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ORIGINAL RESEARCH

Persistence with weekly and monthly bisphosphonates among postmenopausal women: analysis of a US pharmacy claims administrative database

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Background: Bisphosphonates are available in daily, weekly, and monthly dosing formulations to treat postmenopausal osteoporosis. Some researchers suggested that adherence to monthly bisphosphonate might be different from that with weekly or daily bisphosphonate because of different dosing regimens. However, the actual persistency rates in regular practice settings are unknown.

Objectives: To compare persistence rates with alendronate 70 mg once weekly (AOW), risedronate 35 mg once weekly (ROW), and ibandronate 150 mg once monthly (IOM) in a US pharmacy claims database.

Methods: In this retrospective cohort study, pharmacy claims data of patients with new bisphosphonate prescriptions were extracted for women aged ≥ 50 years who had an AOW, ROW, or IOM prescription (index prescription) between December 30, 2004 and May 31, 2005 (the index period) and did not have the index Rx during the previous 12 months. Patients' records were reviewed for at least 5 months from their index date to November 2, 2005 (the follow-up period). Patients were considered persistent if they neither discontinued (failed to refill the index Rx within a 45-day period following the last supply day of the previous dispensing) nor switched (changed to another bisphosphonate) during the follow-up period. Medication-possession ratio was defined as days with index prescription supplies/total days of follow-up.

Results: Among 44,635 patients, 25,207 (56.5%) received prescriptions of AOW, 18,689 (41.9%) ROW, and 739 (1.7%) IOM as the index prescription. In all, 35.1% of AOW patients, 32.5% of ROW patients, and 30.4% of IOM patients ($P < 0.0001$ AOW vs ROW or IOM) had persisted with their initial therapy, whereas 64.0% of AOW, 66.4% of ROW, and 68.2% of IOM patients discontinued ($P < 0.0001$) during follow-up. The medication-possession ratio (days with index prescription supplies/total days of follow-up) was significantly higher for AOW (0.55) compared with ROW (0.52) and IOM (0.51, $P < 0.05$). By Kaplan–Meier analysis, the time for 50% of patients to discontinue therapy was also significantly longer with AOW (109 days) compared with ROW (95 days, $P < 0.05$) or IOM (58 days, $P < 0.05$).

Conclusion: In a real-world clinical setting, although persistence with all treatments was suboptimal, patients receiving prescriptions for once-weekly alendronate were more likely to be persistent than those receiving prescriptions for once-weekly risedronate or once-monthly ibandronate.

Keywords: adherence, alendronate, bisphosphonates, ibandronate, osteoporosis, risedronate

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Introduction

Osteoporosis is a chronic disease characterized by increased bone fragility and susceptibility to fracture. Western industrialized societies with increasing median ages are

on the verge of an osteoporosis pandemic.[1] Approximately 44 million Americans aged > 50 years have osteoporosis (10 million) or are at elevated risk (34 million).[2,3] Osteoporosis accounts for 1.5 million to 2 million fractures and $17 billion to $18 billion in direct health-care costs annually in the United States.[2,4,5]

Bisphosphonates are well-tolerated inhibitors of osteoclast-mediated bone resorption, which can significantly decrease bone turnover, increase bone density, and reduce fracture risk, and are considered therapeutic mainstays for postmenopausal osteoporosis.[6–12] Both alendronate and risedronate reduce risk of hip and spine fractures, while ibandronate has evidence of reducing spine fracture only.

Long-term adherence with bisphosphonates is instrumental in optimizing treatment outcomes but can be problematic, especially given the chronic nature of osteoporosis.[13] Of all medication-related hospitalizations, up to 69% are attributed to poor medication adherence, at an annual cost of approximately $100 billion, chiefly due to lost productivity and preventable hospitalizations.[13,14] By one estimate, ≥10% of all hospitalizations and nearly 25% of all nursing home admissions can be ascribed to poor medication adherence.[14] Up to 75% of patients with osteoporosis are nonadherent with their treatment regimens within 12 months.[15–21]

Suboptimal long-term adherence (ie, persistence) with osteoporosis therapies has adverse health consequences, and if persistence can be improved, many more postmenopausal women might experience reduced risks of fractures and other improved outcomes.[22–25] The Alendronate Phase III Osteoporosis Treatment Study determined that discontinuation of the bisphosphonate alendronate sodium over a 10-year period was associated with gradual loss of clinical effects on bone density and biochemical markers of bone remodeling.[26] Therefore, it is important to better appreciate factors associated with (or predictive of) bisphosphonate treatment persistence.

Bisphosphonates have been formulated for once-weekly (alendronate, risedronate sodium) and once-monthly (ibandronate sodium) administration. Prior studies have demonstrated that patients with osteoporosis prefer a treatment with documented efficacy in significantly reducing the risk of fractures of the hip, vertebrae, and other bones over a treatment with evidence of protecting against vertebral fractures only.[27] However, no study has been conducted to compare real-life persistence with once-weekly and once-monthly bisphosphonate regimens among patients with osteoporosis. The objective of the present analysis was to estimate and compare rates of persistence with alendronate once weekly (AOW), risedronate once weekly (ROW), or ibandronate once monthly (IOM) in a real-life setting according to US pharmacy claims data.

Methods

Data sources

Data were extracted from the Intelligent Health Repository (IHR) database of Wolters Kluwer (Amsterdam, Netherlands), formerly of NDCHealth (Atlanta, GA, USA). The IHR is one of the largest patient-level data repositories in the United States, including longitudinal prescription activity for approximately 157 million patients. This database contains pharmacy claims data adjudicated from 49,000 US retail pharmacies, including available transaction data from >500,000 prescribers using 42,500 pharmacies. The database contains claims from 40% of the nation's large hospitals (25% of total hospitals) and >100,000 physician offices, clinics, and other sites. Co-pay information from this database derives directly from adjudicated claims.

In the IHR database, prescription pharmacy claims data are linked to provide a vast source of longitudinal patient information linked to diagnosis, prescription, and hospital activity. Advanced methods of deidentification and record linkage are used to optimize the number of records that can be accurately linked to a unique patient, physician, hospital, or payer. Resulting data are validated against hundreds of health-care-specific business edits, duplicate record elimination, code standardization, and enhancements through the use of industry reference databases on drugs, physicians, facilities, health-care services, and geographies.

Study design

In this retrospective study, the IHR pharmacy claims administrative database was utilized to identify a cohort of patients to whom initial prescriptions of one of three prescription bisphosphonates were dispensed: 70 mg AOW, 35 mg ROW, or 150 mg IOM. Prescription records of women aged ≥ 50 years who had a prescription for AOW, ROW, or IOM filled during the period from December 30, 2004 to November 2, 2005 were eligible for review. Women who had had an AOW, ROW, or IOM prescription (ie, index prescription) filled between December 30, 2004 and May 31, 2005 (ie, index period) and had not received the index prescription during the prior 12 months were included. Patients with at least 5 months of enrollment history were included and followed for at least 5 months, from the index date to November 2, 2005 (ie, follow-up period).

Definitions of terms

Persistence with therapy was defined as the refilling of bisphosphonate prescriptions without discontinuing (failing to refill index prescription) within 45 days after the last supply day of the previous dispensing at any time during the follow-up period.

Discontinuation of treatment was defined as either "switching therapy" or "stopping therapy." Switching therapy was defined as dispensing an osteoporotic drug other than the index drug while not obtaining a refill of the index prescription within 45 days after the last supply day of the previous dispensing at any time during the follow-up period.

Stopping therapy was defined as failure to dispense any osteoporotic drug within 45 days after the last supply day of the previous dispensing at any time during the follow-up period. Duration of therapy was computed as the last date of dispensing before either discontinuation of the index treatment or study end point. Medication-possession ratio was computed by dividing the total number of days with index prescription supplies by the total number of days of follow-up.

Statistical analyses

Numbers and proportion of patients receiving prescriptions for each bisphosphonate regimen were computed. Proportions of patients who were persistent with or discontinued each treatment were compared by χ^2 tests. Analysis of variance and Duncan's multiple range test were conducted to compare the medication-possession ratio for AOW with data for ROW and IOM. All tests were two tailed at $\alpha = 0.05$. A Kaplan–Meier survival analysis[28] was conducted to estimate the time for 50% of patients to discontinue each index prescription. A Cox proportional hazards model controlling for age was used to compare the likelihood of discontinuation among treatment groups over the follow-up period.

Sensitivity analyses were performed to estimate the rate of persistence with a gap of 60 days (rather than 45 days) between refilling prescriptions. In these assessments, patients were considered persistent if they neither discontinued (failed to refill index prescription within 60 days of the date of previous dispensing) nor switched to another bisphosphonate during the follow-up period. In addition, separate analyses were performed for the large subgroup of patients (n = 40,514) who were new to osteoporosis therapy. These patients had not been given any prescription for the treatment of osteoporosis in the 12-month period prior to receiving the index prescription.

SAS software version 8 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

Results

A total of 44,635 patient claim records met selection criteria and were included for analysis: 25,207 (56.4%) prescriptions for AOW, 18,689 (41.9%) for ROW, and 739 (1.7%) for IOM as the index prescription. The distribution of patients by age range is shown in Table 1. Approximately one-third of participants were ≥75 years of age. Among 40,514 patients considered to be new to osteoporosis therapy, 23,383 (57.7%) were given AOW as their index prescription, 16,597 (41.0%) ROW, and 534 (1.3%) IOM.

By the end of follow-up, 35.1% of all AOW patients, 32.5% of ROW patients, and 30.4% of IOM patients had persisted with their initial therapies ($P < 0.001$ for comparison among three regimens; Table 2), whereas 64.0% of AOW, 66.4% of ROW, and 68.2% of IOM patients had discontinued their index treatment ($P < 0.0001$ for comparison among three regimens). In addition, 0.9% of all AOW patients, 1.1% of ROW patients, and 1.4% of IOM patients had switched to other bisphosphonates.

As shown in Figure 1, the medication-possession ratio among all patients was significantly higher for AOW (0.55) compared with ROW (0.52) and IOM (0.51, $P < 0.05$) regimens. By using the Kaplan–Meier method, the estimated time for 50% of patients to discontinue therapy was significantly longer ($P < 0.05$) with AOW (109 days) compared with ROW (95 days) or IOM (58 days) (Figure 2).

According to the Cox proportional hazards models controlling for age, the likelihood of discontinuing bisphosphonate regimens was significantly higher ($P < 0.0001$) for ROW (adjusted hazard ratio 1.10, 95% confidence interval [CI] 1.06–1.11) and IOM (adjusted hazard ratio 1.30, 95% CI 1.20–1.40) compared with AOW (Table 3). Findings were similar for patients who were new to osteoporosis therapy.

Similar trends were observed when the sensitivity analysis was carried out using a 60-day (rather than 45-day) gap for refilling prescriptions. The proportion of persistent patients was still significantly higher ($P < 0.05$) for patients who received AOW (39.8%) than for those who received ROW (37.6%) or IOM (34.8%).

Discussion

This is one of the first retrospective cohort analyses of a US pharmacy claims administrative database that compared compliance rate between weekly and monthly bisphosphonates.

The overall persistence rate with bisphosphonates was quite suboptimal, with >60% discontinuation rates for each medication. Because pharmacy claims data are indirect

Table 1 Age distribution by index prescription

Index prescription	Age, years						Total
	50–54	55–59	60–64	65–69	70–74	≥75	
n	4468	7165	6671	5612	5206	15,513	44,635
AOW, n (%)	2416 (9.6)	4035 (16.0)	3740 (14.8)	3136 (12.4)	2952 (11.7)	8928 (35.4)	25,207 (56.5)
ROW, n (%)	1978 (10.6)	3032 (16.2)	2820 (15.1)	2373 (12.7)	2157 (11.5)	6329 (33.9)	18,689 (41.9)
IOM, n (%)	74 (10.0)	98 (13.3)	111 (15.0)	103 (13.9)	97 (13.1)	256 (34.6)	739 (1.7)

Abbreviations: AOW, alendronate once weekly; ROW, risedronate once weekly; IOM, ibandronate once monthly.

indices of actual medication-taking behaviors, our observed persistence rates of <40% for all three bisphosphonates may underestimate actual persistence. The presence of a pharmacy claims record does not guarantee that patients actually took medications. However, such data have demonstrated favorable correlations with actual drug exposure.[17,29–31]

Our data showed that in the daily clinical practice setting, persistence with AOW among postmenopausal women was significantly higher than with ROW or IOM. In addition, patients receiving prescriptions for AOW had significantly higher medication possession ratios and longer time to discontinuation, which was approximately twofold longer (109 days) with AOW than for patients receiving IOM (58 days).

Our findings of significantly higher persistence with AOW compared with ROW or IOM are consistent with prior studies on patients' preference for osteoporosis therapies when full therapy profile, including efficacy, safety, and dosing, was provided to patients. However, findings from this study may contradict findings from another study that observed higher preference by patients for monthly bisphosphonate regimens over weekly bisphosphonates.[32] Our results probably reflected the dynamics in the regular practice setting, which might be different patterns of drug utilizations in the randomized controlled clinical trials.

In medical practice, therapeutic adherence is a complex, multifactorial process that can be influenced by a wide range of factors in addition to regimen frequency and simplicity. These considerations include objective patient factors, such as age, sex, presence or absence of incident nonvertebral fracture, and number of comorbid conditions; factors more related to processes of patient care, such as bone mineral density testing and the number of osteoporosis medications; and more subjective patient variables, such as treatment preferences[33–36] and perception of risk.[16,18,37–41] Other factors that can influence medication adherence relate to the physician, including sex, race, and age; physician treatment preferences; and the overall nature of the physician–patient alliance and communication,[14] including the congruence of patients' and physicians' preferences for patient involvement in decision-making.[42]

Therapeutic adherence could be the result of patients' preference. Perhaps predictably, in a recent randomized open-label crossover study showing a significant patient preference for IOM therapy compared with AOM, "ease of following a treatment regimen for a long time" was a leading reason cited by postmenopausal women with osteoporosis.[43] On the other hand, patients in other studies have cited effectiveness of medications in reducing fracture risk at multiple anatomic sites and medication tolerability and safety profiles as leading reasons for preferring certain osteoporosis treatments.[44–50] In a recent study, medication effectiveness emerged as the most highly ranked and rated of eight attributes in determining treatment preferences of women with (or at elevated risk of) osteoporosis.[27] Side effects and drug interactions were

Table 2 Treatment status at end of follow-up period among those in Table 1

Index prescription	Persisted	Discontinued	Switched
AOW, n (%)*	8837 (35.1)	16,132 (64.0)	238 (0.9)
ROW, n (%)*	6066 (32.5)	12,418 (66.4)	205 (1.1)
IOM, n (%)*	225 (30.4)	504 (68.2)	10 (1.4)

Note: *Significantly different among three groups, $P < 0.05$.
Abbreviations: AOW, alendronate once weekly; ROW, risedronate once weekly; IOM, ibandronate once monthly.

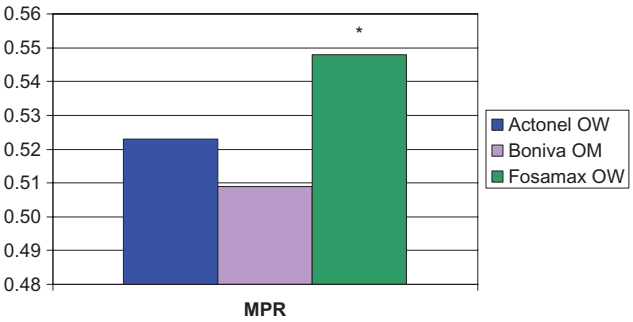

Figure 1 Medication-possession ratio (MPR, %) with alendronate 70 mg once weekly (AOW), risedronate 35 mg once weekly (ROW), and ibandronate 150 mg once monthly (IOM) in all patients.
Notes: MPR was computed as days with index prescription supplies/total days of follow-up. *$P < 0.05$ for comparison between AOW and ROW + IOM.

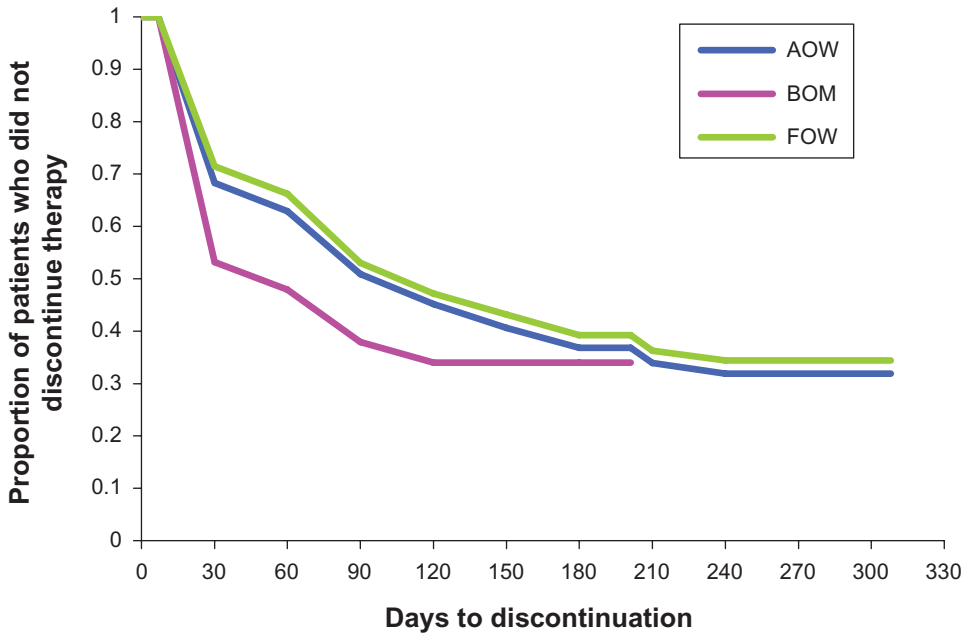

Figure 2 Kaplan–Meier curves for patients who discontinued therapy during the follow-up period.
Note: The time for 50% of patients to discontinue therapy was significantly longer with AOW than with either ROW or IOM.
Abbreviations: AOW, alendronate once weekly; BOM, boniva once monthly; FOW, fosamax once weekly; ROW, risedronate once weekly; IOM, ibandronate once monthly.

also highly ranked and rated, whereas dosing frequency, procedure, and formulation were considered much less important in determining osteoporosis-treatment preference. Similarly, effectiveness in preventing fractures, as well as tolerability and safety profiles, have emerged as leading reasons cited by physicians for prescribing osteoporosis medications.[51]

Patients' preferences for and adherence with osteoporosis treatments may be especially influenced by their individual perceptions of short- and long-term risk.[40,52] In a community focus-group study of women ages ≥ 60 (mean 74.8) years of diverse race/ethnicity, patients who preferred calcium supplementation cited this as a low-cost, low-risk alternative.[39] Patients indicating a preference for alendronate noted its greater protection against fractures and relative freedom from potentially serious adverse health effects such as thromboembolism compared with estrogen or raloxifene.[39] Such a benefit–risk analysis is consistent with Anderson's health-belief model, in which a patient's decision to take action depends largely on the perceived benefits and costs of the action, including perceived advantages and disadvantages of treatments.[53]

In addition to the aforementioned indirectness of pharmacy claims assessments as a means of quantifying actual medication-taking behaviors, the retrospective nature of our study did not allow us to control for treatment selection bias beyond the variables captured in the pharmacy claims database. A number of patient demographic and clinical factors, such as insurance status, number of medications, comorbidities, educational levels, and nursing home residency, that might influence medication adherence were not captured. Other aspects of the database may constitute study limitations. Pharmacy claims data may be susceptible to administrative (billing and coding) errors that might be less likely in a rigorous clinical trial.[17]

Our analysis also could not control for the imbalance in proportions of patients receiving each type of bisphosphonate prescription, particularly the fact that <2% of patients received prescriptions for IOM, which had been approved by US regulators relatively recently before the onset of the present study.

Table 3 Likelihood of bisphosphonate nonpersistence over time: proportional hazard model (all patients)*

Factor	Hazard ratio (95% confidence interval)
ROW index prescription†	1.10 (1.06–1.11)
IOM index prescription†	1.30 (1.20–1.40)
55–59 years of age‡	0.95 (0.90–0.99)
60–64 years of age‡	0.96 (0.92–1.01)
65–69 years of age‡	1.00 (0.99–1.09)
70–74 years of age‡	1.07 (1.02–1.12)
≥75 years of age‡	1.09 (1.05–1.13)

Notes: *Similar findings were observed in patients new to osteoporosis therapy; †$P < 0.0001$ vs AOW (alendronate 70 mg once weekly; reference); ‡age 50–54 years was the reference for age comparison.
Abbreviations: AOW, alendronate once weekly; ROW, risedronate once weekly; IOM, ibandronate once monthly.

Patients new to bisphosphonates may have lower medication adherence.[19,21] Further, a 45-day lapse in medication supplies may be somewhat less important for patients taking a longer-lived medication such as ibandronate compared with shorter-lived agents. On the other hand, it is reassuring that our findings from a sensitivity analysis using a longer (60-day) gap between dispensing were similar to the data observed using the 45-day gap. Finally, our findings cannot be generalized to other forms of osteoporosis treatment, distinct administration routes (eg, subcutaneous, intravenous[54,55]), or treatment of men with osteoporosis; 33% of all fractures occur in men, and morbidity and mortality following fracture are higher among men.[56,57] Measures such as disease-management programs, customized patient education, and patient outreach programs, eg, patient reminder services, will be able to improve patients' medication adherence and overall outcomes.

In conclusion, it is observed that in real-life treatment settings, postmenopausal women receiving prescriptions for AOW were significantly more likely to persist with their regimens than those receiving prescriptions for ROW or IOM. Further studies should be done with more patients who use monthly therapy, and therefore we would have sufficient sample size to control for the factors that could bias the association under study.

Overall, persistence with all three treatments was suboptimal. Efforts should be made to improve the compliance rate among osteoporotic patients. Studies have suggested that monitoring bone mineral density or other biomarkers (eg, serum carboxyterminal collagen cross-link markers) to monitor adherence to bisphosphonates before and after initiating osteoporosis treatment is one way to enhance osteoporosis treatment adherence.[16,18]

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