Anti-Osteoporotic Medication-Related Jaw Osteonecrosis: A Descriptive Analysis of the European EudraVigilance Database

Osteonecrose da Mandíbula Associada a Terapêuticas Anti-Osteoporóticas: Análise Descritiva da Base de Dados Europeia EudraVigilance

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Dear Editor,

Osteoporosis is a chronic disease affecting bone microstructure and facilitating fractures following low-impact trauma. It represents a growing public health concern, impacting patients' quality of life and functionality, and posing an economic burden to healthcare systems.[1,2] Pharmacological therapies for osteoporosis include antiresorptive therapies, such as bisphosphonates and denosumab (DNS), and osteoanabolic agents, such as teriparatide (TP), abaloparatide (AP), and romosozumab (RMZ), which has a dual-action effect that additionally includes antiresorptive properties. While antiresorptives remain more commonly used, osteoanabolics are gaining relevance and may be considered as part of the initial treatment strategy, as acknowledged in recent guidelines.[3] Antiresorptives are also used in other clinical contexts, including metastatic bone cancer and prevention of treatment-induced bone loss.[4,5]

Jaw osteonecrosis (ONJ) is a rare, yet potentially serious adverse event associated with antiresorptive treatments. Its incidence is difficult to determine due to inconsistent definitions across studies.[5] This and other potential adverse events have been reported in global pharmacovigilance databases like EudraVigilance,[6] compiling suspected adverse reaction (SAR) reports for drugs approved in the European Union. The individual case safety reports (ICSRs) can be submitted by both healthcare and non-healthcare professionals directly through the EudraVigilance web portal, managed by the European Medicines Agency (EMA). While these reports cannot establish causality, they help to detect safety signals that warrant further investigation.

We aimed to compare the occurrence of ONJ in patients treated with DNS, alendronate (ALN), zoledronate (ZOL), TP, AP, and RMZ using real-world data from the EudraVigilance database.[6] We extracted all ICSRs reporting cases of ONJ submitted by healthcare professionals within the European Economic Area, between January 2021 and December 2023. Duplicates and cases potentially related to other drugs were excluded. Collected data included patient demographics, seriousness criteria, outcome, and treatment indication, route, dose, and duration. We compared different variables and the SARs outcome, followed by the Reporting Odds Ratio (ROR) for each drug.[7]

Between 2021 and 2023, 24 755 reports of SARs related to these treatments were recorded in EudraVigilance.[6] Of these, 676 (2.8%) involved ONJ and met our inclusion criteria. No ONJ reports pertained to TP, and no SARs related to AP were reported by healthcare professionals in the European Economic Area in this period. Most cases occurred in women aged 65 - 85 years (Table 1). Romosozumab, DNS, and ALN were mainly prescribed for osteoporosis (100%, 58.5% and 86.4%, respectively), while ZOL was mostly used in oncologic settings (69.2%). In all cases with available data, ALN was administered *per os*, DNS and RMZ subcutaneously, and ZOL intravenously. The most frequent doses were ALN 70 mg (100%), ZOL 4 mg (74.4%), DNS 60 mg (100%), and RMZ 210 mg (100%). Mean treatment duration was 69.3 ± 74.2 months for ALN, 32.7 ± 25.3 months for ZOL, and 58.8 ± 32.6 months for DNS; duration data for RMZ was unavailable. Among DNS reports, most patients had recovered or were recovering at the time of the report (56.9%), with older patients being less likely to recover ($p < 0.05$). In contrast, most patients on ALN or ZOL had not recovered (66.7%). No associations were found between the outcome and treatment duration or dose.

When comparing different treatments, ONJ was more frequently reported for ZOL [ROR 2.03, CI (1.72 - 2.39)], followed by ALN [ROR 1.40, CI (1.13 - 1.73)]. Romosozumab and TP had the lowest reporting rates [ROR 0.02, CI (0.00 - 0.11) and ROR 0.01, CI (0.00 - 0.07), respectively]. No statistically significant association was observed for DNS [ROR 1.07, CI (0.90 - 1.26)]. The calculation of ROR was not possible to perform for AP due to the absence of any SARs during this period.

Our findings align with existing evidence on the rarity of ONJ.[5,8] Nevertheless, this study stands out, to our knowledge, as the first to compare these treatments using the EudraVigilance database and the ROR, providing unique insights from a globally representative dataset. Among antiresorptives, ZOL showed a higher reporting frequency of ONJ, which may be influenced by its more intensive use in oncologic settings, as suggested by other authors.[5] In contrast, DNS did not associate with an increased probability of reporting. These findings are based on spontaneous reporting data and cannot infer definitive causality. Nonetheless, they provide relevant insights into clinical decision-making and may offer some reassurance regarding the safety profile of these treatments for this specific adverse event.

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AUTHOR CONTRIBUTIONS

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Table 1 – Characteristics of Individual Case Safety Reports in the EudraVigilance database, containing a suspected adverse reaction of osteonecrosis of jaw from January 1st, 2021, to December 31st, 2023, attributed to alendronate, zoledronate, and denosumab.

Characteristic	Alendronate (n, %)	Zoledronate (n, %)	Denosumab (n, %)	Teriparatide (n, %)	Abaloparatide (n, %)	Romosozumab (n, %)
Year of Reporting						
2021	39 (31.2)	116 (39.7)	78 (30.2)	0 (0.0)	0 (0.0)	0 (0.0)
2022	51 (40.8)	105 (36.0)	76 (29.5)	0 (0.0)	0 (0.0)	0 (0.0)
2023	35 (28.0)	71 (24.3)	104 (40.3)	0 (0.0)	0 (0.0)	1 (100.0)
Sex						
Female	107 (85.6)	176 (60.3)	224 (86.8)	-		1 (100.0)
Male	17 (13.6)	112 (38.4)	31 (12.0)		-	0 (0.0)
Not specified	1 (0.8)	4 (1.4)	3 (1.2)			0 (0.0)
Age range						
Younger than 18 years	0 (0.0)	1 (0.3)	0 (0.0)			0 (0.0)
18 to 64 years	21 (16.8)	86 (29.5)	42 (16.3)			0 (0.0)
65 to 85 years	83 (66.4)	174 (59.6)	126 (48.8)			0 (0.0)
Older than 85 years	13 (10.4)	11 (3.8)	32 (12.4)	-	-	0 (0.0)
Not specified	8 (6.4)	20 (6.8)	58 (22.5)			1 (100.0)
Suspected adverse reaction considered serious	125 (100.0)	288 (98.6)	251 (97.3)	-	-	1 (100.0)
Seriousness criteria[a]						1 (100.0)
Resulting in medically important conditions	100 (80.0)	234 (80.1)	221 (85.7)			0 (0.0)
Requiring or prolonging hospitalization	23 (18.4)	44 (15.1)	33 (12.8)			0 (0.0)
Resulting in disability/incapacity	9 (7.2)	12 (4.1)	4 (1.6)			0 (0.0)
Resulting in death	0 (0.0)	1 (0.3)	3 (1.2)			0 (0.0)
Life threatening	0 (0.0)	1 (0.3)	1 (0.4)	-	-	0 (0.0)
						0 (0.0)
Reaction outcome at the time of the report						0 (0.0)
Not recovered	54 (43.2)	86 (29.5)	47 (18.2)			0 (0.0)
Recovering	7 (5.6)	29 (9.9)	19 (7.4)			0 (0.0)
Recovered	18 (14.4)	36 (12.3)	43 (16.7)			0 (0.0)
Recovered with sequelae	2 (1.6)	4 (1.4)	4 (1.6)			0 (0.0)
Fatal	0 (0.0)	1 (0.3)	3 (1.2)	-	-	0 (0.0)
Unknown	44 (35.2)	136 (46.6)	142 (55.0)			1 (100.0)
Indication for drug use						
Osteoporosis	108 (86.4)	47 (16.1)	151 (58.5)			1 (100.0)
Osteoporosis prophylaxis	4 (3.2)	11 (3.8)	8 (3.1)			0 (0.0)
Oncologic context	1 (0.8)	202 (69.2)	12 (4.7)			0 (0.0)
Other indications	2 (1.6)	4 (1.4)	0 (0.0)	-	-	0 (0.0)
Unknown	10 (8.0)	28 (9.6)	87 (33.7)			0 (0.0)

a: Each case might meet more than one criterion.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. Singer A, McClung MR, Tran O, Morrow CD, Goldstein S, Kagan R, et al. Treatment rates and healthcare costs of patients with fragility fracture by site of care: a real-world data analysis. Arch Osteoporos. 2023;18:42.
2. Barcelos A, Gonçalves J, Mateus C, Canhão H, Rodrigues AM. Costs of incident non-hip osteoporosis-related fractures in postmenopausal women from a payer perspective. Osteoporos Int. 2023;34:2111-9.
3. National Osteoporosis Guideline Group. Clinical guideline for the prevention and treatment of osteoporosis. 2024. [cited 2025 Oct 04]. Available from: https://www.nogg.org.uk/sites/nogg/download/NOGG-Guideline-2024.pdf?v4.
4. Mbese Z, Aderibigbe BA. Bisphosphonate-based conjugates and derivatives as potential therapeutic agents in osteoporosis, bone cancer and metastatic bone cancer. Int J Mol Sci. 2021;22:6869.
5. Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, et al. Osteonecrosis of the jaw and antiresorptive agents in benign and malignant diseases: a critical review organized by the ECTS. J Clin Endocrinol Metab. 2022;107:1441-60.
6. European Medicines Agency. EudraVigilance – European database of suspected adverse drug reaction reports. 2024. [cited 2025 Oct 04]. Available from: https://www.adrreports.eu.
7. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. 2011;72:905-8.
8. Kawahara M, Kuroshima S, Sawase T. Clinical considerations for medication-related osteonecrosis of the jaw: a comprehensive literature review. Int J Implant Dent. 2021;7:47.

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