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ORIGINAL ARTICLE

Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users

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Abstract
Summary Osteonecrosis of the jaw (ONJ) is rare (2.53/10,000 person-years) among alendronate users, but long-term and compliant use are associated with an increased risk of surgically treated ONJ. Risk of surgically treated ONJ is higher in patients with rheumatoid diseases and use of proton pump inhibitors.
Introduction ONJ is a rare event in users of oral bisphosphonates. Our aims were to evaluate if the risk of surgically treated ONJ increases with longer or more compliant treatment with alendronate for osteoporosis and to identify risk factors for surgically treated ONJ.
Methods Open nationwide register-based cohort study containing one nested case-control study. Patients were treatment-naïve incident users of alendronate 1996–2007 in Denmark, both genders, aged 50–94 at the time of beginning treatment (N = 61,990). Participants were followed to 31 December 2013.
Results Over a mean of 6.8 years, 107 patients received surgery for ONJ or related conditions corresponding to an incidence rate of 2.53 (95% confidence interval (CI) 2.08 to 3.05) per 10,000 patient years. Recent use was associated with an adjusted odds ratio (OR) 4.13 (95% CI 1.94 to 8.79) compared to past use. Similarly, adherent users (medication possession ratio (MPR) >50%) were at two to threefold increased risk of ONJ compared to low adherence (MPR <50%), and long-term (>5 years) use was related with higher risk (adjusted OR 2.31 (95% CI (1.14 to 4.67)) than shorter-term use. History of rheumatoid disorders and use of proton pump inhibitors were independently associated with surgically treated ONJ.
Conclusions Our data suggest that recent, long-term, and compliant uses of alendronate are associated with an increased risk of surgically treated ONJ. Nevertheless, the rates remain low, even in long-term adherent users. ONJ risk appears higher in patients with conditions likely to indirectly affect the oral mucosa.

Keywords Alendronate · Biphosphonates · Epidemiology · Osteomyelitis of the jaw · Osteonecrosis of the jaw · Risk factors · Surgery

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Introduction

Oral bisphosphonates (BPs) are the most commonly used medications for osteoporosis but no trials extended beyond 10 years [1]. BP-related osteonecrosis of the jaw (ONJ) was first reported by dentists and oral surgeons more than a decade ago [2–4] occurring much more commonly in cancer patients receiving higher cumulative doses of BPs used at frequent intervals than in patients with osteoporosis [5].

The incidence of ONJ in the osteoporosis patient population has previously been estimated to be between 0.001 and 0.01%, and is only a little higher than the apparent ONJ incidence in the general population (<0.001%) [5–7]. It is unclear if the duration of osteoporosis therapy with BPs affects the risk of developing ONJ, but some studies indicate that [8, 9]. Most patients with ONJ have been managed conservatively [5] with surgery remaining an option for non-responsive and more severe cases [7, 9]. However, the fraction of patients with ONJ who undergo surgery varies from one clinical setting to another. For example, of 88 patients with ONJ treated at a highly specialized department of Maxillofacial Surgery in Copenhagen, 61 (69%) underwent surgery [10] while 95% of ONJ patients in an analysis of ONJ in three cancer trials were managed conservatively [11]. The latter is almost certainly influenced by the overall frailty and in most cases limited survival prospects of the patients—both of which may be a barrier to surgery—and the former by management of the mildest cases in dental practices or primary care.

We focused on surgically treated ONJ because only surgical treatment of ONJ can be expected to be captured fully in hospital registers—conservative treatment is generally managed in primary dental care which is generally a private practice—and only surgically treated ONJ is a sufficiently severe condition to be compared to an osteoporotic fracture. Hence, the objective of this study was to determine if the risk of surgically treated ONJ increases with increasing treatment time with alendronate for osteoporosis. Secondly, we aimed to identify risk factors for surgically treated ONJ among alendronate users.

Material and methods

Denmark has a population size of 5.7 million [12]. All Danish citizens are assigned a unique 10-digit personal registration number Central Person Register (CPR) number at birth or immigration. This personal number also serves as the social security number and must be provided in all contacts with the health care system, which ensures that all contacts with the system are registered, and duplicate registrations of the same patient avoided.

Using the registration number (CPR), complete data on hospital discharge diagnoses and prescription information can be obtained. The National Hospital Discharge Register has recorded all somatic hospital admissions since 1977, and from 1995 outpatient and emergency contacts were also included. The register includes all hospital admissions nationwide and discharge diagnoses (International Classification of Diseases 10th revision (ICD-10) codes); the data is linked to the CPR number. From 1995 and onwards, data on all prescriptions dispensed from Danish pharmacies have been collected in the National Prescription Database. This database is also linked to the CPR number and contains data on anatomical therapeutic classification (ATC) code, number of tablets, dose, and date of redemption.

The study population consisted of new, treatment-naïve users of alendronate for the prevention of osteoporotic fractures. The study is an investigator-initiated, nationwide population-based open registry cohort study, containing one nested case-control study, to determine the risk of surgically treated ONJ as a function of cumulative alendronate use, time, and adherence.

The included population has been described earlier [13] in our study of femur and hip fracture outcomes and consisted of 61,990 women and men aged 50 or over who began alendronate in 1996–2007 in Denmark. Patients in the cohort were followed from the start of treatment (first prescription) until the earliest of death, transfer out (migration out of the country), or end of study (31 December 2013), regardless of treatment compliance/persistence. The case-control study was nested within the cohort of alendronate users. Patients who experienced surgically treated ONJ were identified as cases in the case-control dataset and matched to five controls by the age, sex, year of start of treatment, and follow-up time.

Outcomes

Operational definition of surgically treated ONJ: The main outcome was incident ONJ using the following approach as ICD-10 code indicating inflammatory conditions of the jaw or oral cavity: K102, K102B, K102C, K102D, K102G, K102I, K102J and excluding osteoradionecrosis (K102E and K102F). ICD-10 code indicating osteonecrosis or osteomyelitis at any anatomical location: M861, M862, M864, M866, M868, M869C, M870, M871, M873, M878, M879. For inclusion as an outcome in the operational diagnosis in the present study, a procedure code indicating surgeries to jaws or oral cavity coded on the same hospital contact was also required (SKS code KE indicating surgery to mandible, maxilla, or oral cavity including all subcodes). All patients with these conditions are referred to specialized wards (including ear, nose, and throat specialists and oral and maxillofacial surgeons) for care and are thus registered in the system. In Denmark, there are 6 departments of oral and maxillofacial surgery managing ONJ patients (November 2013) and 23 private clinics/offices that may generally refer their ONJ patients to one of the six departments [14] and all used the disease codes. This referral procedure is known to dentist [15].

Exposures

The key exposure was pharmacy dispensations for alendronate (ATC (Anatomical Therapeutic Chemical) codes M05BA04 and M05BB03) filled in 1996–2013. The Medication Possession Ratio (MPR) was calculated as the number of WHO-ATC (World Health Organization Anatomic Therapeutic Classification) defined daily doses (DDD) divided by the length of time in days for each year of treatment, transferring any excess doses (>365 DDD in a year) into the next year, where it was added to prescriptions filled. The dose of alendronate used in Denmark is always 70 mg a week—that is, a DDD of 10 mg. If the patients filed prescriptions over time equivalent to 1 DDD per day, they were considered 100% adherent to the drugs prescribed. In our cohort study, patients were classified as compliant to treatment if they had an MPR ≥80%.

Statistical methods

We used SAS version 9.4 (SAS Institute, Cary, NC) for matching for the nested case-control study using the gmatch macro (Mayo Clinic, 2003). Surgically treated ONJ cases were individually matched 5:1 for year of birth (maximum distance 1 year), sex, and year of initiation of alendronate treatment to non-cases. Both cases and non-surgically ONJ cases were drawn from the cohort of alendronate users with no requirement to still be using alendronate as this is handled as an exposure variable in the subsequent logistic regression analysis. We used the TIME variable in the matching routine to ensure controls remained alive at the time that cases experienced their surgically ONJ outcome. Case-control analyses were done with conditional logistic regression analysis (SPSS v 19.0) with results shown as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). We pre-specified MPR and dose year cut-off points based on previous analyses of observational data [16, 17], where MPR <80% (and <50%) with alendronate have been associated with a reduced antifracture efficacy. There were no post hoc or unplanned subgroup analyses. Comedications considered for multivariable adjustment in the case-control studies included prednisolone, prednisone, and proton pump inhibitors. Chronic comorbid conditions were identified by ICD-8 (1977-93) and ICD-10 (1994-) codes and included all those listed in the Charlson comorbidity indices [18]. Baseline characteristics for the longitudinal cohort were those present at the time of the first alendronate prescription (cohort method), while characteristics (that is, confounders) adjusted for in the nested case-control study were defined at the time of surgically ONJ event to adhere to case-control methods.

The study design was intended to avoid confounding by indication through inclusion of patients who had been prescribed only alendronate, a drug that is exclusively used for osteoporosis and for which Danish reimbursement criteria require patients to have low bone mineral density or have experienced low trauma fractures (hip and/or mild spine fracture) [19].

Residual unbalancing in baseline comorbid conditions, history of fracture before treatment, and key drug exposures were addressed by including these as covariates in the multivariable conditional logistic regression analyses. Adjusted OR are reported as an approximation for risk reduction (where OR <1) or increase (where OR >1) as a function of duration, compliance, and timing of alendronate use.

We compared baseline descriptive characteristics with t tests and χ^2 tests as appropriate, using a critical significance level of 5% and two-sided tests throughout. Analyses were done using SPSS version 19.0.

Results

Study cohort and event rates

Table 1 shows the baseline descriptive characteristics for the cohort of 61,990 treatment-naive alendronate users at treatment initiation. Over a mean observation period of 6.8 years (422,850 patient years in total, median 7.0 per participant, IQ range 4.2 to 9.1), 107 patients received surgery for ONJ or

Table 1 Baseline descriptive characteristics at start of treatment with alendronate. Figures are numbers (percentage) of patients unless specified otherwise

	N = 61,990
Mean (SD) age (year)	72.1 ± 10.0
Gender (female)	51,558 (83.2)
Charlson index	
0	30,150 (48.6)
1	4247 (6.9)
2	13,953 (22.5)
3+	13,640 (22.0)
Main comorbid conditions	
Major osteoporotic fracture	19,261 (31.1)
Diabetes	3085 (5.0)
Chronic kidney disease	449 (0.7)
Chronic pulmonary disease	11,942 (19.3)
Prior myocardial infarction	3998 (6.4)
Malignancy	7908(12.7)
Medication history	
Prednisolone in last year	15,377 (24.8)
Proton pump inhibitors in last year	12,552 (20.2)

related conditions corresponding to an incidence rate of 2.53 (95% CI 2.08 to 3.05) per 10,000 patient years. In the year preceding initiation of alendronate, seven people (1.13 per 10,000 patient years, 95% CI 0.45 to 2.33) had received surgery under the same ICD-10 and procedure codes. As discussed below, this rate can be viewed as the noise rate, i.e., the rate of surgical procedures than cannot be distinguished from ONJ under the operational definition used in this observational study but which took place prior to the beginning of alendronate treatment. Out of the ONJ cases, 88 had only used weekly alendronate, 7 only daily alendronate, and 12 had used both. There was no difference in risk of surgically treated ONJ attributable to this difference in exposure ($p = 0.96$). Among the ONJ cases, one patient had shaft fracture and two patients had subtrochanteric fracture. The proportion with such fractures did not differ from the non-ONJ controls, however ($p = 0.40$ for subtrochanteic and $p = 0.60$ for shaft factures, respectively).

Risk of surgically treated ONJ

This analysis aims to identify factors associated with increased risk of developing surgically treated ONJ, including the magnitude of alendronate exposure whether defined by adherence, dose years, or recent exposure at the time of event. Table 2 shows the characteristics of the 107 patients (cases) who experienced a surgically treated osteomyelitis or osteonecrosis of the jaw and their 534 ages and sex matched (5:1) cohort controls (alendronate users from the cohort who did not experience the outcome of interest) during the follow-up period. The mean age at ONJ surgery was 74.9 years. Cases that had a significantly higher Charlson comorbidity index, were more likely to have diabetes, rheumatoid disorder, chronic pulmonary disease, malignancy, and peptic ulcer disease. The use of proton pump inhibitors and prednisolone during the year before the ONJ event was higher among cases.

Conditional logistic regression analysis (Table 3) shows that recent alendronate users (who had ceased treatment for more than 3 months but less than 1 year) were identified as being at fourfold increased risk over past users (OR 4.13 (95% CI 1.94 to 8.79). Adherent users were at increased risk (MPR >80% OR 2.25 (95% CI 1.22–4.18) $p = 0.01$ and MPR >50–80% OR 3.01 (95% CI 1.40–6.50) $p = 0.005$) of ONJ compared with those who failed to adhere (MPR <50%), and use for more than 5 years' being associated with higher risk (5–10 years: OR 2.31 (95% CI 1.14–4.67) $p = 0.02$, >10 years: OR 1.79 (95% CI 0.36–8.96) $p = 0.48$) than use for a shorter period of time. A history of rheumatoid disorders was independently associated with ONJ. The frequency of use of proton pump inhibitors was also higher among cases.

Table 2 Comorbid conditions and comedications at time of event. Figures are numbers (percentage) of patients unless specified otherwise

	Cases $N = 107$	Controls $N = 534$	p
Mean (SD) age (year) at ONJ diagnosis	74.9 ± 9.5	74.9 ± 9.5	Matched
Mean (SD) age (years) aln start	69.1 ± 9.6	69.1 ± 9.7	$p = 0.989$
Gender (female)	85 (79.4)	425 (79.6)	Matched
Aln user status			
Past user (≥1 year before)	26 (24.3)	171 (32)	$p = 0.114$
Recent user (≥3 months to 1 year before)	27 (25.2)	53 (9.9)	$p < 0.001$
Current user (<3 months)	54 (50.5)	310 (58.1)	$p = 0.148$
MPR			
<50%	22 (20.6)	180 (33.7)	$p = 0.008$
50–80%	21 (19.6)	64 (12.0)	$p = 0.033$
>80%	64 (59.8)	290 (54.3)	$p = 0.296$
Dose years of alendronate			
<5	66 (61.7)	372 (69.7)	$p = 0.105$
5–10	37 (34.6)	146 (27.3)	$p = 0.130$
≥10	4 (3.7)	16 (3.0)	$p = 0.687$
Charlson index			
0	18 (16.8)	232 (43.3)	$p < 0.001$
1	5 (4.7)	46 (8.6)	
2	31 (29.0)	120 (22.5)	
3+	53 (49.5)	136 (25.5)	
Main comorbid conditions			
Major osteoporotic fracture	46 (43)	193 (36.1)	$p = 0.181$
Fracture other	19 (17.8)	78 (14.6)	$p = 0.407$
Diabetes	21 (19.6)	27 (5.1)	$p < 0.001$
Chronic kidney disease	3 (2.8)	5 (0.9)	$p = 0.13$
Rheumatoid disorders	41 (38.3)	110 (20.6)	$p < 0.001$
Chronic pulmonary disease	40 (37.4)	104 (19.5)	$p < 0.001$
Dementia	6 (5.6)	13 (2.4)	$p = 0.077$
Peptic ulcer disease	19 (17.8)	46 (8.6)	$p = 0.004$
Malignancy	26 (24.0%)	73 (13.7%)	$p = 0.008$
Proton pump inhibitors in last year	55 (51.4)	124 (23.2)	$p < 0.001$
Prednisolone in last year	37 (34.6)	98 (18.4)	$p < 0.001$

We found no cases with concurrent non-jaw fractures or other evidence that the contacts were trauma related. Two cases of jaw fractures in conjunction with tooth extraction were identified. As jaw fracture is a rare but known complication to ONJ, we kept these cases in the main analysis but also repeated the analyses as a sensitivity analysis where these two cases were removed. This did not alter the conclusions; the OR for surgically treated ONJ with 5–10 years of used changed minimally to 2.33 (95% CI 1.15–4.76), $p = 0.019$ and with 10+ years OR 1.76 (95% CI 0.35–8.90) $p = 0.49$.

Table 3 Nested case-control analysis (107 cases and 534 control subjects) of surgically treated ONJ within a user-only cohort of 61,990 incident alendronate users. Figures are numbers (percentage) of patients

	Number	OR for probable ONJ unadjusted (107 cases and 534 control subjects)	OR for probable ONJ adjusted[a] (107 cases and 534 control subjects)
User status			
Past user (≥1 year before)	197 (30.7)	Reference	
Recent user (≥3 months to 1 year before)	80 (12.5)	3.56 (1.86–6.79) $p < 0.001$	4.13 (1.94–8.79) $p < 0.001$
Current user (<3 months)	364 (56.8)	1.15 (0.68–1.95) $p = 0.61$	1.37 (0.73–2.56) $p = 0.33$
MPR			
<50%	202 (31.5)	Reference	
50–80%	85 (13.3)	2.72 (1.40–5.28) $p = 0.003$	3.01 (1.40–6.50) $p = 0.005$
>80%	354(55.2)	1.84 (1.09–3.12) $p = 0.024$	2.25 (1.22–4.18) $p = 0.01$
Dose years			
<5	438 (68.3)	Reference	
5–10	183 (28.5)	1.86 (1.00–3.44) $p = 0.049$	2.31 (1.14–4.67) $p = 0.02$
≥10	20 (3.1)	1.81 (0.49–6.66) $p = 0.37$	1.79 (0.36–8.96) $p = 0.48$
Comorbid conditions and comedications			
Major osteoporotic fracture	239 (37.3)	1.36 (0.88–2.10) $p = 0.17$	1.24 (0.75–2.06) $p = 0.40$
Fractures, other	97 (15.1)	1.27 (0.73–2.20) $p = 0.41$	0.75 (0.38–1.48) $p = 0.41$
Diabetes	48 (7.5)	5.03 (2.62–9.67) $p < 0.001$	2.85 (1.28–6.35) $p = 0.11$
Chronic kidney disease	8 (1.2)	3.18 (0.70–14.48) $p = 0.14$	1.26 (0.18–9.14) $p = 0.82$
Rheumatoid disorders	151 (23.6)	2.41 (1.54–3.76) $p < 0.001$	2.14 (1.22–3.76) $p = 0.008$
Chronic pulmonary disease	144 (22.5)	2.59 (1.63–4.13) $p < 0.001$	1.46 (0.72–2.95) $p = 0.30$
Dementia	19 (3.0)	2.33 (0.87–6.26) $p = 0.09$	1.35 (0.34–5.37) $p = 0.67$
Peptic ulcer disease	65 (10.1)	2.27 (1.27–4.06) $p = 0.006$	1.03 (0.50–2.10) $p = 0.95$
Malignancy	99 (15.4)	2.06 (1.23–3.42) $p = 0.006$	1.67 (0.81–3.42) $p = 0.17$
Proton pump inhibitors in last year	179 (27.9)	3.56 (2.29–5.53) $p < 0.001$	3.16 (1.87–5.34) $p < 0.001$
Prednisolone in last year	135(21.1)	2.49 (1.54–4.00) $p < 0.001$	1.10 (0.60–2.04) $p = 0.75$

[a] Adjusted for Charlson index, prior fractures, diabetes, renal disease, rheumatoid disorders, chronic pulmonary diseases, dementia, ulcer disease, malignancy, recent prednisolone, and proton pump inhibitors use

Discussion

The rate of surgically treated ONJ is low, even in long-term adherent alendronate users. However, recent users are at four times the risk of past users and the risk is higher after more than 5 years of exposure, as it is in those with good (>80%) compliance. Our results also suggest that the risk of surgically treated ONJ is higher in patients with conditions likely to indirectly affect the oral mucosa or oral bone such as patients with rheumatoid diseases and is according to risk factors described for ONJ in other studies [20, 21].

Milder stages of ONJ are usually treated conservatively [5–7, 9] and the events tracked in this study likely represent more advanced ONJ (stages 2 and 3). It is also recent rather than current use that tracks with surgical ONJ risk and it probably simply means that patients come off alendronate when ONJ is diagnosed and that they have probably been off alendronate for weeks when coming in for surgery. Indeed, the clinical diagnosis requires that 8 weeks have passed since the first observation of the mucosal lesion by a health professional and patients would not be expected to fill additional prescriptions of BPs in these circumstances. This may also be in accordance with the earlier suggestion of a drug holiday, temporary cessation of oral BP therapy before dental procedures, will reduce the risk of ONJ [9].

It is not clear from previous studies if every patient treated with alendronate for osteoporosis could develop ONJ requiring surgery or if only a small minority is at risk. Previous case-control and cohort studies have relieved on patients with ONJ and controls to determine risk factors for ONJ, e.g., the association between BP use and risk of ONJ [22]. Our study is a classic case-control design in which patients with ONJ outcome were compared with similar patients having osteoporosis (for instance, users of same drug (alendronate), were of same age, sex and who started alendronate treatment same year) without ONJ to identify factors associated with the risk

of developing the outcome in question. Our study shows that the risk factors of surgically ONJ in patients is a history of rheumatoid disorders and more likely to use proton pump inhibitors. The risk of ONJ and progression to surgery needs to be explained to the all patients but patients with the mentioned comorbidity conditions and long-term treatment with alendronate should be shown extra attention in the context of, e.g., tooth extraction.

There is solid evidence from randomized placebo-controlled that up to 3–5 years' duration supports the efficacy of alendronate in decreasing the risk of vertebral fractures, hip fractures, and non-vertebral fractures in patients with osteoporosis. Extension trials have suggested efficacy of prolonged alendronate therapy in maintaining bone density for up to 10 years [23, 24], but evidence regarding fracture risk reduction with prolonged therapy is less convincing. Although Merck reported no cases of ONJ among controlled clinical trials more than 28,000 patients (over 17,000 of whom were treated with FOSAMAX, alendronate), including 3000 patients with 3 to 5 years of exposure and 800 patients with 8 to 10 years of exposure [25], our study suggests that the risk of surgically treated ONJ increases with alendronate treatment compliance and duration. In a multicenter retrospective cohort study including only patients with ONJ, time to onset of BP-related ONJ was 6.0 years in patients treated with alendronate [26]. In a mailed survey study to 13,946 patients who had received chronic oral bisphosphonate therapy, 8572 responded. Only nine ONJ cases were identified and thus finding the prevalence of ONJ significantly larger among cases with longer (more than 4 years of oral BP exposure) compared less than 4 years 0.21 vs 0.04%, respectively [8]. Although there appears from studies to be a trend for an increased risk of ONJ with duration of BP use, the quality of the evidence for such association is poor [22], but our study supported the trend of a higher risk of surgically ONJ after more than 5 years of alendronate exposure.

Being treated for osteoporosis may itself be associated with dental problems [27], but studies have also indicated a reduced incidence rate ratio of dental periodontal treatments after initiation of, e.g., alendronate treatment [28] indicating an improved patients' periodontal health. In this study, all patients are treated for osteoporosis and could not be compared with untreated patients—either with or without osteoporosis—but we could identify patients at risk whom should be payed extra attention. For all patients on BP treatment, the importance of oral hygiene and dental health should always be underlined [9]. Patients should be educated to the risk of developing ONJ such as instructed to report signs and symptoms.

Among established risk factors for ONJ in patients with osteoporosis or cancer are beside BP, tooth extraction drug related as corticosteroid therapy, chemotherapeutic agents, other local factors as concomitant oral disease, poor oral hygiene, poor fitting dentures, intraoral trauma as well as age, being Caucasian, cancer diagnosis, and comorbidity [11, 29–36]. An increased risk of surgically ONJ in prednisolone users in this study was seen only in the unadjusted analyses but it was attenuated in the multivariable models. This could be explained by a lower intervention threshold in these patients. Current Danish guidelines [19] advocate BP intervention at a T-score below −1 in patients exposed to glucocorticoids, compared to a threshold of T-score below −2.5 for all others.

Limitations and strengths

Our study population was almost exclusively North European and the results might not apply to other ethnic groups. Denmark is a welfare state and physicians and patients might pay more attention to oral health and identify more cases of ONJ while on treatment with alendronate. Further limitation is that at the time of the analysis, there was no specific disease code available for ONJ. As the first reports of ONJ emerged in 2003, some events observed in this study were seen before this. A previous study validating ICD-10 codes for identifying cases of ONJ in Danish registers have shown ICD-10 codes used alone to perform relatively poorly [37]. In the oncology setting [15], the ICD10 code K102, indicating inflammatory conditions of jaws, had a sensitivity of 60 and 63% for two validated ONJ populations while M878, "unspecified osteonecrosis," had a sensitivity of 16.8% in both. For this reason, the current study did not rely on ICD-10 coding alone, but required the simultaneous presence of procedure codes for surgery to the oral cavity of jaws. We do not have access to individual patient notes to validate this approach and believe the rates found here should be viewed as an upper boundary of harm estimate with a certain noise rate as exemplified by the event rate in the year preceding the start of BP treatment. In this study, we have only focused on alendronate use (treatment naïve patients) but other drugs have (other BPs and denosumab) or have not (parathyroid hormone analogues, raloxifene, strontium ranelate) been linked to development of ONJ [5]. Potentially, the first class of drugs could add additional risk whereas the second class of drugs would either be neutral or, in the case of teriparatide, potentially reduce risk or promote healing [7]. Tooth extraction is a common predisposing event to ONJ [9]; we had no such information in this study. Further, we did not have information in the dataset about radiation therapy (these are non-surgical codes that were not in the analysis plan we submitted to the authorities). We did however exclude all events that were coded as radiation induced. Observational studies of ONJ may be susceptible to

ascertainment bias as clinicians and patients will be aware of the potential for development of jaw lesions as a consequence of treatment. We would expect this source of bias to be very limited in the present study where all subjects were BP exposed.

The strength is that as our databases are event based and capture hospital contacts and filled prescriptions, there were no identifiably missing data. Further, the quality and duration of drug exposure data allow almost two decades of drug prescription data. We used an elaborate user-only study design to eliminate drug channeling bias and embedded one case-control study in a longitudinal open study of alendronate use to achieve optimal statistical power for rare outcomes.

Conclusion and perspective

The rate of surgically treated ONJ is low, even in long-term adherent users. However, recent users are at four times the risk of past users and the risk is higher after more than 5 years of exposure and in more compliant users. Our results also suggest that surgically treated ONJ risk is higher in patients with conditions likely to indirectly affect the oral mucosa such as patients with rheumatoid diseases and use of proton pump inhibitors.

Many of the elderly patients with osteoporosis seen in the dental clinic are currently on oral BPs for osteoporosis or osteopenia. Because of the extremely low incidence of ONJ in patients on oral BPs, it is important to pay extra attention to the risk groups (rheumatoid disease and use of proton pump inhibitor in the last year), especially if treatment has had duration for more than 5 years.

Compliance with ethical standards

Conflicts of interest PE reports grant support from Eli Lilly and payment for educational presentations for Amgen and Eli Lilly, payment for membership of advisory boards from Amgen, Eli Lilly, and Merck, and stock ownership in Novo Nordisk. DP-A reports institutional research grants from Amgen, Servier and UCB, and support for conference attendance and speaker fees paid by Amgen to his institution. RE reports institutional research grants and personal fees from Amgen, IDS, Alexion, and Roche, institutional research grants from Astra Zeneca, and speaker or consulting fees from Bayer, Fonterra, Janssen, Eli Lilly, Ono Pharma, Alere, Teijin Pharm, D-STAR, and GSK nutrition. BA reports institutional research contracts with Novartis and UCB.

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