Bone Reports 5 (2016) 208–213

Contents lists available at ScienceDirect

Bone Reports

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

Association of gastrointestinal events with osteoporosis treatment initiation and treatment compliance in Germany: An observational study

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ARTICLE INFO

Article history:
Received 17 December 2015
Received in revised form 29 April 2016
Accepted 6 June 2016
Available online 07 June 2016

Keywords:
Osteoporosis
Postmenopausal
Bisphosphonates
Germany
Gastrointestinal diseases
Patient compliance
Medication adherence

ABSTRACT

Background: Gastrointestinal (GI) events are common in postmenopausal women treated for osteoporosis. The influence of GI events on treatment initiation and treatment compliance is the subject of ongoing research.
Objective: The objectives of this study were (i) to determine the association of GI events with receipt of treatment in patients newly diagnosed with osteoporosis, and (ii) among treated patients, to determine the association of GI events with treatment compliance.
Methods: This was a retrospective analysis of claims data carried out in Germany using the Mediplus database. Data were collected from January 1992 through December 2010. The dual-objective study design required two distinct cohorts. Cohort 1 comprised women aged ≥55 with a diagnosis of osteoporosis. GI events were recorded for the 12 month periods before and after the date of diagnosis. Time-varying Cox regression and discrete choice models were used, respectively, to assess the association of post-diagnosis GI events with the initiation of pharmacologic treatment (yes versus no) and the type of treatment initiated (bisphosphonates versus non-bisphosphonates). Cohort 2 comprised women aged ≥55 who initiated an oral bisphosphonate (alendronate, ibandronate, or risedronate). GI events were recorded for the 12 month periods before and after the date of bisphosphonate initiation, and a logistic regression model was employed to determine if pre-treatment or post-treatment GI events were associated with patient compliance, defined as a medication possession ratio (MPR) of ≥60%, with sensitivity analyses at MPR ≥ 80%.
Results: In cohort 1 (N = 18,813), 13.8% of patients had GI events in the pre-diagnosis period, and 14.8% had GI events in the post-diagnosis period. Among the patients with post-diagnosis GI events, 93.2% remained untreated during the post-index year, 6.2% were treated with bisphosphonates, and 0.6% received non-bisphosphonates. The respective percentages in patients without post-diagnosis GI events were 81.3%, 16.7%, and 1.9%. A post-diagnosis GI event decreased the likelihood of receiving any osteoporosis treatment (versus no treatment) by 83% (HR 0.17, 95% CI 0.14–0.20) and also decreased the likelihood of receiving a bisphosphonate (versus a non-bisphosphonate) by 39% (OR 0.61, 95% CI 0.54–0.68). In cohort 2 (N = 6040), 17.1% of patients had GI events in the year before treatment initiation, and 19.1% had GI events in the year after treatment initiation. At 12 months post-treatment initiation, GI events were more frequent in patients with pre-treatment GI events (53.2%) than in those without pre-treatment GI events (12.0%). Post-treatment GI events decreased the likelihood of attaining compliance defined as an MPR ≥ 60% (OR 0.84, 95% CI 0.73–0.97) but not an MPR ≥ 80% (OR 0.91, 95% CI 0.79–1.06).
Conclusions: In German women newly diagnosed with osteoporosis, GI events decreased the likelihood of receiving treatment and were associated with the choice of treatment. In women initiating oral bisphosphonates, post-treatment GI events were associated with reduced patient compliance.

1. Introduction

Osteoporosis is present in an estimated 25% of women aged ≥50 in Germany (Gauthier et al., 2012). Findings from a national analysis of medical claims indicated that, among German patients being treated pharmacologically for osteoporosis, approximately half were prescribed oral bisphosphonates (Haussler et al., 2007).

Abbreviations: CCI, Deyo-Charlson comorbidity index; GI, gastrointestinal; ICD, International Classification of Diseases; MPR, medication possession ratio; NSAID, non-steroidal anti-inflammatory drug.

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http://dx.doi.org/10.1016/j.bonr.2016.06.001

Gastrointestinal (GI) symptoms (e.g., heartburn, reflux, nausea, vomiting) have been observed in up to 52% of German users of bisphosphonates (primarily women over age 45) (Ringe and Moller, 2009; Bauer et al., 2012), but GI symptoms are common among postmenopausal women (Freemantle et al., 2010; Infantino, 2008), making it difficult to ascribe such symptoms to bisphosphonate use. Indeed, observational case-control studies have demonstrated that there is no significant relationship between bisphosphonate use and upper GI complications (Etminan et al., 2009; Vestergaard et al., 2010; Ghirardi et al., 2014). Nevertheless, GI adverse events (or the use of gastroprotective agents) have often been found to be associated with lower rates of compliance with osteoporosis therapy (Rossini et al., 2006; Penning-van Beest et al., 2008; Gallagher et al., 2008), and GI problems may affect the decision to treat osteoporosis (Colon-Emeric et al., 2007).

The impact of GI events on treatment decisions and patient compliance has not been studied in Germany. The objectives of this study were therefore (i) to determine whether GI events were associated with the decision to treat and the choice of treatment in female osteoporosis patients in Germany, and (ii) among treated patients, to estimate the association of GI events with compliance while on treatment.

2. Materials and methods

2.1. Data source and study design

Data for this analysis were abstracted from the Mediplus database of Germany, a longitudinal physician-based database containing demographic, medical, pharmaceutical, and lab test results for patients. The database is representative of the German population with regard to the regional distribution of physicians, prescriptions, and diagnostic groups of patients.

Each objective required a distinct patient cohort and study design based on distinct index events. For objective 1, the index event was a diagnosis of osteoporosis, and subjects identified with this index event were defined as cohort 1. In this cohort, we observed GI events in the post-index period up until treatment initiation, for a maximum time of 12 months, and assessed the association of post-index GI events with the odds of treatment initiation and choice of treatment. For objective 2, the index event was the initiation of an oral bisphosphonate, and subjects identified with this event were defined as cohort 2. For this cohort, we estimated the proportion of patients with GI events at 3, 6, and 12 months following the index date and assessed the association of post-index GI events with patient compliance as of the 12-month time point.

2.2. Study samples and variables

All subjects in the analysis were women aged ≥55 years on the index date. Women who were diagnosed with a malignant neoplasm (International Classification of Diseases [ICD]-10 codes C00-C42, C44-C96, D00-D09, and D37-D49) or Paget's disease (ICD-10 code M88) were excluded from this study.

In cohort 1, women were selected who: received a diagnosis of osteoporosis on an index date between January 1, 1993 and December 31, 2009; were naïve to osteoporosis medication any time prior to the index date and to estrogen for one year prior to the index date; and had ≥12 months of continuous eligibility before and after the index date. An osteoporosis diagnosis was defined by the presence of an ICD-10 code of M80 (osteoporosis with current pathological fracture) or M81 (osteoporosis without current pathological fracture). Osteoporosis medications were defined as either bisphosphonates or non-bisphosphonates and were identified in the data registry by their Anatomical Therapeutic Chemical codes. The bisphosphonates were alendronate, ibandronate, risedronate, and zoledronate, and the non-bisphosphonates were calcitonin, raloxifene, strontium ranelate, and teriparatide/parathyroid hormone. Both oral and injectable forms of all drugs were considered. GI events were identified by ICD-10 codes (see Supplementary Table S1) 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. Pre-diagnosis GI events were assessed in the 1-year pre-index period. Post-diagnosis GI events were assessed from the index date until treatment initiation or the end of follow-up, whichever came first.

In cohort 2, women were selected who initiated a single oral bisphosphonate on an index date within the period 1996–2009, had ≥12 months of continuous eligibility before and after the index date, and were naïve to all osteoporosis medications in the year before the index prescription. Oral bisphosphonates of interest were alendronate, ibandronate, and risedronate, and GI events were the same as those listed for cohort 1. Compliance was defined as a medication possession ratio (MPR; the percentage of days in the post-index period on which patients were in possession of the prescribed medication) of ≥60%, with sensitivity analyses at MPR ≥ 80%.

2.3. Statistical analysis

Demographic and clinical characteristics (e.g., age; pre-index medication use (non-steroidal anti-inflammatory drugs [NSAIDs], gastroprotective agents, and glucocorticoids), fractures, and GI events; comorbidity profiles) were analyzed descriptively and are presented as numbers and percentages or means and standard deviations, as appropriate.

For cohort 1, the distribution of receipt of treatment and type of treatment was compared across the subgroups with and without GI events using a chi-square test. When quantifying the association of post-diagnosis GI events with treatment, a two-stage analysis accounted for the varying exposure time between the osteoporosis diagnosis and treatment initiation. In the first stage, a time-dependent Cox regression model was used to estimate the odds of receiving any treatment versus no treatment. In this model, patients were stratified according to the presence or absence of pre-diagnosis GI events. In the second stage, a discrete choice model with a conditional logit was used to estimate the odds of receiving bisphosphonates versus non-bisphosphonates. For both models, the independent variables included post-diagnosis GI events, age group, Deyo-Charlson comorbidity index (CCI) score, common comorbidities, and pre-diagnosis medication use. In the second model, pre-diagnosis GI events were added to the list of independent variables.

In cohort 2, the frequency of post-treatment GI events in patients with and without pre-treatment GI events was compared descriptively at 3, 6, and 12 months post-index. Logistic regression was used to estimate the odds of medication compliance. Independent variables included in this model were pre-treatment and post-treatment GI events, age group, pre-treatment medication use, pre-treatment osteoporosis-related fractures, and CCI score.

3. Results

3.1. Association of GI events with treatment for osteoporosis

A total of 18,813 women diagnosed with osteoporosis were included in cohort 1 (Table 1). The average age in this cohort was 71.4 years. During the pre-diagnosis period, 35.3% of the patients used NSAIDs and 16.9% used glucocorticoids, 18.1% used gastroprotective agents, and 13.8% experienced a GI event. The mean (SD) CCI score was 0.79 (1.11), and the most common comorbidity was hypertension (42.8%).

Among patients diagnosed with osteoporosis, 3181 (16.9%) received pharmacotherapy in the year following the diagnosis (Table 2). Bisphosphonates were prescribed to 89.8% of treated patients and non-bisphosphonates to 10.2%. Alendronate was the most frequently