ORIGINAL ARTICLE

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Risk of Osteonecrosis of the Jaw Under Denosumab Compared to Bisphosphonates in Patients With Osteoporosis

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ABSTRACT

Osteonecrosis of the jaw (ONJ) is a rare but serious adverse event associated with antiresorptive treatment. There is little evidence regarding the incidence of ONJ among patients with osteoporosis who are treated with denosumab versus bisphosphonates (BPs). The aim of this study was to determine the risk of ONJ in a real-world population. Subjects who underwent at least one dual-energy X-ray absorptiometry (DXA) examination were included in the osteoporosis register of the Swiss Society of Rheumatology between January 1, 2015, and September 30, 2019. Statistical analyses included incidence rates, rate ratios, and hazard ratios for ONJ, considering sequential therapies and drug holidays as covariates. Among 9956 registered patients, 3068 (89% female, median age 69 years [63 to 76]) were treated with BPs or denosumab for a cumulative duration of 11,101 and 4236 patient-years, respectively. Seventeen cases of ONJ were identified: 12 in patients receiving denosumab at the time of ONJ diagnosis and 5 in patients receiving oral or intravenous BP therapy. The diagnosis of ONJ was confirmed by independent and blinded maxillofacial surgeons, using the American Association of Oral and Maxillofacial Surgeons case definition of ONJ. The incidence of ONJ per 10,000 observed patient-years was 28.3 in patients receiving denosumab and 4.5 in patients with BP-associated ONJ, yielding a rate ratio of 6.3 (95% confidence interval [CI] 2.1 to 22.8), $p < 0.001$. Nine of 12 patients who developed ONJ during denosumab treatment had been pretreated with BPs, but none of the 5 patients with BP-related ONJ had previously received denosumab. The risk of ONJ was higher in patients receiving denosumab therapy compared with BPs (hazard ratio 3.49, 95% CI 1.16 to 10.47, $p = 0.026$). Previous BP therapy before switching to denosumab may be an additional risk factor for ONJ development. © 2021 American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: OSTEONECROSIS OF THE JAW; ONJ; DENOSUMAB; OSTEOPOROSIS; BISPHOSPHONATES

Introduction

Bisphosphonates (BPs) and denosumab reduce bone loss and prevent fractures in patients with osteoporosis and those receiving glucocorticoid treatment or hormone ablative therapy. In the past few decades, medication-related osteonecrosis of the jaw (ONJ) has been reported as a rare but serious adverse effect of BPs and, more recently, denosumab therapy.[1] ONJ is characterized by persistent, often painful necrosis of bone in the maxillofacial region, which reduces quality of life and is associated with significant morbidity.[2] It was first described in 2003 in patients receiving high doses of BPs, mostly as a result of cancer-related hypercalcemia.[3] Later, it was also observed in patients receiving lower BP doses for the treatment of osteoporosis.[4] The pathogenesis of ONJ remains poorly understood, but several potential mechanisms have been discussed, including oversuppression of bone remodeling, local infection, inhibition of angiogenesis, soft tissue toxicity, and immune dysfunction.[2,4] A medication-related ONJ is defined by the

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American Society for Bone and Mineral Research as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after diagnosis in a patient currently or previously treated with antiresorptive therapy in the absence of radiation therapy of the craniofacial region.[2,4] Besides antiresorptive drugs, triggers such as tooth extractions or prosthesis pressure points, as well as other risk factors (glucocorticoids, poor oral hygiene, chronic inflammatory disease, smoking, and diabetes mellitus) can contribute to the development of ONJ.[5]

The incidence of ONJ is highest in the oncology patient population (1% to 15%), where high doses of antiresorptive drugs are used at frequent intervals. In patients receiving low-dose BPs for osteoporosis, the risk of ONJ is estimated to be 1/10,000 to 1/100,000 patient-years (0.001% to 0.01%),[4,6] which is marginally higher than the incidence in the general population (<0.001%). A higher recurrence was observed in the Extension phase of the pivotal FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months). A total of 13 denosumab-associated ONJ cases (5.2 per 10,000 patient-years) were identified[7] and were strongly associated with invasive oral procedures.[8]

The aim of this study was to analyze the incidence of ONJ in patients with osteoporosis. Since we have observed an increasing number of ONJ cases in our clinical practice during the past 5 years, we systematically evaluated our patients in the osteoporosis register from the Swiss Society of Rheumatology. Because the database derives from a real-world population receiving individualized therapeutic modalities, the analysis specifically focused on different sequences of antiresorptive therapies and temporary discontinuations (''drug holidays'').

Subjects and Methods

Study design

This study was conducted at a single non-academic outpatient center in Switzerland, named OsteoRheuma Bern (ORB). Patients reviewed in this cohort study were included in a national register for osteoporosis maintained by the Swiss Society of Rheumatology (https://osteorheuma.ch/top). This register was founded in 2014 with the primary aim of evaluating the risk of osteoporotic fractures. Subjects with suspected osteoporosis (because of fractures and/or specific risk factors) who were referred for a dual-energy X-ray absorptiometry (DXA) scan and clinical evaluation are included in the register. Age, sex, height, weight, and information about risk factors for osteoporotic fractures are collected, as well as *T*-scores, trabecular bone scores, clinical and morphometric fracture data, and anti-osteoporotic therapies. Data on ONJ were recorded for patients treated at OsteoRheuma Bern but not at other inclusion sites. Eligible cohort members were subjects followed from January 1, 2015, to September 30, 2019, who were evaluated and treated at OsteoRheuma Bern. Both retrospective data about past anti-osteoporotic therapies as well as prospective data after cohort entry were collected. All subjects underwent at least one DXA scan and were usually followed up every 2 to 3 years depending on their individual fracture risk and therapeutic strategy. An anti-osteoporotic drug therapy was administered in case of a fragility fracture or high fracture risk. The choice of medication was at the discretion of the treating physician, with certain constraints stipulated by the health authorities.

The study was approved by the Ethics Committee of the Canton of Bern, Switzerland (KEKBE 2019–01037), and all subjects provided written informed consent.

Outcomes

The primary outcome was the incidence of ONJ. Medical records of all subjects (not just those receiving antiresorptive therapies) were reviewed for the mention of ONJ or dental procedures with complications. If any of these were present, health-related data were collected from the medical reports of dentists and/or maxillofacial surgeons, along with corresponding radiographs and histological results. Potential cases of ONJ were independently adjudicated by two maxillofacial surgeons who were unaware of the type of antiresorptive treatment, using the American Association of Oral and Maxillofacial Surgeons (AAOMS) staging criteria.[2,9] Secondary outcomes were risk factors for the development of ONJ and the influence of sequential therapeutic modalities, including drug holidays. Drug holidays were defined as long breaks of several months or years between two anti-osteoporotic treatment cycles, not as short-term delays in dosing, which are sometimes implemented in cases of oral procedures in patients under antiresorptive therapy. A drug holiday was defined as beginning at the end of the dosing interval of each substance (eg, 12 months after zoledronate or 3 months after intravenous ibandronate).

Statistical analyses

We analyzed the association of BPs and denosumab with the risk of ONJ in a time-to-event manner, including both treatments and drug holidays as time-varying covariates in a Cox regression model. Specifically, we expressed the administration of BPs or denosumab as a single categorical variable, with categories of ''none,'' ''BP,'' and ''denosumab.'' We chose this approach because observation times varied greatly between patients in our study cohort, so odds ratios would yield biased results. We

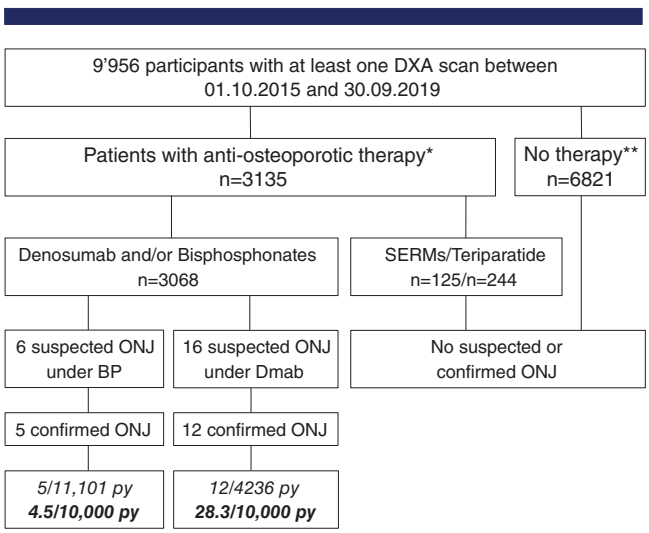

Fig. 1. Flow chart with outcome. Flow chart of the study cohort, including outcome. *One patient can receive more than one therapy; **except calcium, vitamin D, or hormone replacement therapy. BP = bisphosphonate; Dmab = denosumab; ONJ = osteonecrosis of the jaw; py = patient-years; SERM = selective estrogen receptor modulator.

calculated event rates, rate ratios, and hazard ratios, using continuity correction by 0.1 at the level of events and denominator person-time to derive rates, and applied the rule of three as described by Hanley and Lippman-Hand to derive the upper end of the confidence interval (CI) in case of no event.[10] Proportional hazard assumptions were checked using Schoenfeld residuals. Continuous variables were presented as median with interquartile range (IQR) with *p* values calculated using the Wilcoxon rank-sum test. Categories were presented as numbers and percentages, with *p* values from Fisher's exact test for binary variables or the chi-square test for variables with more than two categories. Statistical analyses were performed using Stata 16 (StataCorp, College Station, TX, USA).

Results

Study cohort

The study cohort included 9956 subjects enrolled between October 1, 2015 (the implementation date of the osteoporosis register of the Swiss Society of Rheumatology) and September 30, 2019. A total of 3068 patients received BPs, denosumab, or both sequentially. Seventeen cases of medication-related ONJ were diagnosed: 12 in patients receiving denosumab therapy and 5 in patients receiving BPs at the time of ONJ diagnosis. No cases of ONJ were diagnosed in patients being treated with selective estrogen receptor modulators (SERMs; 472 observed patient-years) or teriparatide (400 observed patient-years), or in subjects receiving no anti-osteoporotic drug (Fig. 1). {FIG1}

The median age of all patients receiving denosumab and/or BP therapy ($n = 3068$; 89% female) was 69 years (63 to 76). Of these individuals, 1.2% were younger than 45 years, and the most common reason for therapy was premenopausal osteoporosis or, in a few cases, pregnancy and lactation-associated osteoporosis. All patients included in the analysis were white. Regarding comorbidities, those of patients treated with BPs, denosumab, or both sequentially are described in Table 1. {TBL 1} Several differences were noted: The percentages of patients who received glucocorticoids or aromatase inhibitors were highest in the BP and denosumab groups, respectively. Further, the prevalence of rheumatoid arthritis was lower in patients with denosumab therapy than in either of the other two groups.

Description of ONJ cases

Of 22 patients identified as possibly having ONJ, 6 were receiving BP therapy and 16 were being treated with denosumab at the time that ONJ was initially suspected. All patients were reviewed by two independent maxillofacial surgeons using the AAOMS case definition for ONJ, and a diagnosis of ONJ was finally confirmed in 17 patients (16 female, 1 male). The two maxillofacial surgeons were blinded regarding the treatment regimen in each case. In the excluded patients, the radiological or clinical criteria for ONJ were not met and/or the diagnosis could not be confirmed histologically. In two patients, mandibular abscesses were

Table 1. Patient Characteristics by Treatment

	BP only($n = 1802$)	Dmab only($n = 422$)	Both($n = 844$)	*p* Value
Male	271 (15%)	24 (5.7%)	34 (4.0%)	**<0.001**
Age (years)	69 ± 10	69 ± 10	70 ± 8.9	0.18
BMI (kg/m^2)	25 ± 4.8	24 ± 4.8	24 ± 4.1	**<0.001**
Premenopausal	59 (3.3%)	16 (3.8%)	25 (3.0%)	0.65
Family history of osteoporosis	206 (11%)	40 (9.5%)	81 (10%)	0.26
Use of glucocorticoids (≥5 mg/d for ≥3 months)	239 (13%)	21 (5.0%)	47 (5.6%)	**<0.001**
Prostate cancer with hormone ablative therapy	4 (0.22%)	2 (0.47%)	2 (0.24%)	0.53
Use of aromatase inhibitors	32 (1.8%)	57 (14%)	46 (5.5%)	**<0.001**
Use of antiepileptic medication	10 (0.55%)	1 (0.24%)	4 (0.47%)	0.87
Rheumatoid arthritis	87 (4.8%)	8 (1.9%)	27 (3.2%)	**0.007**
Axial spondylarthritis	10 (0.55%)	1 (0.24%)	1 (0.12%)	0.26
Immobility/need for a walking aid	95 (5.3%)	28 (6.6%)	33 (3.9%)	0.10
Type 1 diabetes	20 (1.1%)	6 (1.4%)	4 (0.47%)	0.15
Chronic obstructive pulmonary disease	66 (3.7%)	10 (2.4%)	17 (2.0%)	0.050
Hypogonadism in males	11 (0.61%)	1 (0.24%)	1 (0.12%)	0.17
Early menopause in females (<45 years)	109 (6.0%)	29 (6.9%)	51 (6.0%)	0.79
Primary hyperparathyroidism	16 (0.89%)	4 (0.95%)	4 (0.47%)	0.45
Current smoking	184 (10%)	45 (11%)	52 (6.2%)	**0.001**
Alcohol intake >30 g/d	30 (1.7%)	2 (0.47%)	2 (0.24%)	**0.001**
T-score lumbar spine	−1.8 ± 1.4	−2.3 ± 1.5	−2.4 ± 1.3	**<0.001**
T-score femoral neck	−2.1 ± 0.73	−2.2 ± 0.79	−2.2 ± 0.73	**<0.001**
T-score total hip	−1.8 ± 1.2	−1.9 ± 0.92	−1.9 ± 0.84	**0.009**
T-score radius	−2.2 ± 1.4	−2.7 ± 1.4	−2.2 ± 1.6	0.18
T-score minimum	−2.5 ± 1.2	−2.8 ± 0.98	−2.8 ± 0.84	**<0.001**
Trabecular bone score	1.2 ± 0.16	1.2 ± 0.15	1.2 ± 0.17	**0.023**
Vertebral fracture(s)	534 (30%)	126 (30%)	264 (31%)	0.68
Hip fracture(s)	93 (5.2%)	17 (4.0%)	36 (4.3%)	0.49
Non-vertebral fracture(s)	494 (27%)	100 (24%)	244 (29%)	0.14

BP = bisphosphonate; Dmab = denosumab; BMI = body mass index.
Continuous variables: median with interquartile range (IQR); categorical variables: percentages of total of each subgroup.

Table 2. Clinical Details of Patients With Osteonecrosis of the Jaw (ONJ)

Patient no.	Age[a]	Causative event	BP therapy[b]	Drug holiday	Dmab[c]	Time to healing	Therapy	Risk factors	Location	Stage AAOMS[c]
12 ONJ under Dmab therapy										
1	76	Peri-implantitis	4 years ALN, 2 years ZOL	4 months	6 years	1 year	Surgical (>1 OP)	Smoking	Maxilla	2
2	59	Dental extraction	9 years ALN	2 years	6 years	1 year	Surgical	None	Mandible	2
3	74	Periodontitis			4.5 years	4 months	Surgical	Smoking	Mandible	1
4	74	Periodontitis			3.5 years	5 months	Surgical	None	Maxilla	2
5	79	Denture pressure points	8 years ALN	4 years	3 years	2 months	Surgical	None	Mandible	1
6	84	Periodontitis	3 years IBN iv	1 year	3 years	3 years	Surgical (>1 OP)	None	Mandible	2
7	63	Denture pressure points	7 years ALN/IBN iv	2 years	2.5 years	1 month	Conservative	None	Mandible	1
8	84	Dental extraction	6 years ALN/IBN iv	15 months	2.5 years	4 months	Surgical	Breast cancer, AI	Mandible	2
9	77	Dental extraction			2 years	2 months	Surgical	Smoking, RA	Mandible	2
10	71	Dental extraction	5 years ALN	6 years	1.5 years	14 months	Surgical	Smoking	Mandible	3
11	66	Dental extraction	9 years ALN	5 years	1.5 years	3 months	Surgical	Breast cancer, AI	Mandible	1
12	67	Periodontitis	6 years ALN	2 years	1 year	14 months	Surgical	None	Mandible	2
5 ONJ under BP therapy										
1	82	Denture pressure points	11 years ALN			2 years	Surgical (>1 OP)	None	Mandible	1
2	60	Peri-implantitis	8 years ALN/IBN iv			6 months	Surgical (>1 OP)	Smoking	Maxilla	1
3	62	Dental extraction	11 years ALN/IBN iv			6 months	Surgical	Smoking	Maxilla	2
4	54	Dental extraction	3 years ZOL			3.5 years	Surgical	RA, diabetes, glucocorticoids	Mandible	2
5	71	Peri-implantitis	5 years ZOL			4 months	Conservative	None	Mandible	1

AI = aromatase inhibitor; ALN = alendronate BP = bisphosphonate; Dmab = denosumab; IBN = ibandronate; iv = intravenous; OP = operation; RA = rheumatoid arthritis; ZOL = zoledronate.

[a]Age (years) at onset.

[b]Therapy before ONJ was diagnosed.

[c]Official staging according the American Association of Oral and Maxillofacial Surgeons (AAOMS).[9]

found in already advanced periodontitis that showed inflammation but no avital bone on histological examination, and these abscesses healed after initial infection control and periodontal treatment. In addition, three patients with periapical osteolysis received root canal treatment due to pulp necrosis. One of these patients had undergone recent apical root resection that was misinterpreted by the treating physician as possible ONJ. The five patients in whom ONJ was initially suspected but not confirmed were included in the group without ONJ.

The clinical characteristics of the 17 patients with ONJ are described in Table 2. {TBL 2} More than half of the affected subjects had relevant risk factors, in particular smoking ($n = 6$), glucocorticoid therapy and type 2 diabetes ($n = 1$), rheumatoid arthritis ($n = 2$; one treated with methotrexate monotherapy and one with abatacept monotherapy), and two women with breast cancer receiving aromatase inhibitors. Notably, the two women with breast cancer did not have skeletal metastases, and they were receiving antiresorptive therapy at low doses for osteoporosis treatment and prevention of bone loss.

Twelve of the 17 patients with confirmed ONJ were on denosumab, and 9 of these patients had been pretreated with BPs (mean 6.7 years). The intermediate drug holiday between BPs and denosumab ranged between 4 months and 6 years. The remaining five patients with BP-related ONJ had not undergone prior antiresorptive therapy with denosumab. ONJ associated with BPs developed during intravenous ibandronate or zoledronate therapy in four patients, and during oral alendronate treatment in one patient. The individual sequences of different therapies and drug holidays in all 17 patients are shown in Fig. 2. {FIG2} Clinical characteristics of patients with ONJ ($n = 17$) versus patients without ONJ ($n = 3051$) are described in Supplemental Table S1, with little evidence for differences between the ONJ and non-ONJ groups aside from antiresorptive treatment.

Description of sequential therapies and drug holidays

A total of 3068 patients received BPs, denosumab, or both sequentially. The median cumulative duration of BP therapy was 3.3 years (2.1 to 5.6), while for denosumab therapy it was 2.9 years (2.2 to 4.7). Thus, we assessed 11,101 observed patient-years for BP therapy (41% alendronate, 36% ibandronate, and 23% zoledronate) and 4236 for denosumab therapy. Eight hundred forty-four patients (28%) received sequential therapies (first a BP and then denosumab, or vice versa) with or without drug holidays. Overall, drug holidays comprised only a small proportion of the observation time (2614 patient-years; 15%), and no cases of ONJ occurred during a drug holiday. In total, 1048 (34%) patients had a drug holiday, and its median duration was 1.9 years (0.5 to 3.6).

Incidence rates and risk of ONJ depending on different therapies

Among 3068 patients receiving BP and/or denosumab therapy, five BP- and 12 denosumab-related ONJ cases were found, yielding an incidence rate per 10,000 patient-years of 4.50 (95% CI 1.87 to 10.82) for BP and 28.3 (16.09 to 49.9) for denosumab. The rate ratio between denosumab and BP was 6.29 (95% CI 2.06 to 22.79), $p < 0.001$ (Table 3*A*). {TBL 3} Nine of the 12 patients who developed ONJ under denosumab had undergone prior therapy with BPs. Thus, we studied hazard ratios in a multivariate analysis, considering sequential therapies and drug holidays as covariates (Table 3*B*). The risk of ONJ was significantly higher under denosumab therapy compared with BP treatment (hazard ratio 3.49, 95% CI 1.16 to 10.5, $p = 0.026$). Since there were differences between patients treated with BPs versus denosumab, the corresponding variables are listed in Table 3*C*. None of these variables demonstrated an association with the risk of ONJ, and adjusted hazard ratios revealed no relevant changes.

Because BPs have been used for a much longer time than denosumab, we performed a sensitivity analysis that ignored any treatments before August 1, 2010 (the date on which denosumab was approved in Switzerland and also the date on which denosumab was first used as a treatment in our study cohort). For this purpose, the same observational time for BPs and denosumab is warranted. The incidence rates and hazard ratios for this equalized period are described in Table 4. {TBL 4} The results

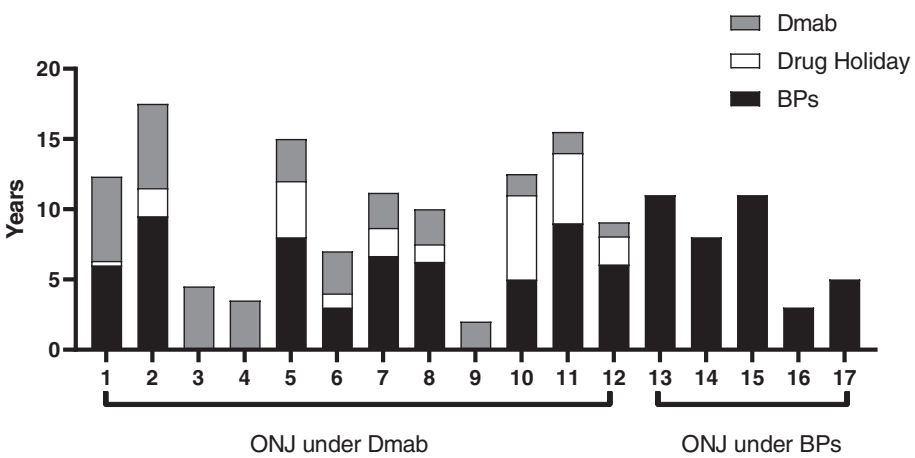

Fig. 2. Overview of cumulative treatment duration and treatment sequences of patients with ONJ. BPs = bisphosphonates; Dmab = denosumab; ONJ = osteonecrosis of the jaw. The bars represent the treatment sequences of all patients with ONJ ($n = 17$; ONJ developed during denosumab therapy in 12 patients and during BP treatment in 5 patients). Nine of the 12 patients with denosumab-related ONJ had previous BP treatment and a drug holiday between therapies, but no patients with BP-related ONJ had any prior therapy.

Table 3. Rates and Ratios of Osteonecrosis of the Jaw (ONJ)

A. ONJ event rates[a]			
	Patient-years	No. of events	Rate per 10,000 patient-years (95% CI)
Entire cohort	17,951	17	9.47 (5.89 to 15.23)
Treatment			
Drug holidays	2614	0	0.00 (0.00 to 0.001)
BPs	11,101	5	4.50 (1.87 to 10.82)
Denosumab	4236	12	28.3 (16.09 to 49.9)

B. Risk of ONJ by treatment			
		HR (95% CI)	*p* Value
Crude analysis	Drug holidays	0[b]	
	BPs	Reference	
	Denosumab	3.49 (1.16 to 10.5)	0.026

C. Adjusted hazard ratios for ONJ risk					
		Association with ONJ		Adjusted effect of Denosumab	
	n	HR (95% CI)	*p*	HR (95% CI)	*p*
BP		Reference			
Denosumab		3.49 (1.16 to 10.5)	0.026		
Age (years)	3068	0.99 (0.94 to 1.04)	0.656	3.47 (1.16 to 10.41)	0.027
Male	3068	0.83 (0.11 to 6.31)	0.860	3.49 (1.16 to 10.48)	0.026
BMI (kg/m^2)	2858	0.93 (0.82 to 1.05)	0.219	3.34 (1.10 to 10.09)	0.033
Use of glucocorticoids	3068	0.69 (0.09 to 5.24)	0.723	3.47 (1.15 to 10.46)	0.027
Aromatase inhibitors	3068	0.69 (0.00 to 4.22)	1.000	4.38 (1.38 to 16.28)	0.009
Rheumatoid arthritis	3068	3.68 (0.84 to 16.1)	0.084	3.56 (1.18 to 10.70)	0.024
Chronic obstructive pulmonary disease	3068	1.98 (0.26 to 15.2)	0.511	3.50 (1.17 to 10.50)	0.025
Alcohol intake >30 g/d[c]	3068	6.12 (0.00 to 40.0)	1.000	4.14 (1.30 to 15.41)	0.013
Smoking	3068	4.42 (1.43 to 13.6)	0.010	3.58 (1.20 to 10.70)	0.022
T-score lumbar spine	2884	1.01 (0.67 to 1.52)	0.954	3.88 (1.16 to 13.00)	0.028
T-score femoral neck	2767	0.65 (0.32 to 1.34)	0.246	2.85 (0.93 to 8.73)	0.066
T-score total hip	2678	0.90 (0.69 to 1.18)	0.445	2.92 (0.96 to 8.91)	0.059
Trabecular bone score	1948	0.15 (0.02 to 1.09)	0.061	1.30 (0.27 to 6.33)	0.748

CI = confidence interval; BP = bisphosphonate; HR = hazard ratio; BMI = body mass index.

Incidence rates (*A*) and hazard ratios (*B*) of ONJ. With BPs as the reference, denosumab is associated with a higher risk of ONJ, even after adjustment for clinical characteristics (*C*). Note that some estimates in *C* might be biased because of missing values: *T*-scores of lumbar spine or femoral neck and trabecular bone scores are missing in 2 and 10 patients with ONJ, respectively.

[a]Rate ratio of denosumab versus BPs: 6.29 (95% CI 2.06 to 22.79), $p < 0.001$.

[b]CI not estimable because of zero events.

[c]Calculated using exact logistic regression due to zero events in one category; the estimates hence represent odds ratios with 95% CI.

were robust in this sensitivity analysis and not substantially different from those in the main analysis.

Discussion

In this observational study, we investigated the incidence of ONJ in a real-world population. Patients were treated sequentially with different anti-osteoporotic therapies, including BPs, denosumab, SERMs, or teriparatide. ONJ occurred in patients who received BPs or denosumab, but not during drug holidays or in those administered SERMs or teriparatide.

The occurrence of BP-related ONJ in patients with osteoporosis is well established, with an incidence of 1 per 10,000 to 100,000 patient-years. Eiken and colleagues reported an incidence rate of 2.53 per 10,000 patient-years in a Danish register-based cohort study.[11] Similarly, the sex- and age-standardized ONJ incidence rate was 2.6 per 10,000 patient-years in a retrospective cohort study by Tennis and colleagues.[12] Ulmner and colleagues conducted a survey-based study in hospital dental clinics in Sweden and found that the incidence of BP-associated ONJ was 6.7 per 10,000 patient-years.[13] In another survey-based study, Khan and colleagues reported a cumulative ONJ incidence of 1.04 per 100,000 patient-years in Ontario.[14] On the other hand, little is known about the incidence of ONJ under denosumab treatment against osteoporosis (60 mg every 6 months). In the 7-year extension of the FREEDOM study, 13 patients with ONJ were identified, yielding an incidence of 5.2 per 10,000 patient-years.[7,8] In contrast, the incidence of denosumab-related ONJ in our patients was markedly higher (28.3 per 10,000 patient-years). Moreover, the risk of ONJ under denosumab was significantly higher than under BPs. This discrepancy was also found in previous studies, but they were performed in patients with malignant diseases who received high doses of antiresorptive agents.[15-17]

Table 4. Rates and Risk of Osteonecrosis of the Jaw (ONJ), Ignoring Treatments Before August 1, 2010

A. ONJ events rates, ignoring treatments before August 1, 2010[a]			
	Patient-years	No. of events	Rate per 10,000 patient-years (95% CI)
Drug holidays	1571	0	0.00 (0.00 to 0.002)
BPs	7673	5	6.52 (2.71 to 15.66)
Denosumab	4239	12	28.3 (16.08 to 49.8)

B. Risk of ONJ by treatment, ignoring treatments before August 1, 2010		
	HR (95% CI)	*p* Value
Drug holidays	0.00[b]	
BPs	Reference	
Denosumab	3.14 (1.08 to 9.17)	0.036

CI = confidence interval; BP = bisphosphonate; HR = hazard ratio.

Incidence rates (*A*) and hazard ratios (*B*) of ONJ. With BPs as the reference, denosumab is associated with a higher risk of ONJ. In these sensitivity analyses, treatments before August 1, 2010, were ignored. Thus, equivalent observational periods for both denosumab and BPs were warranted.

[a]Rate ratio denosumab versus BPs: 4.34 (95% CI 1.42 to 15.74), $p = 0.002$.

[b]Not estimable because of zero events.

Switching from BPs to denosumab has been hypothesized to raise the risk of ONJ development.[18-23] Nine of the 12 patients who developed ONJ under denosumab were previously treated with BPs for a mean duration of 6.7 years. Because of the long-term effects of BPs and their incorporation into bone mineral, it can be assumed that these drugs increase the risk of ONJ development during subsequent therapy with denosumab, at least in patients with only short breaks between treatment sequences. In the FREEDOM trial and its extension, the drug holiday between BP treatment and the initiation of denosumab was >5 years for intravenous BPs, and >12 months and a maximum treatment duration of 3 years for oral BPs.[7,24] In contrast, drug holidays were shorter in most of our patients who underwent sequential therapy with BPs and denosumab. Delays in dosing or short drug holidays of up to 1 year after BP therapy seem to have no influence on the incidence of ONJ,[25,26] but longer breaks probably reduce its risk.[27] Apart from drug holidays, evidence is lacking on whether long-term administration of antiresorptive agents increases the risk of ONJ[28] and whether there is a duration-dependent association. In our study, 9 of 17 patients with ONJ had a cumulative duration of antiresorptive treatment of 8 years or more, but 5 patients were treated for less than 5 years before ONJ was diagnosed. Thus, factors other than drug holidays and the cumulative treatment duration appear to influence the risk of ONJ, for instance, chronic diseases or specific risk factors like smoking, diabetes, or glucocorticoid use.[29,30]

About a quarter of our patients with BP and/or denosumab therapy suffered from various comorbidities, which is common in real-world populations.[31] This may have contributed to our high incidence rates of ONJ. Of four patients who developed ONJ while on antiresorptive therapy, two were being treated with immunosuppressive agents and two with aromatase inhibitors. ONJ related to medications other than BPs or denosumab is uncommon but has been reported before.[32,33] However, it is difficult to establish a causal relationship between other drugs and the risk of ONJ.[34] Furthermore, comorbidities or additional therapies do not explain the different incidence rates of ONJ under denosumab versus BPs, as these factors were present in both patients with BPs and those with denosumab therapy. None of these comorbidities or additional therapies demonstrated an association with ONJ in the regression model, and adjusted hazard ratios were not substantially changed. Therefore, our findings are more likely due to specific differences in the pathogenesis of BP- versus denosumab-associated ONJ. It was recently reported that ONJ in patients receiving denosumab or BPs differed regarding histopathological and radiologic features, and in some studies, also in terms of outcome.[35-38] Denosumab-associated ONJ demonstrated significantly lower numbers of osteocytes per area,[35] whereas persistent bone resorption lacunae on the necrotic bone surface were found only in BP-associated ONJ.[36] Further, the radiologic features of denosumab-related ONJ may be different from those of BP-associated ONJ, with fewer sequesters and less cortical lysis.[37] It has also been hypothesized that denosumab-related ONJ heals faster,[38] which may be explained by the short treatment effect of denosumab. However, if patients under denosumab have undergone prior BP therapy, cumulative toxic effects on various bone cells and/or keratinocytes in the oral mucosa could increase the risk of ONJ.

Our observations may directly impact the therapeutic strategy in osteoporosis. Long-term BP treatment could increase the risk of rare events such as atypical femoral fractures and ONJ.[28] On the other hand, it is unclear whether drug holidays of several years between BP and denosumab therapy reduce the risk of ONJ. It is recommended that a drug holiday should be considered after 5 years of oral BPs or 3 years of intravenous BPs in women who are not at high risk of fracture.[28] However, the situation with denosumab is different: Because of the rebound effect after its discontinuation, immediate subsequent therapy with a BP is strongly recommended.[39] It has also been reported that BP therapy before denosumab reduces fracture risk and bone loss after denosumab discontinuation.[40,41] With respect to our observations, uninterrupted sequential therapy with BPs and denosumab could be associated with an increased risk of ONJ. Nevertheless, ONJ is a rare side effect, and the treatment benefits of antiresorptive agents presumably outweigh the risk of ONJ by far.[42]

Our observational study has several limitations. First, we did not routinely screen for ONJ, as is usually done in prospective trials. Thus, the incidence of oral complications and early stages of ONJ may have been underestimated. More than half of our patients with ONJ demonstrated an AAOMS stage of 2 or

3, although stages 1 and 2 are usually more frequent.[43] Second, the prevalence of ONJ in subjects without anti-osteoporotic drugs may have been underestimated, as the awareness of early or stage 1 ONJ in the general population is lower than in patients receiving BP or denosumab therapy. However, our patients with ONJ (all of whom were treated) had relatively advanced disease, which should have been recorded in the medical charts of untreated patients as well. Third, our study group included patients with secondary osteoporosis (eg, glucocorticoid-induced osteoporosis) or other comorbidities. These comorbidities may constitute an additional risk factor for ONJ. Fourth, treatment modalities were heterogeneous, making the statistical evaluation challenging. We addressed bias with statistical corrections, namely with time-dependent covariates for treatment sequences and adjustments for patient characteristics. Fifth, only a few patients received SERMs or teriparatide, so the results should be interpreted with caution in this regard. In the literature, ONJ have also been reported in patients receiving SERMs.[44] Sixth, only limited information about preventive strategies was available.

In our group of patients with osteoporosis, the risk of ONJ was higher in those who received denosumab than those treated with BPs. Previous BP therapy before switching to denosumab may be an additional risk factor for ONJ development.

Disclosures

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Peer Review

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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