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ONJ in Two Dental Practice-Based Research Network Regions

ABSTRACT

The incidence of osteonecrosis of the jaw (ONJ) in the population is low, but specifics are unknown. Potential risk factors include bisphosphonate treatment, steroid treatment, osteoporosis, and head/neck radiation. This Dental Practice-Based Research Network study estimated ONJ incidence and odds ratios from bisphosphonate exposure and other risk factors using a key word search and manual chart reviews of electronic records for adults aged ≥ 35 yrs enrolled during 1995–2006 in two large health-care organizations. We found 16 ONJ cases among 572,606 cohort members; seven additional cases were identified through dental plan resources. Among 23 cases (0.63 *per* 100,000 patient years), 20 (87%) had at least one risk factor, and six (26%) had received oral bisphosphonates. Patients with oral bisphosphonates were 15.5 (CI, 6.0–38.7) more likely to have ONJ than non-exposed patients; however, the sparse number of ONJ cases limits firm conclusions and suggests that the absolute risks for ONJ from oral bisphosphonates is low.

KEY WORDS: osteonecrosis, bisphosphonates, cohort study, Dental PBRN.

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INTRODUCTION

Recent reports have documented osteonecrosis in the jaw of patients treated with bisphosphonates (Marx *et al*., 2005; Fresco *et al*., 2006; Hewitt and Farah, 2007; Mavrokokki *et al*., 2007; Murad *et al*., 2007; Pazianas *et al*., 2007; Yarom *et al*., 2007; Grbic *et al*., 2008). ONJ has been defined as an area of exposed, non-vital bone in the maxilla or mandible that persists over 6-8 wks (Bilezikian, 2006; Cartsos *et al*., 2008). Bisphosphonates are typically administered intravenously to metastatic cancer patients and orally to osteoporosis patients to prevent bone loss (Marx *et al*., 2005; Migliorati *et al*., 2005; Wilkinson *et al*., 2007). These drugs are believed to affect the jaw because of the higher remodeling and turnover rate in this area of the skeleton (Reszka and Rodan, 2003; Marx *et al*., 2005; Reid *et al*., 2007). ONJ incidence and risks associated with oral bisphosphonates remain undefined in the population (McMahon *et al*., 2004; Woo *et al*., 2006; Pazianas *et al*., 2007; Cartsos *et al*., 2008; Rizzoli *et al*., 2008).

This study's objectives were to estimate the incidence of ONJ in two large Health Maintenance Organizations (HMOs) participating in The Dental Practice-Based Research Network (DPBRN), and assess the impact of oral bisphosphonate exposure on the development of ONJ. We used an automated review of outpatient electronic medical records (EMR) to identify suspected ONJ cases, which were confirmed through manual chart review. Chart notes review was necessitated by the lack of an existing diagnostic code for this condition at the time the study was performed (Edwards *et al*., 2008).

METHODS

Setting

The Institutional Review Board at each institution approved this study. Kaiser Permanente Northwest (KPNW) is an integrated, group model HMO serving about 465,000 members in Oregon and southwest Washington. HealthPartners of Minnesota (HP) is a mixed-model HMO serving nearly 800,000 enrollees in the Minneapolis/St. Paul metropolitan area. Both organizations provide comprehensive dental care to about half of their HMO populations. Each HMO makes available for research electronic data captured from outpatient and inpatient encounters, including physician chart notes, pharmacy dispenses, home health care, and out-of-plan services. Complete electronic dental records were not available for the entire study period and were not used. The authors of this

Table 1. Diagnoses and Procedure Codes That Could Indicate Osteonecrosis of the Jaw

Diagnoses (ICD-9)	Included Codes
Inflammatory conditions of the jaw	526, 526.1–526.9
Other unspecified disorders of bone and cartilage, including cyst of bone, aseptic necrosis of bone	733, 733.2–733.29, 733.4, 733.40–733.49, 733.9, 733.95
Other open wound of the head, jaw, internal structures of the mouth	873, 873.4–873.9
Late effects of treatment	909, 909.0–909.9
Fracture of the face bones with pathologic designation	802.20–802.39, 802.4, 802.5, 802.8
Procedures (CPT-4)	
Excision of bone or tumor (jaw or face)	21025, 21026, 41830, 41850, 21029–32, 21044
Malignancy treatment procedures	21015, 21034, 21040, 21045–47

study have extensive experience using these data to address a wide range of medical and dental care topics.

Study Population

The population included adults, aged ≥ 35 yrs, with ≥ 1 yr of concurrent medical plan and pharmacy benefit coverage during 1/1/1995–9/30/2006 (most recent available) for HP members and 1/1/1998–9/30/2006 for KPNW members, excluding sickle cell anemia patients.

Design

We used a retrospective cohort model to assess ONJ incidence in the two HMO populations and estimate odds ratios (OR) and confidence intervals (CI) for ONJ from exposure to oral bisphosphonates and other hypothesized risk factors (Migliorati *et al*., 2005; Estefania-Fresco *et al*., 2006; Hewitt and Farah, 2007; Khosla *et al*., 2007; Marx *et al*., 2007; Hess *et al*., 2008). A five-step process identified ONJ cases from the study population. First, we flagged potential ONJ cases among patients with a diagnostic (ICD-9) or procedure (CPT-4) code that could have been used to describe or treat a necrotic lesion in the jaw (Table 1). Second, we extracted digitized physician chart notes from encounters for patients identified in step 1 and used a natural language processing (NLP) program to conduct a key-word search for codes and terms describing a necrotic bone lesion (*e.g*., ONJ, osteonecrosis, necrosis, osteomyelitis, bone lesion) in the maxilla, mandible, or jaw. Third, chart notes flagged by the NLP program were reviewed by study staff for case relevance. Fourth, patients considered to have a relevant chart received a comprehensive manual chart review to confirm their ONJ case status. Last, to guard against false-negatives, we performed steps 2-4 for all cohort members who were excluded in Step 1 (*i.e*., those with no diagnosis or procedure code suggesting a possible ONJ lesion). We mailed inquiries about ONJ among patients to 170 dentists and oral surgeons within both health plans and oral surgeons from the University of Minnesota (UM) who regularly receive HP surgical referrals. We also obtained case information from ONJ case registries at UM and KPNW.

Measures

We defined ONJ as a clinically diagnosed exposed necrotic lesion in the mandible or maxilla. Only patients with ONJ confirmed by manual chart review were considered cases. Trained reviewers completed chart audits under study investigator's guidance. Study team dentists adjudicated indeterminate cases. We used visit dates with ONJ notation or diagnosis to determine lesion onset and healing. We collected outpatient information about steroids, oral and intravenous (IV) bisphosphonates, and pharmacy dispenses (dates, dosage, days' supply). We also collected encounters with diagnosis and procedure codes for other hypothesized risk factors: cancer, osteoporosis, osteopenia, diabetes, immune disorders (*e.g*., HIV/AIDS), and head and neck radiation treatment. Those occurring before the ONJ diagnosis date were considered potential risk factors and were included in the evaluation. We also created an indicator for individuals with any risk factor. Age at entry, sex, and dental plan coverage were also collected.

Statistical Analysis Plan

We estimated univariate and adjusted ORs and 95% confidence intervals (CI) for the likelihood of ONJ using PROC LOGISTIC (SAS 9.1.3). Maximum-likelihood estimates and p-values were estimated separately for binary indicators of any cancer, osteoporosis, diabetes, immune disorders, oral bisphosphonate dispense, steroid dispense, head/neck radiation, and the any-risk-factor score. The main-effects model included any cancer diagnosis, osteoporosis, diabetes, immune disorders, oral bisphosphonate dispense, and steroids dispense prior to ONJ diagnosis date, and controlled for sex and dental insurance.

RESULTS

We identified 572,606 health plan members who met the eligibility requirements (367,082 KPNW members beginning 1/1/1998; 205,524 HP members beginning 1/1/1995). Age, sex, HMO dental insurance coverage, and time enrolled were similar for the two plans (Table 2). Overall, cohort members were about age 50; roughly half were female or had dental insurance. Race and ethnicity were available for 57% of KPNW and 39% of the HP cohorts, of whom 91% were Non-Hispanic white.

Approximately 25,000 cohort members' (4.4%) EMR contained at least one encounter having a diagnosis or procedure code that suggested a necrotic bone lesion, including 'inflammatory jaw condition' (n = 3156), 'cyst of bone' (n = 705), 'aseptic necrosis of the bone' (n = 1038), and 'open wound of the jaw' (n = 349). The NLP review of these records identified 73 suspected ONJ cases, of which 16 (all KPNW) were confirmed by manual chart review (Table 3). We identified six additional HP cases through UM oral surgeons and one more KPNW case through the Peer Review Committee. ONJ episodes appeared to be longer than 8 wks for all cases.

Table 2. Demographic Characteristics of the Cohort Population

Cohort Characteristics	Kaiser Permanente Northwest	HealthPartners	Total
Total population	367,082	205,524	572,606
Mean age (SD)	49.8 (13.2)	49.1 (12.2)	49.5 (12.8)
Female (%)	52.4	52.7	52.5
Hispanic* (%)	3.8	1.8	3.1
Race* (%)			
White	92.1	88.2	91.0
African American	2.4	7.0	3.7
Other	5.5	4.8	5.3
Mean months enrolled (SD)	62.8 (34.0)	65.1 (45.8)	63.7 (38.7)
Health plan dental coverage (%)	50.5	49.7	50.2

*Percent with known ethnicity and race. The percent with known race-ethnicity is 56.5% in KPNW, 39.2% in HP, and 49.9% overall.

Table 3. Demographic and Risk Factor Characteristics of Cohort Members with and without ONJ

	Kaiser Permanente Northwest				HealthPartners			
	Cases		Non-cases		Cases		Non-cases	
	N = 17		N = 367,065		N = 6		N = 205,518	
	N	% or Mean (SD)	N	% or Mean (SD)	N	% or Mean (SD)	N	% or Mean (SD)
Mean age (yrs) (SD)		62 (13)		50 (13)		54 (12)		49 (12)
Female	13	76.5%	192,497	52.4%	3	50.0%	108,213	52.7%
Dental insurance	9	52.9%	185,200	50.5%	4	66.7%	102,094	49.7%
Mean months enrolled (SD)		76 (35)		63 (34)		82 (52)		65 (46)
Cancer								
Any cancer	8	47.1%	44,075	12.0%	4	66.7%	27,693	13.5%
Multiple myeloma	1	5.9%	286	0.1%	3	50.0%	460	0.2%
Breast	1	5.9%	6552	1.8%	1	16.7%	4842	2.4%
Oral	5	29.4%	8206	2.2%	0	0.0%	760	0.4%
Osteoporosis	6	35.3%	10,641	2.9%	1	16.7%	12,746	6.2%
Osteopenia	1	5.9%	2974	0.8%	2	33.3%	16,019	7.8%
Diabetes mellitus	3	17.7%	42,006	11.4%	1	16.7%	25,863	12.6%
Immune disorders*	1	5.9%	1402	0.4%	0	0.0%	1745	0.9%
Head and neck radiation	2	11.8%	4246	1.2%	2	33.3%	4142	2.0%
Oral bisphosphonates	6	35.3%	12,954	3.5%	0	0.0%	8203	4.0%
Mean days (SD)		1465 (964)		617 (656)		–		643 (655)
Mean dispenses (SD)		26 (17)		11 (12)		–		14 (15)
IV bisphosphonates†	2	11.8%	369	0.1%	NA		NA	
Corticosteroids	6	35.3%	87,580	23.9%	5	33.3%	46,220	22.5%
Mean days (SD)		363 (471)		84 (298)		120 (74)		93 (323)
Mean dispenses (SD)		15 (21)		4 (7)		14 (3)		4 (8)
Any risk factor	14	82.4%	117,903	32.1%	6	100.0%	72,608	35.3%

*Immune mechanism disorders, includes diagnoses of AIDS/HIV and lupus.
†Noted in the outpatient medical records only.

Over the two cohorts, patients with confirmed ONJ were predominantly female and about 10 years older than those without ONJ. Most patients with ONJ (87.0%) had at least one of the hypothesized risk factors we examined. The most common diagnoses in the subgroup with ONJ were cancer and osteoporosis. The most common cancer diagnoses for ONJ cases were oral cancer among KPNW members and multiple myeloma among HP members; nine of 12 cases with cancer had multiple diagnoses. Four ONJ patients (17.4%) received head and neck radiation treatment.

Large portions of the cohort had oral bisphosphonate or corticosteroid exposure. Overall, 21,164 patients (3.7%) had at least 1 oral bisphosphonate dispense, and 133,800 (23.4%) had a corticosteroid dispense. KP members averaged 11 dispenses

(SD 12) for 618 days' supply (SD 656, median 390); HP members averaged 14 dispenses (SD 15) for 643 days' supply (SD 655, median 420). Six patients with ONJ had an oral bisphosphonate dispense earlier than ONJ onset; all were KPNW members. Days' supply ranged from 154 to 2400 (mean, 1465; SD, 964; median, 1692). Steroid days' supply for 133,800 patients without ONJ averaged 87 (SD 307), while 17 cases received an average 232 days' supply (SD 338) prior to ONJ onset. Two cases had an IV bisphosphonate dispense noted in the KPNW outpatient EMR; however, inpatient data from each health plan did not indicate whether any bisphosphonate was part of the inpatient drug treatment regimen.

Univariate logistic regression results identified 4 significant risk factors for ONJ over both sites and at each site ($p < 0.0001$) (Table 4). Cohort members with cancer were 7.6 times more likely (CI, 3.4-17.3) to have ONJ than those without cancer, whereas patients who had head and neck radiation treatment *vs*. none had an OR for ONJ of 14.2 (CI, 4.8-41.6). Having osteoporosis increased the odds of ONJ by 10.3 times (CI, 4.2-25.0). No HP member with ONJ had an oral bisphosphonate dispense, but KPNW members with oral bisphosphonate exposure were more likely to have ONJ than members with no oral bisphosphonate dispenses (OR 14.9; CI, 5.5-40.3). Steroid exposure appeared to be related to ONJ among KPNW patients only (OR 2.8; CI, 1.1-7.4).

The small number of ONJ cases prevented us from estimating adjusted models that controlled for multiple covariates, and many patients had more than one risk factor. Patients with any risk factor were 13.4 times (CI, 4.0-45.0) more likely to have ONJ overall than patients with no risks.

DISCUSSION

Our examination found few confirmed ONJ cases among 572,000 HMO cohort members, despite the fact that a third of our cohort had at least one presumed ONJ risk factor, and about 10% had a medical diagnosis or procedure that warranted examination by the study team. ONJ incidence in the cohort was 0.63 (0.39-1.59) *per* 100,000 person-years. This is less than the 1/10,000-1/100,000 range found by Khosla and colleagues (Khosla *et al*., 2007), but close to the 0.7 *per* 100,000 reported by Merck (American Association of Oral and Maxillofacial Surgeons, 2007). Among oral bisphosphonate users, however, ONJ incidence was 4.1 (3.0-6.3) *per* 100,000 person-years.

Analysis of our data supports the notion that many factors may contribute to ONJ (McMahon *et al*., 2004). Of the 23 ONJ cases identified, four patients had head and neck radiation therapy, and two others are known to have had IV bisphosphonate dispenses. Head and neck radiation is a primary risk factor for osteoradionecrosis (McMahon *et al*., 2004; Marx *et al*., 2005). Other cancer patients may have received IV bisphosphonates, separately or in combination with oral treatments, as part of their inpatient chemotherapy regimens, but data were not available to address this question. About 10% of patients treated with IV bisphosphonates are estimated to develop ONJ (Woo *et al*., 2006).

This study was limited by the extent that patients' health and treatment histories were documented in the EMR, before an ONJ diagnosis code was available. Most data we examined were entered before the first published indication of an ONJ-bisphosphonate relationship in 2003, and 'ONJ' was not specifically mentioned in our medical records until 2005. Consequently, we used the NLP key word search to identify potential ONJ discussions from provider chart notes, such as descriptions of open, slow-healing necrotic bone lesions, and conducted comprehensive reviews of all patients having any mention of these terms, as a guard against false-positives. This was the first large cohort study to include chart review. For example, 3156 cohort members were diagnosed with an inflammatory condition of the jaw, mainly osteomyelitis, yet only 12 were confirmed ONJ cases. We guarded against false-negatives by conducting an NLP review of chart notes for cohort members with no identified ONJ risk factor. No additional cases were confirmed through this process.

Even with these steps, the data systems are limited by the detail and quality of the data entered into the system. We identified six additional ONJ cases among HP patients through UM oral surgeons. One of the three KPNW members with ONJ who was known to a dental system peer review committee was not flagged by our EMR review. We re-examined the medical charts for these seven patients and found no information that would have been captured by our NLP review. For the HP cohort, we found that oral surgery records were not captured by the EMR, primarily because patients were referred for treatment to UM oral surgeons not charting in the HP EMR. Oral surgery is also provided to KPNW Dental Care Plan members, and the EMR includes this information. Overall, we are confident that our search strategy was able to capture most ONJ cases at both sites.

Both health systems had little information about hospital dispenses. This restricted our ability to evaluate IV bisphosphonate exposure. Cancer patients typically receive IV bisphosphonates as inpatients, so it is possible that the IV form of the drug played a role in ONJ development in confirmed cases among cancer patients.

The accepted definition of ONJ suggests a minimum duration of 6-8 wks (Bilezikian, 2006; Cartsos *et al*., 2008), and case reports describe the condition as slow-healing (Ruggiero *et al*., 2006; Khosla *et al*., 2007). All ONJ lesions persisted beyond the 8-week threshold, though we rarely saw mention of healing in the charts.

The small number of confirmed cases limited our regression results. We found univariate ORs suggesting that cancer, osteoporosis, radiation treatment, and oral bisphosphonates predict ONJ. These results should be interpreted with caution because of the wide confidence intervals and the possibility of confounding by indication. More importantly, the low numbers limited our ability to test the association of predicted probabilities and observed responses for the univariate analyses.

This study is consistent with previous findings suggesting an increased risk of ONJ for oral bisphosphonate users (Migiorati *et al*., 2005; Hewitt and Farah, 2007; Marx *et al*., 2007; Pazianas *et al*., 2008), but our confidence in the association is limited by the small proportions of ONJ patients exposed to oral bisphosphonates (6/23) and oral bisphosphonate users who developed ONJ (6/21,163). While it may be prudent for patients to address dental needs before starting oral bisphosphonates (Pazianas

Table 4. Univariate Odds Ratio (OR) Estimates for Predictors of Osteonecrosis of the Jaw, Overall and by Site

	Kaiser Permanente Northwest	HealthPartners	Overall
Predictor	OR (CI)	OR (CI)	OR (CI)
Any cancer	6.5 (2.5–16.9)	12.8 (2.4–70.1)	7.6 (3.4–17.3)
Osteoporosis	18.3 (6.8–49.4)	3.0 (0.4–25.9)	10.3 (4.2–25.0)
Diabetes	1.7 (0.5–5.8)	1.4 (0.2–11.9)	1.6 (0.5–4.6)
Immune disorder	16.3 (2.2–123.0)	—*	8.2 (1.1–61.0)
Head/neck radiation	11.4 (2.6–49.8)	24.3 (4.5–132.8)	14.2 (4.8–41.6)
Oral BPs	14.9 (5.5–40.3)	—*	9.2 (3.6–23.3)
Corticosteroids	2.8 (1.1–7.4)	3.4 (0.7–17.1)	3.0 (1.3–6.8)
Any risk factor	9.8 (2.8–34.3)	—*	13.4 (4.0–45.0)

OR = odds ratio, CI = confidence interval, BPs = bisphosphonates.
*ORs could not be calculated due to zeros in the numerator for oral BPs and denominator for any risk factor.

et al., 2007; Khan *et al*., 2008; Qaseem *et al*., 2008), suggestions to interrupt oral bisphosphonate treatment to receive dental care may be unwarranted. The small number of cases precludes further clinical recommendations from this study. The potential for interaction between bisphosphonate exposure and concurrent serious medical illness to increase the likelihood of ONJ warrants continued study and more extensive monitoring by medical and dental practitioners. In October 2007, ICD-9 733.45, "aseptic necrosis of bone, jaw," was introduced. This new code should help clinicians to document and researchers to identify ONJ cases. We further recommend that health systems and providers also document onset dates, exposure to potential risks, and healing time.

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