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Risk of Osteonecrosis of the Jaw under Denosumab Compared to Bisphosphonates in Patients with Osteoporosis

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Data Sharing

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

1. 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 9'956 registered patients, 3'068 (89% female, median age 69 years [63 to 76]) were treated with BPs or denosumab for a cumulative duration of 11'101 and 4'236 patient-years, respectively. Seventeen cases of ONJ were identified; 12 in patients receiving denosumab at the time of ONJ diagnosis and five 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% 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 five patients with BP-related ONJ had previously received denosumab. The risk of ONJ was higher in patients receiving denosumab therapy compared to 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.

2. 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 characterised 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 hypercalcaemia.[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 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 (1-15%), 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 cohort study was to analyse 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 individualised therapeutic modalities, the analysis specifically focused on different sequences of antiresorptive therapies and temporary discontinuations (“drug holidays”).

3. Methods

3.1. Study design

This study was conducted at a single non-academic outpatient centre 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 DXA scan and clinical evaluation are included in the register. Age, gender, 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 dual-energy X-ray absorptiometry (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.

3.2. 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 (e.g., 12 months after zoledronate or 3 months after intravenous ibandronate).

3.3. Statistical analyses

We analysed 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 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 $\chi 2$-squared test for variables with more than two categories. Statistical analyses were performed using Stata 16 (StataCorp, College Station, TX, USA).

4. Results

4.1. Study cohort

The study cohort included 9'956 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 3'068 patients received BPs, denosumab, or both sequentially. Seventeen cases of medication-related ONJ were diagnosed; 12 in patients receiving denosumab therapy and five in patients receiving BPs at the time of ONJ diagnosis. No cases of ONJ were diagnosed in patients being treated with SERMs (472 observed patient-years) or teriparatide (400 observed patient-years), or in subjects receiving no anti-osteoporotic drug **(Figure 1).**

The median age of all patients receiving denosumab and/or BP therapy (n=3'068; 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**. 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.

4.2. Description of ONJ cases

Of 22 patients identified as possibly having ONJ, six 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. 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 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**. More than half of the affected subjects had relevant risk factors, in particular smoking (n=6), glucocorticoid therapy and type II 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 nine 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 **Figure 2**. Clinical characteristics of patients with ONJ (n=17) versus patients without ONJ (n=3’051) are described in **Suppl. Table 1**, with little evidence for differences between the ONJ and non-ONJ groups aside from antiresorptive treatment.

4.3. Description of sequential therapies and drug holidays

A total of 3'068 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 4'236 for denosumab therapy. 844 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 (2'614 patient-years; 15%), and no cases of ONJ occurred during a drug holiday. In total, 1'048 (34%) patients had a drug holiday, and its median duration was 1.9 years [0.5 to 3.6].

4.4. Incidence rates and risk of ONJ depending on different therapies

Among 3'068 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% confidence interval (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 3a**). 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 3b**). The risk of ONJ was significantly higher under denosumab therapy compared to 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 3c**. 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**. The results were robust in this sensitivity analysis and not substantially different from those in the main analysis.

5. Discussion

In this cohort 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 et al. 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 et al.[12] Ulmner et al. 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 et al. 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]

Switching from BPs to denosumab has been hypothesised 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. Due to 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 following 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, nine of 17 patients with ONJ had a cumulative duration of antiresorptive treatment of 8 years or more, but five 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 hypothesised 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 may 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]

5.1. Limitations

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 II or III, although stages I and II 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 I 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 (e.g., 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.

5.2. Conclusion

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.

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Author contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Study conception and design: JE, SR, TL. Acquisition of data: TL, JE, US, HRZ, JPB, BS. Analysis and interpretation of data: JE, SR, DL, JPB, HJH and BS. BG and JE take responsibility for the integrity of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

6. References

1. 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 Oct;72(10):1938-56.

2. 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 Jan;30(1):3-23.

3. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg.* 2003 Sep;61(9):1115-7.

4. 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 Oct;22(10):1479-91.

5. Fassio A, Bertoldo F, Idolazzi L, Viapiana O, Rossini M, Gatti D. Drug-induced osteonecrosis of the jaw: the state of the art. *Reumatismo*. 2017 May 22;69(1):9-15.

6. Grbic JT, Black DM, Lyles KW, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: Data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. *J Am Dent Assoc*. 2010 Nov;141(11):1365-70.

7. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017 Jul;5(7):513-523.

8. Watts NB, Grbic JT, Binkley N, et al. Invasive oral procedures and events in postmenopausal women with osteoporosis treated with denosumab for up to 10 years. J *Clin Endocrinol Metab*. 2019 Jun 1;104(6):2443-2452.

9. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws-2009 Update. *Journal of Oral and Maxillofacial Surgery*. 2009 May;67(5 Suppl):2-12.

10. Hanley JA, Lippman Hand A. If Nothing Goes Wrong, Is Everything All Right?: Interpreting Zero Numerators. *JAMA*. 1983 Apr 1;249(13):1743-5.

11. Eiken PA, Prieto-Alhambra D, Eastell R, Abrahamsen B. Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users. *Osteoporosis International*. 2017 Oct;28(10):2921-2928.

12. Tennis P, Rothman KJ, Bohn RL, et al. Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. *Pharmacoepidemiology and Drug Safety*. 2012 Aug;21(8):810-7.

13. Ulmner M, Jarnbring F, Törring O. Osteonecrosis of the jaw in Sweden associated with the oral use of bisphosphonate. *Journal of Oral and Maxillofacial Surgery*. 2014 Jan;72(1): 76-82.

14. Khan AA, Rios LP, Sándor GKB, et al. Bisphosphonate-associated osteonecrosis of the jaw in Ontario: A survey of oral and maxillofacial surgeons. *Journal of Rheumatology*. 2011;38(7):1396-402.

15. Limones A, Sáez-Alcaide LM, Díaz-Parreño SA, Helm A, Bornstein MM, Molinero-Mourelle P. Medication-related osteonecrosis of the jaws (MRONJ) in cancer patients treated with denosumab VS. zoledronic acid: A systematic review and meta-analysis. *Med Oral Patol Oral Cir Bucal*. 2020 May 1;25(3):e326-e336.

16. Jakob T, Tesfamariam YM, Macherey S, et al. Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a network meta-analysis. *Cochrane Database Syst Rev*. 2020 Dec 3;12(12):CD013020.

17. Jiang L, Cui X, Ma H, Tang X. Comparison of denosumab and zoledronic acid for the treatment of solid tumors and multiple myeloma with bone metastasis: a systematic review and meta-analysis based on randomized controlled trials. *Journal of Orthopaedic Surgery and Research*. 2021 Jun 22;16(1):400.

18. Srivastava A, Nogueras Gonzalez GM, Geng Y, et al. Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. *Support Care Cancer*. 2021 May;29(5):2305-2317.

19. Voss PJ, Steybe D, Poxleitner P, et al. Osteonecrosis of the jaw in patients transitioning from bisphosphonates to denosumab treatment for osteoporosis. *Odontology*. 2018 Oct;106(4):469-480.

20. Yarom N, Lazarovici TS, Whitefield S, Weissman T, Wasserzug O, Yahalom R. Rapid onset of osteonecrosis of the jaw in patients switching from bisphosphonates to denosumab. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018 Jan;125(1):27-30.

21. Ikesue H, Doi K, Morimoto M, et al. Switching from zoledronic acid to denosumab increases the risk for developing medication-related osteonecrosis of the jaw in patients with bone metastases. *Cancer Chemother Pharmacol.* 2021 Jun;87(6):871-877.

22. Loyson T, Van Cann T, Schöffski P, et al. Incidence of osteonecrosis of the jaw in patients with bone metastases treated sequentially with bisphosphonates and denosumab. *Acta Clin Belgica Int J Clin Lab Med*. 2018 Apr;73(2):100-109.

23. Ehrenstein V, Heide-Jørgensen U, Schiødt M, et al. Osteonecrosis of the Jaw among patients with cancer treated with denosumab or zoledronic acid: Results of a regulator-mandated cohort postauthorization safety study in Denmark, Norway, and Sweden. *Cancer.* 2021 Jul 26. Online ahead of print.

24. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009 Aug 20;361(8):756-65.

25. Ottesen C, Schiodt M, Gotfredsen K. Efficacy of a high-dose antiresorptive drug holiday to reduce the risk of medication-related osteonecrosis of the jaw (MRONJ): A systematic review. *Heliyon*. 2020 Apr 27;6(4):e03795.

26. Hasegawa T, Hayashida S, Kondo E, et al. Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study. *Osteoporos Int*. 2019 Jan;30(1):231-239.

27. Jung SY, Suh HS, Park JW, Kwon JW. Drug holiday patterns and bisphosphonate-related osteonecrosis of the jaw. *Oral Dis*. 2019 Mar;25(2):471-480.

28. 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 Jan;31(1):16-35.

29. Chang J, Hakam AE, McCauley LK. Current Understanding of the Pathophysiology of Osteonecrosis of the Jaw. *Curr Osteoporos Rep*. 2018 Oct;16(5):584-595.

30. Kim SH, Lee YK, Kim TY, Ha YC, Jang S, Kim HY. Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: A nationwide cohort-study. *Bone*. 2021 Feb;143:115650.

31. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence — What Is It and What Can It Tell Us? *N Engl J Med*. 2016 Dec 8;375(23):2293-2297.

32. Teoh L, Moses G, Nguyen AP, McCullough MJ. Medication-related osteonecrosis of the jaw –analysing the range of implicated drugs from the Australian Database of Adverse Event Notifications. *Br J Clin Pharmacol*. 2021 Jul;87(7):2767-2776

33. Aljohani S, Fliefel R, Ihbe J, Kühnisch J, Ehrenfeld M, Otto S. What is the effect of anti-resorptive drugs (ARDs) on the development of medication-related osteonecrosis of the jaw (MRONJ) in osteoporosis patients: A systematic review. *J Cranio-Maxillofacial Surg*. 2017 Sep;45(9):1493-1502.

34. Neha R, Beulah E, Anusha B, Vasista S, Stephy C, Subeesh V. Aromatase inhibitors associated osteonecrosis of jaw: signal refining to identify pseudo safety signals. *Int J Clin Pharm*. 2020 Apr;42(2):721-727.

35. Yuan A, Munz A, Reinert S, Hoefert S. Histologic analysis of medication-related osteonecrosis of the jaw compared with antiresorptive-exposed bone and other infectious, inflammatory, and necrotic jaw diseases. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020 Feb;129(2):133-14040.

36. Aoki K, Matsunaga S, Ito S, et al. Persistent bone resorption lacunae on necrotic bone distinguish bisphosphonate-related osteonecrosis of jaw from denosumab-related osteonecrosis. *J Bone Miner Metab*. 2021 Apr 8. Online ahead of print.

37. Pichardo SEC, Broek FWT, Fiocco M, Appelman-Dijkstra NM, van Merkesteyn JPR. A comparison of the cone beam computed tomography findings in medication-related osteonecrosis of the jaws related to denosumab versus bisphosphonates: an observational pilot study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020 Apr;129(4):411-417.

38. Ikesue H, Mouri M, Tomita H, et al. Associated characteristics and treatment outcomes of medication-related osteonecrosis of the jaw in patients receiving denosumab or zoledronic acid for bone metastases. *Support Care Cancer.* 2021 Aug;29(8):4763-4772.

39. Tsourdi E, Zillikens MC, Meier C, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. *J Clin Endocrinol Metab*. 2020 Oct 26;dgaa756.

40. Everts-Graber J, Reichenbach S, Gahl B, Ziswiler HR, Studer U, Lehmann T. Risk factors for vertebral fractures and bone loss after denosumab discontinuation: A real-world observational study. *Bone*. 2021 Mar;144:115830.

41. Burckhardt P, Faouzi M, Buclin T, Lamy O. Fractures After Denosumab Discontinuation: A Retrospective Study of 797 Cases. *J Bone Miner Res*. 2021 May 19. Online ahead of print.

42. Ferrari S, Lewiecki EM, Butler PW, et al. Favorable skeletal benefit/risk of long-term denosumab therapy: A virtual-twin analysis of fractures prevented relative to skeletal safety events observed. *Bone*. 2020 May;134:115287.

43. Lerman MA, Xie W, Treister NS, Richardson PG, Weller EA, Woo S Bin. Conservative management of bisphosphonate-related osteonecrosis of the jaws: Staging and treatment outcomes. *Oral Oncol*. 2013 Sep;49(9):977-983

44. Lin TC, Yang CY, Kao Yang YH, Lin SJ. Incidence and risk of osteonecrosis of the jaw among the Taiwan osteoporosis population. *Osteoporosis International*. 2014;25(5) 1503-11.

7. Legends

Figure 1: Flow chart with outcome

Flow chart of the study cohort, including outcome.

* One patient can receive more than one therapy

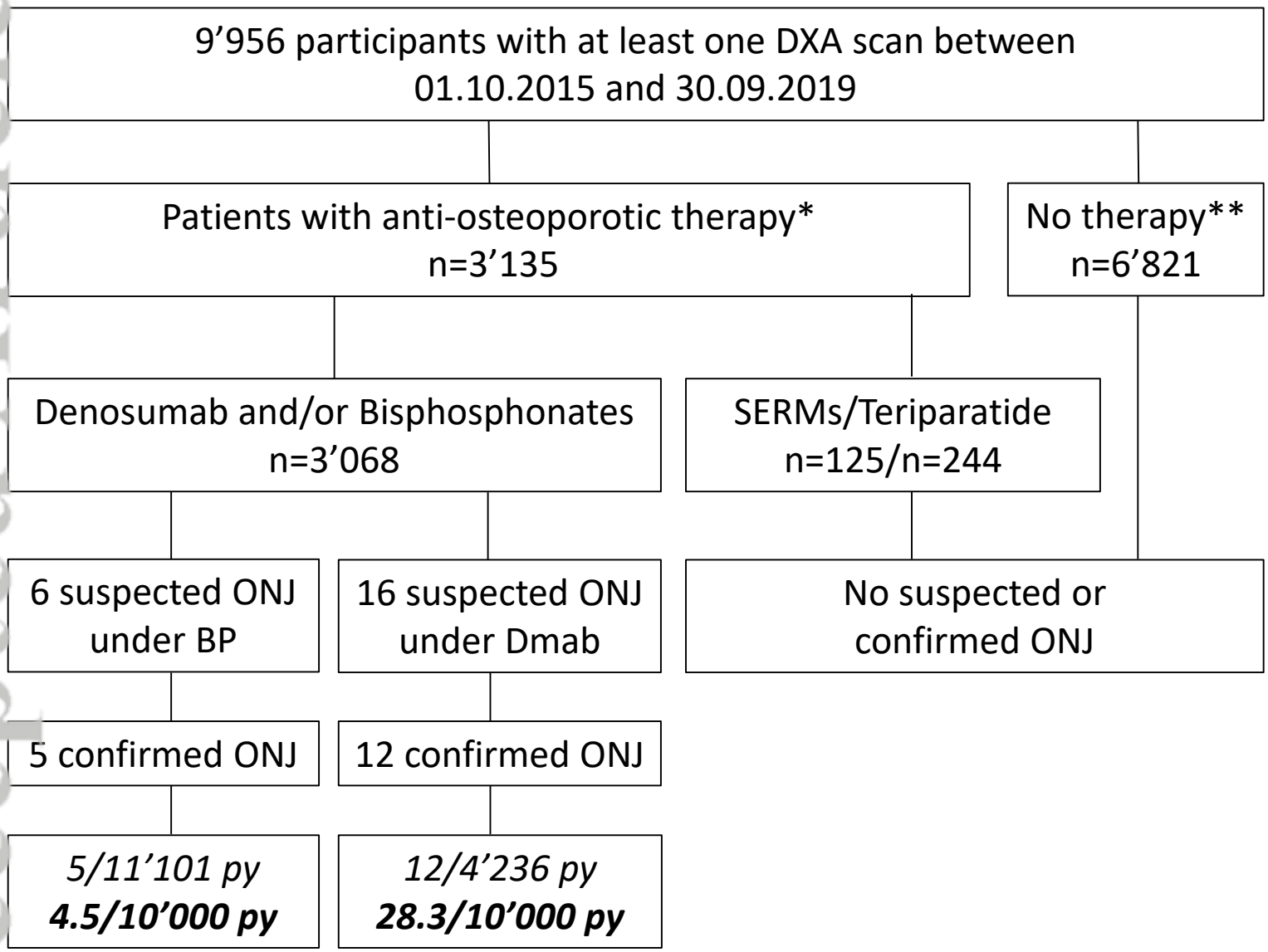
** except calcium, vitamin D, or hormone replacement therapy

Abbreviations: BPs: bisphosphonates; Dmab: denosumab; ONJ: osteonecrosis of the jaw; py: patient-years; SERM: selective estrogen receptor modulator

Figure 2: Overview of cumulative treatment duration and treatment sequences of patients with ONJ

Abbreviations: 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 five 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.



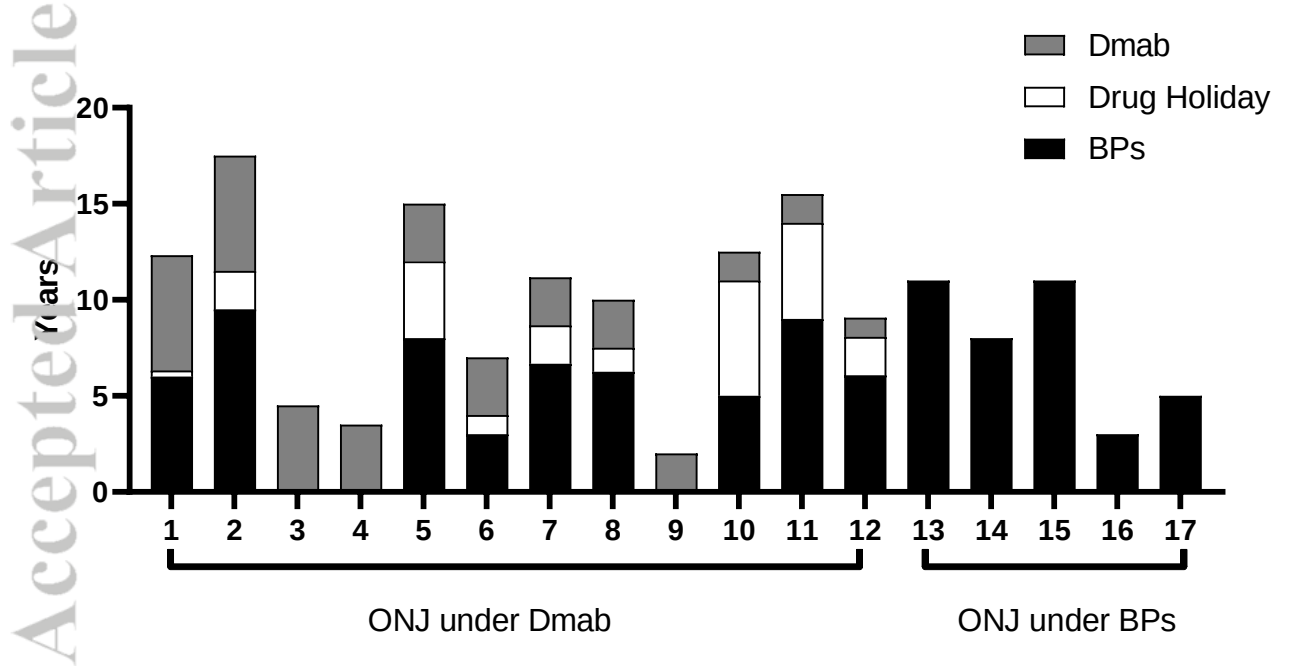


Table 1: Patient characteristics by treatment

	BP only (n=1'802)	Dmab only (n=422)	Both (n=844)	*p*-value
Male	271 (15%)	24 (5.7%)	34 (4.0%)	**<0.001**
Age	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

Abbreviations: BMI: body mass index; BP: bisphosphonate; Dmab: denosumab

Continuous variables: Median with interquartile range [IQR], categorical variables: Percentages of total of each subgroup.

Table 2: Clinical details of patients with ONJ

#	Age[1]	Causative event	BP therapy[2]	Drug holiday	Dmab[2]	Time to healing	Therapy	Risk factors	Location	Stage AAOMS[3]
12 ONJ under Dmab therapy										
1	76	Peri-implantitis	4y ALN, 2y ZOL	4 months	6 years	1 year	Surgical (>1 OP)	Smoking	Maxilla	II
2	59	Dental extraction	9y ALN	2 years	6 years	1 year	Surgical	None	Mandible	II
3	74	Periodontitis			4.5 years	4 months	Surgical	Smoking	Mandible	I
4	74	Periodontitis			3.5 years	5 months	Surgical	None	Maxilla	II
5	79	Denture pressure points	8y ALN	4 years	3 years	2 months	Surgical	None	Mandible	I
6	84	Periodontitis	3y IBN iv	1 year	3 years	3 years	Surgical (>1 OP)	None	Mandible	II
7	63	Denture pressure points	7y ALN/IBN iv	2 years	2.5 years	1 month	Conservative	None	Mandible	I
8	84	Dental extraction	6y ALN/IBN iv	15 months	2.5 years	4 months	Surgical	Breast cancer, AI	Mandible	II
9	77	Dental extraction			2 years	2 months	Surgical	Smoking, RA	Mandible	II
10	71	Dental extraction	5y ALN	6 years	1.5 years	14 months	Surgical	Smoking	Mandible	III
11	66	Dental extraction	9y ALN	5 years	1.5 years	3 months	Surgical	Breast cancer, AI	Mandible	I
12	67	Periodontitis	6y ALN	2 years	1 year	14 months	Surgical	None	Mandible	II
5 ONJ under BP therapy										
1	82	Denture pressure points	11y ALN			2 years	Surgical (>1 OP)	None	Mandible	I
2	60	Peri-implantitis	8y ALN/IBN iv			6 months	Surgical (>1 OP)	Smoking	Maxilla	I
3	62	Dental extraction	11y ALN/IBN iv			6 months	Surgical	Smoking	Maxilla	II
4	54	Dental extraction	3y ZOL			3.5 years	Surgical	RA, diabetes, glucocorticoids	Mandible	II
5	71	Peri-implantitis	5y ZOL			4 months	Conservative	None	Mandible	I

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

[1] Age at onset

[2] Therapy before ONJ was diagnosed

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

Table 3: Rates and ratios of osteonecrosis of the jaw (ONJ)

A. ONJ event rates

	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	2'614	0	0.00 (0.00 to 0.001)
BPs	11'101	5	4.50 (1.87 to 10.82)
Denosumab	4'236	12	28.3 (16.09 to 49.9)

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

B. Risk of ONJ by treatment

		HR (95% CI)	*p*-value
Crude analysis	Drug holidays	0*	
	BPs	Reference	
	Denosumab	3.49 (1.16 to 10.5)	0.026

*CI not estimable due to zero events. HR: hazard ratio

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	3'068	0.99 (0.94 to 1.04)	0.656	3.47 (1.16 to 10.41)	0.027
Male	3'068	0.83 (0.11 to 6.31)	0.860	3.49 (1.16 to 10.48)	0.026
BMI (kg/m^2)	2'858	0.93 (0.82 to 1.05)	0.219	3.34 (1.10 to 10.09)	0.033
Use of glucocorticoids	3'068	0.69 (0.09 to 5.24)	0.723	3.47 (1.15 to 10.46)	0.027
Aromatase Inhibitors	3'068	0.69 (0.00 to 4.22)	1.000	4.38 (1.38 to 16.28)	0.009
Rheumatoid arthritis	3'068	3.68 (0.84 to 16.1)	0.084	3.56 (1.18 to 10.70)	0.024
Chronic obstructive pulmonary disease	3'068	1.98 (0.26 to 15.2)	0.511	3.50 (1.17 to 10.50)	0.025
Alcohol intake >30 g/d*	3'068	6.12 (0.00 to 40.0)	1.000	4.14 (1.30 to 15.41)	0.013
Smoking	3'068	4.42 (1.43 to 13.6)	0.010	3.58 (1.20 to 10.70)	0.022
T-score Lumbar spine	2'884	1.01 (0.67 to 1.52)	0.954	3.88 (1.16 to 13.00)	0.028
T-score Femoral neck	2'767	0.65 (0.32 to 1.34)	0.246	2.85 (0.93 to 8.73)	0.066
T-score Total hip	2'678	0.90 (0.69 to 1.18)	0.445	2.92 (0.96 to 8.91)	0.059
Trabecular bone Score	1'948	0.15 (0.02 to 1.09)	0.061	1.30 (0.27 to 6.33)	0.748

*calculated using exact logistic regression due to zero events in one category; the estimates hence represent odds ratios with 95% CI.

Incidence rates (A) and hazard ratios (B) of ONJ. With bisphosphonates (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 Table C might be biased due to missing values: T-scores of lumbar spine or femoral neck and trabecular bone scores are missing in two and 10 patients with ONJ, respectively.

Table 4: Rates and risk of osteonecrosis of the jaw (ONJ), ignoring treatments before 1.8.2020

A. ONJ events rates, *ignoring treatments before 1.8.2010*

	Patient-years	# events	Rate per 10'000 patient-years (95% CI)
Drug holidays	1'571	0	0.00 (0.00 to 0.002)
BPs	7'673	5	6.52 (2.71 to 15.66)
Denosumab	4'239	12	28.3 (16.08 to 49.8)

Rate ratio denosumab vs BPs: 4.34 (95% CI 1.42 to 15.74), p=0.002.

B.* Risk of ONJ by treatment, *ignoring treatments before 1.8.2010

	HR (95% CI)	*p*-value
Drug holidays	0.00*	
BPs	Reference	
Denosumab	3.14 (1.08 to 9.17)	0.036

*not estimable due to zero events.

Incidence rates (A) and hazard ratios (B) of ONJ. With bisphosphonates (BPs) as the reference, denosumab is associated with a higher risk of ONJ. In these sensitivity analyses, treatments before 01.08.2010 were ignored. Thus, equivalent observational periods for both denosumab and BPs were warranted.