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Adverse drug events of denosumab: Data-mining based on the United States Food and Drug Administration Adverse Event Reporting System database

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ABSTRACT: Objective: This study seeks to analyze data from the United States (U.S.) Food and Drug Administration Adverse Event Reporting System (FAERS) to identify potential adverse drug event (ADE) signals associated with denosumab and provide valuable insights into the clinical safety of denosumab usage. Methods: Data on denosumab-related ADEs reported from the FAERS between the second quarter of 2010 to the first quarter of 2022 were extracted using OpenVigil 2.1. The Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) were calculated as measures to detect potential ADE signals. Results: The analysis of FAERS data uncovers potential ADE signals associated with the use of denosumab. These signals encompass a spectrum of adverse effects, including well-established risks such as musculoskeletal pain, hypocalcemia, and osteonecrosis of the jaw. Moreover, novel potential adverse events emerge, including oral diseases, fractures occurring in various locations, and signals indicating tumors beyond the drug's approved indications. Conclusions: This study highlights the significance of closely monitoring patients for potential adverse events during denosumab treatment. Healthcare professionals should exercise heightened vigilance for the development of oral diseases, fractures, and tumors in individuals receiving denosumab therapy. The identification of these additional ADE signals should inform clinical decision-making, patient risk assessments, and ongoing efforts in pharmacovigilance, thereby ensuring the safe and effective utilization of denosumab.

KEYWORDS: Denosumab; adverse drug events; FAERS; drug safety; signal detection.

1. INTRODUCTION

Denosumab is a humanized IgG2 monoclonal antibody and an inhibitor of the RANK ligand that acts by binding specifically and with high affinity to the receptor activator of nuclear factor-κB ligand (RANKL). By inhibiting RANKL, denosumab reduces bone resorption, increases bone mass, and improves bone strength by preventing the formation and activity of osteoclasts [1]. It is currently the only available RANKL inhibitor for human therapy. Denosumab differs from traditional bisphosphonates in several ways. It provides benefits such as extended dosing intervals, ease of administration, and, notably, its use is not restricted by impaired renal function [2]. Denosumab received its initial approval from the U.S. FDA in June 2010 for the treatment of osteoporosis in postmenopausal women at high risk of fracture [3]. In June 2020, it was approved in China for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Denosumab is currently recommended for the treatment of osteoporosis, bone metastasis, and giant cell tumors in mature bone patients [4-6].

Denosumab has been in clinical practice for over a decade, with more than 10 clinical studies having accumulated a wealth of clinical data on the drug's safety and efficacy. Among these studies, the largest is the phase 3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study and its ten-year extension study [7, 8]. The FREEDOM study, spanning three years, found taht

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denosumab significantly reduces the risk of various fractures but does not increase the risk of cancer, infections, cardiovascular diseases, delayed fracture healing, or hypocalcemia. Cases of jaw osteonecrosis were not observed. However, in the 10-year extension study, cases of femoral fractures and jaw osteonecrosis were identified. While the incidence of adverse events remains low, there is a trend of increasing risk with prolonged exposure over time. Although the efficacy and safety of denosumab have been established, rare and severe adverse reactions such as jaw necrosis and atypical femoral fracture [9, 10], have also been reported in other studies. Due to the limited sample size and observation time in clinical trials, potential safety issues have not been fully clarified. The potential adverse reactions of denosumab, such as fractures and osteonecrosis of the jaw, which are currently reported, may lead to severe adverse consequences if not effectively monitored and promptly treated, significantly affecting patients'quality of life. Therefore, monitoring the adverse reactions of denosumab is of paramount significance for its rational and safe clinical use. The United States (U.S.) Food and Drug Administration Adverse Event Reporting System (FAERS) [11] is responsible for gathering adverse event and medication error reports submitted to the U.S. Food and Drug Administration. Because of its expansive dataset and free accessibility to the public, FAERS is frequently employed in pharmacovigilance research to detect signals related to drug adverse events [12]. Therefore, in this study, we conducted data mining and analysis on the adverse events of denosumab in the FAERS database. By analyzing large sample data after marketing, our aim is to explore the safety profile of denosumab in the real world, perform pharmacovigilance safety monitoring, and provide references for safe and rational drug use.

2. RESULTS

A total of 119,125 reports of ADEs associated with denosumab were analyzed in this study. The top 40 ADEs with the highest reporting frequency at the preferred term (PT) level were used for signal mining. ADEs reported with frequencies exceeding 1000 cases and simultaneously identified as signals include: back pain, bone pain, jaw pain, osteonecrosis of the jaw, tooth disorder, myalgia, hypocalcemia, spinal fracture, and death. The results were sorted by reporting frequency and presented in Table 1.

Table 1 contains four ADEs related to fractures, all of which have been identified as signals. The frequency distribution of these four ADE signals in female patients, as well as a comparison between the≤50 years and>50 years age groups, is presented in Figure 1. Based on Figure 1, it can be observed that spinal fractures are the most common fracture-related PT in female patients, and the ≤50 years age group has significantly fewer occurrences of any fracture-related PT compared to the >50 years age group.

Using the proportional reporting ratio (PRR) and reporting odds ratio (ROR) methods, 84 high-level term (HLT) signals were obtained, including biochemical markers of bone metabolism, bone neoplasms unspecified malignancy, dental and gingival therapeutic procedures, musculoskeletal necrosis and vascular insufficiency, and parathyroid analysis. After removing non-informative ADEs, we sorted the remaining ADEs in descending order of PRR signal strength and retained the top 60 ADEs at the HLT level, which are presented in Table 2.

Based on our analysis at the standardized MedDRA query (SMQ) level, we have identified five signal terms. These include osteonecrosis, gingival disorders, prostate tumors of unspecified malignancy, and other signals. These signals are presented in descending order of PRR signal intensity in Table 3**.** Furthermore, the proportion of several detected SMQ signals in the overall population and specific gender subgroups is displayed in Figure 2. It can be observed that Osteonecrosis is the most frequently reported SMQ signal, both in the overall population and in male and female subgroups. Among all the subpopulations analyzed, excluding cases with missing gender information, females significantly outnumber males (62.06% vs. 26.50%).

Table 1. PT sequence of top 40 in the list of the ADE report number for denosumab

PTs	n	Proportion (%)	Signal
Death*	15301	12.84	Y
Osteonecrosis of jaw	5223	4.38	Y
Arthralgia	3480	2.92	N
Back pain	2899	2.43	Y
Pain	2834	2.38	N
Pain in extremity	2775	2.33	N
Fatigue	2144	1.80	N
Rash	2039	1.71	N
Bone pain	1927	1.62	Y
Tooth disorder*	1871	1.57	Y
Myalgia	1867	1.57	Y
Hypocalcaemia	1772	1.49	Y
Malaise	1729	1.45	N
Fall	1693	1.42	N
Nausea	1550	1.30	N
Diarrhoea	1332	1.12	N
Asthenia	1321	1.11	N
Pain in jaw	1275	1.07	Y
Spinal fracture	1273	1.07	Y
Pruritus	1182	0.99	N
Dyspnoea	1099	0.92	N
Headache	1099	0.92	N
Pneumonia	1026	0.86	N
Muscle spasms	989	0.83	N
Dizziness	925	0.78	N
Urinary tract infection	921	0.77	N
Fracture	904	0.76	Y
Alopecia	900	0.76	N
Gait disturbance	822	0.69	N
Musculoskeletal pain	789	0.66	Y
Tooth extraction*	746	0.63	Y
Pyrexia	737	0.62	N
Vomiting	728	0.61	N
Feeling abnormal	727	0.61	N
Femur fracture	717	0.60	Y
Mobility decreased	715	0.60	Y
Hypertension*	686	0.58	N
Weight decreased	679	0.57	N
Hip fracture*	637	0.53	Y
Constipation	628	0.53	N

Note：* the corresponding ADE is not included in the drug instruction of denosumab."Y" means "Yes", and "N" means "No".
Abbreviation：PT, preferred term; ADE, adverse drug event.

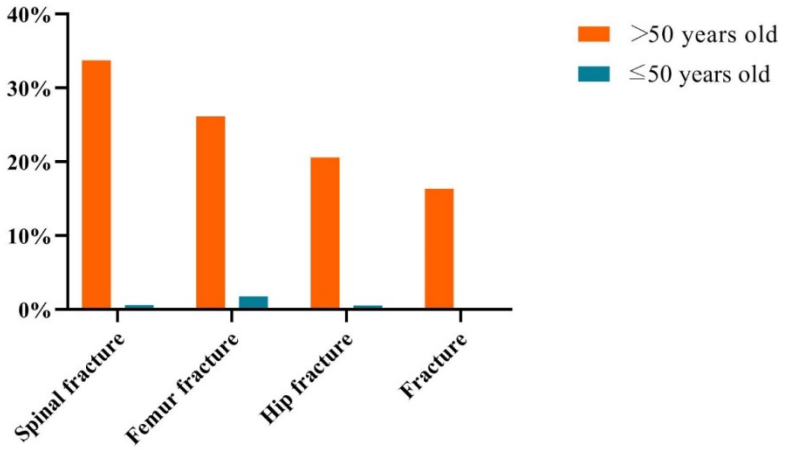

Figure 1. The distribution of ADE signals related to fractures in females aged ≤50 years and >50 years. The fracture-related ADEs mentioned here are selected from Table 1 (the top 40 in terms of the number of reports) and have been identified as signals.

Table 2. Results of signal detection of HLT sequence

HLT	n	PRR	χ^2_{Yates}	ROR $_{205}$
Biochemical markers of bone metabolism	52	39.70	1293.85	28.51
Bone neoplasms unspecified malignancy *	116	18.47	1549.09	15.11
Dental and gingival therapeutic procedures *	1674	17.55	21516.48	16.87
Musculoskeletal necrosis and vascular insufficiency	5575	14.24	58664.81	14.47
Parathyroid analyses *	344	14.24	3596.06	12.73
Facial therapeutic procedures	96	14.18	990.86	11.43
Dental disorders NEC *	2631	13.04	25249.40	12.77
Calcium metabolism disorders	2214	12.72	20715.41	12.37
Spinal column fracture	1962	12.48	17988.34	12.08
Spinal fractures and dislocations	1967	12.13	17505.15	11.74
Bone disorders NEC	7422	11.11	60479.64	11.49
Parathyroid gland therapeutic procedures *	28	10.49	204.65	7.08
Musculoskeletal and connective tissue neoplasms NEC*	118	9.00	748.64	7.45
Dental pulp disorders*	30	8.31	168.38	5.71
Parathyroid disorders NEC *	80	8.00	439.81	6.36
Endocrine abnormalities of gonadal function NEC*	85	7.34	421.25	5.88
Bone related signs and symptoms	3266	7.26	16259.09	7.18
Aural neoplasms benign*	10	6.48	37.98	3.41
Dental pain and sensation disorders *	572	6.20	2316.55	5.72
Hyperparathyroid disorders	436	5.98	1680.74	5.44
Fractures NEC	1957	5.96	7540.44	5.77
Hypoparathyroid disorders *	111	5.83	409.83	4.81
Ovarian therapeutic procedures	37	5.82	133.47	4.17
Leukemia chronic NEC *	6	5.77	17.80	2.52
Malignant musculoskeletal and connective tissue neoplasms *	753	5.33	2483.45	4.97
Dental and periodontal infections and inflammations *	837	5.31	2748.75	4.98
Fractures and dislocations NEC	1958	5.31	6442.69	5.14
Pleural therapeutic procedures	4	5.27	9.26	1.92
Skeletal cysts benign	23	5.22	69.77	3.42
Phosphorus metabolism disorders	178	5.03	537.90	4.33
Gingival infections *	168	5.02	505.49	4.30
Head neck and oral cavity therapeutic procedures NEC	98	4.98	290.19	4.07
Gingival disorders signs and symptoms NEC	532	4.82	1518.67	4.43
Dental and oral soft tissue infections	849	4.80	2413.44	4.51
Bone sarcomas	28	4.38	66.15	3.00
Paraendocrine neoplasms NEC*	4	4.08	6.15	1.50
HLT	n	PRR	χ^2_{Yates}	ROR $_{205}$
Bone and joint infections (excl arthritis)	461	4.08	1019.91	3.73

Pelvic fractures and dislocations *	167	4.06	364.62	3.48
Pelvic fractures *	167	4.06	364.62	3.48
Musculoskeletal and soft tissue imaging procedures	992	3.96	2096.48	3.74
Fracture complications	41	3.88	80.79	2.83
Chemotherapies	64	3.85	126.05	3.00
Spine and neck deformities	384	3.76	740.88	3.40
Limb fractures	2946	3.66	5496.11	3.59
Limb fractures and dislocations	2946	3.66	5495.12	3.59
Metastases to specified sites	1034	3.65	1904.78	3.45
Bone and joint infections	474	3.65	870.37	3.34
Vitamin analyses	213	3.60	379.82	3.14
Cartilage neoplasms benign	6	3.43	7.68	1.51
Bone therapeutic procedures NEC	73	3.37	114.75	2.67
Fat soluble vitamin deficiencies and disorders	153	3.32	236.71	2.83
Healing abnormal NEC	415	3.15	583.18	2.86
Lip and oral cavity neoplasms benign	15	2.97	17.00	1.77
Bone neoplasms benign (excl cysts) *	8	2.96	8.18	1.46
Dietary and nutritional issues	16	2.87	17.08	1.75
Bone metabolism disorders	1032	2.84	1190.00	2.68
Soft tissue disorders NEC	365	2.79	403.04	2.52
External ear disorders NEC*	43	2.79	45.86	2.06
Pleural neoplasms*	36	2.73	36.46	1.96

Note: * not included in the drug instructions.
Abbreviation: HLT, high-level term; PRR, proportional reporting ratio; χ^2_{Yates}, Chi-squared values corrected as recommended by Yates; ROR_{205}, the lower limit of the 95% confidence interval; NEC, not elsewhere classified.

Table 3. Results of signal detection of standardized MedDRA queries

SMQ	n	PRR	χ^2_{Yates}	ROR_{205}
Osteonecrosis	6010	17.34	76596.32	17.70
Gingival disorders *	714	3.86	1443.30	3.60
Osteoporosis/osteopenia	1330	2.97	1677.82	2.83
Prostate tumours of unspecified malignancy *	210	2.85	241.53	2.48
Tumour markers	341	2.16	204.83	1.94

Note: Events marked with "*"are events not included in the drug instructions.
Abbreviation：MedDRA, Medical Dictionary for Drug Regulatory Activities; SMQ, standardized MedDRA queries; PRR, proportional reporting ratio;ROR_{205}, the lower limit of the 95% confidence interval.

3. DISCUSSION

In this study, we utilized both the ROR and PRR methods to analyze the ADEs associated with denosumab, and the results obtained from both methods exhibited a high level of consistency. The signal detection results were in line with the specification and literature reports [7, 8], thus validating the reliability of our study. Furthermore, our analysis identified certain ADEs that were not mentioned in the drug instructions, highlighting the importance of addressing these events in clinical practice. It is noteworthy that bone or muscle pain was identified as the most common adverse effects associated with denosumab. At the PT level, back pain (n=2899), bone pain (n=1927), myalgia (n=1867), pain in jaw (n=1275) and musculoskeletal pain (n=789) were observed as adverse reaction signals. Some clinical trials have indicated that musculoskeletal pain is commonly experienced by the denosumab and placebo groups, and occasional discontinuation of treatment due to musculoskeletal pain has been observed [7, 8, 13].

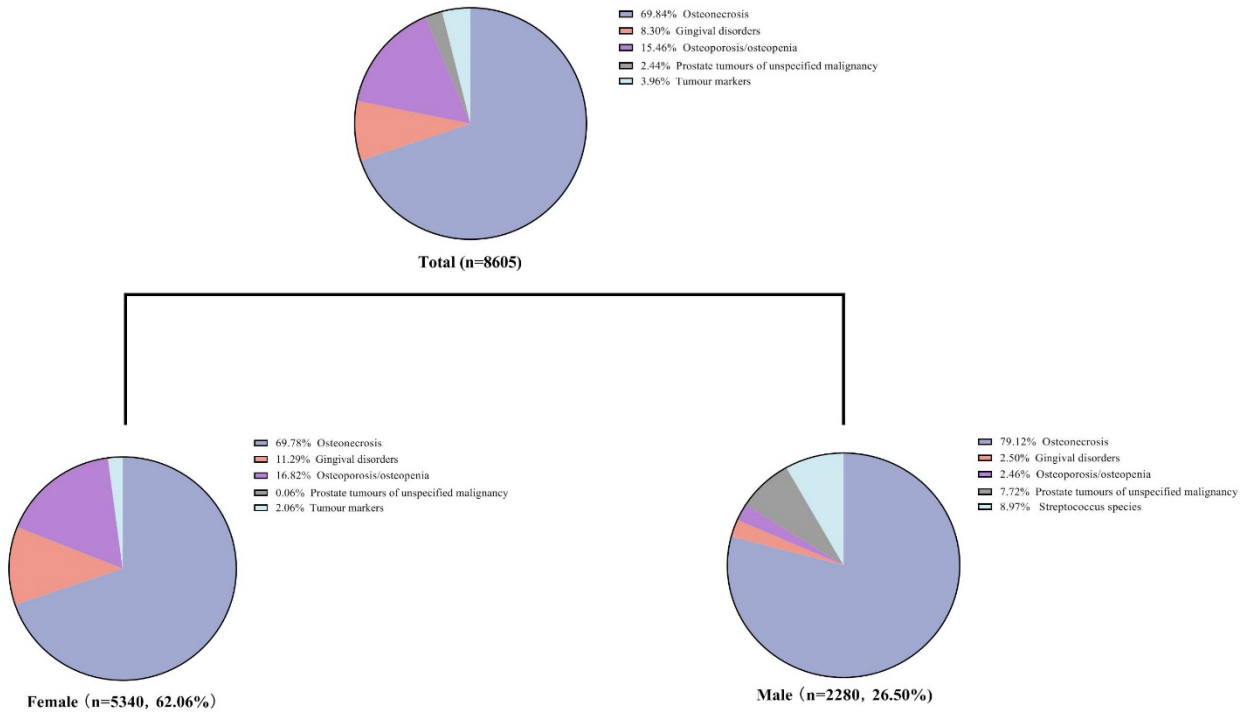

Figure 2. The proportion of several detected SMQ signals in the overall population and specific gender subgroups.

Therefore, it is important to consider the possibility of pain caused by the primary disease to avoid unnecessary treatment discontinuation prompted by pain. Additionally, hypocalcemia, in particular, is a significant adverse reaction signal of denosumab, with PT level hypocalcemia (n=1772), and HLT level calcium metabolic diseases (PRR=12.72, ROR_{025} =12.37). Research has indicated that the real-world incidence of denosumab-induced hypocalcemia is higher than previously reported [14]. One study suggests that renal insufficiency may be a risk factor for severe hypocalcemia after denosumab treatment, possibly due to impaired 1, 25-dihydroxyvitamin synthesis caused by decreased 1a hydroxylase activity, which affects blood calcium balance [15]. While hypocalcemia induced by denosumumab is usually transient, it can have serious consequences such as arrhythmia or even death [16]. Therefore, it is recommended to evaluate patients' blood calcium level before starting denosumab treatment and address any risk factors for hypocalcemia. Additionally, patients undergoing denosumab treatment, especially those with renal insufficiency, should receive sufficient calcium and vitamin D supplements and their blood calcium levels should be monitored throughout the treatment period. Vigilance is necessary for the occurrence of rebound hypercalcemia upon discontinuation of denosumab therapy [17].

Common infections, such as urinary tract infections, upper respiratory tract infections and skin infections, are listed in the drug instructions for denosumab. A meta-analysis showed that compared to placebo, denosumab increased the risk of serious adverse reactions associated with infection [18]. In our study, bone and joint infections (excluding arthritis) (PRR=4.08, ROR_{025} =3.73) and bone and joint infections (PRR=3.65, ROR_{025} =3.34) were identified as significant but relatively infrequent adverse reaction signals at the HLT level, except for some oral infections. This suggests that these infections caused by denosumab are present but rare in the real world. Nevertheless, individuals at a high risk of immune deficiency should remain vigilant regarding the occurrence of infections.

Osteonecrosis of the jaw (ONJ) is a rare but severe adverse effect of denosumab [19]. This study revealed a significant signal of ONJ, with a high number of reported cases at the PT level (n=6065, PRR=45.50). Furthermore, musculoskeletal necrosis and vascular dysfunction at the HLT level (PRR=12.43, ROR=13.08) and osteonecrosis at the SMQ level (PRR=14.78, ROR=15.06) were also observed. Notably, jaw pain (n=1251, PRR=5.02) with high numbers of reports and signal values was identified as an early sign of ONJ. In the FREEDOM study, no cases of osteonecrosis of jaw were found in the denosumab treatment group [7]. However, during the 10-year extended study, 13 cases of ONJ were reported [7], suggesting that prolonged

exposure to denosumab may increase the risk of ONJ. The pathophysiological mechanism of ONJ primarily revolves around five factors: bone remodeling disorders, changes in immune function, soft tissues toxicity, angiogenesis inhibition, and inflammation or infection. Dental infection and oral microorganisms are considered to be the core of ONJ [20]. Therefore, it is advisable for patients to undergo a preventive dental examination before initiating denosumab therapy. If any unhealed lesions are present in the mouth, patients should consider postpone denosumab treatment. To ensure the effectiveness of the treatment, patients are encouraged to maintain good oral hygiene habits throughout the course of denosumab treatment, undergo regular oral check-ups and avoid invasive dental surgeries. Additionally, ONJ may develop rapidly in patients who switch from bisphosphonates to denosumab [21], so prescribing physician should pay special caution in such cases.

This study identified significant signals of various oral disorders associated with denosumab, which were not previously included in the drug label and literature, but serve as precursors to ONJ. Specifically, the study found significant signals for tooth disorder (n=1871) and tooth extraction (n=746) at the PT level, as well as dental and gingival therapeutic procedures (PRR=17.55, ROR_{025} =16.87), dental disorders (not elsewhere classified, NEC) (PRR=13.04, ROR_{025} =12.77), dental pulp diseases (PRR=8.31, ROR_{025} =5.71), dental pain and sensation disorders (PRR=6.20, ROR_{025} =5.72), dental and periodontal infections and inflammations (PRR=5.31, ROR_{025} =4.98), gingival infections (PRR=5.02, ROR_{025} =4.30) at the HLT level, and gingival disorders (PRR=3.86, ROR_{025}=3.60) at the SMQ level. Although a mouse model has shown that the use of denosumab alone does not impair the growth of gingival fibroblasts, it suggests that denosumab administration leads to delayed repair of damaged connective tissue and sustained inflammation [22]. Furthermore, when denosumab is used in combination with other drugs, such as corticosteroids, may exacerbate the negative effects on oral mucosal cells [23]. Previous studies have reported that one-third of patients experienced tooth extraction, tooth loss, and dental implants during denosumab treatment, and those who experienced these conditions were at a higher risk for jaw necrosis [13]. Animal experiments have also demonstrated that jaw bone necrosis is more likely to occur in animals with gingival and periodontal infections [24]. Therefore, it is crucial to carefully consider the use of denosumab in patients with pre-existing oral disease and to monitor their oral conditions during treatment. If oral disease does occur, it is especially important to remain vigilant for signs of ONJ.

This study also identified significant safety signals for denosumab related to various fractures. These included spine fracture (n=1273), fracture (n=904), femur fracture (n=717), and hip fracture (n=637) at the PT level. Additionally, spinal column fractures (PRR=12.48, ROR_{025} =12.08), spinal fractures and dislocations (PRR=12.13, ROR_{025} =11.74), fractures NEC (PRR=5.96, ROR_{025} =5.77), fractures and dislocations NEC (PRR=5.31, ROR_{025} =5.14), pelvic fractures (PRR=4.06, ROR_{025} =3.48) and limb fractures (PRR=3.66, ROR_{025} =3.59), at the HLT level. The drug instructions state that the risk of multiple vertebral fractures and atypical femur fractures may increase after discontinuation of denosumab therapy, particularly in patients with prior vertebral fractures. The 10-year FREEDOM extension study reported one atypical femur fracture in each of the long-term and crossover groups, with an incidence of 0.8 cases per 10,000 subject-years, indicating an extremely rare adverse reaction [7]. However, our study revealed a significant number of femur fractures, specifically 717 cases, which emphasizes the need for urgent clinical attention. Other types of fractures are not included in the instructions, and the possibility of fractures due to osteoporosis cannot be excluded. Therefore, it is recommended that patients undergo further examination to exclude the possibility of fracture in addition to experiencing general adverse reactions, such as pain, during medication. Patients should not discontinue the medication without consulting their healthcare provider, and should be switched to other anti-bone resorption agents after discontinuation.

In addition to its approved use for osteoporosis, denosumab is now indicated for various conditions such as solid tumors with bone metastases, multiple myeloma, giant cell tumors of bone, prostate cancer in men receiving androgen deprivation therapy, and breast cancer in women receiving aromatase inhibitor therapy and at high risk of fracture. Our study identified denosumab-related ADEs in tumors -related conditions, including musculoskeletal and connective tissue neoplasms NEC, chronic leukemia, paraendocrine neoplasms NEC, pleural neoplasms, aural neoplasms benign, bone neoplasms malignant (excl sarcomas), bone sarcomas, and benign lip and oral cavity neoplasms.While the overall risk-benefit ratio of denosumab has been shown to be favorable in patients with giant cell tumors of bone [25, 26] , studies have suggested that denosumab use in treating bone giant cell tumors may increase safety signals for other types of tumors [27-29]. Therefore, close monitoring for the occurrence of tumor diseases is recommended when using

denosumab for osteoporosis treatment. For patients with osteoporosis and tumors other than bone giant cells, the clinical benefit should be thoroughly evaluated, and cautious use of the drug is advised. Furthermore, our study identified high frequencies or signals of off-label use and product dose omission, indicating the need for regulatory measures in clinical medication.

This study utilized the FAERS database to analyze the real-world data on the use of denosumab, effectively addressing the limitations of small sample sizes and limited observation time in clinical trials. However, this approach has certain limitations. Firstly, the spontaneous reporting system within the database has inherent flaws [30]. This is because adverse events are voluntarily submitted not only by healthcare professionals but also by consumers such as patients, family members, and lawyers. As a result, there are issues such as non-professional reporting, non-standard data sources, biased partial reports, underreporting, and missing clinical information, among others. All of these can impact the accuracy of the data mining results. Secondly, the safety signals generated by the PRR and ROR methods employed in this study indicate a statistical correlation between denosumab and ADE signals, but do not necessarily establish a definitive causal relationship between the drug and ADEs. Further clinical studies are required to determine the causality between the target drug and the identified ADEs. Lastly, the FAERS database primarily contains data from European and American populations, with limited representation from Asian populations. Therefore, the results may vary among different ethnic groups. Nevertheless, data mining with a large sample size still serves as a valuable tool for identifying potential safety concerns associated with drug usage and provides a reference for exploring drug safety.

4. CONCLUSION

Denosumab has emerged as a key drug in treating malignant and benign bone diseases, but its safety profile has raised concerns. This study utilized the FAERS database in the United States and employed the disproportionality analysis method to identify ADEs associated with denosumab post-marketing. The safety signals identified in this study, such as musculoskeletal pain, hypocalcemia, and jaw necrosis, were consistent with those mentioned in the drug instructions. Furthermore, new ADE signals, such as various oral diseases, certain fractures, and off-label tumor indications were detected, providing valuable insights for clinical decision-making and adverse drug reaction research. To ensure patient safety, it is recommended to strengthen pharmaceutical care practices during the clinical use of denosumab. It is also important to complement the findings of this study with other research methods to further elucidate the safety profile of denosumab and gather more comprehensive evidence.

5. MATERIALS AND METHODS

5.1 Data source

The data used in this study were obtained from the FAERS database, which is a voluntary reporting system that collects information on adverse events and medication errors reported to the FDA, and provides an important basis for monitoring and evaluating post-marketing safety risks. Graph construction were conducted using GraphPad Prism (ver.9, GraphPad Software, La Jolla, USA).

5.2 Analysis tool

To access and analyze the FAERS database, we utilized OpenVigil 2.1(https://openvigil.sourceforge.net/), which is an open-source tool designed for collating, analyzing, and extracting information from pharmacovigilance databases. OpenVigil 2.1 includes drug mapping and duplicate detection features, ensuring reliable access to the underlying adverse events reporting system and accurate counting of reports based on extraction conditions. We extracted data from the FAERS database, covering the period from the second quarter of 2010 to the first quarter of 2022, which corresponds to the period during which denosumab was marketed. Reports in which denosumab was the primary suspected drug were focused on, while reports of other drugs, duplicates, non-informative ADEs and uncertain names were excluded. ADEs were screened and standardized by mapping PTs to Medical Dictionary for Drug Regulatory Activities (MedDRA) terms. MedDRA is a globally recognized medical terminology dictionary used for classifying and coding adverse event data related to medical products, especially in pharmacovigilance and drug safety. Within the MedDRA hierarchy, PTs are the most specific level, representing individual medical terms or expressions describing clinical symptoms, diagnoses, or conditions. HLTs sit one level above PTs, grouping

related PTs into broader medical categories. HLTs provide a more generalized perspective on adverse events and conditions, simplifying data analysis while preserving some level of detail. SMQs are predefined collections of PTs and HLTs organized around specific medical themes or interests. SMQs aid in systematically reviewing and analyzing safety data. Specifically, we mapped all PTs obtained from data mining to 1856 HLTs and 106 SMQs language groups to detect potential safety signals in the data. The specific steps for operating on the OpenVigil 2.1 website are as follows: Click on the "Search" section of the website, choose "Drug" under "OpenVigil Search," and enter "Denosumab," "Xgeva," "Prolia" in the "'Drug" field, connecting these three words with "OR." Then, select "Role of Drug" as "Primary Suspect," restrict the time range in the Advanced Search from the second quarter of 2010 to the first quarter of 2022, choose the desired data presentation and statistics for export, and click "Search" to export the results.

5.3 Data mining algorithms

Disproportionality analysis is a widely used method to detect potential ADE signals by identifying the relationship between target drugs and target ADEs [31]. In this study, we applied the frequentist approach, including the ROR method, PRR method and Yates-corrected chi-squared values (χ^2_{Yates}), to conduct signal mining. The lower limit of the 95% confidence interval (CI) of the ROR (ROR_{025}) was calculated using the formula: $e^{\ln(ROR)-1.96\sqrt{1/a+1/b+1/c+1/d}}$. We used the following signal detection threshold criteria: (1) Report number "a"≥3; (2) PRR > 2, χ^2_{Yates} > 4, ROR_{025} > 1, indicating signal generation. The calculation methods for the frequentist approach are shown in Table 4 and Table 5. The calculation principles of the values in this study were implemented using the OpenVigil - 2x2 contingency table calculator (https://openvigil.pharmacology.uni-kiel.de/contingency-table-calculator.php). This is a free online statistical calculator designed for analyzing 2x2 contingency tables, specifically tailored for pharmacovigilance data analysis. The signal value represents the strength of the statistical association between denosumab and the target ADE. The higher signal value indicates a stronger signal, meaning that the target drug is more closely associated with adverse reactions.

Table 4. Fourfold table of disproportionality measurement

	Number of target ADE reports	Number of other ADE reports	Sums
Target drug	a	b	a + b
Other drugs	c	d	c + d
Sums	a + c	b + d	a + b + c + d

Abbreviation：ADE, adverse drug event.

Table 5. Calculation formulas for disproportionality measurement

Detection method	Calculation formula
ROR	$\mathrm{ROR} = (a/c)/(b/d)$
PRR	$\mathrm{PRR} = [a/(a+c)]/[b/(b+d)]$
ROR_{205}	$95\%\mathrm{CI}=e^{\ln(ROR)-1.96\sqrt{1/a+1/b+1/c+1/d}}$

Note: Detection threshold criteria: (1) the number of reports a ≥ 3; (2) PRR > 2, lower 95%CI > 1, and signal generation will be prompted in the case above.

Abbreviation : ROR, reporting odds ratio; PRR, proportional reporting ratio; ROR_{205}, the lower limit of the 95% confidence interval; CI, confidence interval.

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