Is Intravenous Bisphosphonate Use Associated with a Higher Risk of a Flare in Inflammatory Bowel Disease Patients?

Bharati Kochar
Jeff Y. Yang
Jennifer L. Lund
Hans H. Herfarth

Study Protocol v11.01.19

We declare that we have no knowledge, through advance exploratory analyses, of the likely ultimate findings of the study at the time that this protocol is submitted.

Background

The number of older adults with inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), is rising over time due to an increased incidence and prevalence of the diseases.[1, 2] The management of a chronic disease, such as IBD, in older adults is complicated by an increased number of comorbidities and concomitant medications.[3]

Osteoporosis is a common morbidity of older adults. One prospective European study reported that the prevalence of osteoporosis in women aged 50-60 years was 15% and in women over 70 years was 45%. While osteoporosis is more common in women, the same study reported a prevalence of osteoporosis of 17% in men over 70 years.[4] There are numerous cross sectional studies of bone mineral density in IBD patients. The majority of these studies conclude that there is an increased risk for low bone mineral density in IBD patients, which could be attributed to corticosteroid use and decreased intestinal absorption of calcium and Vitamin D.[5, 6] There is even a recommendation to check bone mineral density in IBD patients with certain risk factors.[7] However, the effect of the treatments for osteoporosis on patients with IBD are not well described in the literature.

The most common treatment for osteoporosis is the bisphosphonate drug class. These are medications that can be administered orally and intravenously. Bisphosphonate therapy stimulates a cytokine-mediated acute phase response that induces activation of tumor necrosis factor (TNF)-α and interferon (IFN)-γ.[8, 9] In some patients, this response manifests as a reaction characterized by fever, chills, arthralgias and myalgias.[10, 11] Oral bisphosphonates are less frequently associated with such an acute clinical response because absorption from the gastrointestinal tract is more gradual. A recent retrospective case-series in a rheumatology practice suggested that intravenous bisphosphonate administration may trigger a flare of chronic autoimmune syndromes, including two patients who had a flare of Crohn's disease.[12] However, this phenomenon has not been systematically investigated in a cohort of IBD patients.

Specific Aims:

1. To describe patients with inflammatory bowel disease that are being treated with intravenous and oral bisphosphonate therapy

   <u>Hypothesis:</u> We hypothesize that the majority of IBD patients treated with bisphosphonates are older and receive oral bisphosphonates

2. To determine if intravenous bisphosphonate therapy is associated with an increased risk of flare of IBD activity, as measured by a new prescription for a corticosteroid or an IBD-related emergency room visit or hospitalization, compared with oral bisphosphonate therapy

   <u>Hypothesis:</u> We hypothesize that intravenous bisphosphate therapy will be significantly associated with a flare of disease activity

Methods:

We will conduct this study using the active comparator, new-user design.[13]

Data Source

We propose using the MarketScan Commercial Claims and Encounters administrative claims database from 2006 – 2017.

Study Population

The base population for the study will consist of all patients in the MarketScan database who have been treated with a bisphosphonate, oral and intravenous, between January 1st, 2006 and December 31st, 2017. The study start date of January 1, 2006 was selected to reflect the market entry of intravenous bisphosphonates to the US market. Receipt of bisphosphonates will be identified using a combination of National Drug Codes (NDCs) for individual agents as well as Healthcare Common Procedure Codes (HCPCS) for administration of intravenous bisphosphonates. Oral bisphosphonates will include alendronate, ibandronate and risedronate; intravenous bisphosphonates will include ibandronate and zolendronic acid.

Inclusion Criteria

1. We will identify a cohort of prevalent IBD patients. The cohort will be defined by patients who have at least 3 International Classification of Disease (ICD)-9 or 10 codes on different days for Crohn's disease (555.x or K50.x) or ulcerative colitis (556.x or K51.x) or those who have one ICD code for an IBD and a prescription for an IBD-related medication defined as mesalamine, olsalazine, balsalazide, sulfasalazine, 6-mercaptopurine, azathioprine, infliximab, adalimumab, golimumab, certolizumab or enteral budesonide. This is a definition used in previous studies of IBD patients in administrative claims databases, updated to include medications that have been approved since the original study.[14]
2. 180 days of continuous enrollment before bisphosphonate use and 30 days of continuous enrollment after bisphosphonate use for a total of 210 days of continuous enrollment

Exclusion Criteria

To ensure new use of bisphosphonates, we will exclude all individuals who do not have at least 6 months of continuous enrollment in the MarketScan database prior to the first prescription or administration claim, during which no other prescription/administration for any bisphosphonate formulation is observed (washout period).

Exposure

Exposure will be defined as one dose of an IV or oral bisphosphate, which will be the index date. The decision to compare those receiving an IV bisphosphonate to those who are receiving an oral bisphosphonate was made a priori in an attempt to minimize confounding by indication.

Outcomes

The listed outcomes are surrogate markers of flares of IBD activity. Outcomes will be measured in the 30 days following bisphosphonate use

1. Urgent care or emergency department use with IBD as a primary or secondary diagnosis code
2. IBD-related hospitalization, identified as an inpatient admission with a primary or secondary diagnosis of IBD
3. Systemic corticosteroid or enteral budesonide prescription in those who were not treated with corticosteroids in the 30 day period before the index date

Covariates

1. Age
2. Sex
3. Geographic location
4. Baseline IBD diagnosis
5. Charlson Co-Morbidity Index[15]
6. Baseline anti-TNF use
7. Healthcare utilization in the baseline period (before index date):
    a. number of hospitalizations
    b. number of GI-related surgeries
    c. number of IBD-related urgent care/emergency department visits
    d. number of CT/MRI scans
    e. Number of unique prescription drugs received
    f. Number of IBD-related outpatient visits

Analysis

1. After identifying the IBD Cohort, we will compare the demographics, such as age, sex, geographic location and Charlson co-morbidity index, as well as available disease related variables, such as type of IBD, medications used in the 90 days prior to bisphosphonate use, IBD related hospitalizations, surgery and health care utilization of IBD patients using IV versus oral bisphosphonates
2. We will construct a propensity score model to compare IBD patients receiving IV bisphosphonates to those receiving oral bisphosphonates. All above covariates will be included in the propensity score model. We will implement standardized mortality ratio (SMR) weighting using estimated propensity scores to achieve covariate balance between the IV and oral bisphosphonate cohorts, to control for measured confounding. The estimand of interest will be the average treatment effect among the treated (IV bisphosphonates users).
3. We will compare the crude and adjusted 30-day incidence of outcomes in the IV bisphosphonate group and oral bisphosphonate group.

Subgroup Analyses & Sensitivity Analyses:

1. We will perform a subgroup analysis comparing younger (age <50) to older (age 50-64) patients.

2. We will perform a subgroup analysis restricting the analysis only to female users.
3. We will perform a sensitivity analysis using multivariable binomial regression instead of propensity-score weighting to assess the impact of confounding control.
4. We will perform a sensitivity analyses estimating 90-day incidence of outcomes.

References

1. Ananthakrishnan AN, Donaldson T, Lasch K, et al. Management of Inflammatory Bowel Disease in the Elderly Patient: Challenges and Opportunities. Inflamm Bowel Dis 2017;23:882-893.
2. Shivashankar R, Tremaine WJ, Harmsen WS, et al. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clin Gastroenterol Hepatol 2017;15:857-863.
3. Anderson G HR, Zeffiro T, Johnson N. Chronic Conditions: Making the Case for Ongoing Care. Princeton, NJ: , 2004.
4. European Prospective Osteoporosis Study G, Felsenberg D, Silman AJ, et al. Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res 2002;17:716-24.
5. Targownik LE, Bernstein CN, Nugent Z, et al. Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clin Gastroenterol Hepatol 2013;11:278-85.
6. Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 2003;48:3224-9.
7. Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. Am J Gastroenterol 2017;112:241-258.
8. Nerdal PT, Peters C, Oberg HH, et al. Butyrophilin 3A/CD277-Dependent Activation of Human gammadelta T Cells: Accessory Cell Capacity of Distinct Leukocyte Populations. J Immunol 2016;197:3059-3068.
9. Roelofs AJ, Jauhiainen M, Monkkonen H, et al. Peripheral blood monocytes are responsible for gammadelta T cell activation induced by zoledronic acid through accumulation of IPP/DMAPP. Br J Haematol 2009;144:245-50.
10. Reid IR, Gamble GD, Mesenbrink P, et al. Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab 2010;95:4380-7.
11. Welton JL, Morgan MP, Marti S, et al. Monocytes and gammadelta T cells control the acute-phase response to intravenous zoledronate: insights from a phase IV safety trial. J Bone Miner Res 2013;28:464-71.
12. Markovits N, Loebstein R, Bank I. Immune-mediated syndromes following intravenous bisphosphonate therapy. Inflammopharmacology 2017;25:665-671.
13. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep 2015;2:221-228.
14. Kappelman M. D R-SSL, Kleinman K, Ollendorf D, Bousvaros A, Grand R. J, Finkelstein, J. A. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol 2007;5:1424-9.
15. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.