

Surgically Treated Osteonecrosis and Osteomyelitis of the Jaw and Oral Cavity in Patients Highly Adherent to Alendronate Treatment: A Nation-wide User-only Cohort Study Including Over 60,000 Alendronate Users

Pia A Eiken^{1,2}, Daniel Prieto-Alhambra,^{3,4} Richard Eastell⁵, Bo Abrahamsen^{6,7}

(1)Dept of Cardiology, Nephrology and Endocrinology, North Zealand Hospital, Hillerød , Dyrehavevej 29, 3400 Hillerød, Denmark, Pia Eiken Consultant Endocrinologist

(2)Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark, Pia Eiken Clinical Associate Professor Senior Lecturer

(3)Musculoskeletal Pharmaco- and Device Epidemiology, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford. Botnar Research Centre, Windmill Road, OX3 7LD, Oxford, United Kingdom, Daniel Prieto-Alhambra Associate Professor.

(4)GREMPAL Research Group and CIBERFes, Idiap Jordi Gol, Universitat Autònoma de Barcelona and Instituto Carlos III (FEDER Research Funds), Av Gran Via Corts Catalanes 185, 08003 Barcelona, Spain, Daniel Prieto-Alhambra Post-Doctoral Clinical Researcher.

(5)Academic Unit of Bone Metabolism (AUBM), University of Sheffield, Herries Road, S5 7AU Sheffield, United Kingdom Richard Eastell Professor

(6) Odense Patient Data Explorative Network, Department of Clinical Research, University of Southern Denmark, J.B. Winsløws Vej 9 A, 3. Sal, DK-5000, Odense, Denmark, Bo Abrahamsen Professor

(7)Dept of Medicine, Holbæk Hospital, Smedelundsgade 60, 4300 Holbæk, Denmark, Bo Abrahamsen Consultant Endocrinologist

Corresponding author: Pia Eiken. Email: piei@regionh.dk, Phone: +4548294441

Disclosures: 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.

KEY WORDS

Epidemiology; **Biphosphonates**; Alendronate; osteonecrosis of the jaw, osteomyelitis of the jaw; surgery; risk factors

Abstract

Purpose/Introduction: Osteonecrosis of the jaw (ONJ) is a rare event in users of oral bisphosphonates. Our aim was 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 Nation-wide 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 three fold 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.

Mini abstract: (word 43, max 50). Osteonecrosis of the jaw (ONJ) is rare (2.3/100,000 person-years) amongst 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

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% to 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 amongst 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 filled 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 one 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 anti-fracture 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-naïve 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 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, 7 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 1 patient had shaft fracture and 2 patients had subtrochanteric fracture. The proportion with such fractures did not differ from the non-ONJ controls, however ($p=0.40$ for subtrochanteric and $p=0.60$ for shaft fractures, 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 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 four-fold 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 five 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.

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) $p=0.49$.

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 five 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 (stage 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 eight 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 BPs 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 are 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 nonvertebral 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 3,000 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, 8,572 responded. Only 9 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 five 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 paid 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 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 allowing 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 last year), especially if treatment has had duration for more than 5 years.

References:

- (1) Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2016; 31: 1910.
- (2) Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; 61: 1115-7.
- (3) Ruggiero SL, Mehrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; 62: 527-34.
- (4) Marx RE, Sawatari Y, Fortin M, et al. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005; 63: 1567-75.
- (5) Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015; 30: 3-23.
- (6) Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007; 22: 1479-91.
- (7) Khan AA, Morrison A, Kendler DL, et al. Case-Based Review of Osteonecrosis of the Jaw (ONJ) and Application of the International Recommendations for Management From the International Task Force on ONJ. *J Clin Densitom* 2017; 20: 8-24.
- (8) Lo JC, O'Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg* 2010; 68: 243-53.
- (9) Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg* 2014; 72: 1938-56.
- (10) Schiodt M, Reibel J, Oturai P, et al. Comparison of nonexposed and exposed bisphosphonate-induced osteonecrosis of the jaws: a retrospective analysis from the Copenhagen cohort and a proposal for an updated classification system. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; 117: 204-13.
- (11) Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann Oncol* 2012; 23: 1341-7.
- (12) Population and elections. <http://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=22256&sid=pop>. Accessed March 8, 2017.
- (13) Abrahamsen B, Eiken P, Prieto-Alhambra D, et al. Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case-control study. *BMJ* 2016; 353: i3365.
- (14) Schiodt M, Larsson Wexell C, Herlofson BB, et al. Existing data sources for clinical epidemiology: Scandinavian Cohort for osteonecrosis of the jaw - work in progress and challenges. *Clin Epidemiol* 2015; 7: 107-16.
- (15) Ehrenstein V, Gammelager H, Schiodt M, et al. Evaluation of an ICD-10 algorithm to detect osteonecrosis of the jaw among cancer patients in the Danish National Registry of Patients. *Pharmacoepidemiol Drug Saf* 2015; 24: 693-700.

- (16) Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc* 2006; 81: 1013-22.
- (17) Caro JJ, Ishak KJ, Huybrechts KF, et al. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int* 2004; 15: 1003-8.
- (18) Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43: 1130-9.
- (19) <http://laegemiddelstyrelsen.dk/da/nyheder/2012/aendrede-kriterier-for-enkeltilskud-til-ovrigte-osteoporosemidler-end-alendronat/~media/072DF0C8F48540F2964EAB109CB2D1D6.ashx>. Accessed March 8, 2017.
- (20) de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *J Rheumatol* 2008; 35: 70-6.
- (21) Malden N, Lopes V. An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence. *J Bone Miner Metab* 2012; 30: 171-82.
- (22) Lee SH, Chang SS, Lee M, et al. Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. *Osteoporos Int* 2014; 25: 1131-9.
- (23) Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; 296: 2927-38.
- (24) Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res* 2010; 25: 976-82.
- (25) Statement by Merck & Company. Incorporated: Regarding Fosamax (alendronate sodium) and rare cases of osteonecrosis of the jaw. Product News. 9 March 2010. Available from: <http://www.mercknewsroom.com/news/statement-merck-regarding-fosamax-alendronate-sodium-and-rare-cases-osteonecrosis-jaw>. Accessed December 19, 2016.
- (26) Fung P, Bedogni G, Bedogni A, et al. Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study. *Oral Dis* 2016.
- (27) Dervis E. Oral implications of osteoporosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 100: 349-56.
- (28) Vestergaard P, Schwartz K, Rejnmark L, et al. Oral bisphosphonate use increases the risk for inflammatory jaw disease: a cohort study. *J Oral Maxillofac Surg* 2012; 70: 821-9.
- (29) Yamashita J, McCauley LK. Antiresorptives and osteonecrosis of the jaw. *J Evid Based Dent Pract* 2012; 12: 233-47.
- (30) Dodson TB. The Frequency of Medication-related Osteonecrosis of the Jaw and its Associated Risk Factors. *Oral Maxillofac Surg Clin North Am* 2015; 27: 509-16.
- (31) Yamazaki T, Yamori M, Ishizaki T, et al. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *Int J Oral Maxillofac Surg* 2012; 41: 1397-403.
- (32) Tsao C, Darby I, Ebeling PR, et al. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. *J Oral Maxillofac Surg* 2013; 71: 1360-6.

- (33) O'Ryan FS, Lo JC. Bisphosphonate-related osteonecrosis of the jaw in patients with oral bisphosphonate exposure: clinical course and outcomes. *J Oral Maxillofac Surg* 2012; 70: 1844-53.
- (34) Yazdi PM, Schiodt M. Dentoalveolar trauma and minor trauma as precipitating factors for medication-related osteonecrosis of the jaw (ONJ): a retrospective study of 149 consecutive patients from the Copenhagen ONJ Cohort. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; 119: 416-22.
- (35) Otto S, Schreyer C, Hafner S, et al. Bisphosphonate-related osteonecrosis of the jaws - characteristics, risk factors, clinical features, localization and impact on oncological treatment. *J Craniomaxillofac Surg* 2012; 40: 303-9.
- (36) Taylor T, Bryant C, Popat S. A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital. *Br Dent J* 2013; 214: E18.
- (37) Gammelager H, Svaerke C, Noerholt SE, et al. Validity of an algorithm to identify osteonecrosis of the jaw in women with postmenopausal osteoporosis in the Danish National Registry of Patients. *Clin Epidemiol* 2013; 5: 263-7.