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SHORT SCIENTIFIC COMMUNICATION

Adherence to bisphosphonates in the general population: a study in patients referred to a primary care service

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Abstract

Purpose The aim of the study was to evaluate the adherence to treatment with bisphosphonates in women with postmenopausal osteoporosis referred to a primary care clinic.

Methods A total of 7257 outpatients were referred to the primary care service where the study was conducted. We retrieved data of postmenopausal women to which bisphosphonates have been prescribed in the period January 1, 2000–December 31, 2014, and analyzed the group of patients who had discontinued the drug.

Results The total number of women treated with bisphosphonates was 285 (mean age 72 ± 9.8 years). At the time the data were retrieved, 157 (55% of the total) had discontinued therapy. Among them, 119 (41.7%) agreed to participate in the study. They reported the following reasons for treatment discontinuation: withdrawal by another physician (40%), lack of motivation (20%), absence of BMD improvement (14%), uncomfortable way of drug administration (11%), side effects (6%), fear of side effects (1.6%), high number of concomitant medications (0.8%), and others (6.6%). Sixty patients (50.4%) discontinued therapy within 2 years, 27 patients (23%) > 2 and ≤ 5 years and 32 (27%) after 5 years.

Conclusions Our study demonstrates that more than half of women with postmenopausal osteoporosis referred to a primary care service discontinued bisphosphonates before the clinical effect can be seen and mostly because of advice by physicians not initially prescribing the drug. There is an inappropriate management of bisphosphonate therapy in terms of therapeutic efficacy and strategies aimed at ameliorating clinical management of osteoporosis patients are warranted.

Keywords Bisphosphonates · Adherence · Primary care · General practitioners

Introduction

Osteoporosis is a common skeletal disorder characterized by reduced bone mass and altered bone microarchitecture with a consequent increased risk of fragility fractures. Major osteoporosis-related fractures are associated with increased morbidity and mortality and represent a major health problem worldwide. Data from the US National Health and Nutrition Examination Survey (NHANES) have documented a 16% and 29.9% prevalence of osteoporosis in men and women 50 years and older, respectively, in the period 2005–2008 [1]. Similar data from a recent multicenter cross-sectional study conducted in Italy have shown a 36.6% prevalence of osteoporosis and a rate of 23% of major osteoporotic fractures [2]. In particular, 2.5% of postmenopausal women of this cohort aged 50 and older has experienced a hip fracture [2]. These data are in line with previous ones showing how major osteoporotic fractures represent a growing but often underestimated burden for the hospital care worldwide [3–5]. In the European Union, the costs for hip, vertebrae, and wrist fractures was about 37 billion Euros for 2010 and is expected to increase by 25% in 2025 [5]. Hence, the major treatment goal in patients with osteoporosis is fracture prevention [6]. Bisphosphonates are among the oldest drugs used in the treatment of osteoporosis, having demonstrated their efficacy in several clinical trials, as well as in clinical practice. Despite these numerous advantages, a significant decline in the use of bisphosphonates in the last decade has been observed both for oral and intravenous drugs [7]. Prevalence of

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oral bisphosphonate use among women older than 55 increased from 1996 to 2001 and maintained until 2008, with a significant decline afterward [7]. Similar data are reported for the intravenous bisphosphonates use [7].

As poor adherence to osteoporosis treatment is associated with smaller BMD gains, increased fracture or re-fracture risk, and eventually increased mortality, there have been several studies investigating the factors associated with low compliance [8–11]. Among them, issues related to safety and low level of awareness of osteoporosis compared to other chronic conditions were reported as strongly influencing patient perception on osteoporosis treatment [11]. The study of Rossini et al. in a cohort of 9851 postmenopausal women referred to Italian specialized centers has shown that the most common causes of discontinuation of osteoporosis drugs were drug-related side effects [9]. Of note, 19% of patients discontinued the treatment in the first 6 months after prescription [9].

The majority of the published reports focused on the evaluation of the adherence to therapy in patients referred to specialized centers, and to our knowledge, there have been no studies assessing the adherence and factors associated with drug discontinuation in a less selected cohort. Owing to the limitations in the access to tertiary care centers, patients with osteoporosis are frequently managed by general practitioners, particularly after prescription of therapy.

In this study, we sought to investigate patient adherence to treatment with bisphosphonates in a cohort of women with postmenopausal osteoporosis referred to a primary care service.

Methods

The study was conducted in a primary care medical clinic in Cerveteri, a town located about 50 km far from Rome, Italy. The total amount of outpatients of the clinic is 7257 (3474 men and 3783 women). Five general practitioners were involved and retrieved from the records of the clinic data of all postmenopausal women to which bisphosphonates (alendronate, clodronate, ibandronate, risedronate, and neridronate) have been prescribed in the period from January 1, 2000, through December 31, 2014. We collected the computerized records of bisphosphonates prescriptions from 2000 through 2015. Data from a total population of 285 women were retrieved. Among them, we selected the group of patients who had discontinued the drug at the time the study was performed (March 31, 2015). In particular, we selected subjects who had no prescription in the 3 months after the last prescription considered (December 31, 2014). Indeed, as a total of eight capsules of weekly oral alendronate and risedronate, two capsules of monthly oral ibandronate, six vials of weekly intramuscular clodronate, and two vials of monthly intramuscular neridronate can be prescribed with a single prescription, we could assume that patients could not be on treatment for 3 months with a single prescription. The (*Koiné* ®) software was used to retrieve data. The software is generally used for prescription and for electronic charts by primary care physicians in Italy.

Patients who discontinued therapy were offered a questionnaire with the following items to specify the main reason for drug's discontinuation: side effects, worries about possible side effects, uncomfortable way of drug's administration, withdrawal by other physician, cost of the therapy, lack of BMD improvement, lack of motivation, high number of concomitant drugs in addition to osteoporosis treatment, persistence of pain, and others. Furthermore, we collected anthropometric data and information about medical history, as follows: age, time of menopause, presence of fragility fractures occurred after the age of 40, age at diagnosis of osteoporosis, number of concomitant drugs, and specialization of the physician who first prescribed osteoporosis drug.

All subjects gave written informed consent to participate in the study. The mean time from bisphosphonate initiation to questionnaire completion was 6.5 years.

Statistical analysis

Percentage of women who have discontinued bisphosphonates at the time the study was performed over the total number of women was calculated. We therefore evaluated the percentage of patients for any cause of drug discontinuation over the number of patients who discontinued therapy. Patients who have discontinued therapy were divided in three groups according to treatment duration, as follows: < 2 years, > 2 and ≤ 5 years, and > 5 years, and percentage of patients in any group was evaluated.

Results

We studied 285 postmenopausal women (mean age ± SD 72 ± 9.8) who have been prescribed bisphosphonates in the period of interest. At the time the study was performed, 157 (55%) had discontinued therapy, while 128 (45%) were still on treatment.

We tried to contact all patients who had discontinued therapy. Among them, 119 (41.7% of the total; 75.8% of those discontinuing therapy) were reached out and agreed to fill in the questionnaire. Table 1 shows demographic and clinical data of the cohort of patients, as well as the prevalence of specialties among physicians who first prescribed bisphosphonates. Sixty-six (55.5%) of patients discontinued alendronate, 28 (23.5%) clodronate, 12 (10.1%) risedronate, eight (6.7%) ibandronate, and five (4.2%) neridronate. By the date the questionnaire was administrated, 13% of women reported previous fractures (16.7% vertebral and 22% femoral fractures).

Figure 1 shows the percentage of causes for bisphosphonates discontinuation as reported in the

Table 1 Demographic and clinical data, specialties of the prescriber physicians and treatment duration

Women, *n* (%)	119
Age (years, mean ± SD)	72 ± 9.8
Age at menopause (years, mean ± SD)	47.9 ± 4.3
Age range at diagnosis (years, % of patients in any age range)	
40–50	11 (3.8%)
51–60	73 (25.6%)
61–70	27 (9.4%)
71–80	8 (2.8%)
> 80	0 (0%)
Fragility fracture (*n*, %)	
Vertebral	3 (1%)
Femur	5 (1.7%)
Humerus	0 (0%)
Wrist	3 (1%)
Other sites	9 (3.1%)
Concomitant therapy[a] ≤ 2, *n* (%)	50 (42%)
Patients who discontinued drug[b], *n* (%)	128 (45%)
Physicians who prescribed the drug:	
Orthopedic surgeon, *n* (%)	50 (42%)
Gynecologist, *n* (%)	22 (18%)
General practitioner, *n* (%)	17 (14%)
Rheumatologist, *n* (%)	9 (8%)
Physiatrist, *n* (%)	8 (7%)
Endocrinologist, *n* (%)	1 (1%)
Others, *n* (%)	12 (10%)
Treatment duration < 2 years, *n* (%)	60 (50%)
Treatment duration > 2 and ≤ 5 years, *n* (%)	27 (23%)
Treatment duration > 5 years, *n* (%)	32 (27%)

[a] Including drugs taken on a chronic basis (excluding bisphosphonates)

[b] At the time data were retrieved

questionnaire by the 119 patients who discontinued therapy; the results were compared to data from Rossini et al. reporting similar results in a cohort of patients referred to centers specialized in metabolic bone disease [9]. As shown, the most frequent reason for drug discontinuation was the indication by physician other than the one who prescribed therapy (49 patients, 40.6%), followed by lack of motivation (24 patients, 20%) and absence of BMD improvement (17 patients, 14%). Owing to the high prevalence of drug discontinuation by physicians other than the first prescriber, we then asked patients to specify the specialization of the physician who suggested to stop treatment. Results were as follows: orthopedic surgeon (17, 34.6% of cases), general practitioner (12, 24.5%), rheumatologist (8, 16.3%), gynecologist (3, 6%), others (3, 6%), physiatrist (3, 6%), and endocrinologist (3, 6%). Furthermore, it is important to highlight that among patients who discontinued therapy on the basis of another physician's advice, three (6.2%) have at least one vertebral or femur fracture.

Among patients who indicated "others" as reason for drug discontinuation, one patient specified that the dentist discontinued the medication.

Sixty out of 119 patients (50%) discontinued therapy within 2 years, 27 patients (23%) > 2 and ≤ 5 years and 32 (27%) after 5 years of treatment. Among those discontinuing therapy within 2 years, four (6.6%) have at least one vertebral or femur fragility fracture.

As far as treatment adherence, 87.5% of patients declared to have continuously taken the drug until discontinuation, while 12.5% took the medication irregularly.

Discussion

Adherence to osteoporosis treatment is currently one major clinical issue in the field of metabolic bone disease. There have been numerous reports of alarming reduction of both compliance and adherence to bisphosphonates, whose prescription also decreased, thus showing the widespread low awareness of the need to treat osteoporosis among patients and healthcare professionals [11]. Our study showed that more than half of the patients referred to general practitioners for osteoporosis care discontinued treatment before the usual time course suggested by many international guidelines and in a sizable proportion of cases after an irregular administration of therapy. These results are consistent with previous studies showing the high rate of early discontinuation of osteoporosis treatments in the last decade [9, 11]. As far as reason for discontinuation, many authors focused on patient safety concerns as the primary cause of decline in bisphosphonates use [11]. Publication of studies raising concerns on the potential risk of osteonecrosis of the jaw, atrial fibrillation, and atypical femur fractures in association with alendronate therapy in the years 2006–2010 encountered the interest of public opinion, as demonstrated by the spike in the Internet search terms for alendronate in the same period [11]. Accordingly, the media reports in the field have strongly influenced patient perception of osteoporosis therapy and consequent behavior [11, 12]. Data from Rossini et al. confirmed that the occurrence of side effects and worries about possible side effects are common reasons for drug discontinuation in patients referred to specialized centers [9]. In the USA, Jha et al. reported a decline in the prevalence of oral bisphosphonates use among women and men between 2008 and 2010, with higher prevalence among white women, the rural population, and in association with low education level, while no influence of age, gender, employment, or the presence of a primary care physician was observed [11].

Different results arise from our study; indeed, recommendation by physicians other than the initial prescriber was the main factor influencing bisphosphonate discontinuation.

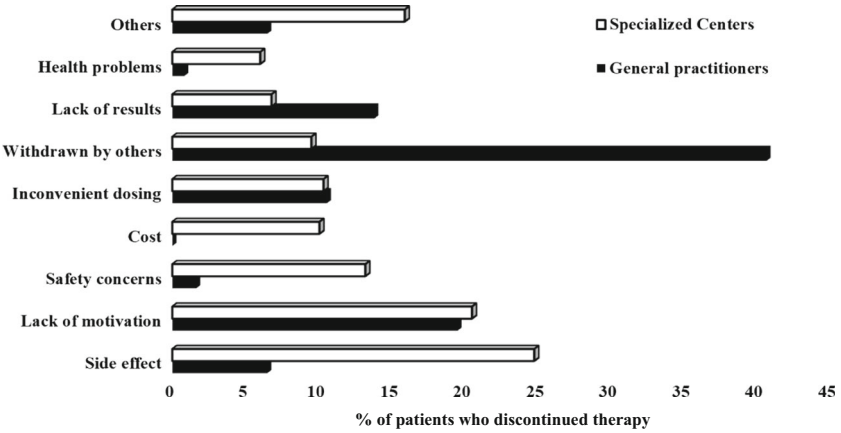

Fig. 1 Reasons for bisphosphonates discontinuation (%) as reported in the cohort of 119 patients referred to a primary care service and compared to data from Rossini et al. in patients referred to specialized centers [9]

Although performed a decade apart, comparison between data from our cohort and those from Rossini et al. raises the hypothesis that there is a difference in causes of non-adherence between patients referred to specialized centers vs those referred to primary care physicians in Italy. As it was beyond the scope of the study, we did not collect clinical and densitometric data that would have been useful to assess whether these findings could be related to a not appropriate indication for treatment, particularly in those women in which the treatment was stopped in the first 2 years. Notwithstanding, 13% of women discontinuing the drug-reported previous fragility fractures, and vertebral and femur fracture were reported in four out of 60 patients who discontinued therapy within 2 years. These data indicate that discontinuation was not motivated by the absence of indication for treatment in a relevant proportion of patients. The possibility of a not appropriate management of therapy is therefore the most likely and the main causes need to be defined. This point could be related to the lack of agreement and communication among physicians dealing with osteoporosis care. Also, the low level of awareness of osteoporosis and safety concerns about osteoporosis medications that were generated in the last years not only in the general population but also among the healthcare providers have a prominent role [12, 13]. The pervasive belief among a relevant proportion of physicians of a low efficacy of osteoporosis therapy, particularly compared to the risk of side effects has indeed a strong influence on patient adherence [13]. Also, we cannot exclude that a proportion of these patients have discontinued bisphosphonates for a drug holiday. Finally, communication between patients and physicians is a main determinant in osteoporosis care. A survey study by Copher et al. reported a 20.5% difference in physician perception of adherence vs. observed patient adherence to osteoporosis medication among 412 US physicians in the period 2002–2006 [14]. The primary involvement of physicians dealing with osteoporosis care has been therefore advocated by several proposed strategies to solve the problem of under-treatment of osteoporosis [13]. Application of such strategies has an enormous relevance also in consideration of the low level of patient motivation in continuing therapy reported in our study, as well as in studies in specialized centers [9].

Another aspect differing from studies in specialized centers is the very low proportion of patients in our cohort whose primary reason for discontinuation was the cost of the drug [9]. As osteoporosis medication reimbursement is regulated by the Italian Medicines Agency laws, the vast majority of patients in our cohort presumably satisfied criteria for reimbursement and prescriptions by the general practitioners were applied accordingly. The last point further corroborates the hypothesis that indication for treatment was met in the majority of patients.

Limitations of our study are related to the retrospective selection of the sample and single-center nature, as well as the lack of data on other antiresorptive drugs, calcium, and vitamin D. As the referral to the primary care physician in Italy is mostly made on a local basis, we could speculate that the population studied is representative of the specific area but cannot drive definitive conclusion for the general population. Additionally, data on the reasons for discontinuation are self-reported and recall biases cannot be totally excluded. Notwithstanding, this is, to our knowledge, the first report on the adherence to osteoporosis treatment in a cohort of patients referred to general practitioners. We considered that subjects who had no prescription in the 3 months after the last prescription have certainly stopped the treatment, even though we have no proof that patients who received prescription have taken the drug. Moreover, prescriptions can be provided also by specialists in Italy, but we reviewed the patients' records to exclude the possibility that they have been seen by specialized centers during the period of interest. Finally, when we contacted patients to administer the questionnaire, they have confirmed the time when therapy was discontinued.

The overall evidence suggests that patients referred to a primary service for osteoporosis care are usually appropriately prescribed with specific drugs, but the following management

is not adequate nor appropriate, as a high proportion discontinues treatment before clinical and densitometric effects can be appreciated. Differently to patients referred to specialized centers, that are more likely to gather information on osteoporosis medication and therefore presumably make autonomous choice, the role of physicians is crucial in influencing adherence in patients referred to primary care service, as demonstrated also by the low prevalence of patients who discontinued therapy because of own safety concerns. The high level of confidence of such a group of patients in physicians' advice represents a good point to start from in order to apply strategies aimed at ameliorating adherence of osteoporosis medications. All these strategies need to involve patients and physicians and are aimed at minding the treatment gap in osteoporosis care, as well as the gap between physician perception of patient adherence and actual patients' adherence to osteoporosis therapy [14]. Public campaigns involving media (journals, television, Internet) need to refer to patients and physicians, particularly those not specialized in metabolic bone disease, but frequently dealing with patients with osteoporosis.

In conclusion, our results demonstrate that there is a high rate of inappropriate bisphosphonate discontinuation among women with postmenopausal osteoporosis referred to a primary care service in Italy. Physicians need to face the issue of low adherence to bisphosphonate therapy primarily by their own involvement in the clinical management of osteoporosis patients and the role of the primary care services will be prominent in this context.

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Compliance with ethical standards

Conflict of interest SM served as speaker for Abiogen, Bruno Farmaceutici, Diasorin, Eli Lilly, Italfarmaco, Shire. He also served in the advisory board of Abiogen. He received consultancy from Bruno Farmaceutici. All other authors declare that they have no conflict of interest.

References

1. Wright NC, Saag KG, Dawson-Hughes B, Khosla S, Siris ES (2017) The impact of the new National Bone Health Alliance (NBHA) diagnostic criteria on the prevalence of osteoporosis in the USA. Osteoporos Int 28:1225–1232. https://doi.org/10.1007/s00198-016-3865-3
2. Cipriani C, Pepe J, Bertoldo F, et al (2018) Theepidemiology of osteoporosis in Italian postmenopausal women according to the National Bone HealthAlliance (NBHA) diagnostic criteria: a multicenter cohort study J Endocrinol Invest 41:431–438. https://doi.org/10.1007/s40618-017-0761-4
3. Romagnoli E, Carnevale V, Calandra P, D'Erasmo E, De Geronimo S, Pepe J, Manfredi G, Maranghi M, Aliberti G, Minisola S (2003) Impact of fractures on health care in a major university hospital in Rome. Aging Clin Exp Res 15:505–511
4. Strom O, Borgstrom F, Kanis JA, Compston J, Cooper C, McCloskey EV, Jonsson B (2011) Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 6:59–155
5. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jonsson B, Kanis JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8:136
6. Binkley N, Blank RD, Leslie WD, Lewiecki EM, Eisman JA, Bilezikian JP (2017) Osteoporosis in crisis: it's time to focus on fracture. J Bone Miner Res 32:1391–1394
7. Wysowski DK, Greene P (2013) Trends in osteoporosis treatment with oral and intravenous bisphosphonates in the United States, 2002-2012. Bone 57:423–428
8. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL (2009) Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med 122:S3–S13
9. Rossini M, Bianchi G, Di Munno O, Giannini S, Minisola S, Sinigaglia L, Adami S, Treatment of Osteoporosis in clinical Practice Study G (2006) Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int 17:914–921
10. Degli Esposti L, Sinigaglia L, Rossini M, Adami S, Cagnoni C, Magliaro C, Veronesi C, Buda S, Minisola S (2012) Adherence to therapeutic and diagnostic recommendations in patients with femur fracture and at risk of re-fracture or death: results of an analysis of administrative databases. Reumatismo 64:18–26
11. Jha S, Wang Z, Laucis N, Bhattacharyya T (2015) Trends in media reports, oral bisphosphonate prescriptions, and hip fractures 1996-2012: an ecological analysis. J Bone Miner Res 30:2179–2187
12. Cipriani C, Pepe J, Minisola S, Lewiecki EM (2018) Adverse effects of media reports on the treatment of osteoporosis. J Endocrinol Investig 41:1359–1364
13. Khosla S, Cauley JA, Compston J, Kiel DP, Rosen C, Saag KG, Shane E (2016) Addressing the crisis in the treatment of osteoporosis: a path forward. J Bone Miner Res. https://doi.org/10.1002/jbmr.3074
14. Copher R, Buzinec P, Zarotsky V, Kazis L, Iqbal SU, Macarios D (2010) Physician perception of patient adherence compared to patient adherence of osteoporosis medications from pharmacy claims. Curr Med Res Opin 26:777–785