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ABSTRACT

Case reports and cohort studies have linked bisphosphonate therapy and osteonecrosis of the jaws (ONJ), but neither causality nor specific risks for lesion development have been clearly established. We conducted a 1:3 case-control study with three dental Practice-based Research Networks, using dentist questionnaires and patient interviews for collection of data on bisphosphonate therapy, demographics, co-morbidities, and dental and medical treatments. Multivariable logistic regression analyses tested associations between bisphosphonate use and other risk factors with ONJ. We enrolled 191 ONJ cases and 573 controls in 119 dental practices. Bisphosphonate use was strongly associated with ONJ (odds ratios [OR] 299.5 {95%CI 70.0-1282.7} for intravenous [IV] use and OR = 12.2 {4.3-35.0} for oral use). Risk markers included local suppuration (OR = 7.8 {1.8-34.1}), dental extraction (OR = 7.6 {2.4-24.7}), and radiation therapy (OR = 24.1 {4.9-118.4}). When cancer patients (n = 143) were excluded, bisphosphonate use (OR = 7.2 {2.1-24.7}), suppuration (OR = 11.9 {2.0-69.5}), and extractions (OR = 6.6 {1.6-26.6}) remained associated with ONJ. Higher risk of ONJ began within 2 years of bisphosphonate initiation and increased four-fold after 2 years. Both IV and oral bisphosphonate use were strongly associated with ONJ. Duration of treatment > 2 years; suppuration and dental extractions were independent risk factors for ONJ.

KEY WORDS: osteonecrosis, jaws, bisphosphonates, risk factors.

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Risk Factors for Osteonecrosis of the Jaws: a Case-Control Study from the CONDOR Dental PBRN

INTRODUCTION

Osteonecrosis of the jaws (ONJ) is a rare clinical entity, which has historically been described in the context of severe local or systemic disease or after iatrogenic intervention (Almazrooa and Woo, 2009). Beginning in 2003, case reports, case-series, and cohort studies linked ONJ with bisphosphonate treatment, with prevalence varying from less than 1% to 28% (Wang *et al.*, 2003; Ruggiero *et al.*, 2004; Woo *et al.*, 2006).

Bisphosphonates are indicated mainly for osteolytic conditions associated with cancer (Berenson *et al.*, 1996, 2002; Hillner *et al.*, 2003; Body, 2009) and osteoporosis (Devogelaer, 2000; Stafford *et al.*, 2004), with efficacy in prevention of vertebral and hip fractures (Hortobagyi *et al.*, 1996; Ross *et al.*, 2003). Several bisphosphonates are available in the US, including alendronate, etidronate, ibandronate, pamidronate, risedronate, and zoledronic acid. Alendronate and risedronate alone accounted for > 3 million prescriptions in 2003, and this number has been steadily increasing, warranting rigorous study of potential side-effects (Stafford *et al.*, 2004).

We conducted a case-control study in dental practices to determine the risk associated with bisphosphonates and to identify other risk factors for ONJ, including dental diseases and procedures. This article presents our main findings related to demographics, medical conditions, dental procedures, and systemic medications. Further information on specific dental diseases and procedures is presented elsewhere.

METHODS

Study Design

We designed a protocol across the three National Institutes of Health-funded dental Practice-based Research Networks (PBRNs), headquartered in New York, NY (PEARL), Seattle, WA, and Portland, OR (Northwest PRECEDENT), and Birmingham, AL (DPBRN). General dentists and dental specialists from within and outside the network membership were informed about the study through mass mailings. Practitioners who had diagnosed ONJ cases and were interested in participating were asked to contact the respective network. Power analyses indicated that 170 ONJ cases would be necessary for detection of differences with a power of 80%. The joint protocol was approved by each PBRN's Institutional Review Board.

Case Selection

The study population was drawn from dental practices within the geographic areas of the PBRNs. Inclusion criteria were age > 40 yrs old, no history of facial

trauma or sickle cell disease, and diagnosis of ONJ with onset after January 1, 2003. ONJ was defined as maxillary or mandibular exposed bone of any size that clinically appeared necrotic, without regard to duration or cause. Since we included all osteonecrotic jaw lesions, we neither restricted cases to a minimum duration of 8 wks, nor excluded those with a history of radiation therapy (Khosla *et al.*, 2007). Cases originated from primary, secondary, and tertiary care centers. Subsequent to identification of a case, practitioners were asked to contact the patient verbally and ask permission for contact by the researchers, who then obtained informed consent.

Control Selection

We enrolled three controls for each ONJ case, aiming to select them from the same primary care practice where a case was diagnosed. The inclusion criteria were age > 40 yrs old and no history of bone necrosis. For cases obtained from secondary or tertiary care centers, controls were selected from the general dental practice that referred the case or, if this was not possible, from a practice in the same geographic area. We performed no further matching.

Data Collection

Standardized dentist forms queried dental signs, symptoms, diagnoses, and procedures between 2000 and 2008 that preceded the diagnosis of ONJ by a maximum of 3 yrs. For example, for patients diagnosed with ONJ in 2007, the questionnaire covered the period 2004 to 2007. We recorded tooth loss, periodontal disease, caries, endodontic problems, gingival bleeding, suppuration, pain or sensitivity, neurosensory disturbances, and information on dental procedures and dates of their performance. For controls, we collected the same data beginning 3 yrs prior to interview date. ONJ-specific issues did not apply to controls. Dental records were accessed by the dentist or his/her designee, and data forms were completed and returned to the PBRN for analyses. For quality assurance, 10% of the records from each PBRN were re-abstracted by a research assistant and compared with the original.

Patients underwent a structured telephone interview conducted by trained research assistants at each PBRN, assessing ONJ characteristics (mouth location, date of onset, size, pain, duration, healing), oral hygiene, medical history (cancers, radiotherapy, bone diseases), occupational exposures (chemical industry, phosphorus exposure), demographics, education and lifestyle (race/ethnicity, alcohol and smoking history), and medications (oral and/or IV bisphosphonates, chemotherapy, antiretroviral medication, steroids, regular use of other drugs). ONJ-related questions did not apply to controls.

Exposures

The primary exposure of interest was bisphosphonate therapy. Secondary exposures included therapeutic radiation to the jaws, diagnosis of cancer or osteoporosis, dental diagnoses and procedures, co-existing chronic diseases, and long-term use of systemic corticosteroids. These factors were selected based on their previous association with osteonecrosis. Duration, frequency,

dose, and scheduling of each bisphosphonate and other details of exposure were collected during the patient interview. For cases, dental procedures occurring prior to ONJ development but within the same dental quadrant were labeled as “matched” procedures, while those in uninvolved quadrants were “unmatched”. Cases in which the location of ONJ was not known were excluded from the pertinent analyses. These data were dichotomized for controls as present or absent.

Statistical Considerations

Conditional logistic regression models were used to investigate the association between bisphosphonates and other factors with ONJ (SAS procedure LOGISTIC, SAS Institute, Cary, NC, USA). The case-control sets originating from dental practices were the stratification variables. Data from the three PBRNs were pooled, and OR and 95%CI were calculated. No adjustment for the network clustering was performed. Potentially confounding factors and multicollinearity were evaluated. Propensity score approaches (D’Agostino, 1998; Calvo-Alen *et al.*, 2006) were used in a secondary analysis to control for strong associations between bisphosphonate exposure and the conditions for which bisphosphonates are prescribed. Covariates included general indicators of health, demographics, co-morbidities, dental diagnoses and procedures, and treatment with medications other than bisphosphonates.

RESULTS

We identified 308 cases of ONJ, of which 117 cases either refused participation or could not be contacted. Therefore, 191 cases together with 573 controls were included in the analyses (see Appendix). Bisphosphonate use was reported by 113 cases (83%) and 71 controls (15%), with a mean duration (standard error) of 5.6 (0.7) and 4.2 (0.6) yrs, respectively (Table 1). Duration and numbers and sizes of the ONJ lesions are depicted in Table 2.

Bivariate Analyses

Compared with controls, more cases were aged > 60 yrs (OR 3.1 [95%CI 2.1-4.4]), had not finished high school (3.2 [1.6-6.7]), had income < \$25,000 (2.7 [1.7-4.5]), and had a history of tobacco use (1.7 [1.2-2.3]). Patients with a history of any cancer had OR = 14.3 (95%CI 8.8-23.3) for ONJ compared with those without cancer. Similarly, patients who reported having osteoporosis (OR = 7.0 [95%CI 4.2-11.6]), diabetes (1.7 [1.1-2.8]), and anemia (3.1 [2.1-4.5]) had higher unadjusted associations with ONJ compared with individuals without these conditions.

Both oral (PO) and IV bisphosphonates were associated with ONJ (OR = 9.8 [95%CI 5.3-18.1] and 299.5 [70.0-1282.7], respectively), as were chemotherapy for cancer (25.7 [13.8-48.0]), radiation to the jaws (7.6 [4.3-13.6]), and use of systemic corticosteroids (2.2 [1.6-3.2]). For all cases, bisphosphonate use < 2, 2-5, and > 5 yrs had ORs (95%CI) of 13.9 (6.4-30.2), 32.3 (13.5-77.3), and 29.4 (12.7-68.3), respectively. When those with a history of cancer were excluded, the respective ORs became 5.2 (1.2-22.5), 11.4 (3.2-40.2), and 26.6 (5.3-133.6). Other bivariate analyses for these non-cancer patients (47 cases, 138

Table 1. Distribution (percent) of Participant Characteristics, Co-morbidities, Treatments, and Dental Procedures by Case/Control

Characteristic	Case% (n = 191)	Control% (n = 573)
Mean age (SD) in 2003 (yrs)	62 (11.3)	54 (11.4)
Gender		
Female	71	65
Race		
Caucasian	93	89
African-American	4	6
Other	3	5
Education		
More than high school	56	70
High school	35	27
Less than high school	9	3
Tobacco use	57	45
Any cancer	75	22
Osteoporosis	35	10
Osteopenia	8	6
Anemia	37	16
Diabetes	17	11
Gingival bleeding	42	47
Suppuration	26	8
Steroid use	59	41
Chemotherapy	60	7
Radiation therapy to head and neck	25	5
Bisphosphonate use	83	15
Bisphosphonate agents		
Oral risedronate	8	3
Oral ibandronate	5	2
Oral alendronate	38	11
Intravenous pamidronate	23	0.2
Intravenous zoledronic acid	48	0.7
Bisphosphonate use duration		
None	22	87
> 0-2 yrs	20	6
> 2-5 yrs	29	4
> 5 yrs	29	3
Extraction in ONJ region*	41	9
Endodontic treatment in ONJ region*	14	8
Implant within ONJ region*	3	1
Surgical periodontal treatment within ONJ region*	3	2

ONJ: osteonecrosis of the jaw.

*In the ONJ region for cases only; any region of the mouth (yes or no) for controls.

controls) revealed risk associations similar to those of the whole sample (data not shown).

Multivariate Analyses

In a model including demographics, dental risk factors, treatments and co-morbidities (all participants), oral suppuration (7.8 [95%CI: 1.8-34.1]), matched dental extractions (7.6 [2.4-24.7]), and therapeutic radiation for head and neck cancer (24.1 [4.9-118.4]) were associated with ONJ (Table 3). Use of oral bisphosphonates was a potent risk factor (OR = 12.2 [95%CI

Table 2. Osteonecrosis of the Jaw Natural History Based on Participant Report

	Total (n = 191) %
Year of diagnosis of first lesion	
Missing	16
2003	6
2004	6
2005	17
2006	26
2007	29
Number of quadrants with lesions	
Missing	4
0	4
1	76
2	13
≥ 3	3
Maximum length of bone exposure (wks)	
Missing	22
< 2	1
2-3	3
4-5	4
6-7	7
> 8	64
Maximum size of all lesions	
Missing	24
Dime or smaller	59
Quarter	10
Larger than a quarter	7
Any tingling pain prior to lesion	42
Spontaneous bone exposure	56
Pain at the time bone became exposed	64
Medication use for ONJ	97
Healed	41

ONJ: osteonecrosis of the jaw.

4.3-35.0]). The OR for IV bisphosphonates did not converge due to rare use of this treatment in controls (95%CI 91.0- >999.9). Anemia was the only chronic medical condition with independent association (OR = 5.2 [95%CI 1.7-15.8]). The final model in Table 3 shows that duration of bisphosphonate use < 2 yrs was associated with a ten-fold risk of ONJ, while with duration > 2 yrs, that risk nearly quadrupled. Table 4 shows that among patients without cancer, bisphosphonate use (OR 7.2 [95%CI 2.1-24.7]), suppuration (11.9 [2.0-69.5]), and dental extraction (6.6 [1.6-26.6]) remained independently associated with ONJ.

In the secondary analysis using propensity scores, bisphosphonate use remained associated with ONJ in all (OR = 11.8 [95%CI 5.9-23.6]) and in non-cancer patients (8.0 [2.3-28.2]).

DISCUSSION

Despite numerous publications, risk factors for ONJ, including bisphosphonate treatment, have not been clearly established. While association of ONJ with bisphosphonate use and dental extractions appeared relatively assured (Almazrooa and Woo, 2009), the

Table 3. Multivariate Model Results for All Participants

Factor	Comparison Group	Reference Group	Odds Ratio (95%CI)	P-value	Overall P-value
Bisphosphonate use defined as None/Oral/Intravenous (Case = 137/Control = 367)					
Suppuration	Yes	No	7.8 (1.8, 34.1)	–	0.006
Extraction (matched to quadrant)	Matched extraction	No/mismatched extraction	7.6 (2.4, 24.7)	–	< 0.001
Radiation to head or neck	Yes	No	24.1 (4.9, 118.4)	–	< 0.0001
Bisphosphonate use	Oral	None	12.2 (4.3, 35.0)	< 0.0001	< 0.0001
	Intravenous (includes oral and intravenous)		> 999.9 (91.0, > 999.9)	< 0.0001	
Bisphosphonate defined as containing nitrogen chain or nitrogen ring (Case = 137/Control = 367)					
Suppuration	Yes	No	6.1 (1.7, 22.2)	–	0.006
Extraction (matched to quadrant)	Matched extraction	No/mismatched extraction	11.7 (3.9, 34.9)	–	< 0.0001
Radiation to head or neck	Yes	No	10.1 (3.0, 34.0)	–	< 0.001
Anemia	Yes	No	5.2 (1.7, 15.8)	–	0.004
Bisphosphonate type	Nitrogen chain	None	15.2 (5.2, 44.3)	< 0.0001	< 0.0001
	Nitrogen ring		178.4 (33.1, 960.5)	< 0.0001	
Bisphosphonate defined by duration of use (Case = 109/Control = 292)					
Suppuration	Yes	No	7.5 (2.0, 28.1)	–	0.003
Extraction (matched to quadrant)	Matched extraction	No/mismatched extraction	9.1 (3.0, 27.4)	–	< 0.0001
Radiation to head or neck	Yes	No	13.4 (4.0, 45.4)	–	< 0.0001
Anemia	Yes	No	4.2 (1.3, 13.3)	–	0.017
Bisphosphonate duration	> 0-2 yrs	none	9.9 (2.2, 45.6)	0.003	< 0.0001
	> 2-5 yrs		39.8 (10.0, 158.8)	< 0.0001	
	> 5 yrs		38.6 (9.1, 163.6)	< 0.0001	

Table 4. Multivariate Model Results for Participants without Cancer (Case = 30, Control = 81)

Factor	ONJ Cases	Controls	Odds Ratio (95%CI)	P-value
Suppuration	Yes	No	11.9 (2.0, 69.5)	0.006
Extraction (matched to quadrant)	Matched extraction	Any extraction	6.6 (1.6, 26.6)	0.008
Bisphosphonate use	Yes	No	7.2 (2.1, 24.7)	0.002

strength of these associations remained poorly quantified. Evidence for other risk factors was mixed and weak. This case-control study, conducted in a broad cross-section of dental practices, confirms an elevated risk for ONJ among patients treated with bisphosphonates, with a large effect in the range suggestive of a causal link. All formulations of bisphosphonates (except etidronate, used by three participants only) were associated with ONJ.

Analyses by bisphosphonate agent also confirmed the expected differences by drug potency. The OR for IV zoledronic acid (100,000 times more potent than etidronate) and pamidronate were sizably larger than those for weaker oral formulations (alendronate). The significant association of less potent bisphosphonates with ONJ confirms previous reports (Bamias *et al.*, 2005; Marx *et al.*, 2005; Badros *et al.*, 2006), and has significant clinical implications, since millions of patients have been treated with these drugs (Stafford *et al.*, 2004; Silverman and Maricic, 2007). Our study was not designed to estimate prevalence or incidence; however, while the associations we report are large, the evidence suggests that absolute risks are possibly modest (Silverman and Maricic, 2007).

ONJ has also been associated with duration of bisphosphonate treatment (Woo *et al.*, 2006). The minimum duration of use subsequent to ONJ development was reported to be 6 mos (Bamias *et al.*, 2005; Marx *et al.*, 2005; Badros *et al.*, 2006). The mean duration of bisphosphonate treatments for ONJ diagnosis in these studies ranged from 1.6-4.7 yrs, depending on bisphosphonate type. Our results confirm that risk begins within 2 yrs of treatment, for both cancer and non-cancer patients, showing that even the less potent bisphosphonates are linked to ONJ after a relatively brief treatment period. The ORs for non-cancer patients (the vast majority of whom were taking oral bisphosphonates) increased substantially after 5 yrs, supporting the suggestion that a drug ‘vacation’ after 5 yrs of treatment may be reasonable (Black *et al.*, 2006).

ONJ can occur in the setting of other diseases (Enwonwu *et al.*, 2000; Robin *et al.*, 2005; Sun *et al.*, 2006) or due to iatrogenic factors (Schwartz and Kvorning, 1982; Tarassoff and Csermak, 2003; Najm *et al.*, 2004; Talamo *et al.*, 2005). We did find that ONJ was associated with several risk factors; however, many of these are indications for bisphosphonates, such as various cancers and

osteoporosis. Associations with other systemic diseases like diabetes mellitus (Khamaisi *et al.*, 2007) and anemia require further study. In the current study, only the latter remained an independent risk factor in models including bisphosphonate duration.

Pharmacological agents that have been associated with osteonecrosis at sites other than the jaws include corticosteroids (Almazrooa and Woo, 2009), cytotoxic drugs (Talamo *et al.*, 2005), and multimodal antiretroviral therapies (Reddy *et al.*, 2005). Our results showed that both corticosteroids and cytotoxic drugs were associated with ONJ in bivariate analysis, but after inclusion of dental factors and bisphosphonate use, there were no independent associations. We had too few patients on antiretroviral therapies to examine this association.

Prior to 2003, the most common risk factors for ONJ were ionizing radiation, ingested radioactive elements, and phosphorus (Woo *et al.*, 2006). Data on the incidence of radiation-induced ONJ range from 0.4 to 56% of patients exposed to cancer-curative doses (Jerezek-Fossa and Orecchia, 2002). Our study included 46 cases and 26 controls with a history of radiation therapy to the head and neck, and this history demonstrated an independent association with a large effect size, confirming previous reports of radiation-induced osteonecrosis (osteoradionecrosis).

Our study has both strengths and limitations. Other studies found the prevalence of ONJ in cohorts of patients treated with IV bisphosphonate to be from < 1% to 28% (Badros *et al.*, 2006; Boonyapakorn *et al.*, 2008), depending on the population. Typically, the lower estimates included osteoporosis patients, while the higher figures were obtained in groups of cancer patients. Due to its case-control design, our study cannot contribute to this critical issue.

A second limitation is the fact that information about medication use was obtained from telephone interviews. Though patients were asked in a pre-interview mailing to help the process by listing all their past and current drugs prior to the call, this method is still subject to recall bias. Because bisphosphonates are taken once weekly or once monthly and require specific instructions after administration, it is possible that recall bias may be lessened. Another potential limitation is the three-center design, with data merged for final analysis.

A strength of our study is its conduct in community-based dental practices spanning the US rather than at academic medical centers, increasing the likelihood that our participants were more typical of the general population and strengthening generalizability. Several additional analyses tested the robustness of our findings, including the use of propensity scores to adjust for confounding by indication, supporting our main results.

In conclusion, this case-control study supports a causal link between bisphosphonates and ONJ. The highest risk was found for patients receiving more potent bisphosphonates, but substantial associations existed for oral-bisphosphonate-treated, non-cancer patients as well.

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