Accepted Manuscript

Oral Bisphosphonates and Risk of Wet Age-Related Macular Degeneration

Zaid Mammo, MD, Michael Guo, BSc, David Maberley, MSc, MD, Joanne Matsubara, Ph.D, Mahyar Etminan, PharmD, MSc

PII: S0002-9394(16)30197-0

DOI: 10.1016/j.ajo.2016.04.022

Reference: AJOPHT 9730

To appear in: *American Journal of Ophthalmology*

Received Date: 22 February 2016

Revised Date: 22 April 2016

Accepted Date: 27 April 2016

Please cite this article as: Mammo Z, Guo M, Maberley D, Matsubara J, Etminan M, Oral Bisphosphonates and Risk of Wet Age-Related Macular Degeneration, *American Journal of Ophthalmology* (2016), doi: 10.1016/j.ajo.2016.04.022.

Abstract

PURPOSE: To examine the risk of age related macular degeneration (AMD) with oral bisphosphonates.

DESIGN: Three study designs were used. 1) disproportionality analysis;2) case-control study; 3) Self-controlled case series (SCCS).

METHODS: **Setting:** 1) Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) Database;2) Two patient cohorts from British Columbia, Canada. **Study population:** 1) All reports of AMD to the FDA with oral bisphosphoantes;2) Patients with wet AMD in British Columbia (2009-2013) and one million controls (2000-2007). **Intervention:** Oral bisphosphonates**. Main outcome measures:** 1) Reports of AMD to the FDA;2) First diagnosis of wet AMD verified by a retina specialist in British Columbia.

RESULTS: In the disproportionality analysis there were 133 cases of AMD reported with alendronate, 20 with ibandronate, and 14 with risedronate. The reported odds ratios (RORs) for alendronate, ibandronate and risedronate were 3.82 (2.94-4.96), 2.40 (1.49-3.86) and 2.87 (1.58-5.19) respectively. In the case-control analysis there were 6,367 cases and 6370 corresponding controls. The adjusted OR for wet AMD among regular users of bisphosphonates in the one, two and three years prior to the index date were 1.27 (95%CI: 1.14-1.41), 1.41 (95%CI: 1.25- 1.59) and 1.61 (95%CI:1.40- 1.86) respectively. In the SCCS analysis there were 198 cases of wet AMD on continuous bisphosphonate therapy. The RR for wet AMD for continuous bisphosphonate use was 1.99 (95% CI:1.41-2.79). We did not have information on intravenous bisphosphonates.

CONSLUSIONS: Continuous users of oral bisphosphonates are at a higher risk of developing wet AMD. Given the observational nature of this study and limitation of the data, future studies are needed to confirm these findings.

Oral Bisphosphonates and Risk of Wet Age-Related Macular Degeneration

Zaid Mammo MD[1], Michael Guo BSc[2], David Maberley MSc, MD[1,3], Joanne Matsubara Ph.D[1], Mahyar Etminan PharmD, MSc[1,2,3]

1-Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, Canada

2-Department of Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada

3-Collaboration for Epidemiology of Ocular Diseases (CEPOD), Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, Canada

Corresponding Author:

Mahyar Etminan PharmD, MSc
Assistant Professor of Ophthalmology and Visual Sciences| Faculty of Medicine
Associate Member, Pharmacology and Therapeutics
The University of British Columbia |The Eye Care Center
Room 323-2550 Willow Street, Vancouver BC, V5Z 3N9
Phone 604-875-4725 | Fax 604-875-4663
Email: etminanm@mail.ubc.ca

Abstract word count: 258

Text word count: 2269

Short title: Oral bisphosphonates and risk of wet age related macular degeneration

INTRODUCTION

Bisphosphonates are one of the most prescribed classes of drugs, mainly used for the prevention of osteoporosis. They are complex molecules with pro-inflammatory properties which might explain the mechanism behind some of their adverse events. For example, zolendronic acid, an intravenous bisphosphonate, has been linked to both early and delayed flu-like symptoms due to the release of inflammatory mediators such as interleukins[1], cytokines[1,2] and C-reactive proteins (CRP's)[1,2]. Similarly, oral and intravenous bisphosphonates have been shown to increase the risk of ocular inflammatory conditions such as scleritis[4], uveitis[5,6] and optic neuritis[7]. A case-control study using the Age-Related Eye Disease Study has shown that CRP, an inflammatory marker associated with coronary artery disease, might also be associated with age-related macular degeneration (AMD)[3].

Age-related macular degeneration is an incurable disease that continues to be the leading cause of blindness in older adults. There are two main types: dry and neovascular (also referred to as wet) AMD. Intravitreal injections of anti-vascular endothelial growth factor (VEGF) are the mainstay treatment for wet AMD. Large epidemiologic studies have identified several risk factors that might be important in the pathology of AMD including genetics, smoking[8] and obesity[9]. However, the effects of chronic use of prescription drugs, especially those that can promote inflammation like bisphosphonates, are unknown. We hypothesised that long-term use of oral bisphosphonates can increase the risk of neovascular or wet AMD in older adults and conducted a pharmacoepidemiologic study.

METHODS

Setting and Study Population

We used three distinct study designs including disproportionality analysis, case-control study and a self-controlled case-series (SCCS) in this study.

For the disproportionality analysis we used data from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database that captures all spontaneous adverse drug reactions reported to the FDA. Data was available from the fourth quarter of 2004 to the second quarter of 2014.

For the case-control and self-controlled case series studies, we used the British Columbia (BC) Ministry of Health Databases. The databases are comprised of health related information for approximately 4.8 million residents of BC. Specifically, the data capture all hospitalizations through the Discharge Abstract Database[10], all physician visits through the Medical Services Plan (MSP) data file[10], and all prescription drugs (including date of dispensation, day supply and quantity dispensed) through PharmaNet[10]. The BC Provincial Retinal Disease Treatment Program, part of the BC Ministry of Health, provides anti-VEGF therapies (bevacizumab or ranibizumab) to older adults with wet AMD. Data for all AMD patients are recorded by a retina specialist and inputted to a comprehensive database which captures all intravitreal injections including type of anti-VEGF use and the date of injection

from 2009 to 2013. These data have been used in several epidemiologic studies[11,12]. Ethics approval was obtained from the University of British Columbia Clinical Ethics Board.

Study design

Disproportionality analysis

Disproportionality analysis is a signal detection technique that examines the risk of an adverse event with a target drug by comparing the number of cases of the adverse event reported with the drug in question against the number of cases of the same adverse event reported with all other drugs in the database. This technique uses information from adverse drug reaction databases such as the FAERS[13] database. It allows researchers and drug regulatory agencies to screen potential 'signals' for adverse drug reactions[13].

Case-control study

Cases were identified as those with the first incidence of wet AMD, defined as the first intravitreal injection of anti-vascular endothelial growth factor (VEGF) therapies (mainly bevacizumab or ranibizumab), from 2009 to 2013 in the British Columbia (BC) AMD database. This date was deemed the index date. Controls were selected from a smaller sub-set of the BC Ministry of Health database, which included approximately one million subjects who had visited an ophthalmologist in BC from 2000-2007. Controls had the same opportunity of being diagnosed for AMD by an ophthalmologist as the cases thus minimizing detection bias. Controls were selected if they did not have an *international classification of diseases code ninth revision* (ICD-9) for any retinal disease (362.00) or had not received verteporfin therapy and were alive and at risk of developing AMD at the index date. We matched each case with 10 controls by age, follow-up time, and calendar time to control for prescribing trends.

Self-controlled case series

The SCCS is similar to a retrospective cohort study but only analyzes person-time among the cases[14]. Exposed person-time on bisphosphonate therapy (risk period) is compared to the period without bisphosphonate use in the same subject controlling for time-fixed confounders[14]. Thus the main advantage of the SCCS study is that it eliminates inter-subject variability that might lead to bias. In the SCCS design, confounders that change over time, such as age, were modelled in increments of one-year age-bands.

Among the 7,752 incident wet AMD patients identified from the British Columbia (BC) Ministry of Health Database, we first identified all those with at least one prescription of an oral bisphosphonate available in Canada including *alendronate, etidronate and risedronate*. From this cohort we further identified continuous users of a bisphosphonate defined as an AMD subject with no discontinuation periods longer than 15 days between two bisphosphonate prescriptions. Subjects were censored at the time of a prescription termination or the end of the study period. Since the time to onset of AMD with bisphosphonates is unknown, we followed bisphosphonate users to the first AMD injection date to avoid exposure misclassification. The period prior to the first bisphosphonate prescription was designated as the unexposed period (Figure 1) and thus used as the comparator period.

Statistical analysis

For the disproportionality analysis, we used OpenVigil 2.1, a validated online analytical tool that uses FAERS data for disproportionality analysis. OpenVgil 2.1[15] has been developed specifically for disproportionality analysis and has gone through quality checks to ensure data quality[15]. We computed reported odds ratios (RORs) and 95% confidence intervals (CIs) for the following oral bisphosphonates: *alendronate, risedronate, ibandronate, and etidronate.* The ROR was computed using the number of AMD cases for each bisphosphonate compared to the number of reported AMD events for all other drugs. An ROR of greater than 2.0 was considered the minimum effect size for a positive signal[16].

For the case-control analysis we first identified all bisphosphonate users among the cases and controls in the three years prior to the index date. The possible time to onset of wet AMD with oral bisphosphonates is unknown. However, due to the nature of its pathology and its relatively long latency, we defined regular users of bisphosphonates as those having received at least one bisphosphonate prescription every three months in the year prior to the index date. To further control for long latency and possible reverse causality we also examined the risk during the two and three year periods prior to the index date. Irregular users were those who did not receive regular bisphosphonate prescriptions during the one, two or three years prior to the index date but had received at least two prescriptions annually in the years prior to the index date.

Descriptive statistics was used to compare covariates between the cases and controls. A conditional logistic regression model was constructed to compute odds ratios (ORs) using non-users as the comparator group. In this model, we adjusted for gender, history of myocardial infarction, stroke, diabetes and use of statin drugs. For the self-controlled case-series analysis we used a conditional poisson regression model[14] that computes rate ratios (RRs) in the exposed period compared to the observation period (unexposed) in each case. The effect of age was modelled using one-year age bands. All analyses were done using SAS version 9.4 (Cary, NC)[17].

RESULTS

In the disproportionality analysis there were 58 cases of AMD reported with alendronate, 17 with ibandronate and 11 with risedronate, respectively (Table 1). There were 27 reports of AMD with alendronate for greater than three years of use. The RORs for alendronate, ibandronate and risedronate were 3.82 (2.94-4.96), 2.40 (1.49-3.86) and 2.87 (1.58-5.19) respectively. In the case-control analysis there were 6,367 cases and 63,670 corresponding controls (Table 2). The adjusted OR for regular users of bisphosphonates in one year prior to the index date was 1.27 (95%CI: 1.14-1.41) and 1.61 (95%CI: 1.40- 1.86) for regular users with three years of exposure to an oral (Table 3). In the SCCS analysis there were 193 cases of AMD on continuous bisphosphonate therapy. The average age of AMD cases was 81.2 years and average duration of continuous bisphosphonate use was 2.7 years (± 2.3) (Table 4). The RR for AMD increased as follow up time increased. The RR for one year of

bisphosphonate exposure was 1.22 (95% CI: 0.76-1.95) compared to 1.87 (95% CI: 1.32-2.67) for five years (Table 5) and an average of 1.99 (95% CI: 1.41-2.79) between all groups. The RR for AMD did not differ between males (RR= 2.03, 95% CI: 1.38-2.98) and females (RR= 2.02, 95% CI: 1.38-4.21).

DISCUSSION

The results of our study suggest an increase in the risk of wet AMD with oral bisphosphonates. This risk was observed in the disproportionality analysis of the FAERS database with alendronate having the highest association and the highest number of reported cases, including cases with three years of bisphosphonate use. Similarly, both the case-control and SCCS study also demonstrated an increase in the risk of wet AMD with increasing the duration of use.

The disease mechanism of AMD involves a complex interaction of genetic and environmental factors. Growing evidence suggests that local and systemic inflammation act as a risk factor for AMD[18,19]. Inflammatory states as measured by increased levels of C-reactive proteins (CRP's), interleukins and aberrant complement activation, have been associated with an increased risk for AMD incidence[3,19]. Given the pro-inflammatory properties of bisphosphonates, this might explain the relative increased risk of wet AMD incidence compared to other drugs that we have reported in our study.

Bisphosphonates are known to initiate inflammatory cascades by activating gamma-delta T cells, which leads to increased downstream pro-inflammatory markers[20]. Inflammatory ocular consequences of bisphosphonate use have been well-documented with reported cases of scleritis[4], uveitis[5-6] and orbital inflammation[21]. A number of cases where re-introduction of the bisphosphonates produced a recurrence of ocular inflammation further support this association[5]. In addition, increased expression of inflammatory meditators, including CRP, by bisphosphonates was demonstrated in-vitro[2]. CRP is a common and reliable measure of systemic inflammation. It is ever-present in acute inflammation and its discovery within sub-retinal deposits and drusen further supports the role of inflammation in AMD pathogenesis[22]. A pooled analysis of five large cohort studies showed a similar association between CRP levels and wet AMD[23]. The pooled odds ratio (OR) for those with high CRP levels compared to low CRP levels was 1.49 (95% CI: 1.06-2.08). Other inflammatory cytokines such as Interleukin-6 and interleukin-8 have also been found to be up-regulated by bisphosphonates[24]. The aqueous humor levels of interlukin-6 (IL-6) and interlukin-8 (IL-8) have been found to be elevated in patients with wet AMD. In addition, IL-6 and IL-8 levels have been significantly associated with the volume of macular edema in wet AMD patients with active choroidal neovascular membranes (CNVM)[25].

Elevated levels of the aforementioned inflammatory markers might provide a link between bisphosphonate use and AMD. However, one study has demonstrated a potential protective effect with bisphosphonates through their anti-angiogenic properties in an animal model[26]. The combined pro-inflammatory and anti-angiogenic properties of bisphosphonates were demonstrated concurrently in an in-vitro experiment of retinal pigment epithelium cells[23]. Another study has shown that oral bisphosphonate may improve visual and anatomical

outcomes in a small, non-randomized study involving patients with choroidal neovascular membranes secondary to wet AMD and pathologic myopia[27]. However, this study only followed patients for six months and it is possible that the pro-inflammatory effects of bisphosphonates overcome their anti-angiogenic effects when used over a longer period of time as shown in our study.

The strengths of this study lie in the inclusion of a large number of AMD cases in all three analyses. Moreover, the case-control and SCCS studies were able to differentiate between wet and dry AMD cases identified by retina specialists, eliminating potential misclassification between the wet and dry forms of the disease. Also, the SCCS design controlled for within-subject variability that may lead to differential prescribing of bisphosphonates. Finally, a duration response in both the case-control study and the SCCS demonstrates that the risk of AMD with bisphosphonate increases with long-term use. Both the SCCS study and disproportionality analysis show an increased risk for longer exposure periods as demonstrated by higher RR's and ROR's in longer-exposed groups.

Our study also has some limitation. Disproportionality analysis could not differentiate between wet and dry forms of AMD and also cannot show a causal relationship. This type of analysis is considered weaker than an epidemiologic study as it cannot account for potential confounding variables. However, this was only used as a signal detection tool which allowed for the case-control and SCCS studies to corroborate the signal. However, the SCCS analysis controlled for the absence of these confounders by eliminating inter-patient differences. It is possible that the increase in the risk of AMD observed in older patients taking bisphosphonates for a longer period might be due to progressing disease severity that might be correlated with AMD. We were unable to study the risk of AMD with individual bisphosphonates due to power restrictions (limited number of cases for each drug). Finally, information on the cases and controls was ascertained from different time periods and differences in prescribing time-trends may have influenced the results.

The results of this study demonstrate an increase in the risk of wet AMD with oral bisphosphonate use. Given the observational nature of our study and limitation of the data, future studies are needed to confirm these findings.

Funding/Support: The study was funded by The Foundation Fighting Blindness. The funding agency did not have any role in the design, analysis or interpretation of the data; or preparation or approval of the manuscript.

A. Funding Statement: This study was funded by the Foundation Fighting Blindness.

B. Financial Disclosures:

Zaid Mammo, Michael Guo and Joanne Matsubara have no financial disclosures

Mahyar Etminan has consulted in the Mirena and intracranial hypertension litigation

David Maberley has been on the following advisory boards in the last 3 years: Novartis (Quebec, Canada), Bayer (Mississauga, Ontario, Canada), Allergan (Markham, Ontario, Canada), Alcon (Forth Worth, Texas). Dr Maberley is being compensated financially for the conduct of studies with the following companies: Alcon, Roche (Mississauga, Ontario, Canada), Ophthotech (New York, USA), Novartis (Dorval, Quebec, Canada), AbbVie (Saint-Laurent, Quebec, Canada) Bayer (Mississauga, Ontario, Canada).

References:

1. Kassi G, Papamichael K, Papaioannou G, et al. Cytokines and insulin resistance after zoledronic acid-induced acute phase response. *Immunol Invest* 2014;43(6):544-555.

2. Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. *Clin Exp Immunol* 2005;139(1):101-111.

3. Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration. *JAMA* 2004;291(6):704-710.

4. Etminan M, Forooghian F, Maberley D. Inflammatory ocular adverse events with the use of oral bisphosphonates: a retrospective cohort study. *CMAJ* 2012;184 (8):E431-434.

5. Ghose K, Waterworth R, Trolove P, Highton J. Uveitis associated with pamidronate. *Aust N Z J Med* 1994;24 (3):320.

6. Colucci A, Modorati G, Miserocchi E, Di Matteo F, Rama P. Anterior uveitis complicating zoledronic acid infusion. *Ocul Immunol Inflamm* 2009;17(4):267-268.

7. Brulinski P, Nikapota AD. Zolendronic acid-induced retrobulbar optic neuritis: a case report. *Clin Oncol* (R Coll Radiol) 2013;25 (5):328-329.

8. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA*1996 (14);276:1141-1146.

9. Risk factors associated with age-related macular degeneration: a case-control study in the Age-Related Eye Disease Study: AREDS report 3.*Ophthalmology* 2000;107(12):2224-2232.

10. http://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central (Accessed March 27, 2016).

11. Schneeweiss S1, Walker AM, Glynn RJ, Maclure M, Dormuth C, Soumerai SB. Outcomes of reference pricing for angiotensin-converting-enzyme inhibitors. *N Engl J Med* 2002;346 (11):822-829.

12. Zhang T, Smith MA, Camp PG, Shajari S, MacLeod SM, Carleton BC. Prescription drug dispensing profiles for one million children: a population-based analysis. *Eur J Clin Pharmacol* 2013;69 (3):581-588.

13. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data Mining of the Public Version of the FDA Adverse Event Reporting System. Int J Med Sci 2013;10:796-803. Available at: http://www.medsci.org/v10p0796.htm#B32. (Accessed March 27, 2016).

14. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;25(10):1768-1797.

15. Böhm R, Hocker J, Cascorbi I, Herdegen T. OpenVigil-free eyeballs on AERS pharmacovigilance data. Nature Biotechnology 2012:30:137-138.

16. Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in Pharmacovigilance. *Expert Opinion Drug Safety* 2005;4(5):929-948.

17. SAS Institute Inc., SAS 9.4, Cary, NC: SAS Institute Inc., 2014.

18. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol* 2003;48 (3):257-293.

19. Nussenblatt RB, Lee RW, Chew E, et al. Immune responses in age-related macular degeneration and a possible long-term therapeutic strategy for prevention. *Am J Ophthalmol* 2014;158(1):5-11.

20. Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. *Clin Exp Immunol* 2005;139(1):101-111.

21. Lefebvre DR, Mandeville JT, Yonekawa Y, Arroyo JG, Torun N, Freitag SK. A Case Series and Review of Bisphosphonate-associated Orbital Inflammation. *Ocul Immunol Inflamm* 2014;1-6.

22. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002;134 (3):411-431.

23. Mitta VP, Christen WG, Glynn RJ, et al. C-reactive protein and the incidence of macular degeneration: pooled analysis of 5 cohorts. *JAMA Ophthalmol* 2013;131 (4):507-513.

24. Or C, Cui J, Matsubara J, Forooghian F. Pro-inflammatory and anti-angiogenic effects of bisphosphonates on human cultured retinal pigment epithelial cells. *Br J Ophthalmol* 2013;97 (8):1074-1078.

25. Miao H, Tao Y, Li XX. Inflammatory cytokines in aqueous humor of patients with choroidal neovascularization. *Mol Vis* 2012;18:574-580.

26. Nourinia R, Ahmadieh H, Rezaei-Kanavi M, Shoeibi N, Kamrava K, Karimi S. Safety of Intravitreal Zoledronic Acid, an Anti-angiogenic Bisphosphonate, in a Rat Model. *J Ophthalmic Vis Res* 2013;9 (1):44-49.

27. Honda S, Nagai T, Kondo N, et al. Therapeutic effect of oral bisphosphonates on choroidal neovascularization in the human eye. *J Ophthalmol* 2010;(10);206837.

Table 1: Table 1: Reported odds ratio (ROR) of age related macular degeneration and oral bisphosphonates in the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database from 2004-2014.

Drug Name	AMD Cases	AMD Cases - other drugs*	Events**	Events - other drugs‡	ROR‡‡
All cases					
Alendronate	58	1759	26187	3031972	3.82 (2.94 – 4.96)
Ibandronate	17	1800	12006	3046153	2.40 (1.49 – 3.86)
Risedronate	11	1806	6487	3051672	2.87 (1.58 – 5.19)
≥3 years duration					
Alendronate	27	1790	3178	3054981	14.50 (9.90 – 21.24)
Ibandronate	1	1816	185	3057974	9.10 (1.27 – 65.00)
Risedronate	0	1817	129	3058030	----------

* Cases of macular degeneration associated with all other drugs

** All other adverse events (excluding macular degeneration) reported for drug of interest

‡ All other adverse events reported for all other drugs

‡‡ Reported odds ratios with 95% confidence intervals

Table 2: Characteristics of 6,367 cases of age related macular degeneration (AMD) and 63,670 controls in the British Columbia Ministry of Health Database

	Cases	**Controls**
N	6,367	63,670
Demographics		
Age (mean ± SD)	79.4 ± 10.7	79.3 ± 10.7
Follow-up years (mean ± SD)	6.2 ± 1.1	6.2 ± 1.1
Gender males (%)	39.6	41.0
Covariates (%)		
MI	5.6	6.9
Stroke	12.4	14.9
Diabetes	27.9	28.4
Statin	39.4	26.9

Table 3: Crude and Adjusted Odds ratios (ORs) for regular and irregular use of bisphosphonates with wet age related macular degeneration

Duration of use	Cases	Controls	Crude OR	Adjusted OR
1 year				
No BP* use	81.1	83.8	1.00	1.00
Regular use	7.2	5.9	1.25	1.24 (1.12-1.38)
Irregular use	11.7	10.2	1.18	1.18 (1.08-1.28)
2 years				
No BP use	81.1	83.8	1.00	1.00
Regular use	5.1	3.8	1.40	1.38 (1.22- 1.56)
Irregular use	13.8	12.4	1.15	1.15 (1.06- 1.24)
3 years				
No BP use	81.1	83.8	1.00	1.00
Regular BP use	3.9	2.5	1.61	1.59 (1.38- 1.82)
Irregular use	15.0	13.8	1.14	1.13 (1.05- 1.22)

*BP = bisphosphonates
**Adjusted OR with 95% confidence intervals, adjusted for covariates in Table 2

Table 4: Characteristics of wet age related macular degeneration (AMD) patients on bisphosphonates in the self-controlled case series study using the British Columbia AMD database

Patient group	Patients with AMD	Mean age at start of exposure	N-AMD Before exposure	Follow-up duration before exposure	N-AMD After exposure	Follow-up duration during exposure
Bisphosphonate	193	81.2 ± 7.5	101	4.9 ± 2.4	92	2.7 ± 2.3
Females	148	81.1 ± 7.2	75	4.6 ± 2.4	73	2.1 ± 2.3
Males	45	81.3 ± 7.6	26	5.8 ± 1.8	19	1.3 ± 1.7

Table 5: Age adjusted Rate Ratios (RRs) for the use of a bisphosphonate and risk of age related macular degeneration (AMD) in the self-case control case series analysis stratified by years of exposure

Exposure period	**Unexposed**		**Exposed**		**Age-Adjusted RR (95 % CI)***
	Patient Years	**n AMD**	**Patient Years**	**n AMD**	
1	89.0	56	50.5	34	1.22 (0.76-1.95)
2	277.1	92	111.7	49	1.29 (0.86-1.94)
3	461.8	101	155.0	58	1.53 (1.05-2.25)
4	623.3	101	190.7	65	1.80 (1.25-2.62)
5	761.4	101	271.3	80	1.87 (1.32-2.67)
Overall	942.6	101	369.7	92	1.99 (1.41-2.79)

n=number of AMD cases
*=Age adjusted rate ratio and 95% CI