CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Adoption of Once-monthly Oral Bisphosphonates and the Impact on Adherence

Becky A. Briesacher, PhD, Susan E. Andrade, ScD, Leslie R. Harrold, MD, MPH, Hassan Fouayzi, MS, Robert A. Yood, MD

University of Massachusetts Medical School, Meyers Primary Care Institute, and Fallon Clinic, Worcester, Mass.

ABSTRACT

BACKGROUND: The extent of the adoption of once-monthly bisphosphonates into general clinical practice is not known, nor is it known if the novel formulation improves adherence.

METHODS: We analyzed administrative claims 2003-2006 from a large employer-based health insurance database for incident use of oral bisphosphonates and stratified users by daily, weekly, and monthly dosing regimen. We measured adherence as the medication possession ratio (MPR) during the first year of therapy. We compared patient characteristics by dosing regimen and evaluated how the dosing regimen influenced the MPR.

RESULTS: We identified 61,125 incident users of bisphosphonates (n = 1034 daily, n = 56,925 weekly, n = 3166 monthly). Monthly bisphosphonate users were, on average, slightly older than the other groups (mean age 66 years for monthly users vs 65 years for weekly users or 66 years for daily users, $P < .05$) and more often lived in the North Central or South United States (76% vs 72% weekly users or 69% daily users, $P < .05$). There were no detectable differences among the dosing groups in the history of serious gastrointestinal risk, comorbidity burden, or prior osteoporotic fractures. During the first year of bisphosphonate therapy, 49% of monthly users had MPR ≥ 80% compared with 49% of weekly users (not significant) or 23% of daily users ($P < .0001$).

CONCLUSION: We found little evidence of preferential prescribing of monthly bisphosphonates to certain types of patients. Furthermore, we found no evidence of improved bisphosphonate adherence with monthly dosing relative to weekly dosing, although adherence with either weekly or monthly dosing was significantly better than with daily dosing.

 • *The American Journal of Medicine (2010) 123, 275-280*

KEYWORDS: Bisphosphonates; Novel formulation; Patient compliance

In April 2005, the Food and Drug Administration approved the first once-monthly oral tablet for the treatment of a chronic disease. The once-monthly ibandronate sodium is a bisphosphonate, a class of drugs that inhibit bone resorption and are commonly prescribed for the treatment and prevention of osteoporosis in postmenopausal women.[1,2] The efficacy and safety of once-monthly bisphosphonates were demonstrated in a 1-year, double-blind study of postmenopausal women with osteoporosis whose treatment with 150 mg once-monthly ibandronate (n = 327) was shown to be noninferior to 2.5 mg daily ibandronate (n = 318) in increasing the bone mineral density in the lumbar spine.[3,4]

Previous to the monthly formulation, oral bisphosphonates were available in daily and weekly formulations, although the weekly formulation has dominated the market since its introduction in 2000. For instance, in a 2002-2003 observational cohort study, 84% of 211,319 patients were taking once-weekly bisphosphonates.[5] Once-weekly oral bisphosphonates have been associated with higher adherence over the once-daily formulations, although overall adherence has remained suboptimal in that drug class.[5-7] Between 52% and 87% of patients starting daily or weekly

Funding: This study was funded in part by an unrestricted research grant from Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Conflict of Interest: None of the authors have any conflicts of interest associated with the work presented in this manuscript.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Reprint requests should be addressed to Becky A. Briesacher, PhD, Assistant Professor, University of Massachusetts Medical School, Division of Geriatric Medicine, Biotech Four, Suite 315, 377 Plantation Street, Worcester, MA 01605.

E-mail address: Becky.Briesacher@umassmed.edu

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2009.05.017

oral bisphosphonates discontinue the therapy within 1 year or do not fill enough prescriptions to cover 80% of a year of therapy.[5,8]

The extent of the adoption of once-monthly bisphosphonates into general clinical practice is not known, nor is it known if the novel formulation improves adherence. Research finds consistently that reducing the dosing demands of medications increases medication adherence, although this relationship has not been tested with once-monthly formulations.[9] In addition, recent surveys report conflicting results on patient preferences for the once-monthly formulation over the weekly, which also might influence adherence.[10,11] Furthermore, it is unclear whether prescribers channel the once-monthly bisphosphonates to certain kinds of patients, such as those with gastrointestinal disorders. The adoption patterns of these medications and the impact of a once-monthly dosing schedule on adherence is especially important because once-monthly bisphosphonate costs approximately 40% to 60% more than the generic forms of the daily and weekly oral bisphosphonates, which have been available since early 2008. The objectives of this study were to assess whether once-monthly bisphosphonates are preferentially channeled to certain patients and whether the monthly dosing schedule is associated with improvements in adherence.

CLINICAL SIGNIFICANCE

- Low adherence occurs with all oral dosing formulations of bisphosphonates (daily, weekly, and monthly).
- Merely reducing the dosing frequency of oral bisphosphonates will not improve adherence, although the worst adherence is associated with daily dosing.
- Clinicians need to reinforce the importance of adherence when starting a patient on bisphosphonates, irrespective of the dosing formulation.

MATERIALS AND METHODS

Study Population and Data Sources

This study used the 2001-2006 MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (Medstat: Ann Arbor, MI). This database contains more than 500 million claim records per year from individuals with private health care insurance. Scientific studies based on this data source have been reported in more than 75 peer-reviewed articles.[12] The data come from approximately 45 large employers who self-insure their employees and dependents. The MarketScan database offers advantages over raw administrative claims because data files undergo validity and editing procedures to ensure high-quality and consistency in fields across years.[13] The data are evaluated against population norms, previous year summaries, and validated data subsets. Outliers are flagged and reviewed for coding or processing errors. Encounter data are audited at the health plan level, and plans submitting incomplete data are excluded. Diagnostic and procedural codes are compared against validity algorithms and set to missing values if inconsistent. The encounter files contain age, sex, geographic residence, and eligibility information. The prescription claims include the national drug codes, date of purchase, quantity, days' supply, and expenditure information. The medical claims contain payment information, diagnoses, procedure codes, and type of provider. For this analysis, we pooled annual files to create a dataset of approximately 15 million people.

The study sample included individuals who were aged 50 years or older, had an osteoporosis diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification 733.xx), an incident dispensing of an oral bisphosphonate (ibandronate, alendronate, or risedronate), and least 2 years of observation. Incident use was defined as no bisphosphonate therapy for at least 12 months before initiating therapy. Individuals were excluded if they had Paget's disease (731.0) (n = 242), received transplantations (n = 321), or received an oral solution of bisphosphonates (n = 1210). The institutional review board of the University of Massachusetts Medical School approved this research.

Measures

The main study variable was dosing schedule. We calculated the dosing schedule as the day's supply divided by the metric quantity for each dispensing of the study drugs. Preliminary analyses showed evidence of prescribing outside of dosing guidelines, which made assignment by only tablet strength unreliable. We identified the modal value for each unique generic study drug dispensed to each individual, manually checked outliers for error (<0.5% of patients), and assigned individuals into mutually exclusive dosing schedules based on set thresholds. For instance, if an individual's modal dosing schedule of alendronate dispensed during the year fell within the range of 1/2 to 2 tablets daily, then that individual was assigned to a daily dosing schedule. Individuals receiving more than 1 assignment were categorized by the earliest assignment (eg, switching from weekly to monthly dosing), and all subsequent bisphosphonate use was summed into 1 medication possession ratio (MPR) value.

The dependent variable was adherence measured as MPR. We estimated the MPR as the sum of the day's supply of study medication dispensed during the year divided by the number of days in the year. Overlaps in the dispensing days of different generic drug therapies were eliminated, under the assumption that leftover supplies from earlier refills were discarded to begin the newer medication (eg, a change in therapy). The value of the day's supply was truncated if the supply extended beyond the time period of