Osteonecrosis of the Jaw among Patients with Cancer Treated with Denosumab or Zoledronic Acid: Results of a Regulator-mandated Postauthorization Safety Cohort Study in Denmark, Norway, and Sweden

Running title: Antiresorptive treatment and ONJ

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Conflict of interest statement

VE, UHJ, MS, OA, BBH, CLW, SEN, AK, and HTS are or were at the time of the study employed at their respective institutions, which received institutional research funding from Amgen Inc for conducting this study. SH and ST are or were at the time the study was conducted employed at the Cancer Registry of Norway, which received funding from Aarhus University to perform specific study tasks as a subcontractor and have nothing to disclose. AG and KL are employees and stockholders of Amgen Inc.

Author contributions

All authors made substantial contributions to the conception and design of the study and to interpretation of data. UHJ conducted the data analysis. VE drafted the manuscript, and all authors revised it critically for important intellectual content. All authors gave their final approval of the version to be published and have agreed to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Lay summary (91/100 words)

Denosumab and zoledronic acid reduce risk of bone fractures, pain, and surgery in patients with advanced cancers involving bone. Osteonecrosis of the jaw (ONJ) – death of a jaw bone – is a known side effect of treatment with denosumab or zoledronic acid. We examined almost 2,900 denosumab- or zoledronic acid-treated patients with cancer in Denmark, Norway, and Sweden. Over five years, ONJ developed in 5.7% of patients whose initial treatment was denosumab, 1.4% of patients whose initial treatment was zoledronic acid; and 6.6% of patients who switched from zoledronic acid to denosumab.

Precis for use in the Table of Contents

This was a non-randomized cohort study in Denmark, Norway, and Sweden, estimating incidence proportions and incidence rates of osteonecrosis of the jaw (ONJ) among patients with cancer initiating denosumab or zoledronic acid for prevention of skeletal-related events in routine clinical practice. Over five years following treatment initiation, incidence proportions of ONJ were 5.7% among treatment naïve denosumab initiators, 1.4% among treatment naïve zoledronic acid initiators; and 6.6% among patients switching to denosumab after no more than 24 monthly bisphosphonate doses; the corresponding incidence rates were 3.0, 1.0, and 4.3 per 100 person-years.

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ABSTRACT (247/250 words)

BACKGROUND

Osteonecrosis of the jaw (ONJ) is an adverse effect of antiresorptive treatment. We estimated incidence proportions and incidence rates of ONJ in cancer patients with bone metastases from solid tumors treated for prevention of skeletal-related events in routine clinical practice.

METHODS

We conducted a cohort study in Denmark, Norway, and Sweden, in 2011–2018, including three treatment cohorts: Denosumab Inception Cohort (DEIC), Zoledronic Acid Inception Cohort (ZAIC), and Denosumab-switch Cohort (DESC). We estimated 1- to 5-year incidence proportions and incidence rates of ONJ, overall, by cancer site (breast, prostate, or other solid tumor), and by country. ONJ diagnoses were confirmed by adjudication.

RESULTS

There were 1,340 patients in the DEIC, 1,352 in the ZAIC, and 408 in the DESC. Median age in the three cohorts was 70.4, 68.9, and 70.2 years, the proportions of men were 72.6%, 53.8%, and 48.3%; and median follow-up was 19.8, 12.9, and 13.3 months. The 5-year incidence proportions (95% confidence interval [CI]) of ONJ were 5.7% (4.4, 7.3) in the DEIC, 1.4% (0.8, 2.3) in the ZAIC, and 6.6% (4.2, 10.0) in the DESC. The corresponding incidence rates per 100 person-years were 3.0 (2.3, 3.7), 1.0 (0.6, 1.5), and 4.3 (2.8, 6.3). Incidence proportions and incidence rates were highest in patients with prostate cancer and in Denmark.

CONCLUSIONS

We provide estimates of risk of medically confirmed ONJ among patients initiating denosumab or zoledronic acid in routine clinical practice in three Scandinavian countries. The results varied by cancer site and by country.

Keywords

Bisphosphonates, cohort study, denosumab, osteonecrosis of the jaw, routinely collected health data, real-world data

INTRODUCTION

Zoledronic acid (a bisphosphonate) and denosumab (a monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand) are two different classes of antiresorptive agents, administered every 3-4 weeks, indicated for prevention of skeletal-related events in adults with advanced malignancies involving bone, such as bone metastases from solid tumors and multiple myeloma.[1,2] In randomized trials among patients with bone metastases from solid tumors, denosumab was more efficacious than zoledronic acid in preventing skeletal-related events[3-5] and alleviating pain,[6] while the two agents were associated with similar overall survival.[7,8]

Osteonecrosis of the jaw (ONJ) is an adverse effect of antiresorptive treatment, with dose- and duration-dependent risks.[9] ONJ is diagnosed in the presence of jaw bone that is exposed or can be probed through a fistula, persisting for at least 8 weeks, in patients without history of radiotherapy or jaw metastasis.[9]

Real-world safety of medications may differ from that observed in clinical trials.[10] In this study, we aimed to estimate incidence proportions and incidence rates of ONJ up to 5 years following initiation of denosumab or zoledronic acid for prevention of skeletal-related events among cancer patients treated in routine clinical practice in Denmark, Norway, and Sweden. This was a postauthorization safety study mandated by the European Medicines Agency (EMA).

MATERIALS AND METHODS

Setting, Design, and Data Sources

This population-based cohort study was set in Denmark, Norway, and Sweden – welfare states with universal health care.[11] Use of denosumab for prevention of skeletal-related events in adults with bone metastases from solid tumors in the three countries started in 2011,[12-14] following the EMA approval.[1] We identified treatment and patients' characteristics using routinely collected health and administrative data from previously described sources (Supplemental Table 1), augmented by medical record abstraction. ONJ cases originated from the Scandinavian ONJ Cohort.[15] The ONJ terminology has evolved from "bisphosphonate-related ONJ" to "antiresorptive-agent associated ONJ" to "medication-related ONJ". This paper uses the term ONJ.[9]

Treatment Cohorts

The treatment cohort identification period started on 01 October 2011 and ended on 31 December 2013 in Sweden and Norway and on 31 December 2014 in Denmark. (The period in Denmark was longer due to study size considerations). Eligible patients were

adults (ages ≥18 years) diagnosed with cancer who, subsequently to their cancer diagnosis and during the treatment cohort identification period, initiated treatment with denosumab or zoledronic acid for prevention of skeletal-related events (Figure 1). We excluded patients with a history of radiation therapy to the head and neck region, and patients treated with denosumab or zoledronic acid solely for hypercalcemia of malignancy. We defined three treatment cohorts: the Denosumab Inception Cohort (DEIC); the Zoledronic Acid Inception Cohort (ZAIC), and the Denosumab-switch Cohort (DESC). Patients in the two inception cohorts were naïve to antiresorptive treatment for skeletal related event prevention; patients in the DESC were allowed to have a maximum of 24 monthly bisphosphonate doses for that indication. Date of treatment initiation was the index date. At early stages of inclusion in Denmark, denosumab initiators were predominantly men with prostate cancer while zoledronic acid initiators were predominantly women with breast cancer. To improve comparability of the cohorts, we group-matched the ZAIC to the denosumab cohorts: patients were selected into the ZAIC from among a randomly-ordered list of patients with the same sex and cancer site as the denosumab initiators. If a given candidate was subsequently deemed ineligible (i.e., was not treated with ZA, treated for hypercalcemia or malignancy, or had a history of head and neck radiation), the next patient on the list was evaluated until finding a match or exhausting the pool of candidates.

Osteonecrosis of the Jaw

In the three Scandinavian countries, patients with ONJ are referred to and treated at specialist departments of oral and maxillofacial surgery. In all three countries, ONJ treatment occurs at hospital-based departments (all treatment centralized to six clinics in Denmark); in Norway, ONJ may be also treated at free-standing clinics; and in Sweden ONJ may be also treated at departments of oral medicine, healthcare or dental care. Clinics outside hospitals do not contribute records to the registries (Supplemental Table 1), and even available hospital-recorded ICD-10 codes have low validity in capturing ONJ.[16] To maximize completeness and validity of ONJ identification, we established the Scandinavian ONJ Cohort, which included ONJ cases diagnosed directly at treating clinics independently of treatment cohorts' identification. The Scandinavian ONJ Cohort contains information on ONJ onset date, risk factors, and ONJ treatment.[15] To mimic ONJ identification procedure used in phase 3 trials and further increase specificity of ONJ adjudication, ONJ cases identified in the Scandinavian ONJ Cohort underwent additional independent adjudication by two experts, blinded to treatment cohort membership. Positively adjudicated cases were considered 'medically confirmed' and included in the analysis.

Statistical Analysis

We summarized characteristics of the patients in the treatment cohorts in 24 months before the index date, using medians and quartiles for continuous variables and frequencies and

percent for categorical variables. We also reported proportion of patients dying or emigrating during the follow-up.

In each treatment cohort, we estimated 1-, 2-, 3-, 4-, and 5-year incidence proportions of ONJ and incidence rate of ONJ, overall, by primary cancer site and by country. An n-year incidence proportion is the count of medically confirmed incident ONJ cases observed during n years divided by the number of patients in the cohort with a potential for completing n years of follow-up. An incidence rate is the number of medically confirmed incident ONJ cases observed during the follow-up divided by total person-time. According to the clinical definition of ONJ, only ONJ cases occurring at least 8 weeks following the index date were considered. Patients included in the ZAIC who switched to denosumab during the cohort identification period stopped contributing time to the ZAIC and started contributing time to the DESC 8 weeks after the switch. Patients were followed from the start of the at-risk period in each treatment cohort until the earliest of diagnosis of medically confirmed ONJ, emigration (loss to follow-up), death, 5 years of follow-up, or 31 December 2018. Patients included in either denosumab cohort who subsequently switched to zoledronic acid were censored for ONJ determination in the relevant denosumab treatment cohort 8 weeks after initiating zoledronic acid. Incidence proportions (in percent) and incidence rates (per 100 person-years) were reported with 95% CIs. Incidence proportions were reported with Clopper-Pearson 95% confidence intervals (CIs), and incidence rates, with Poisson CIs. For the ONJ cases included in the analyses, we summarized demographic characteristics, oral risk factors, and treatment.

Supplemental Table 2 lists definitions of the study variables. We used SAS Software Version 9.4 for all analyses.

Ethical Aspects

This study received all required approvals (Denmark: Danish Data Protection Agency record number 2010-41-5171; mandatory registration at Aarhus University 2016-051-000001/417 and approval of the Patient Safety Board record number 3-3013-13/1); Norway: Regional Committee for Medical and Health Research Ethics South East, record numbers 2012/2286/REK sør-øst and 2013/1053/REK sør-øst). Sweden: Regional Ethical Review Board, Stockholm, Karolinska Institutet/Solna, record number 2013/319-31/2. To prevent identification of individuals, exact cell counts below 5 were masked. The study protocol has been published[17] and the study has been registered on ClinicalTrials.gov (registration number NCT01967160).[18]

RESULTS

After applying the eligibility criteria, 2,877 patients were included in the analysis: 1,340 in the DEIC, 1,352 in the ZAIC, and 408 in the DESC, including 223 patients initially included in the ZAIC who subsequently switched to denosumab and were counted in two cohorts. Fifty patients in the DEIC and 92 patients in the DESC switched to zoledronic acid (Figure 1).

Table 1 summarizes patients' characteristics and follow-up by treatment cohort. The median age of the patients was 70 years in the DEIC, 69 years in the ZAIC, and 70 years in the DESC, and the respective proportions of men were 72.6%, 53.8%, and 48.3%. The median follow-up in the three cohorts was 19.8, 12.9, and 13.3 months, and the median number of treatment doses was 10, 5, and 8. The two inception cohorts differed with respect to the distribution of primary cancer sites. Patients initiating denosumab treatment had a longer median time since bone or visceral metastases than patients initiating zoledronic acid, and a slightly higher hospital comorbidity burden (Table 1).

Between 01 October 2011 and 31 December 2018, 137 ONJ cases among the patients of the treatment cohorts were identified in the Scandinavian ONJ Cohort. Of those, 136 (99.3%) were subsequently medically confirmed by expert adjudication. One-hundred and twenty ONJ cases were included in the analyses of incidence proportions and incidence rates, while 16 cases were excluded from the analyses, per protocol, for one of the following reasons: loss to follow-up; ONJ date of diagnosis less than 8 weeks or more than 5 years after the index date; or occurrence among patients who initiated the study in DEIC or DESC and subsequently switched to zoledronic acid. (The exact counts for each reason are not reportable per data protection regulation).

Figure 2 shows incidence proportions of ONJ by treatment cohort, primary cancer site, and country. The 5-year incidence proportions of medically confirmed ONJ were 5.7% (95% CI: 4.4, 7.3) in the DEIC, 1.4% (95% CI: 0.8, 2.3) in the ZAIC, and 6.6% (95% CI: 4.2, 10.0) in the DESC (Figure 2). The incidence rates of medically confirmed ONJ per 100 person-years were 3.0 (95% CI: 2.3, 3.7) in the DEIC, 1.0 (95% CI: 0.6, 1.5) in the ZAIC, and 4.3 (95% CI: 2.8, 6.3) in the DESC (Table 2). Table 3 summarizes characteristics, risk factors and treatments of the 120 patients with medically confirmed ONJ included in the analysis, by country.

DISCUSSION

In this regulator-mandated population-based non-randomized cohort study, 5-year incidence proportions of medically confirmed ONJ were 5.7% among treatment-naïve patients initiating denosumab, 1.4% among treatment-naïve patients initiating zoledronic acid, and 6.6% in among patients switching to denosumab after no more than 24 monthly cancer doses of bisphosphonates. The corresponding incidence rates of ONJ per 100 person-years (accounting for variable follow-up) were 3.0, 1.0, and 4.3. The incidence proportions and

incidence rates of ONJ varied by cancer site and by country, with highest estimates observed among men with prostate cancer and among patients in Denmark. More than half of the patients with medically confirmed ONJ had a history of oral trauma, including extraction or oral surgery. Variability in ONJ occurrence across the treatment cohorts may be partially attributable to differences in patient populations, specifically, distribution of primary cancer sites, and the associated variation in age, sex, comorbidity and cancer treatment. Incidence proportion of ONJ increased with follow-up time in the denosumab cohorts more prominently than in the zoledronic acid cohort, possibly related to a greater median number of monthly doses received by patients in the denosumab cohorts. The median number of monthly treatments in all cohorts was substantially lower than the median months of follow-up, as follow-up was not censored at treatment discontinuation~~., by design, h~~ However, this study was not designed to examine treatment duration, treatment discontinuation or ~~its~~ reasons for discontinuation. In contemporaneous European studies in similar patient populations 24-month persistence with denosumab or zoledronic acid ranged between 19-68%,[19] while the most common reasons for initial treatment discontinuation (other than patient death) were disease progression, physician choice, and toxicity.[20]

Our results are consistent with the earlier findings regarding risk of ONJ in patients treated with denosumab or zoledronic acid. [3-5,21-23] In phase 3 trials among 5,723 patients with bone metastases from solid tumors, ONJ risk was 1.8% with denosumab and 1.3% with zoledronic acid treatment over up to 40 months of follow-up.[3-5] In an open-label extension study, the risks of ONJ were 6.9% among patients continuing in the denosumab arm, and 5.5% among patients switching to denosumab from zoledronic acid over up to 67 months of follow-up.[21] In a meta-analysis of phase 3 trials (including patients with multiple myeloma), treatment with denosumab vs. bisphosphonates over 3 years was associated with an 1.4- fold increase in ONJ risk, corresponding to an absolute increase of 3 cases per 1,000.[22] A limitation of that study is potential inclusion of partially overlapping populations. In an observational cohort study in Belgium, with similar design to our study but without expert ONJ adjudication, the 5-year incidence proportion of ONJ was 10.0% over a median 18-month treatment among denosumab initiators (51% breast cancer), 6.7% over a median 19-month treatment among zoledronic acid initiators (64% breast cancer), and 15.5% over a median of 36-months cumulative sequential exposure to both agents among zoledronic acid-to-denosumab switchers (82% breast cancer).[24] In a cohort study in the US, 3-year cumulative incidence of ONJ was 2.8% for cancer patients on zoledronic acid and 3.2% among cancer patients on denosumab.[23] It has been hypothesized that switching from bisphosphonates to denosumab, in addition to being a marker of treatment duration, is itself a risk factor for ONJ.[25,26] Taken together, evidence from different sources is consistent with denosumab treatment conferring a greater ONJ risk than treatment with zoledronic acid.

Our study has several limitations. First, there is an inherent non-comparability of patients' characteristics in the treatment cohorts, which is expected when one of the treatments newly

marketed.[27] Therefore this study was designed not as a comparative study but as study to assess absolute risks and rates of ONJ in cancer patients initiating denosumab or zoledronic acid in routine clinical practice. Second, some criteria for clinical diagnosis of ONJ have changed over time: for example, in 2009, a diagnosis of ONJ required current or previous treatment with a bisphosphonate, exposed bone in the maxillofacial region for more than 8 weeks, and no history of radiation therapy to the jaw,[28] while in the 2014, a diagnosis of ONJ required current or previous treatment with antiresorptive or antiangiogenic agents, exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks, and no history of radiation therapy to the jaw or obvious metastatic disease of the jaw.[9] Thus, ONJ identified in this study may differ somewhat from that identified earlier, e.g., in trials. Treatment has also changed: with growing ONJ awareness, and oral and maxillofacial surgeons may increasingly prefer surgical removal of necrotic bone to a conservative treatment. If such intervention occurs shortly after a referral, the 8-week exposed/probed bone clinical criterion for ONJ diagnosis may not be fulfilled, and cases would not be counted. This may partially explain greater risk of ONJ observed in the study from Belgium compared with our study.[24] ONJ severity or resolution could not be reliably assessed. Third, the incidence proportions are underestimated in the presence of censoring: for example, patients censored from a cohort by treatment switch were counted as not having a later event. Fourth, there may be immortal time bias in the Danish population, introduced in patients initially eligible for DESC, but after confirmation via medical chart review were also included in the ZAIC. By design, such patients had to survive until the initiation of denosumab to be included in the study; this bias may partially explain low observed ONJ occurrence in the ZAIC. Finally, there was evidence of ONJ ascertainment varying by country, suggestion higher completeness in Denmark than in Norway or Sweden, given that ONJ treatment in Denmark is centralized to 6 hospital clinics.

In conclusion, this study provides estimates, from routine clinical practice, of 5-year risks and incidence rates of osteonecrosis of the jaw among cancer patients with bone metastases who initiate denosumab or zoledronic acid for prevention of prevent skeletal-related events.

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FIGURES AND TABLES

Figure legends

Figure 1. Diagram of Population Identification

Figure 2. Incidence Proportions of Medically Confirmed ONJ by Treatment Cohort, Follow-up Time, Primary Cancer Site, and Country

1

2 **Table 1. Patients' Characteristics and Follow-up, by Treatment Cohort[a]**

Variable	Denosumab Inception Cohort (N=1,340)	Zoledronic Acid Inception Cohort (N=1,352)	Denosumab-switch Cohort (N=408)
Patient status at the end of follow-up, n (%)			
Alive	255 (19.0)	421 (31.1)	118 (28.9)
Dead or emigrated	1,085 (81.0)	931 (68.9)	290 (71.1)
Months of follow-up, median (Q1, Q3)	19.8 (9.6, 40.5)	12.9 (5.5, 27.7)	13.3 (6.8, 28.2)
Monthly recorded treatment doses, median (Q1, Q3)	10 (4, 20)	5 (2, 12)	8 (4, 16)
Men, n (%)	973 (72.6)	727 (53.8)	197 (48.3)
Age, years, median (Q1, Q3)	70 (65, 78)	69 (61, 76)	70 (61, 77)
Age group, years, n (%)			
< 50	56 (4.2)	102 (7.5)	23 (5.6)
50-64	299 (22.3)	360 (26.6)	117 (28.7)
65-74	532 (39.7)	501 (37.1)	146 (35.8)
≥75	453 (33.8)	389 (28.8)	122 (29.9)
Year of cohort entry, n (%)			
2011	49 (3.7)	147 (10.9)	27 (6.6)
2012	453 (33.8)	544 (40.2)	169 (41.4)
2013	546 (40.7)	485 (35.9)	120 (29.4)
2014	292 (21.8)	176 (13.0)	92 (22.5)
Country, n (%)			
Denmark	676 (50.4)	595 (44.0)	209 (51.2)
Norway	314 (23.4)	357 (26.4)	141 (34.6)
Sweden	350 (26.1)	400 (29.6)	58 (14.2)
Hospital department initiating treatment, n (%)			
Oncology	735 (54.9)	992 (73.4)	301 (73.8)
Urology/surgery	536 (40.0)	194 (14.3)	89 (21.8)
Other	69 (5.1)	166 (12.3)	18 (4.4)
Primary cancer site, n (%)			
Prostate	925 (69.0)	661 (48.9)	192 (47.1)
Breast	338 (25.2)	561 (41.5)	203 (49.8)
Other	77 (5.7)	130 (9.6)	13 (3.2)
Months since primary cancer diagnosis, median (Q1, Q3)	27.4 (8.6, 52.2)	21.4 (5.7, 43.1)	35.7 (17.5, 60.9)
Record of bone metastases, n (%)	1,230 (91.8)	1,126 (83.3)	364 (89.2)
Record of visceral metastases, n (%)	224 (16.7)	300 (22.2)	115 (28.2)
Months since bone metastases, median (Q1, Q3)	5.8 (1.4, 17.0)	3.7 (0.9, 12.4)	15.9 (9.1, 25.0)
Months since visceral metastases, median (Q1, Q3)	4.5 (1.1, 17.7)	3.2 (0.7, 11.7)	13.3 (5.0, 20.1)
Charlson Comorbidity Index, n (%)			
0	1,019 (76.0)	1,075 (79.5)	322 (78.9)
1-2	274 (20.4)	244 (18.0)	74 (18.1)
3+	47 (3.5)	33 (2.4)	12 (2.9)

Variable	Denosumab Inception Cohort (N=1,340)	Zoledronic Acid Inception Cohort (N=1,352)	Denosumab-switch Cohort (N=408)
Hospital comorbidity, n (%)			
Diabetes	136 (10.1)	110 (8.1)	36 (8.8)
Secondary anemia	46 (3.4)	50 (3.7)	20 (4.9)
Hospitalization with infection	176 (13.1)	159 (11.8)	71 (17.4)
Severe/febrile neutropenia	55 (4.1)	44 (3.3)	21 (5.1)
Hypothyroidism	15 (1.1)	21 (1.6)	Masked
Chronic lung disease	64 (4.8)	65 (4.8)	19 (4.7)
Cardiovascular disease	81 (6.0)	74 (5.5)	22 (5.4)
Cerebrovascular disease	42 (3.1)	38 (2.8)	14 (3.4)
Autoimmune disease	40 (3.0)	32 (2.4)	7 (1.7)
Cachexia/severe weight loss	46 (3.4)	55 (4.1)	26 (6.4)
Bisphosphonates used prior to treatment initiation, n (%)			
Zoledronic acid	NA	NA	408 (100.0)
Pamidronic acid	NA	NA	5 (1.2)
Cumulative duration of prior oral and IV bisphosphonate treatment			
0 to < 6 months	NA	NA	193 (47.3)
6 to < 12 months	NA	NA	119 (29.2)
12 to ≤24 months	NA	NA	96 (23.5)

[a] 223 patients started follow-up in the Zoledronic Acid Inception Cohort and switched to denosumab during the treatment cohort identification period. They were counted in both cohorts, but their follow-up for the Zoledronic Acid Inception Cohort was censored at the time of the switch. Counts between 1 and 4 are masked to comply with privacy protection regulations.

IV intravenous; Q1 first quartile; Q3 third quartile, NA not applicable

Table 2. Incidence Rates of Medically Confirmed ONJ by Treatment Cohort, per 100 Person-Years, by Treatment Cohort, Primary Cancer Site and Country

	Denosumab Inception Cohort		Zoledronic Acid Inception Cohort		Denosumab-switch Cohort	
Group	Cases/person-years	Incidence rate (95% CI)	Cases/person-years	Incidence rate (95% CI)	Cases/person-years	Incidence rate (95% CI)
Overall	76/2,576.3	3.0 (2.3, 3.7)	19/1,975.1	1.0 (0.6, 1.5)	25/582.2	4.3 (2.8, 6.3)
Primary cancer site						
Prostate	61/1,765.5	3.5 (2.6, 4.4)	Masked/970	0.7 (0.3, 1.5)	13/276.2	4.7 (2.5, 8.0)
Breast	10/695.9	1.4 (0.7, 2.6)	11/911.2	1.2 (0.6, 2.2)	Masked/300	3.6 (1.8, 6.5)
Other	5/114.8	4.4 (1.4, 10.2)	Masked/100	1.0 (0.0, 5.6)	Masked/10	22.1 (0.6, 123.3)
Country						
Denmark	48/1,327.9	3.6 (2.7, 4.8)	10/896.6	1.1 (0.5, 2.1)	Masked/350	3.2 (1.6, 5.7)
Norway	13/532.7	2.4 (1.3, 4.2)	Masked/480	0.8 (0.2, 2.1)	13/202.0	6.4 (3.4, 11.0)
Sweden	15/715.6	2.1 (1.2, 3.5)	Masked/600	0.8 (0.3, 2.0)	Masked/30	2.9 (0.1, 16.4)

CI: confidence interval; ONJ osteonecrosis of the jaw. Patients with ONJ occurring less than 8 weeks after the index date (N=2 in the zoledronic acid inception cohort) do not contribute to the calculation of incidence rates.
Number of cases are masked and the corresponding person-years rounded to comply with privacy protection regulations.

Table 3. Characteristics and Clinical Course of Patients with Medically Confirmed ONJ Included in the Study, by Country

	Denmark N=69	Norway N=30	Sweden N=21
Demographics			
Sex, n (%)			
Men	51 (73.9)	20 (66.7)	16 (76.2)
Women	18 (26.1)	10 (33.3)	5 (23.8)
Age group, years, n (%)			
< 64	22 (31.9)	11 (36.7)	8 (38.1)
65 - 74	30 (43.5)	11 (36.7)	9 (42.9)
≥75	17 (24.6)	8 (26.7)	4 (19.0)
ONJ risk factors, n (%)			
Smoking,	24 (34.8)	Masked	6 (28.6)
Alcohol use,	38 (55.1)	6 (20.0)	Masked
History of oral trauma (including extraction or surgery)	36 (52.2)	24 (80.0)	10 (47.6)
ONJ stage at diagnosis = 2 or 3, n (%)	49 (71.0)	22 (73.3)	20 (95.2)
Treatment of ONJ, n (%)			
Procedures*			
Curettage	15 (21.7)	7 (23.3)	10 (47.6)
Debridement	10 (14.5)	9 (30.0)	12 (57.1)
Medicinal treatment*			
Antibiotics	56 (81.2)	24 (80.0)	19 (90.5)
Oral rinses	43 (62.3)	16 (53.3)	10 (47.6)

*Categories are not mutually exclusive. ONJ osteonecrosis of the jaw. Small counts masked whenever applicable to comply with privacy protection regulations.