Bisphosphonate Treatment Beyond 5 Years and Hip Fracture Risk in Older Women

Background: There have been many clinical trials to show the efficacy of bisphosphonates during the first 3-5 years of treatment. However, duration of appropriate treatment is uncertain.

In late September 2015, the American Society Bone and Mineral Research recommended a drug holiday from bisphosphonates for women who are not of high fracture risk (those without prior fractures and high bone mineral density). However, this recommendation was made based on evidence from multiple trials that focused on prevention of symptomatic vertebral fractures. Another study completed by the Women's Health Initiative of 2017 found that treatment with bisphosphonates beyond 5 years was associated with increased risk of hip fractures. These types of fractures tend to be atypical and difficult to correct.

What They Did: The aim of this study was to examine the association of bisphosphonate exposure for 5 years, 7 years, or 10 years and the risk of hip fracture in older women. In this retrospective study, investigators used data from Kaiser Permanente Northern (KPNC) and Southern California (KPSC). The investigators identified women who initiated oral bisphosphonate therapy with alendronate, risedronate, or ibandronate from January 1, 1997 to September 30, 2009 (n=29,685). Follow-up was conducted from 2002-2014. The index date was considered as the date study follow up began (after 5 years of bisphosphonate therapy). The investigators divided patients into 3 cohorts: cohort 1 discontinued therapy at study entry (5 years of exposure), cohort 2 discontinued therapy after 2 additional years (7 years of exposure), and cohort 3 discontinued therapy after 5 additional years (10 years of exposure). Cohorts 1 and 2 were analyzed with and without a 6-month grace period for discontinuation. Participants were followed from their index date until their earliest occurrence of a hip fracture, death, an exclusionary event (open fractures or fractures associated with trauma), end of plan membership, or study end.

Inclusion Criteria:

- Women, aged 45-80 at bisphosphonate initiation
- Had health plan membership 2 years prior
- Adherence to bisphosphonate therapy of at least 60% in each year after initiation for 5 years
- Received bisphosphonate treatment within 60 days of the index date

Exclusion Criteria:

- Previously received IV bisphosphonate or etidronate
- Received denosumab, teriparatide, raloxifene or estrogen in the 2 years prior to the index date
- Advanced (stage 4 or 5) or end-stage kidney disease
- Diagnosed with a metabolic bone condition (Paget disease, osteogenesis imperfecta, hypophosphatasia, primary hyperparathyroidism)

- Diagnosed with secondary or metastatic cancer or multiple myeloma

Primary Outcome

Incidence of proximal femur (hip) fracture defined by a principal hospital discharge diagnosis of closed fracture of the femur based on *International Classification of Disease*, Ninth Revision codes.

The authors also attempted to adjust for a variety of time dependent co-variates. These co-variates include evidence of diabetes (8%), rheumatoid arthritis (3%), CKD stage 3A or 3B (eGFR 45-59 or 30-44; 16%), previous history of a fracture (28%), most recent T score, and treatment with a proton pump inhibitor, aromatase inhibitor, or systemic glucocorticoids. It was important for the authors to understand the history of each participant to know whether the participants were of higher risk for having a fracture. Proton pump inhibitors, aromatase inhibitors, and systemic glucocorticoids all can lead to increased risks of fractures.

Results

- Average age: 71 years old
- 60% Caucasian, 4% African American, 13% Hispanic, 20% Asian
- 56% normal or underweight, 31% overweight, 14% obese
- 37% diagnosed with osteoporosis, 57% diagnosed with osteopenia

Primary Outcome: 5-year cumulative incidences (risks) of hip fractures:

- Discontinuation at study entry: 23 per 1000 individuals
- Discontinuation after 2 additional years: 20.8 per 1000 individuals
- Discontinuation after 5 additional years: 26.8 per 1000 individuals

There was a statistically significant decrease in the 4-year risk of a hip fracture when comparing women who discontinued at study entry and continued therapy for 2 additional years, only with the 6-month grace period (4-year RD, -10.4 per 1000 individuals: 95% CI, -19.7 to -1.1 per 1000 individuals). No other risk differences were statistically significant.

Strengths:

- Inclusion of a large and diverse population of older women with long term bisphosphonate use
- Use of centralized electronic health databases
- Statistical methods accounting for numerous potential factors that could be associated with both treatment continuation and hip fracture risk

Limitations:

- Use of observational data

- Findings might not be applicable to older women at higher risk of osteoporotic fracture
- Use of an adherence threshold of 60%
- The authors were unable to exclude the possibility that atypical femur fractures may have been included in the observation
- The co-variates were assessed 5 years prior to study entry, but there was no discussion on if women were placed on therapies during the study period that could increase the fracture risk
- This study only included women
- No mention of adverse effects

Study Author Conclusions: No hip fracture benefit or harm was associated with discontinuing therapy at study entry or continuing therapy for an additional 5 years. However, a potential benefit was found when continuing therapy for 2 additional years, but further observational studies are needed.

Discussion: There is no difference in the incidence of hip fractures when therapy is discontinued after 5 years or continued for an additional 5 years (10 years of treatment). However, treatment continued for an additional 2 years (7 years of treatment) showed possible decreased risk of hip fractures. However, this is an observational study, and these results need to be confirmed by additional retrospective studies in men and assessing other fractures.

Clinical Take Home Point: The results of this trial suggest that an optimal duration of treatment with oral bisphosphonates is ~7 years. It was noted that women who had an additional 5 years of therapy (10 years of exposure) did not gain any additional benefit. Studies focusing on other types of fractures (vertebral, atypical) and the length of exposure to bisphosphonates are needed.

Author: Tyler R. Walsh, PharmD, PGY-2 Geriatric Pharmacy Resident, UAMS, Little Rock, AR

Peer Reviewers: Lisa C. Hutchison, PharmD, BCPS, BCGP
Kaci Boehmer, PharmD, BCACP

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