different anti-osteoporotic drugs on fracture. In sensitivity analyses we generated 1:1 matched cohorts of patients with prescription of bisphosphonates, denosumab, teriparatide or without any pharmacological prescription at baseline and 1:1 matched cohort based on the T-score variation over the time (increase in T-score vs decrease or stability in T-score values).

**Results:** Data from 50,862 women were available. Among these, 3,574 individuals had at least 2 consecutive visits. The crude fracture rate was 91.9/1,000 person-year for non-treated patients. The crude fracture rate in bisphosphonate users was 72.1/1,000 person-year, in denosumab users was 58.2/1,000 person-year and in teriparatide users was 19.3/1000 person-year. Overall, we found that bisphosphonates were associated with a 30% lower risk of fracture compared to no treatment (aHR 0.70, 95% CI 0.50-0.98), denosumab and teriparatide were associated with 60% and 90% lower risk of fracture, respectively (aHR 0.43, 95% CI 0.24-0.75 and aHR 0.09, 95% CI 0.01-0.70). Bisphosphonate use was associated with a lower risk of fracture only after one year of treatment. In Figure 1 are presented the Kaplan Meier curves free from fragility fracture after propensity score matching.

**Conclusion:** In conclusion, we found that all anti-osteoporotic medications effectively reduced the risk of fracture in the real-life. Bisphosphonate’s effect on fracture risk was apparent only after the first year of treatment. Our findings do not support the use of bisphosphonates in patients at imminent risk of fracture.

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**Background:** Mediation of bisphosphonate(BP)-related osteonecrosis of the jaw (ONJ) has hampered the treatment of osteoporosis (OP). The risk of ONJ associated with oral BP in OP and zoledronate (ZOL) in oncology has previously been reported. However, the risk of ZOL-related ONJ in OP has only been reported in Randomized clinical trials.

**Objectives:** Therefore, we aimed to characterize ZOL-related ONJ in OP and compare it’s incidence with oral BP in real life setting.

**Methods:** All reports of adverse events (AEs) of BP (ZOL, alendronate (ALN), risedronate (RIS)) were extracted from the French pharmacovigilance database (FPD) since its origin till 2020. For ZOL, cases were separated by indication, rheumatological (ZOL-R) or oncological (ZOL-K). The risk factors analyzed for ONJ were age, sex, active smoking, alcoholism, diabetes, corticotherapy, neoplasia, previous treatment by chemo or immunotherapy, recent dental care and time of exposure to BP. The association between the occurrence of ONJ and the associated BP was assessed by calculating the reporting odds ratio (ROR) in a case/non-case study. Stratification on assumed risk factors was performed to assess their impact on the risk of ONJ.

The incidence of ONJ under BP between 2011 and 2020 was estimated by relating the number of ONJ cases under BP reported to the FPD to the estimated number of patients treated with ZOL, ALN and RIS over the same period according to health insurance reimbursement data of Medic AM database. Incidence rate calculation, confidence interval calculation, and comparison of incidence rates (Fischer exact test) were performed.

**Results:** For ZOL 2254 AEs were reported: 568 ONJ/1103 AEs with ZOL-K and 70 ONJ/1151 AEs with ZOL-R. For ZOL-R-related ONJ, 3070 cases had recent dental care and 48.7 months of mean time of exposure to BP. Risk factors for ONJ were smoking, history of neoplasia and chemotherapy. For ALN, 1,010 AEs were reported, including 188 ONJ. 91/188 ONJ had recent dental care and 70.9 months of mean time of exposure to BP. Risk factors for ONJ were age ≥65 years, diabetes, corticotherapy, and history of neoplasia. For RIS, 771 AEs were reported including 68 cases of ONJ. 28/68 ONJ had recent dental care and 53.6 months the average time of exposure to BP. The risk factors were age ≥65 years, smoking, corticotherapy, history of neoplasia and chemotherapy. ROR calculation shows that corticotherapy was associated more frequently with RIS (2.10 [1.64-2.69]) and ALN (1.33 [1.04-1.70]) as compared with ZOL-R, with no other significant difference.

The incidence of ONJ was significantly higher with ZOL-R than with RIS (p<0.001) and ALN (p<0.001). Indeed, between 2011 and 2020, 614 832 patients were treated with ZOL-R and 59 cases of ONJ reported yielding an incidence of 9.6/100,000 person-years; 2 233 536 patients were treated with RIS and 44 cases of ONJ reported yielding an incidence of 2.0/100 000 person-years; 2 432 373 patients were treated with ALN and 125 cases of ONJ reported yielding an incidence of 5.1/100 000 person-years.

**Conclusion:** Our data confirm in real-life settings and a large population, that BP-related ONJ is a rare event associated with OP. The risk of BP-related ONJ appears related to the potency of bone resorption inhibition, as RIS has the lowest and ZOL-R the highest risk. Smoking appears a consistent risk factor of ONJ, as is recent dental care. However, we must stress out the usual limitations of pharmacovigilance studies, their retrospective nature, common under-reporting of adverse-events, and the fact that the Medic AM database only refers to city reimburments.

To our knowledge, this is the first study reporting the risk of ONJ under ZOL from the national pharmacovigilance database. Our study confirms the rarity, in OP, of BP-related ONJ. The risk of incidence of ONJ on ZOL-R is higher than on RIS and ALN, suggesting a risk associated with the inhibitory power of bone resorption.

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