Original Research

Relationship Between Gastrointestinal Events and Compliance With Osteoporosis Therapy: An Administrative Claims Analysis of the US Managed Care Population

Ankita Modi, PhD[1]; Shiva Sajjan, PhD[1,*]; E. Michael Lewiecki, MD, FACP, FACE[2]; Steven T. Harris, MD, FACP[3]; and Jessica Papadopoulos Weaver, MPH[1]

[1]*Center for Observational and Real-World Evidence, Merck & Co, Inc, Kenilworth, New Jersey;* [2]*New Mexico Clinical Research & Osteoporosis Center, Albuquerque, New Mexico; and* [3]*University of California, San Francisco Medical Center, San Francisco, California*

ABSTRACT

Purpose: A large proportion of women with osteoporosis do not comply with current osteoporosis therapies, resulting in diminished therapeutic effect. Noncompliance may be due to the occurrence of gastrointestinal (GI) events during the course of therapy. The objective of this study was to estimate the rate of GI events among women taking oral bisphosphonates and to determine the association between GI events and compliance with bisphosphonate therapy.

Methods: This was a retrospective analysis of data from a US Medicare claims database (HUMANA). The study period was from January 2007 to June 2013. The index date was the date of the first oral bisphosphonate prescription (alendronate, ibandronate, or risedronate) occurring between January 2008 and June 2012. The pre- and postindex periods were the 1-year periods before and after the index date, respectively. The analysis included women 65 years of age and older who were naïve to all osteoporosis treatments before the index date. GI events included nausea/vomiting; dysphagia; esophagitis; esophageal reflux; esophageal, gastric, duodenal, and peptic ulcer; stricture, perforation, or hemorrhage of the esophagus; acute gastritis; and GI hemorrhage. GI events were assessed during the preindex period and at 3, 6, and 12 months in the postindex period. Compliance was defined as a medication possession ratio of $\geq$80%. The medication possession ratio was calculated as the total days' supply of bisphosphonate in the postindex period divided by 365 days. The association of postindex GI events with compliance was assessed using multivariate logistic regression.

Findings: The analysis included 37,886 women initiating oral bisphosphonate therapy. In the preindex year, 37.5% of the women experienced a GI event, and in the postindex year, 38.9% had a GI event. Patients with preindex GI events had numerically higher rates of postindex GI events than patients without preindex GI events (61.8% vs 25.1% at 12 months postindex). Patients who experienced postindex GI events were less likely to be compliant with bisphosphonate therapy, with odds of compliance of 0.76 (95% CI, 0.72–0.80) after 12 months.

Implications: Among US women who were prescribed oral bisphosphonates, on-treatment GI events were associated with decreased compliance at 1 year. (*Clin Ther*. 2016;38:1074–1080) © 2016 Published by Elsevier HS Journals, Inc.

Key words: adherence, bisphosphonates, compliance, gastrointestinal diseases, persistence, postmenopausal osteoporosis.

INTRODUCTION

Bisphosphonates are the most commonly used pharmacologic agents for the treatment of osteoporosis in

Accepted for publication March 16, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.03.027
0149-2918/$ - see front matter

[*]Deceased.

the United States.[1,2] Compliance with oral bisphosphonates, defined as the mean medication possession ratio (MPR), ranges between 60% and 80%,[3] and the 1-year persistence rate with these drugs is generally <50%.[4] Poor adherence to bisphosphonate therapy, defined as both suboptimal MPRs and low rates of persistence, reduces their effectiveness at preventing osteoporotic fracture and is associated with higher medical costs and hospitalization rates.[5–7]

Discontinuation of bisphosphonate therapy, either intermittently or permanently, may be due to various reasons, one of which is concurrent gastrointestinal (GI) events.[8,9] However, the effect of concurrent GI events on compliance with oral bisphosphonate therapy has not been well characterized in US women with osteoporosis. This study was designed to assess the rate of GI events in US women new to oral bisphosphonate therapy and to quantify the association of those GI events with compliance.

METHODS

Data Source and Study Design

This observational study used data from HUMANA, a US administrative health claims database. The HUMANA database contains health care data gathered from medical and pharmacy claims by HUMANA, the largest publicly traded health benefits company in the United States. The medical claims include International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for all disease states. The pharmacy claims include prescription claims at the National Drug Code level. The most current database spans January 2007 to December 2013. Patient data are deidentified, so informed consent and institutional review board approval were not required for this study.

In this retrospective observational study, patients were identified in the HUMANA database between January 1, 2008 and June 30, 2012. The index date was defined as the date of the first oral bisphosphonate prescription during this period. The preindex and postindex periods were the 12 months before and after the index date, respectively. Patient demographic and clinical characteristics were assessed in the preindex period, and the association of GI events with persistence and compliance was assessed in the postindex period.

Study Sample

The analysis included women 65 years of age and older on the index date whose first-ever osteoporosis treatment was an oral bisphosphonate (alendronate, risedronate, or ibandronate) and who were continuously enrolled in their health plan for at least 1 year before and 1 year after the index date. Patients with a diagnosis of malignant neoplasm (ICD-9-CM code 140-171, 173-208, or 230-239) during the pre- or postindex periods or a diagnosis of Paget's disease (ICD-9-CM code 731.0) any time in the claims history were excluded from the analysis.

Definition of Variables

GI events were identified by ICD-9-CM and Current Procedural Terminology codes and included nausea/vomiting, dysphagia, esophagitis; gastroesophageal reflux disease; ulcer, stricture, perforation, or hemorrhage of the esophagus; gastric, duodenal, or peptic ulcers; acute gastritis; duodenitis; and GI hemorrhage. Likewise, osteoporotic fractures were identified by ICD-9-CM codes.

Compliance was defined by the MPR, which was calculated as the percentage of days within the postindex period that the patient had a supply of the index bisphosphonate (ie, % days' supply). Compliance was assessed at MPR levels of $\geq 80\%$ and $\geq 60\%$.

Statistical Analysis

Preindex patient characteristics (eg, age, prescription medication use [gastroprotective agents, glucocorticoids, nonsteroidal anti-inflammatory drugs, estrogen]; history of GI events, falls, and osteoporosis-related fractures; and comorbidities) were analyzed descriptively, as was the proportion of patients with GI events at 3, 6, and 12 months postindex. χ^2 and t tests were used to compare MPRs between patients with and without postindex GI events. The likelihood of compliance at an MPR $\geq 80\%$ at 12 months postindex was assessed using multivariate logistic regression analysis. The primary variable of interest was postindex GI events; additional variables used for adjustment of the model were preindex GI events, age, prescription medication use, fracture history, and Deyo-Charlson comorbidity index score.

RESULTS

Characteristics of the Study Population

A total of 37,886 women initiating oral bisphosphonate therapy were eligible for the analysis (Figure 1). The average age at the index date was 74.1 years