Bone Reports 4 (2016) 5–10

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Association between gastrointestinal events and compliance with osteoporosis therapy

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ARTICLE INFO

Article history:
Received 5 June 2015
Received in revised form 6 October 2015
Accepted 29 October 2015
Available online 30 October 2015

Keywords:
Compliance
Bisphosphonate
Gastrointestinal event
Medication possession ratio
Osteoporosis

ABSTRACT

Purpose: The aim of this study was to estimate the rate of gastrointestinal (GI) events, and association between GI events and compliance with osteoporosis therapy among osteoporotic women.
Methods: A retrospective cohort study using a large administrative claims database in the United States from 2001 through 2010 was conducted. We studied women ≥55 years old who were continuously enrolled in a health plan for at least 2 years, a baseline year before and a follow-up year after the date of the first prescription of oral bisphosphonate as the first oral osteoporosis treatment. Compliance with osteoporosis therapy was measured using the medication possession ratio (MPR), with compliance defined as MPR ≥0.8. Multivariate logistic regression was used to assess the association between occurrence of GI events and compliance with osteoporosis therapy after controlling for demographic and clinical characteristics.
Results: A sample consisting of 75,593 women taking at least one oral bisphosphonate with mean (SD) age of 64 (8) years was identified. A total of 21,142 (28%) patients experienced at least one GI event during the follow-up period. Only 31,306 (41%) patients were compliant with osteoporosis therapy. Patients who experienced GI events after initiation of oral bisphosphonates were 29% less likely to adhere to osteoporosis therapy as compared to patients who did not experience GI events (odds ratio [95% CI], 0.71 [0.69–0.74]; $P < .001$).
Conclusions: Less than half of the patients were compliant with osteoporosis therapy within one year after initiating oral bisphosphonates, and the likelihood of compliance was significantly lower by 29% among women with GI events.

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1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Primarily occurring in postmenopausal women as they age and to a lesser degree in older men, osteoporosis is typically a disease without symptoms until a fracture occurs (Siris et al., 2001), with resultant pain, decreased quality of life, acute and sometimes chronic disability, and, in the case of hip fracture, an increase in mortality (Dempster, 2011; Adachi et al., 2010). The substantial personal and societal burden of osteoporotic fracture is accompanied by a large and rising economic burden. In the United States (US) alone, the direct medical costs of osteoporotic fracture were estimated at $16.9 billion in 2005 and are projected to rise to $25.3 billion by 2025 (Burge et al., 2007).

An estimated 30% of women and 19% of men 50 years and older in the US are at elevated risk of osteoporotic fracture and are considered eligible for pharmacologic treatment (Dawson-Hughes et al., 2012). There are several available therapies with proven efficacy for reducing fracture risk in patients with osteoporosis. Among them, the oral bisphosphonates, including alendronate, risedronate, and ibandronate, are the most commonly used agents. However, suboptimal compliance with osteoporosis therapies is a common and well-recognized problem in the real world of clinical practice, outside of clinical trials (Cramer et al., 2007; Kothawala et al., 2007; Li et al., 2012); and poor compliance results in increased risk of fracture, higher medical costs, increases in hospitalizations, and wasted medications (Halpern et al., 2011; Sampalis et al., 2011; Ross et al., 2011; Hadji et al., 2012). Improving compliance with osteoporosis therapies is thus an important goal for both policy makers and clinicians.

In randomized controlled trials, oral bisphosphonates are generally well-tolerated, with upper gastrointestinal (GI) events and discontinuation rates similar to those of placebo (Bauer et al., 2000; Liberman, 2006). The occurrence of GI events among patients using oral bisphosphonates is common in real world clinical practice (Hamilton

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http://dx.doi.org/10.1016/j.bonr.2015.10.006
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et al., 2003; Woo et al., 2010; Penning-van Beest et al., 2008) and it is often difficult to determine whether GI events are related to the use of oral bisphosphonates, other medication (e.g., NSAIDs), or are due to another new or preexisting GI condition. However, the understanding of the association between occurrence of GI events and compliance with osteoporosis therapy among patients using oral bisphosphonates, particularly among a US managed care population, is limited.

The objective of this study was to estimate the rate of GI events and the association between GI events and compliance with osteoporosis therapy among osteoporotic women in a US managed care population.

2. Methods

2.1. Data source

A retrospective cohort study was conducted using the i3 Invision Datamart, a large administrative claims database covering 45 million patients from geographically diverse areas in the US. Longitudinal de-identified patient information in the database includes demographic characteristics and claims data for outpatient visits, hospitalizations, and prescriptions. Disease diagnoses and comorbidities are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (http://www.cdc.gov/nchs/icd/icd9cm.htm, n.d.); medications in pharmacy claims are identified using the National Drug Code Directory (NDC) (http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm, n.d.).

2.2. Sample selection

To be included in the sample, a patient had to be female, aged 55 years or older, and had to be prescribed at least one oral bisphosphonate including alendronate, risedronate or ibandronate anytime from January 1, 2001 to December 31, 2010. Index drug was defined as the first oral bisphosphonate prescribed for a patient as the first oral osteoporosis treatment and the index date was defined as the date of the initiation of the oral bisphosphonate from January 1, 2001 to December 31, 2010. A patient also had to be continuously enrolled in the health plan for at least one year before (base year) and one year after index date (follow-up year). Patients who had a diagnosis of Paget's disease of bone (osteitis deformans; ICD-9-CM code 731.0) at any time in the database were excluded from the study, as were patients with a diagnosis of malignant neoplasm (ICD-9-CM codes, 140.xx to 208.xx, 230.xx to 239.xx, or 172.xx) anytime during the 2-year study period (Orsini et al., 2005). Patients who took any oral osteoporosis therapy during one year prior to index date were excluded.

2.3. Study variables

Compliance with osteoporosis treatment after initiation of an oral bisphosphonate was the outcome of interest in this study. We defined compliance with therapy as a medication possession ratio (MPR) of ≥0.8 (Siris et al., 2009). The MPR was calculated as the number of days' supply of all osteoporosis therapies received in the follow-up year divided by 365 days (Peterson et al., 2007).

GI events were identified using ICD-9 diagnosis codes of dysphagia; esophagitis; esophageal ulcer, stricture, perforation, and hemorrhage; gastroesophageal reflux disease (GERD); gastric ulcer; duodenal ulcer; peptic ulcer; acute gastritis; duodenitis; GI hemorrhage; and nausea and vomiting (Appendix). The GI events during the follow-up period could be recurrent or new. Osteoporotic fractures at baseline were identified from primary and/or secondary diagnoses based on inpatient and outpatient service claims during baseline year. Osteoporotic fractures included hip, vertebral, and non-vertebral fractures, including those of the pelvis, humerus, forearm, other femoral sites, tibia and fibula, rib, clavicle, scapula, and sternum. Fractures not considered as osteoporotic fractures were those of the hand, skull, digits, feet, and ankle and any open fractures (Diez-Perez et al., 2012).

2.4. Statistical analyses

Descriptive statistics were used to summarize patient characteristics at baseline. We compared characteristics of patients who had a recorded GI event with those who had no GI event during the follow-up year, using the χ^2 test for binary and categorical variables and Wilcoxon rank sum test for continuous variables.

Multivariate logistic regression was used to examine the association between GI events and compliance (outcome variable) within the follow-up year. The key independent variable in the model was the occurrence of GI events after initiation of an oral bisphosphonate during the follow-up year (1 year). Covariates in the model included age at the index date, presence of any osteoporotic fractures at baseline, occurrence of GI events at baseline, concomitant medication use at baseline (gastroprotective agents, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and estrogen), and comorbidities (inflammatory bowel disease, celiac disease, diabetes, inflammatory joint disease, depression, hypertension, urination problems, chronic kidney disease, hyperparathyroidism, vitamin D deficiency, and fatigue). In addition to the individual comorbidities, we included the Deyo-Charlson comorbidity index (CCI) score, a measure that has been adapted for use with administrative databases (Deyo et al., 1992) and is used to account for comorbidities based on the presence of 19 predefined comorbid conditions, with higher CCI score denoting greater risk of death from comorbid disease (Charlson et al., 1987). Effects of the likelihood of compliance on all independent variables were quantified and reported in terms of odds ratios (ORs) with 95% confidence intervals (CIs). For a continuous independent variable (e.g., CCI), an OR <1.0 indicates a lower likelihood of treatment compliance associated with the independent variable. For a binary or categorical independent variable (e.g., age group), an OR <1.0 indicates a lower likelihood of treatment compliance in comparison with the reference group (i.e., 0 for a binary variable). *P*-values were evaluated using Wald's tests and were considered statistically significant at a 5% level.

Furthermore, two sets of sensitivity analyses were conducted. One set of sensitivity analyses assessed the regression-adjusted association between GI event and compliance within the first 3 and 6 months of the follow-up year; the other set of sensitivity analyses examined the association between GI events and compliance using MPR ≥0.6 as the compliance threshold, a less stringent definition than in the main analysis (MPR ≥0.8). All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

3. Results

We identified 75,593 women who received at least one oral bisphosphonate from 2001 to 2010 after meeting selection criteria (Fig. 1). Patient baseline characteristics and the rate of post-index GI events have been previously reported (Modi et al., 2015). Briefly, the mean (SD) age of eligible women was 64.4 (8.4) years, 20,073 (26.6%) patients experienced at least one baseline GI event and 4531 (6.0%) patients had a recorded baseline osteoporotic fracture. A total of 21,142 (28.0%) patients experienced one or more GI events during the 1-year follow-up. Patients who experienced a GI event during the baseline year had a higher rate of GI events during the follow-up year (51.2% vs. 19.6%) as compared with those who did not (data not shown).

The distribution of patients by both compliance status (MPR ≥0.8 or MPR ≥0.6) and the presence/absence of a GI event during follow-up is shown in Table 1. The proportion of patients with MPR ≥0.8 was lower among patients who experienced a GI event compared with patients who did not experience a GI event (34.1% vs 44.3%, $P < 0.001$). The same pattern of lower compliance among patients with GI events

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