persistence). Time to non-persistence was calculated as the time in days between the date of the first medication and the last day the patient was still classified as persistent. The refill interval to consider in the analysis was calculated using the baseline information of the real prescribed posology, when available. Whenever that information was missing, the refill interval was considered using the information provided by the drug's Summary of Product Characteristics (SmPC). Lost-to-follow-up included subjects no longer captured in the database for the acquisition of any medication after recruitment (cohort 1) and subjects from cohort 2 identified as non-persistent who were not possible to be reached by telephone during the study period.

Adherence was assessed for each study participant based on the Medication Possession Ratio (MPR). MPR was calculated as the number of days of medication supplied within the refill interval divided by the number of days of the observation period. A patient was classified as adherent when MPR $\geq$ 0.8.

STATISTICAL ANALYSES

Regional distribution, setting (urban/semi-urban/rural) and pharmacists' staff of pharmacies with recruited patients was compared with the overall distribution of pharmacies using Chi-square test for adjustment. Discrete variables were summarized by absolute and relative counts and missing values were stated in the corresponding summary table. Continuous variables were summarized using central tendency measures and dispersion, i.e., mean and standard deviation (SD), median and inter-quartile range (IQR). To evaluate differences between cohorts Chi-square test or Fisher's exact test were used for contingency tables whereas Wilcoxon test was used to for ordinal or continuous variables.

The persistence was determined, for overall population and per each cohort. 95% CI were computed. Kaplan-Meier (KM) curves and log-rank test were computed to compare the time to non-persistence between cohort 1 and 2 and the median time on therapy was calculated. Sensitivity analyses were performed and overall persistence was calculated for patients using combination of pharmacy records and patients' self-reported data on persistence. Further sensitivity analyses were performed, specifically using 60 and 90-day grace periods (for cohort 1) and to assess the impact of switching medication. In the later, a new estimate of persistence was obtained, considering the subjects as still persistent if they switched (within the grace period) to a new medication other than one of the study medications, but still indicated for the treatment of PMO (with the exception of calcium and/or vitamin D).

Cox models were used to explore potential factors that could contribute to time to non-persistence. The response/outcome variable was time-to-non-persistence (combining both pharmacy records and self-report information on persistence) and the covariates were baseline characteristics. Univariate and multivariate hazard ratios (HR) were computed and Wald's 95% CI presented. Model diagnoses comprised the computation of likelihood-ratio, Wald and score chi-square statistics, and the Variance Inflation Factor (VIF). In depth, residuals analysis, including plots with the scaled Schoenfeld residuals was performed, the

latter, to assess proportional hazards assumption. Time cut-points were created in variables with non-proportional hazards.

The proportion of adherent patients was determined at 12 and 24 months. The baseline characteristics of adherent/non-adherent patients were compared using chi-square test or Fisher's exact test.

All tests were two-sided and the statistical significance level adopted was 5% without adjusting for multiplicity. Data were analyzed in SAS Enterprise Guide v4.1.

ETHICS AND DATA PROTECTION

This study was reviewed and approved by the Portuguese Data Protection Authority and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Every participant accepted to participate by signing a written informed consent prior to initiation of any study procedures. Participants had the right to withdraw fully or partially from the study at any time for any reason, without jeopardizing patient service, by the pharmacy. All collected data were strictly confidential and databases had all security measures required by Portuguese law and guaranteed logistical separation between health data and other personal data. Participants were attributed a non-identifying numeric code.

RESULTS

PARTICIPANT PHARMACIES AND PATIENTS

A total of 287 (26.9%) out of 1068 invited pharmacies accepted to participate and 169 (15.8%) recruited at least one patient. Regional distribution of pharmacies with recruited patients was similar with the national distribution of the Portuguese pharmacies (p=0.1030) but were more frequently placed in urban areas (p=0.0021) and had significantly more pharmacists in their staff (p<0.0001).

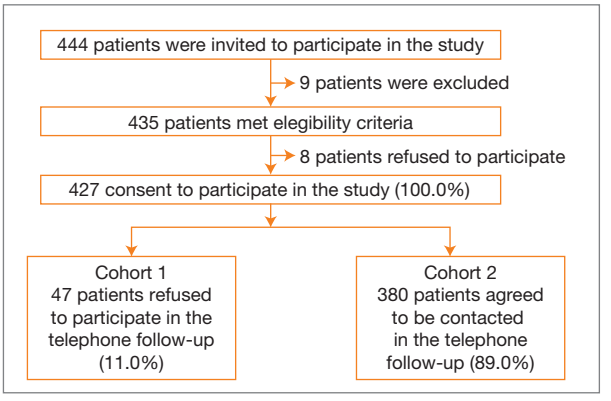

FIGURE 1. Subjects enrolment scheme

A total of 444 patients were invited and 427 eligible patients consented to participate in the study. A total of 380 (89.0%) patients agreed to be contacted through telephone follow-up interviews (cohort 2) (Figure 1).

BASELINE CHARACTERISTICS

Participants' characteristics are presented in Table I. The mean age was 65.0 (SD=9.5) years and 267 (63.0%) had only completed basic education. Most of study participants (n=322; 75.8%) lived in an urban setting, half (n=211; 50.0%) were retired and about 334 (78.2%) were living within household with at least 2 people.

About half (n=214; 50.2%) reported practicing some type of physical exercise (including walking), on average 4.0 (SD=2.0) days per week and 1.1 (SD=0.6) hours per day. Most of the patients had one or more medical appointments per quarter in the 12 months prior to recruitment (n=255; 60.0%). About two-thirds of participants reported to have other chronic diseases (n=289; 67.8%), hypertension (n=186; 64.4%) being the most frequent. A total of 367 (86.8%) subjects reported to take concomitant medication and among those the mean number of different medicines taken was 3.7 (SD=2.4). At least half of patients reported to have reached menopause at age of 51 or older (IQR=48–54). No statistically significant differences were found between cohorts regarding baseline health characteristics (p>0.05), except for the participants who reported having thyroid disorders (p=0.0174) and patients taking medication for Parkinson's disease (p=0.0331), which were more frequent in cohort 1.

At baseline, 245 (57.8%) patients acknowledged having osteoporosis, however the proportion of patients who did not know about their osteoporosis status was significantly higher (p=0.0089) in cohort 1. On average, patients reported the awareness of osteoporosis diagnosis at 61.9 years (SD=9.6). Overall, 332 (78.5%) patients acknowledged having done a BMD test prior to recruitment.

A total of 137 (32.1%) patients reported having a fracture prior to recruitment, of those 71 patients reported having a fracture at menopause age or after. The most prevalent was foot fracture (n=29; 21.2%), followed by wrist fracture (n=23; 16.8%) and femur/hip fracture (n=21; 15.3%).

Regarding the exposure to bisphosphonates therapy,

TABLE I. BASELINE DEMOGRAPHIC AND SELF-REPORTED CLINICAL CHARACTERISTICS

Characteristics	Cohort 1 (n=47)	Cohort 2 (n=380)	Total (n=427)	p-value
Age mean (SD) (NR=0), years	66.0 (11.1)	64.8 (9.3)	65.0 (9.5)	0.6213
< 55	8 (17.0)	53 (13.9)	61 (14.3)	0.2619
55 - 64	14 (29.8)	161 (42.4)	175 (41.0)	
65 - 74	12 (25.5)	98 (25.8)	110 (25.8)	
≥ 75	13 (27.7)	68 (17.9)	81 (18.9)	
Educational level (NR=3)	**n (%)**	**n (%)**	**n (%)**	
No academic degree	10 (21.3)	42 (11.2)	52 (12.3)	0.1652
Basic education (≤ 9 years)	28 (59.5)	239 (63.4)	267 (63.0)	
Secondary education (10-12 years)	6 (12.8)	45 (11.9)	51 (12.0)	
Bachelor/University degree	3 (6.4)	51 (13.5)	54 (12.7)	
Setting of residence (NR=2)	**n (%)**	**n (%)**	**n (%)**	
Urban	33 (70.2)	289 (76.5)	322 (75.8)	0.2790
Suburban	7 (14.9)	59 (15.6)	66 (15.5)	
Rural	7 (14.9)	30 (7.9)	37 (8.7)	
Employment status (NR=5)	**n (%)**	**n (%)**	**n (%)**	
Employed	11 (23.4)	100 (26.6)	111 (26.3)	0.9568
Unemployed	3 (6.4)	25 (6.7)	28 (6.6)	
Retired	24 (51.1)	187 (49.9)	211 (50.0)	
Housewife	9 (19.1)	63 (16.8)	72 (17.1)	
Living alone (NR=0)	**n (%)**	**n (%)**	**n (%)**	
No	38 (80.9)	296 (77.9)	334 (78.2)	0.6432
Yes	9 (19.1)	84 (22.1)	93 (21.8)	
Physical exercise (NR=1)	**n (%)**	**n (%)**	**n (%)**	
No	23 (48.9)	189 (49.9)	212 (49.8)	0.9041
Yes	24 (51.1)	190 (50.1)	214 (50.2)	
Number of days per week (mean [SD])	4.2 [2.4]	3.9 [1.9]	4.0 [2.0]	
Number of hour per day (mean [SD])	1.0 [0.3]	1.1 [0.6]	1.1 [0.6]	
Medical appointments in the last 12 months (NR=2)	**n (%)**	**n (%)**	**n (%)**	
None	0 (0.0)	1 (0.3)	1 (0.2)	0.7330
Once/year	5 (11.1)	46 (12.1)	51 (12.0)	
Once/semester	16 (35.6)	102 (26.8)	118 (27.8)	
Once/quarter	11 (24.4)	110 (29.0)	121 (28.5)	
More than once/quarter	13 (28.9)	121 (31.8)	134 (31.5)	
Chronic illnesses (NR=1)	**n (%)**	**n (%)**	**n (%)**	
No	14 (29.8)	123 (32.5)	137 (32.2)	0.7120
Yes	33 (70.2)	256 (67.5)	289 (67.8)	
Concomitant therapy (NR=4)	**n (%)**	**n (%)**	**n (%)**	
Yes	43 (93.5)	324 (85.9)	367 (86.8)	0.2458
Number of different medicines taking for chronic illnesses				
Mean (SD)	3.8 (2.3)	3.7 (2.4)	3.7 (2.4)	
Median (IQR)	4.0 (2.0-5.0)	3.5 (2.0-5.0)	4.0 (2.0-5.0)	
Age at menopause (NR=45), years	**n (%)**	**n (%)**	**n (%)**	
Mean (SD)	49.4 (4.8)	50.2 (5.6)	50.2 (5.5)	0.3141
Median (IQR)	50.0 (45.5 -53.5)	51.0 (48.0-54.0)	51.0 (48.0-54.0)	

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TABLE I. CONTINUATION

Characteristics	Cohort 1 (n=47)	Cohort 2 (n=380)	Total (n=427)	p-value
Knowledge about osteoporosis status (NR=3)	**n (%)**	**n (%)**	**n (%)**	
No	16 (34.0)	145 (38.5)	161 (38.0)	0.0089
Yes	25 (53.2)	220 (58.3)	245 (57.8)	
Do not know	6 (12.8)	12 (3.2)	18 (4.2)	
Age at first diagnosis (NR=17), years	**n (%)**	**n (%)**	**n (%)**	
Mean (SD)	61.6 (11.0)	62.0 (9.5)	61.9 (9.6)	
Median (IQR)	62.0 (54.9-69.0)	61.8 (54.0-68.9)	61.9 (54.9-68.9)	
Patient's acknowledge about BMD (NR=4)	**n (%)**	**n (%)**	**n (%)**	
No	5 (10.9)	69 (18.3)	74 (17.5)	0.5085
Yes	39 (84.8)	293 (77.7)	332 (78.5)	
Do not know	2 (4.3)	15 (4.0)	17 (4.0)	
Bone fracture after menopause (NR=0)	**n (%)**	**n (%)**	**n (%)**	
No	40 (85.1)	316 (83.2)	356 (83.4)	0.7350
Yes	7 (14.9)	64 (16.8)	71 (16.6)	
Exposure to bisphosphonates therapy (NR=0)	**n (%)**	**n (%)**	**n (%)**	
Treatment naïve (incident cases)	37 (78.7)	290 (76.3)	327 (76.6)	0.7131
Treatment restarters (prevalent cases)	10 (21.3)	90 (23.7)	100 (23.4)	
Year since last bisphosphonates uptake*:				
[6 months-1 year[	1 (10.0)	23 (26.7)	24 (25.0)	
[1 -2 years[	2 (20.0)	17 (19.8)	19 (19.8)	
[2-3 years[	1 (10.0)	18 (20.9)	19 (19.8)	
[3-6 years[	3 (30.0)	14 (16.3)	17 (17.7)	
[6-10 years[	1 (10.0)	10 (11.6)	11 (11.5)	
≥ 10 years	2 (20.0)	4 (4.7)	6 (6.3)	
Bisphosphonate therapy (NR=0)	**n (%)**	**n (%)**	**n (%)**	
Monthly	11 (23.4)	123 (32.4)	134 (31.4)	0.2115
Weekly	36 (76.6)	257 (67.6)	293 (68.6)	
Medical specialty responsible for subject's prescription (NR=2)	**n (%)**	**n (%)**	**n (%)**	
General practitioner	30 (66.7)	259 (68.2)	289 (68.0)	0.0454
Gynecologist and obstetrician	4 (8.8)	42 (11.1)	46 (10.8)	
Orthopedist	3 (6.7)	31 (8.2)	34 (8.0)	
Internal medicine	5 (11.1)	12 (3.2)	17 (4.0)	
Rheumatologist	3 (6.7)	11 (2.9)	14 (3.3)	
Other	0 (0.0)	25 (6.6)	25 (17.9)	

NR – non respondents; BMD – Bone Mineral Density; *Four patients in cohort 2 did not remember the time since the last bisphosphonate uptake, but not within 6 months prior to recruitment.

the majority of patients were treatment naïve (n=327; 76.6%), and 293 (68.6%) and 134 (31.4%) were initiating weekly and monthly therapy, respectively. Regarding prescribed therapy duration, 285 (93.8%) reported chronic/long term OBP use. Medical specialties that issued more OBP prescriptions were general practitioners (n=289; 68.0%) and gynecologists (n=46; 10.8%). No significant differences were found between cohorts.

OVERALL PERSISTENCE

According to ELPT Method, the persistence with oral bisphosphonates therapy after a follow-up of 6, 12, and 24 months was 28.3% (95% CI: [24.0%; 32.6%]),

10.2% (95% CI: [7.3%; 13.1%]) and 4.5% (95% CI: [2.5%; 6.5%]) respectively. Persistence rates were similar between cohorts (p>0.05). Seven patients were lost-to-follow-up (6 in cohort 1 and 1 in cohort 2).

Kaplan-Meier survival analysis at 24 months of follow-up (Figures 2 and 3) demonstrated that overall persistence with OBP therapy was 3.4% (95% CI: [2.0%; 5.6%]) and was similar in the 2 cohorts throughout the study period (p=0.9813). Median time to non-persistence was 70 days (77 in cohort 1 and 67 in cohort 2). The level of persistence of treatment restarters and naïve patients was similar over the study period (p=0.4802).

Sensitivity analysis using data from cohort 2 indicated that the persistence at 24 months estimated exclusively with electronic data from pharmacy records was 3.5% (95% CI: [2.0%; 5.8%]) whereas when including patient self-reported information on persistence was 20.0% (95% CI: [16.1%; 24.2%]) (Figure 4). In cohort 1, a more conservative persistence estimate was evaluated using 60 and 90 days grace periods. KM persistence estimates varied from 20.5% to 35.5% at 6 months, from 5.1% to 15.2% at 12 months and from 2.6% to 7.6% at 24 months. Considering the impact of switching to another osteoporosis medication (not weekly or monthly OBP), the overall persistence did not change at 24 months (3.4%). Over the study period, 44 patients switched to a different osteoporosis medication: 3 in cohort 1 and 41 in cohort 2.

REASONS FOR NON-PERSISTENCE

Over the study period, 361 patients from cohort 2 were identified as potential non-persistent through the pharmacy records database. Of these, 181 confirmed to have stopped taking their OBP medication and 165 patients reported not having stopped the medication, stating that they had acquired OBP medication in another pharmacy. Amongst self-confirmed non-persistent patients, 40 (22.1%) indicated that OBP discontinuation was recommended by the physician and 27.6% (n=50) reported that was due to an adverse event. Gastrointestinal disorders were the adverse events more frequently reported (72.0%; n=36) followed by musculoskeletal and connective tissue disorders (34.0%; n=17) and nervous system disorders (22.0%; n=11). There were no serious adverse events reported by the patients. Other reasons reported for OBP treatment interruption comprised patient's decision to make a pause in the medication (15.5%), "not yet returned to the physician to renew prescriptions" (13.8%) and not be-

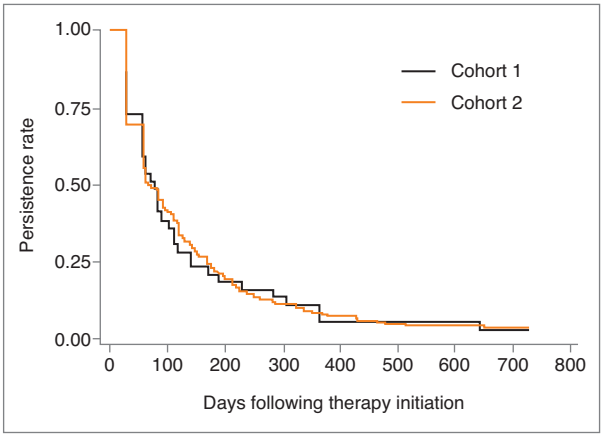

FIGURE 3. Kaplan-Meier curves of persistence with oral bisphosphonates therapy, per cohort

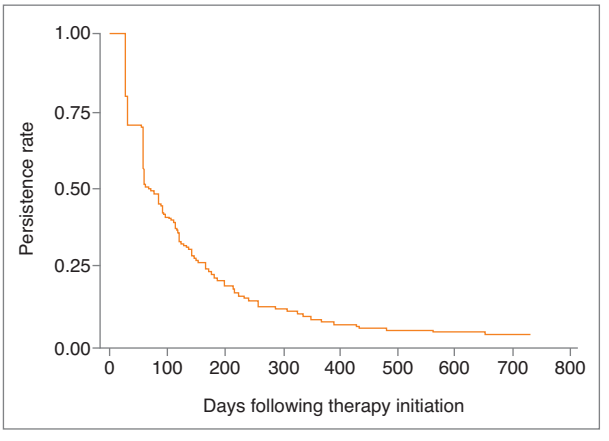

FIGURE 2. Kaplan-Meier curves of overall persistence with oral bisphosphonates therapy

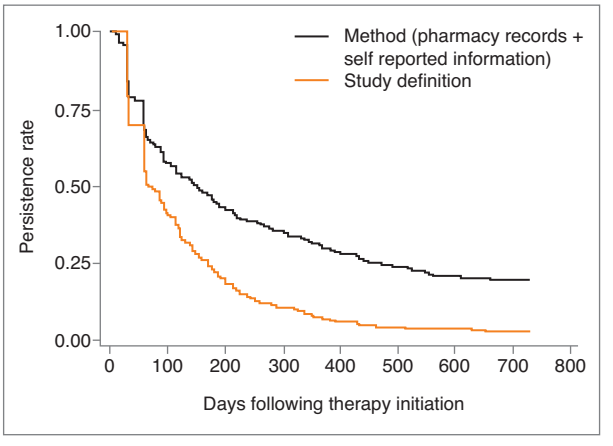

FIGURE 3. Persistence using pharmacy records self-reported information

TABLE II. FACTORS ASSOCIATED WITH TIME TO NON-PERSISTENCE WITH OBP THERAPY FOR THE 24 MONTHS OF FOLLOW-UP PERIOD (PHARMACY RECORDS AND PARTICIPANTS SELF-REPORTED INFORMATION)

	Univariate			Multivariate*		
Baseline characteristics	**HR**	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**
Age group< 75 years	Ref.			Ref.		
≥ 75 years	1.447	1.116-1.876	0.0053	1.260	0.950-1.671	0.1090
Educational level						
No degree and Basic educ. (≤9 years)	Ref.			Ref.		
Sec. and Univ. degree (Follow-up<180 days)	1.287	0.970-1.707	0.0806	1.387	1.035-1.857	0.0283
Sec. and Univ. degree (Follow-up≥180 days)	0.638	0.374-1.088	0.0990	0.531	0.301-0.936	0.0287
Setting of residence						
Urban and Suburban	Ref.			Ref.		
Rural	0.737	0.497-1.092	0.1286	0.738	0.489-1.113	0.1468
Living alone						
No	Ref.			Ref.		
Yes (Follow-up<90 days)	0.988	0.687-1.422	0.9488	0.882	0.608-1.281	0.5111
Yes (Follow-up≥90 days)	1.853	1.313-2.615	0.0005	1.822	1.270-2.614	0.0011
Bisphosphonate therapy						
Monthly	Ref.			Ref.		
Weekly	1.358	1.076-1.715	0.0100	1.295	1.019-1.647	0.0347
Medical specialty responsible for subject's prescription						
General practitioner	Ref.			Ref.		
Other (Follow-up<180 days)	0.730	0.548-0.971	0.0305	0.711	0.531-0.953	0.0224
Other (Follow-up≥180 days)	1.416	0.955-2.099	0.0832	1.832	1.200-2.798	0.0051
Number of different medicines taking for chronic illnesses						
0	Ref.			Ref.		
1 or more (Follow-up<90 days)	1.763	1.038-2.994	0.0360	1.695	0.994-2.891	0.0527
1 or more (Follow-up≥90 days)	0.825	0.558-1.219	0.3343	0.697	0.467-1.040	0.0774

* Wald test: p-value < 0.0001; VIF ≤ 1.1489

ing aware to continue treatment with OBP after the first prescription (12.7%).

POTENTIAL FACTORS ASSOCIATED WITH TIME TO NON-PERSISTENCE

In the multivariate Cox model (Table II), analysis combining both pharmacy records and self-report information on persistence indicated that patients with higher educational level (secondary and university degree) had a higher risk of persistence failure in the first 6 months of follow-up (HR=1.387; 95% CI [1.035; 1.857]; p=0.0283) and lower risk after 6 months of follow-up (HR=0.531; 95% CI [0.301; 0.936]; p=0.0287) and patients living alone had a higher risk of persistence failure after 3 months of follow-up (HR=1.822; 95% CI [1.270; 2.614]; p=0.0011). Results also demonstrated that patients having weekly therapy had a higher risk of persistence failure (HR=1.295; 95% CI [1.019; 1.647]; p=0.0347).

ADHERENCE

At the end of the study, only 7.5% [4.9%; 10.1%] of the patients were adherent (MPR ≥80%). More than a half of the patients (52.6%) had a MPR less than 20% at 24 months of follow-up. Non-adherence at 12 months was found to be higher in patients living alone (p=0.0285) and in patients under a weekly therapy (p=0.0300). However, at 24 months of follow-up these differences were not significant (p>0.05).

DISCUSSION

As part of the real-world practice evidence generation data, it is acknowledged that it is of utmost importance to have methods for monitoring patients' drug usage landscape as well as its outcomes and determinants. Contrasting with the majority of the published studies that used claims databases, the present study represents an important contribution to assess medication-taking behaviour. Through the implementation of a research design that combines, pharmacy records and self-reported information, persistence with osteoporosis medication was measured and reasons for discontinuation at a patient level were identified. An overall persistence rate with weekly and monthly OBP over 24 months from therapy initiation of 4.5% was found, considering information exclusively from pharmacy records. It is worth mentioning that the overall risk of persistence failure was 71.7% at 6 months and 89.8% at 12 months, revealing the highest decrease in persistence during the first year of treatment follow-up.

Several sensitivity analyses were performed in order to assess the impact of different assumptions on OBP persistence rates. In general, regardless of the sensitivity analysis conducted, persistence estimates were very low. At the end of the study period, when extending the permissible gap length to 60 or 90 days, persistence estimates at 24 months was slightly higher (5.1% and 7.6%, respectively). Considering the switching to other osteoporosis medication (other than the study medication), the overall persistence did not change at 24 months. Additionally, even when including patient self-reported data, OBP persistence rate increased but was still very low (20.0%). Even though most of patients were treatment naïve (76.6%) at baseline, similar OBP lower persistence levels were found between treatment restarters and naïve patients.

Overall, taking into account study persistence estimates together with sensitivity analysis results, it is believed that the "true" OBP persistence rate might possibly be between the lower limit of persistence estimate retrieved from pharmacy records exclusively and the upper limit of persistence estimate retrieved from the combination of pharmacy records and patient self-reported information. In this frame, it is assumed that, on one hand, patient's self-reported persistence could be overestimated. However, on the other hand, for a 24 months' time period persistence estimates retrieved exclusively from pharmacy records could be underestimated since patients can go to more than one pharmacy and there is not a Portuguese database that comprises all prescriptions refills from different pharmacies at an individual patient level.

In general, this study revealed lower persistence rates than other studies published elsewhere[14,22–24] based on similar population inclusion criteria and considering information based on administrative or health records databases exclusively. Only a study conducted in Taiwan, based on claims databases, showed a comparable persistence rate of 4.07% at 24 months[25]. Even when considering self-reported data and pharmacy records, persistent rates continued to be lower than what was found within most literature[22,26]. An European study conducted in Germany[23] showed similar persistence rates (12.9% at 24 months), when considering the persistence estimate between the two study methods boundaries results: pharmacy records exclusively and its combination with self-report information data.

Concerning adherence, at the end of the study, more than a half of the patients (52.6%) had a MPR < 20% and only 7.5% of the patients were identified as adherent (MPR > 80%). In cohort 2, considering self-report information, adherence rate increased up to 21.4%. In line with persistence estimates, adherence rates observed were lower when compared to other studies either based on surveys[27] or on electronic medical records[13,14,23,28]. However, it should be mentioned that Portuguese patients reveal, in general, lower adherence rates to chronic therapy than what it was found worldwide[29–32].

When analyzing factors that could contribute to non-persistence overtime, it was found that patients living alone had a higher risk of persistence failure after 3 months of follow-up and patients with higher educational level had a higher risk of persistence failure in the first 6 months of follow-up. Also, it was observed that persistence failure risk was higher for patients on weekly therapy. The OBP persistence failure determinants found in this study are globally in line with what was described elsewhere[14,21,33–35].

Reported adverse events was the most frequent reason reported to discontinue OBP treatment. The most frequent adverse events reported are in accordance with the literature[24]. Improving adherence to OBP require health care providers to proactively address adverse drug events[36,37] in order to prevent OBP risk treatment failure.

The results of this study should be viewed in light of the following limitations. First, pharmacies self-selection could have occurred since participation was not mandatory. Nevertheless, the regional distribution of participating pharmacies was similar to the national distribution of Portuguese pharmacies. However, pharmacies with recruited patients had significantly a higher number of community pharmacists in their staff, which, given the need of complying with study requirements, showed no surprise. Secondly, clinical data collected at baseline were reported by the patient and could be associated with some degree of inaccuracy. Even though a study conducted in Portugal showed a concordance rate of 90% between self-report information and diagnosed health condition, regarding postmenopausal state (38). The fact that a lower proportion of patients acknowledged having a diagnose of osteoporosis communicated by the medical doctor (57.8%) as compared with the patients having done a BMD (78.5%) could be intriguing. A possible explanation could be that the BMD test is not exclusively used for the diagnosis of osteoporosis, as it is used in the diagnosis/complimentary diagnosis test on other musculoskeletal disorders. Beyond that, the BMD test could have been counselled by other healthcare professionals (e.g. gynecologists, through screening programs) and being performed in a routine fashion along women's life, concretely after the commencement of menopause. Despite this, these findings might require improvements in patient-health care provider communication as well as between health-care providers.

Thirdly, the use of self-report information to ascertain persistence could also be biased by a reluctance to admit an inappropriate behavior (social desirability bias). However, inaccuracies in reported persistence are believed to be minimized since independent research interviewers and not patients' healthcare providers were responsible to conduct the follow-up interviews[39,40]. Furthermore, even when including patient self-reported data, the OBP persistence rate found was still very low, that is to say, the majority of patients did not show reluctance to declare they have stopped taking the medication. Beyond that, in order to minimize potential recall bias, a maximum period of 4 week was allowed to contact the patient. From the patient's perspective, when reporting OBP persistence information, it is believed that OBP was easily identified during the telephone follow-up due to its unique characteristics, either concerning posology (weekly or monthly) or the recommended instructions of utilization (e.g. patient must take the tablet with a full glass of water, at least 30 minutes before any food, drink or other medicines, etc.).

Despite the limitations, this study has several strengths. The two cohorts (those who did not accept to be contacted and those who accepted to be contacted) were similar with regard to baseline characteristics and no differences between persistence or adherence rates estimated through pharmacy records exclusively were observed over the study period. During the enrolment phase, eligibility criteria were assessed by a trained pharmacist and then double checked by the research team, which provided additional quality to information retrieved. Missing data, concerning self-report baseline information and telephone follow-up survey, were low presenting high quality of information, in respect to validity and completeness. Data from patient self-report may well capture and further explore some features of medication use and behaviour landscape, namely reasons for treatment discontinuation, when compared to administrative databases. As a final

point, regarding sample size, the number of patients enrolled in this study, allowed to estimate persistence rates with an absolute error of less than 5%.

Overall, regardless of the method used, either pharmacy records exclusively or their combination with patient self-reported information, low levels of OBP persistence and adherence were found. Our results not only confirmed findings from other countries, by identifying sub-optimal rates of persistence with OBP, but also add knowledge by implementing an innovative study design in Portugal that combines pharmacy records and self-report information, to measure persistence and adherence to chronic therapy. These results may be used to develop potential effective interventions that aim to improve the length of persistence to osteoporosis therapy. Furthermore, this study suggested that strategies to improve persistence should be implemented during the first year of therapy and that is of utmost importance to inform patients about their long-term treatment plan, highlighting the role of adherence and persistence with therapy and compliance with dosing recommendations.

Although this study was conducted some years ago, we do believe that the global results still remain today. The present study was the first study tackling persistence and adherence with OBP medication in Portugal, and to the best of our knowledge no other study assessing these medication-taking behaviour domains has been published or conducted so far. Furthermore, OBP remain currently the most frequent treatment in Portugal and the national clinical guideline issued by the Directorate General of Health in 2011 has not been updated.

CONCLUSIONS

Low persistence and adherence levels to OBP treatment were found. Exploratory analysis suggested that low persistence was associated with more OBP frequent dosing and living alone status. Continuing attention should be given to non-serious adverse events of OBP, because they represented the most common reported reason for discontinuation.

Since low persistence is associated with lack of effectiveness, barriers and reasons leading to the discontinuation of anti-PMO therapies should be addressed, especially during the first year of therapy, to promote persistence and adherence and consequently the level of anti-fracture protection in the PMO population.

DISCLOSURES

JG, ZM and AM are currently employed/receive support from CEFAR/ANF and have no conflict of interest to declare. CT was working at CEFAR/ANF when the study was performed and is currently Invited Assistant Professor at the Faculty of Pharmacy of University of Lisbon and employed by the Portuguese Pharmaceutical Society and has no conflict of interest to declare. FB is employee of Amgen and may own stock in Amgen Inc. During the time the study was conducted JC was an employee of Amgen and held stock, but is now Novartis Pharma AG employee. HC and JB have no conflict of interest to declare.

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