Journal of Clinical Gerontology & Geriatrics 6 (2015) 54–58

Contents lists available at ScienceDirect

Journal of Clinical Gerontology & Geriatrics

journal homepage: www.e-jcgg.com

Original article

Prolonged risk of subtrochanteric and diaphyseal femur fractures after discontinuing alendronate treatment: A nationwide nested case-control study in Taiwan

Weng-Foung Huang, PhD [a, b], Li-Chuang Chang, MS [a], Yu-Hsiang Kao, MS [a], Yu-Wen Wen, PhD [c], Fei-Yuan Hsiao, PhD [d, e, f], Li-Ning Peng, MD [b, g], Yi-Wen Tsai, PhD [a, b, **], Liang-Kung Chen, MD, PhD [a, b, g, *]

[a] Institute of Health Welfare and Policy, Taipei, Taiwan
[b] Aging and Health Research Center, National Yang Ming University, Taipei, Taiwan
[c] Clinical Informatics and Medical Statistics Research Center, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[d] Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
[e] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
[f] Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan
[g] Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 7 September 2014
Accepted 20 September 2014
Available online 27 November 2014

Keywords:
alendronate
bisphosphonate
osteoporosis
subtrochanteric femoral fracture

ABSTRACT

Background: The aim of this study is to evaluate the risk of subtrochanteric and diaphyseal femur fractures and the persistence of this risk after discontinuation among elderly alendronate users in Taiwan.
Methods: This is a population-based, nested case–control study collecting data from the Taiwan's National Health Insurance. The study population consisted of patients aged 65 years or older who were first diagnosed with osteoporosis between 2001 and 2008. Cases of subtrochanteric femoral fractures were defined as such if these individuals were hospitalized with a primary diagnosis of subtrochanteric or diaphyseal femur fractures during the study period. Based on risk-set control sampling, 10 matched controls for each case by age, sex, cohort entry year, and the comorbidities of stroke, diabetes mellitus, and osteoarthritis were obtained.
Results: A total of 2859 patients (mean age, 76.0 ± 6.7 years; 82% females) with subtrochanteric femoral fractures were identified. Cases were more likely to use antiosteoporosis drugs, and they tend to use alendronate longer (mean, 236 days vs. 215 days), with higher defined daily dose (243.28 vs. 219.95) than controls. Use of alendronate significantly increased the risk for subtrochanteric femoral fractures: 0–3 years of follow-up [adjusted odds ratio (OR), 1.74; 95% confidence interval (CI), 1.47–2.06], 3–5 years of follow-up (adjusted OR, 1.74; 95% CI, 1.35–2.24), and >5 years of follow-up (adjusted OR, 1.50; 95% CI, 1.09–2.07). Use of alendronate for >1 year significantly increased the risk of subtrochanteric femoral fractures (adjusted OR, 1.64; 95% CI, 1.44–1.87); such association persisted longer than expected (3–5 years of follow-up: adjusted OR, 1.67; 95% CI, 1.27–2.19; >5 years: adjusted OR, 1.50; 95% CI, 1.07–2.11).
Conclusion: Discontinuation of alendronate therapy did not reduce the risk of subtrochanteric femoral fractures until it was discontinued for >5 years. In conclusion, alendronate use significantly increased the risk of subtrochanteric femoral fractures, and the risk may persist for 5 years after discontinuation.

1. Introduction

Bisphosphonates (BPs) have been extensively used for the treatment of osteoporosis and prevention of osteoporotic fractures over the past 2 decades.[1–4] Alendronate, the first BP to be approved, also significantly increases bone mineral density and reduces the risk of osteoporotic fractures.[1,3–5] However, a case study published in 2005 suggested a possible link between prolonged use of BPs and

* Corresponding author. Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Number 201, Section 2, Shih-Pai Road, Taipei, Taiwan.
** Corresponding author. Institute of Health Welfare and Policy, National Yang Ming University, Number 155, Section 2, Li-Nong Street, Taipei, Taiwan.
E-mail addresses: ywtsai@ym.edu.tw (Y.-W. Tsai), lkchen2@vghtpe.gov.tw (L.-K. Chen).

http://dx.doi.org/10.1016/j.jcgg.2014.09.002

atypical femoral fractures (located in the subtrochanteric region or the proximal femoral diaphysis); this report has drawn widespread attention to BP use. Most of the previous cohort studies[7–10] or *post hoc* clinical trials[11] reported no association between BP use and atypical femoral fractures. However, results of those studies were obtained without radiographic confirmation of atypical femoral fractures. One case–control study, which included age- and sex-matched participants, examined BP use in 63 patients who have atypical femoral fractures with typical hip fractures. The study found no significant risks of atypical femoral fractures associated with BP use.[12] By contrast, another case–control study showed a strong association between BP use and atypical femoral fractures by comparing the individual radiographs of 41 patients with atypical femoral fractures with those of intertrochanteric fractures from 82 age-, sex-, and body mass index-matched controls.[6] The other recent case–control study of a large Canadian cohort of 205,466 women aged 68 years or older, matched 716 cases with five controls and reported a slight association between treatment with use of BPs for >5 years and increased the risk of atypical femoral fractures.[13] Lastly, a recent population-based case–control study has reported a significantly higher dose-dependent relationship between BP exposure and atypical femoral fractures.[14]

To summarize the above-mentioned lines of evidence, most case–control studies with radiographic confirmation that was not universally observed by large-scale database-based studies, supported the connection between BP use and subtrochanteric femoral fractures. The inconsistent findings of these observational studies and case reports have left clinicians and patients uncertain about the safety of prescribing BPs. Moreover, because of the long half-life of alendronate, the risk may persist longer than expected, which also deserves further studies for clarification. Therefore, the main purpose of this study is to clarify the risk of subtrochanteric femoral fractures among BP users and how long this risk persists after withdrawal of alendronate.

2. Materials and methods

2.1. Data source and study design

This is a population-based, nested case–control study using the Taiwan's National Health Insurance Research database, a nationwide database comprising anonymous enrollment information and all insurance claims for visits, procedures, and medication prescriptions for >99% of Taiwan's entire population (nearly 23 million). Inaugurated in 1996, Taiwan's National Health Insurance (NHI) program is a mandatory social insurance program providing Taiwan's residents with universal coverage for most medical care services. For each outpatient visit or hospitalization, NHI collects the date of visit, admission, and discharge on the patient's claims record. Each claims record also contains up to five diagnoses coded by physicians according to the *International Classification of Disease, 9th Edition* (ICD-9 CM codes) and all medical service items, such as medication, examinations, test, and rehabilitation, are claimed by health care providers. Most of Taiwan's residents were enrolled in 1996 or at the time of their birth and remained insured for life. This social health insurance program, therefore, maintains longitudinal follow-up information for each person. The database, which has been described in detail elsewhere,[12] is routinely reviewed by the Bureau of NHI of Taiwan to ensure its completeness and accuracy[13] and has been the source for numerous epidemiological studies published in peer-reviewed journals.

2.2. Study cohort

The study cohort consisted of patients aged 65 years or older who were first diagnosed to have osteoporosis between January 1, 2001 and December 31, 2008. These patients might have received any of the BPs, selective estrogen-receptor modulator (raloxifene), hormone replacement therapy, calcitonin, or were not pharmacologically treated. Cohort entry date was defined as the date of first-time diagnosis of osteoporosis during the study period, based on 1-year washout criteria. Patients were excluded if they had been hospitalized for any form of cancer 1 year prior to the entry date.

2.3. Cases with subtrochanteric femoral fractures and their controls

Cases of subtrochanteric femoral fractures in this osteoporotic cohort were defined as having subtrochanteric fractures if they had been hospitalized at least once with a primary diagnosis of subtrochanteric fracture of the femur (ICD-9-CM code: 820.22 fracture of subtrochanteric section of femur closed) or fracture of other and unspecified parts of the femur (ICD-9-CM code: 821) during the study period. The index date of incidence was defined as the date of first hospitalization for subtrochanteric femoral fractures during the study period. Based on risk-set control sampling, we randomly matched 10 controls for each subtrochanteric femoral fracture case by age, sex, cohort entry year, and the comorbidities of stroke, diabetes mellitus, and osteoarthritis. The controls were assigned an index date for outcome observation identical to the date when the matched case was first hospitalized for subtrochanteric femoral fractures during the study period.

2.4. Alendronate exposure

We examined the association between the use of alendronate and the incidence of subtrochanteric femoral fractures. Use of alendronate was analyzed in relation to the index date of subtrochanteric femoral fractures, and use of alendronate before subtrochanteric femoral fractures was categorized by the time from last use (1 month, 1–6 months, from 6 months to 1 year, or >1 year). The total duration of alendronate use was first calculated as defined daily dose (DDD) prescribed during the cohort entry date and index date of outcome and also the total medication days during the observation period. The duration of each prescription was determined by the “days of supply” field of the prescriptions shown on the NHI claims records for each patient. Duration of usage was calculated as cumulative days of total alendronate prescriptions (<6 months, from 6 months to 1 year, and >1 year).

2.5. Statistical analyses

We first explored the relationship between alendronate and subtrochanteric femoral fractures by examining the association between alendronate use and hospitalizations for subtrochanteric femoral fractures. To explore the potential dose effect, we compared patients with subtrochanteric femoral fractures who had taken alendronate for <1 year with those who had taken it for >1 year. Among alendronate users, we also examined the potential risk reduction after discontinuation of alendronate by classifying its use according to the time since last use: 1 month, 1–6 months, from 6 months to 1 year, and >1 year. Because of the nature of matching in case–control studies, not every matched case–control pair had used alendronate for the same exact length of time. We repeated all above-mentioned analyses on subpatient groups stratified by their follow-up period (0–3 years, 3–5 years, and >5 years) instead of prescription duration (Fig. 1).[13]

Because this study had a 1-to-10 matching design, we used conditional logistic regressions to control the correlation within the matched sample. Then, we estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between use of alendronate and subtrochanteric fractures among all patients and