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ORIGINAL ARTICLE

Marginal structural model to evaluate the association between cumulative osteoporosis medication and infection using claims data

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Abstract

Summary Due to the suboptimal persistence to osteoporosis (OP) treatment, factors triggering treatment discontinuation/switching may be causing time-varying confounding. BP treatment was associated with the risk of overall infection in opposite directions in the unweighted Cox model versus the weighted MSM. The discrepancy of effect estimates for overall infection in the MSM suggested there may be time-varying confounding.

Introduction Due to the suboptimal persistence to osteoporosis (OP) treatment, factors triggering treatment discontinuation/switching may be affected by prior treatment and confound the subsequent treatment effect, causing time-varying confounding.

Methods In a US insurance database, the association between joint treatment of bisphosphonates (BP) and other OP medication and the incidence of infections among postmenopausal women was assessed using a marginal structural model (MSM). Stabilized weights were esti-

mated by modeling treatment and censoring processes conditioning on past treatment, and baseline and time-varying covariates.

Results BP treatment was associated with the risk of overall infection in opposite directions in the unweighted Cox model {incidence rate ratio [IRR] [95% confidence interval (CI)] = 1.15 [1.14–1.17]} versus the weighted MSM [IRR (95% CI) = 0.79 (0.77–0.81)], but was consistently associated with a lower risk of serious infection in both the unweighted Cox model [IRR (95% CI] = 0.79 (0.78–0.81)) and the weighted MSM [IRR (95% CI) = 0.71 (0.68–0.75)]. Similar results were found when current and past treatments were simultaneously assessed.

Conclusions The discrepancy of effect estimates for overall but not serious infection comparing unweighted models and MSM suggested analyses of composite outcomes with a wide range of disease severity may be more susceptible to time-varying confounding.

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Abbreviations

BP	Bisphosphonates
CI	Confidence interval
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
IRR	Incidence rate ratio
MSM	Marginal structural model
ONJ	Osteonecrosis of the jaw
OP	Osteoporosis
PH	Proportional hazards
PMO	Postmenopausal osteoporosis

Introduction

Bisphosphonates (BP) are the most commonly prescribed medications to treat osteoporosis (OP). They are potent anti-resorptive agents that maintain or increase bone strength by slowing or preventing the dissolving of bone [1]. BP treatment has been associated with an increased risk of osteonecrosis of the jaw (ONJ) [2, 3]. While the underlying mechanism for anti-resorptive therapy to cause ONJ is unknown, infection was suggested to play a pivotal role in the pathogenesis of ONJ and persistent infection may prevent bone and soft tissue lesion from healing [4]. A histological analysis of ONJ cases treated with BP also suggested that the development of ONJ appears to be an inflammation-associated process [5]. It remains unclear whether BP treatment affects the risk of infection. Despite a few case reports, there is no population-based study that systematically evaluated the potential effect of BP treatment on the risk of infection.

One challenge in assessing treatment effects of BP is the poor persistence with these medications as a result of inconvenient dosing regimens, drug side effects or other comorbid conditions, especially in women with postmenopausal osteoporosis (PMO) [6]. Therefore, the likelihood of time-varying confounding is increased when comparing the long-term treatment effect of BP versus other OP medications since earlier OP medications may affect occurrence of the study outcome as well as subsequent OP treatments. For instance, BP and other OP medications may have different potency in reducing the risk of fragility fracture, and fracture is known to be a risk factor for infection. Time-varying confounding by fragility fracture for the association between sequential OP treatments and the risk of infection is depicted in the causal directed acyclic graph in Fig. 1. Because fragility fracture is both a mediating factor for the potential effect of the OP treatment 1 on the risk of infection, and a time-dependent confounder for the association between the OP treatment 2 and the
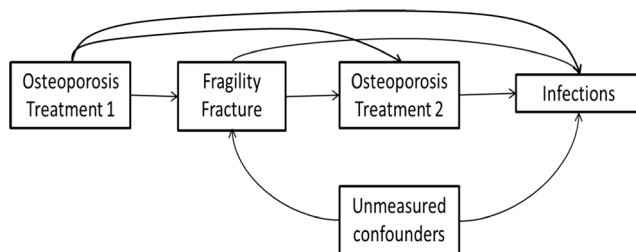

Fig. 1 Directed acyclic graph demonstrating time-varying confounding by fragility fracture of the association between sequential OP treatments and risk of infections

risk of infection, either adjusting or not adjusting for fragility fracture using standard confounding adjustment methods (e.g., covariate-adjustment regression model or stratification) will generate biased effect estimates [7, 8]. In the presence of unmeasured confounders on the association between fragility fracture and risk of serious infections that cannot be ruled out with certainty, such as cigarette smoking or malnutrition, fragility fracture can be a collider (i.e., outcome of two or more variables) [9, 10] and thus conditioning on it in a regression model would open a back-door path, producing additional bias [11]. Instead the influence of such time-varying confounder(s) on the overall sequential treatment effects can be accounted for by inverse probability of treatment weighted (IPTW) estimation of the parameters in a marginal structural model (MSM) for the joint effect of treatment history on the incidence of infection [7, 12]. In the example described above, conceptually, a pseudo-population can be created through weighting each subject in the study population by the inverse probability of receiving the OP treatment history they indeed received, conditional on their history of time-fixed and time-varying confounders (e.g., fragility fracture). In the resulting pseudo-population, fragility fracture no longer affects the probability of the subsequent OP treatment, and therefore is no longer a time-varying confounder; however, the causal association between treatment history and infection risk remains as in the original population. Thus, an analysis that does not adjust for time-varying confounders in the pseudo-population will generate an unbiased effect estimate of the joint causal effect of sequential OP treatment, assuming no other unmeasured confounders are present. A similar approach can also be used to handle censoring due to loss to follow-up by conceptualizing censoring as another time-varying treatment [7, 13]. Numerous other time-varying variables affected by earlier OP treatment may directly or indirectly influence patients' future choice of OP treatment and causing time-varying confounding. The potential channeling bias that BP treatment is more likely to be prescribed to heathier patients who are perceived to be at lower risk of known related adverse events may also contribute to time-varying confounding as prior BP versus other OP treatment may have different potency in improving the bone and overall health of a patient.

In the current study, we evaluated the association between treatment history (BP and other OP medication) and the incidence rate of infections using marginal structural Cox proportional hazards (PH) models adjusting for fragility fracture and other time-varying covariates. As there is no anticipation of treatment effect with regard to specific anatomic site or pathogen

type, overall infection identified by any infection diagnosis from a large insurance claims database was assessed. Serious infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication use were also evaluated for better specificity of outcome assessment. To assess the impact of time-varying confounding in this study, the same association was also estimated through regular unweighted multivariate-adjusted Cox PH models.

Methods

Study population

The analyses were conducted in the commercial claims and Medicare Coordination of Benefits databases from MarketScan, including data from 01 January 2004 through 30 June 2011. The MarketScan database captures person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations.

Women with PMO were included in the study based on the following inclusion criteria during the study period: postmenopausal age (≥55 years); had ≥12 months of continuous enrollment in the health plan; and had a diagnosis of OP or osteoporotic fracture or treatment with an OP medication. The PMO index date of an eligible woman was defined by the earliest date when she satisfied all of the above inclusion criteria during the study period. The 12-month period before the PMO index date was defined as the PMO baseline period, during which patient characteristics including exposure to OP medications and time-fixed covariates were assessed (Fig. 2). Women with a diagnosis for Paget's disease or a diagnosis or treatment related to malignancy (excluding non-melanoma skin cancer) during the PMO baseline period were excluded.

Exposure assessment

OP treatment including BP and other OP medications were assessed through drug codes or procedure codes. BP were restricted to those indicated for the treatment of PMO, i.e., IV BP including zoledronic acid infusion (Reclast) and ibandronate injection, and oral BP including alendronate sodium, alendronate sodium/vitamin D tablet (Fosamax plus D), ibandronate sodium, risedronate and risedronate sodium/calcium carbonate. Other OP medications included teriparatide injection, raloxifene tablet, and calcitonin.

The lack of regularly scheduled visits in studies based on administrative claims data poses a challenge that standard epidemiologic cohort studies do not face. To address this issue, an unstructured "visit process" was used to assess time-varying treatment with OP medications (BP or other) during the follow-up for all patients. From the PMO index date until the end of follow-up, each OP medication received was flagged. In our study design, a visit was defined by the initiation of an OP treatment, switching to the other treatment or reaching 6-month following switching to no treatment (see Fig. 2 footnote for definition of switching), diagnosis of fragility fracture, diagnosis of study outcome (infection) or end of follow-up (see the "Methods" section on follow-up for details). These specific events are likely to indicate or influence the decision on patients' choice of OP medication and thus updating covariates prior to these events provides important assessment of potential time-varying confounding variables. Associated with each visit is a look-back period defined as the 6-month prior to the visit (including the visit date). The look-back period was used to assess exposure to OP medications, as well as time-varying covariates for each visit. PMO baseline period can be the earliest look-back period for a patient.

Figure 2 displays visits and look-back periods for a hypothetical patient. In this example, the patient received a BP at visit 1 (PMO index date) and other OP medication at visit 2 (month 2), then switched back to BP at visit 3 (month 5). Assuming that the days supplied for the second BP is 30 days and with a buffer of 60 days, the patient is deemed to have switched to no treatment at month 8.

The exposure to OP medications was classified using the following two approaches to account for treatment history of OP medications:

1. Categorical classification based on the treatment received in the current look-back period (BP including both BP and other OP medication, other OP medication only and no OP medication) as well as treatment received in the current period and any of the past look-back periods (current BP treatment only, current and past BP treatment, past BP treatment only, current other OP medications only, current other OP medications and past BP treatment, and no OP medication).
2. Quintiles of cumulative dosage of BP treatment received during all previous look-back periods calculated through standardizing the received dose of various BP to alendronate-equivalent daily dose (Appendix A). The midpoint of each quintile was also used as a categorical variable to test the significance of trend.
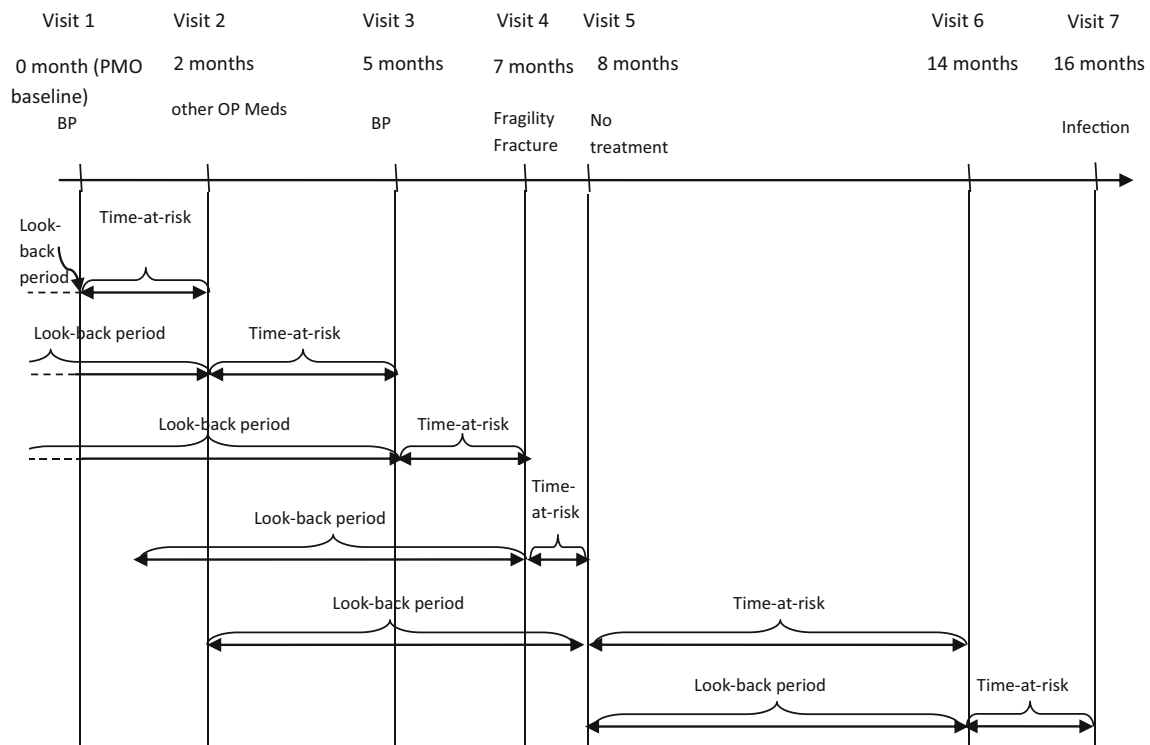
Fig. 2 An example of how to flag "visit" for a patient by switching of treatments, occurrence of a fragility fracture, and experience of the outcome of interest (infection). Schematic view of the 6-month look-back period (from the current visit) and the time-at-risk for the outcome (i.e., the day after the current visit up to and including the day of the next visit). Treatment switching status was defined as follows: (1) If a patient continuously received multiple treatment of the same class of drugs (BP or other OP medications) with a gap between two doses of less than the number of days supplied of the previous dose plus 60 days, the patient was deemed as staying on the same treatment. (2) If a patient received OP medication other than BP before the end of days supplied of the previous BP treatment plus 60 days or vice versa, the patient was deemed as having switched to the other treatment. (3) If a patient did not receive the same or different OP medication after the end of days supplied plus 60 days of the previous treatment, the patient was deemed as having switched to no treatment. (4) If a patient received BP or other OP medication after having switched to no treatment, the patient was deemed as having switched to the BP or other OP medication, respectively

Outcome assessment

Diagnosis of overall infection and serious infection was identified through relevant International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), treatment codes, and procedure codes throughout the eligible follow-up period for each patient. Overall infections included a wide range of infection types without restriction by specific pathogen or anatomic site, and serious infections included the same infection types but required the infection was severe enough to lead to hospitalization, ER visit, or administration of parenteral anti-infective medication use. The requirement of additional claims-identifiable medical procedures or drug treatment for the assessment of serious infection is intended to enhance the specificity and reduce false-positive of study outcome. The outcome status was updated and time at risk was calculated as the time from current visit to next visit (Fig. 2).

Covariate assessment

A variety of time-fixed and time-varying covariates were assessed, including demographic characteristics, comorbidities and concomitant medications which are potential risk factors for infection as well as healthcare utilization variables (Appendix B). The time-fixed covariates were evaluated only once during the PMO baseline period and time-varying covariates were updated during each look-back period. If the time-varying covariate was a chronic disease (e.g., diabetes), once the diagnosis was identified, it was carried forward throughout the remaining follow-up period.

Follow-up

All women with PMO were followed from the PMO index date until the first of the following: disenrollment from the data system, diagnosis or treatment related to malignancy (excluding non-melanoma skin cancer), diagnosis of Paget's disease, or end of the study period (30 June 2011). The follow-up for the occurrence of overall infection and serious infection was independently conducted, so that the occurrence of one outcome did not censor the follow-up for the other outcomes.

Statistical analysis

The association between OP treatment and the incidence of overall infection and serious infection was evaluated through MSM based on IPTW. The stabilized weight for MSM was calculated in the steps described in the Appendix C [14].

The incidence rate ratio (IRR) of overall infection and serious infection comparing the OP treatment groups was estimated using a Cox regression MSM model. Time-fixed covariates and time since start of follow-up (modeled as natural cubic splines) were also included in the model as time-dependent intercepts. Robust standard errors were used to construct confidence interval (CI) for MSM parameter estimates. The association between treatment with OP medications and the incidence of overall infection and serious infection was also estimated through standard Cox regression models without weighting by $SWi(t)_{treatment}$ or $SWi(t)_{censoring}$. Unadjusted and two sets of multivariate-adjusted analyses were performed. In the first set of analyses, only time-fixed covariates were adjusted for, while in the second set of analyses, both time-fixed and time-varying covariates were adjusted for.

Results

During the study period, a total of 469,432 women with PMO were identified from the MarketScan insurance claims database and contributed 1,050,567 person-years of follow-up. Among them, 464,728, 67,860 and 517,979 person-years received BP, other OP medications, and no OP medication, respectively, during the look-back period before each visit (Table 1). Women who received a BP or other OP treatment were younger and had a lower prevalence of several comorbidities such as diabetes, end stage renal disease, chronic obstructive pulmonary disease, chronic lung disease, serious infection, fragility fracture and other fracture than women who received no OP treatment. When cohorts were classified based on BP and other OP medications received in the current period and any of the past look-back periods, the same pattern was observed that treated cohorts were younger, and less likely to have comorbidities than the untreated cohort (Table 1).

The polytomous logistic regression models used to estimate treatment weights are displayed in Appendix D. Since including extreme weights would cause instability of weighted estimates of the MSM, the stabilized weights were truncated at a threshold percentile level (i.e., 0.5 and 99.5% in primary analysis and 1 and 99% in sensitivity analysis), so that patients with stabilized weight more extreme than the threshold level were set to the threshold level (Table 2). In additional analyses, treatment and

censoring models derived from the most recent four previous visits only were used to construct the stabilized weight to limit the influence of extreme weights and explore whether recent diagnoses and treatment are more influential on OP treatment and censoring.

In the analysis for overall infection, treatment with BP and other OP medications during the 6-month look-back period was associated with an increased risk in the unweighted Cox regression model [IRR (95% CI) = 1.15 (1.14–1.17) and 1.25 (1.23–1.27), respectively] relative to the untreated cohort (Table 3). The association became weaker for both treatments after adjustment for time-fixed variables only or both time-fixed and time-varying variables. The direction of the association between treatment and the risk of overall infection was reversed in the MSM for BP [IRR (95% CI) = 0.79 (0.77–0.81)] and other OP medications [IRR (95% CI) = 0.86 (0.82–0.90)]. The results on combinations of cumulative OP treatment followed the same pattern that the categories with current and/or past BP treatment were associated with a lower risk of overall infection in the MSM while the association between current BP treatment and overall infection was reversed in the unweighted Cox regression models. Furthermore, higher dose quintiles of cumulative BP treatment was found to be associated with a lower risk of overall infection [IRR (95% CI) = 0.98 (0.95–1.01), 0.96 (0.93–0.98), 0.91 (0.88–0.93), 0.81 (0.79–0.84) for 300–859 mg, 860–1799 mg, 1800–4039 mg and ≥4040 mg relative to 1–299 mg, respectively, in MSM] (P for trend <0.001).

In the analysis for serious infection, current and past BP treatment was consistently associated with a lower risk relative to those untreated in unweighted Cox regression models as well as MSM (Table 4). A dose-response trend was also observed in the association between cumulative dose of BP treatment and the lower risk of serious infection in the unweighted analysis (P for trend <0.001) but the association was not present in the MSM (P for trend = 0.63).

Sensitivity analysis of MSM by truncating stabilized combined weight at 1 and 99 percentile or based on stabilized weights derived from the most recent four visits produced similar results to the primary analysis.

Discussion

In this retrospective cohort study among women with PMO, patients treated with BP were found to have a lower risk of serious infection leading to hospitalization or ER visit in both unweighted multivariate-adjusted models and the MSM weighted analysis. The same association between treatment with BPs and a lower risk of overall infection was observed with the MSM but not unweighted models.

The descriptive analysis of baseline characteristics suggested patients treated with BP and other OP medications were

Table 1 Distribution of selected baseline covariates by exposure to various medications updated at each visit throughout follow-up among women with PMO

	Treatment assessed in 6-month before the current visit			Treatment updated cumulatively up until the current visit					
	BP (total N = 464,728 Ptyrs[a])	Other OP medications (total N = 67,860 Ptyrs)	No BP or other OP medications (total N = 517,979 Ptyrs)	With current BP Only (total N = 258,594 Ptyrs)	With current and past BP (total N = 206,134 Ptyrs)	With past BP only (total N = 203,991 Ptyrs)	With current other OP medications only (total N = 59,264 Ptyrs)	With current other OP medications and past BP Only (Total N = 8596 Ptyrs)	With no BP or other OP medications (N = 313,988 Ptyrs)
	%	%	%	%	%	%	%	%	%
Age (years) on PMO index date									
55–59	29.6	30.5	24.7	29.0	30.3	29.5	30.8	28.3	21.5
60–64	22.0	22.0	17.5	23.0	20.8	18.6	22.4	18.9	16.8
65–69	12.8	12.2	11.9	12.8	12.7	13.5	11.9	14.8	10.8
70–74	11.9	11.5	12.1	11.8	12.1	12.8	11.2	13.4	11.6
75–79	11.0	9.9	12.5	10.9	11.1	11.7	9.6	11.9	13.1
80+	12.8	13.9	21.4	12.6	13.0	13.8	14.1	12.8	26.3
Comorbidities									
Type 1 diabetes	2.1	2.2	3.9	1.6	2.6	3.5	2.1	2.7	4.2
Type 2 diabetes	12.8	13.2	19.1	11.0	15.1	18.0	13.1	13.8	19.8
End-stage renal disease	1.5	2.5	4.2	1.0	2.1	3.5	2.4	3.4	4.7
Chronic obstructive pulmonary disease	4.7	5.5	8.2	3.5	6.1	8.2	5.1	8.0	8.3
Chronic lung disease	5.7	6.9	11.4	4.2	7.5	10.3	6.4	10.2	12.1
Rheumatoid arthritis	2.3	1.8	2.1	1.9	2.7	2.7	1.6	3.3	1.8
Serious infection	4.2	5.0	5.4	4.4	4.0	4.0	5.0	4.4	6.4
Fragility fracture	3.7	5.5	15.5	2.8	4.8	1.6	5.4	6.1	24.5
Other fracture	5.8	5.9	6.6	4.3	7.7	2.6	5.9	5.9	9.1
Charlson comorbidity index (mean, SD)	0.5 (0.8)	0.5 (1.0)	0.6 (1.0)	0.5 (0.9)	0.4 (0.8)	0.4 (0.9)	0.5 (1.0)	0.5 (0.9)	0.6 (1.0)
Medications									
Corticosteroid (oral or injectable)	26.3	27.0	22.2	27.7	24.5	22.0	27.1	26.4	22.4
Anti-diabetics	10.8	10.6	12.8	9.9	11.8	11.6	10.8	9.4	13.5
Immunosuppressant drugs	1.1	0.9	0.8	1.0	1.3	1.0	0.8	1.4	0.7
Healthcare utilization									
Number of office/outpatient visits to other physicians (mean, SD)	7.2 (6.1)	7.7 (6.6)	7.5 (6.4)	7.1 (6.0)	7.2 (6.1)	7.1 (6.1)	7.6 (6.6)	7.7 (6.4)	7.8 (6.6)
Number of types of different drug classes dispensed (mean, SD)	8.3 (5.2)	8.9 (5.6)	7.9 (5.5)	8.0 (5.1)	8.4 (5.2)	8.3 (5.1)	8.9 (5.6)	8.9 (5.4)	7.6 (5.7)
Number of emergency room visits (mean, SD)	0.4 (1.1)	0.5 (1.4)	0.8 (1.6)	0.4 (1.1)	0.4 (1.1)	0.4 (1.1)	0.6 (1.4)	0.5 (1.3)	1.0 (1.8)
Days of hospitalization (mean, SD)	0.6 (0.5)	0.6 (0.5)	0.5 (0.5)	0.7 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.5 (0.5)	0.4 (0.5)

[a] Patient-years

SD standard deviation

Table 2 Distribution of log-stabilized combined weights at each visit for the analysis of serious infection and overall infection with and without truncation at the 0.5% and 99.5% percentile

Outcome		Minimum	25% percentile	Mean	Median	75% percentile	Maximum
Overall infection	Original	0	0.26	1.79	0.59	0.94	201,071.49
	Truncated	0	0.26	0.89	0.59	0.94	19.74
Serious infection	Original	0	0.19	1.25	0.52	0.91	32,770.96
	Truncated	0	0.19	0.85	0.52	0.91	18.71

younger and had a lower prevalence of selected risk factors of infection. The identification of serious infections leading to hospitalization, ER visit, or administration of parenteral anti-infective medication use is less susceptible to false-positive than overall infections. Nonetheless, overall infections, as a more sensitive outcome, was included in this study to evaluate the consistency of the association of OP treatment with the risk of a broader range of infectious conditions including less severe and local infections. Direct adjustment for potential risk factors of infection in the regression models generated opposite results on

the association of BP with overall infection versus serious infection. These results were not anticipated given that serious infections are the more severe types of overall infection and they are expected to share a similar etiology and risk factors. On the other hand, when these risk factors were used in the weights for IPTW estimation of a MSM, treatment with BP was consistently associated with a decreased risk of overall infection and serious infection. The reduced risk of infection associated with BP was further supported by the dose-response observed for both serious infection and overall infection. These

Table 3 IRR and 95% CI of overall infection comparing OP medication cohorts derived from MSM and regular Cox regression model

OP treatment	Number of patient-years	Number of cases	Unadjusted Cox PH regression model		Multivariate Cox PH regression model I*		Multivariate Cox PH regression model II†		MSM‡	
			IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Treatment assessed in 6 months before the current visit										
Without treatment	330,429	78,634	1	–	1	–	1	–	1	–
BP only	335,976	82,963	1.15	(1.14–1.17)	1.11	(1.10–1.13)	1.07	(1.05–1.08)	0.79	(0.77–0.81)
Other OP medication only	47,433	12,882	1.25	(1.23–1.27)	1.17	(1.14–1.19)	1.11	(1.08–1.13)	0.86	(0.82–0.90)
Treatment updated cumulatively up until the current visit										
Without treatment	221,126	58,148	1	–	1	–	1	–	1	–
With current BP only	211,083	54,117	1.15	(1.13–1.17)	1.11	(1.09–1.12)	1.02	(1.01–1.04)	0.86	(0.84–0.88)
With current and past BP only	124,893	28,846	0.93	(0.97–0.94)	0.95	(0.93–0.96)	1.04	(1.03–1.06)	0.75	(0.72–0.78)
With Past BP only	109,302	20,486	0.71	(0.70–0.73)	0.77	(0.76–0.79)	0.88	(0.86–0.89)	0.75	(0.72–0.78)
With current other OP medication only	43,134	11,968	1.18	(1.15–1.20)	1.11	(1.09–1.13)	1.09	(1.06–1.11)	0.89	(0.85–0.93)
With current other OP medication and past BP Only	4299	914	0.88	(0.82–0.94)	0.91	(0.86–0.98)	1.02	(0.95–1.09)	0.79	(0.66–0.95)
Cumulative BP dose—standardized to alendronate										
1–299 mg	41,591	10,340	1	–	1	–	1	–	1	–
300–859 mg	55,002	12,875	0.94	(0.92–0.97)	0.94	(0.92–0.97)	0.96	(0.94–0.99)	0.98	(0.95–1.01)
860–1799 mg	49,490	10,564	0.86	(0.84–0.88)	0.88	(0.86–0.90)	0.91	(0.89–0.94)	0.96	(0.93–0.98)
1800–4039 mg	47,500	9175	0.78	(0.76–0.80)	0.83	(0.80–0.85)	0.86	(0.84–0.88)	0.91	(0.88–0.93)
≥4040 mg	45,188	7381	0.66	(0.64–0.68)	0.75	(0.72–0.77)	0.78	(0.76–0.81)	0.81	(0.79–0.84)
P for trend	238,771	50,335	<0.001		<0.001		<0.001		<0.001	

*Adjusted for time-fixed variables including geographic region, length of enrollment in the data system, calendar year, number of office/outpatient visits, number of type of different drugs dispensed, number of emergency room visits, and days of hospitalization.

† Adjusted for above mentioned time-fixed variables and time-varying variables including age, diabetes (type I and type II), end stage renal disease, HIV/AIDS, liver cirrhosis, cystic fibrosis, chronic obstructive pulmonary disease, lupus, multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, inflammatory bowel disease, psoriasis, rheumatic fever, overweight/obesity, serious infection, serious neutropenia, decubitus ulcer, fragility fracture, Charlson comorbidity index, bisphosphonate treatment, corticosteroid (oral or injectable), anti-diabetics and immunosuppressant drugs, and malnutrition.

‡ Adjusted for abovementioned time-fixed variables with stabilized weight truncated at 0.5th and 99.5th percentile.

Table 4 IRR and 95% CI of serious infection comparing OP medication cohorts derived from MSM and regular Cox regression model

OP treatment	Number of patient-years	Number of cases	Unadjusted Cox PH regression model		Multivariate Cox PH regression model I*		Multivariate Cox PH regression model II†		MSM‡	
			IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Treatment assessed in 6-month before the current visit										
Without treatment	448,182	37,316	1	–	1	–	1	–	1	–
BP only	430,433	25,191	0.79	(0.78–0.81)	0.78	(0.77–0.79)	0.91	(0.89–0.93)	0.71	(0.68–0.75)
Other OP medication only	62,122	4263	0.92	(0.89–0.95)	0.86	(0.83–0.89)	0.97	(0.93–1.01)	0.77	(0.71–0.83)
Treatment updated cumulatively up until the current visit										
Without treatment	276,254	26,945	1	–	1	–	1	–	1	–
With current BP only	253,210	14,257	0.68	(0.67–0.70)	0.68	(0.66–0.70)	0.84	(0.82–0.86)	0.65	(0.62–0.68)
With current and past BP Only	177,223	10,934	0.67	(0.66–0.69)	0.68	(0.67–0.70)	0.90	(0.88–0.93)	0.96	(0.90–1.01)
With past BP only	171,927	10,371	0.62	(0.61–0.63)	0.66	(0.65–0.68)	0.86	(0.84–0.88)	0.89	(0.84–0.94)
With current other OP medication only	54,945	3829	0.80	(0.77–0.83)	0.76	(0.73–0.78)	0.94	(0.91–0.97)	0.86	(0.79–0.93)
With current other OP medication and past BP only	7178	434	0.67	(0.61–0.74)	0.69	(0.62–0.75)	0.87	(0.79–0.95)	1.09	(0.88–1.36)
Cumulative BP dose—standardized to alendronate										
1–430 mg	73,520	5233	1	–	1	–	1	–	1	–
430–900 mg	69,134	4370	0.89	(0.85–0.93)	0.91	(0.87–0.94)	0.92	(0.88–0.96)	0.97	(0.93–1.01)
900–2240 mg	76,171	4746	0.88	(0.85–0.92)	0.90	(0.86–0.93)	0.91	(0.88–0.95)	0.99	(0.95–1.03)
2240–4780 mg	73,769	4103	0.79	(0.76–0.82)	0.83	(0.80–0.87)	0.85	(0.82–0.89)	1.01	(0.97–1.05)
≥ 4780 mg	64,072	3311	0.74	(0.70–0.77)	0.81	(0.78–0.85)	0.81	(0.78–0.85)	0.98	(0.94–1.03)
P for Trend	356,666	21,763	<0.001		<0.001		<0.001		0.63	

*Adjusted for time-fixed variables including geographic region, length of enrollment in the data system, calendar year, number of office/outpatient visits, number of type of different drugs dispensed, number of emergency room visits, and days of hospitalization.

† Adjusted for abovementioned time-fixed variables and time-varying variables including age, diabetes (type I and type II), end stage renal disease, HIV/AIDS, liver cirrhosis, cystic fibrosis, chronic obstructive pulmonary disease, lupus, multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, inflammatory bowel disease, psoriasis, rheumatic fever, overweight/obesity, serious infection, serious neutropenia, decubitus ulcer, fragility fracture, Charlson comorbidity index, bisphosphonate treatment, corticosteroid (oral or injectable), anti-diabetics and immunosuppressant drugs, and malnutrition.

‡ Adjusted for abovementioned time-fixed variables with stabilized weight truncated at 0.5th and 99.5th percentile.

results suggest that time-varying confounding is only present in the comparison of the infection risk between treated and untreated OP patients. Furthermore, given the wide range of conditions included in the assessment of overall infection, specific time-varying confounders may only be present for less severe infections and thus only MSM rather than regular multivariate-adjusted model can generate a valid effect estimate.

Though the underlying mechanism for the reduced risk of infection associated with BP treatment is unknown, potential influence of BP on the immune system has been documented based on animal studies and in vitro studies. Administration of clinically relevant doses of BP in mice increases antibody response to live and inactive viruses, proteins, haptens, and existing commercial vaccine formulations. It was found that BP target B cells and enhance B cell expansion and antibody production upon encounter, suggesting BP are an additional class of adjuvants that boost humoral immune responses [15]. In addition, BP may exert several effects on the immune system. In particular, pamidronate stimulates the production of a T cell subset that specifically inhibits bone resorption and may activate the production of antigenic receptor T cells, leading to the release of cytokines [16, 17]. Other studies also reported other effects of BP in increasing the production of interleukin-1, interleukin-6, and C-reactive proteins [16–19]. Future human studies including population-based studies are warranted to confirm whether these changes in the immune system induced by BP treatment convey a protective effect against infection.

Several additional limitations of the current study should be noted when interpreting the results. First, claims databases have inherent limitations because the claims are collected for the purpose of payment rather than research. For instance, the presence of a diagnosis code on a medical claim may not represent the true presence of a disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Secondly, the assessment of cumulative dose of BP was based on treatment received during all previous look-back periods, and

thus the length of available look-back period partially determines the total cumulative dose. Therefore, the assessment of dose-response relationship with BP treatment may be biased towards the null given the likely non-differential misclassification of the cumulative dose. Thirdly, the unstructured "visit process" used in the study does not differentiate the temporal sequence between the time-varying confounders and time-varying exposure during the look-back period. Therefore, for some patients time-varying confounders may be affected by received OP treatment. Fourthly, because time at risk is defined as the interval between two adjacent visits, it may not reflect the actual etiologically relevant time window. Finally, the estimated effect in this study was based on the observed visit process and therefore may not be generalized to a population with different visit process.

A reduced risk of serious and overall infection associated with BP treatment in women with PMO was identified in this study using MSM to adjust for time-varying confounders. The discrepancy of effect estimates for overall infection but not serious infection comparing unweighted multivariate-adjusted models and MSM suggested the analysis of composite outcomes with a wide range of disease severity may be more susceptible to time-varying confounding. Further studies need to confirm these findings and investigate potential underlying mechanisms.

Compliance with ethical standards

Conflicts of interest Fei Xue, Vamshidar Goli, Paul Petraro, Trevor McMullan, and J. Michael Sprafka were employees of Amgen at the time of this manuscript preparation. Fei Xue and J. Michael Sprafka held Amgen stocks/stock options when the manuscript was prepared. Eric Tchetgen Tchetgen declares that he has no conflict of interest.

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