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Research Article

Real-world study of medication-related osteonecrosis of the jaw from 2010 to 2023 based on Food and Drug Administration Adverse Event Reporting System

Yuhao Zhong[1], Wei Dai[2], Lin Yin[3], Guomin Wu[1], Xiaoying Wang[3,4,*]

[1]Department of Oral, Plastic, and Aesthetic Surgery, Hospital of Stomatology, Jilin University, Changchun 130021, China
[2]Department of Otorhinolaryngology—Head and Neck Surgery, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, China
[3]Information Center, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, China
[4]Guangdong Key Laboratory of Blockchain Security, Guangzhou University, Guangzhou 510006, China
*Corresponding author: Xiaoying Wang, Information Center, Third Affiliated Hospital of Sun Yat-sen University, 600 Tianhe Road, Guangzhou 510630, Guangdong, China (wxying@mail.sysu.edu.cn).

Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a rare and severe adverse drug reaction (ADR) commonly seen in people taking drugs prescribed for metastatic cancer and osteoporosis. Prior studies only analyzed this ADR utilizing the public database Food and Drug Administration Adverse Event Reporting System (FAERS) by different stages (2010-2014, 2015-2021); a more comprehensive study is needed to analyze the MRONJ cases and the associated drugs from a longer time span. We conducted a retrospective pharmacovigilance analysis for all reported MRONJ cases between 2010 and 2023 in FAERS, using preferred terms and the primary suspect drug as searching conditions. Thus, this study aimed to analyze the MRONJ cases and the associated drugs more comprehensively. The reporting odds ratios (RORs) and 95% CIs were calculated for each queried drug. To distinguish the signal levels, we calculated the expected information component (EIC) and its 95% CI, using the Bayesian confidence propagation neural network (BCPNN) methods. We identified 22 846 MRONJ cases. A total of 15 drug classes including 30 suspect drugs showed different positive signal levels; among these drugs, 8, 5, and 17 had strong, medium, and weak intensity signals (+++, ++, and +), respectively. Drug classes involved bisphosphonate, RANKL inhibitor, radiotherapy drug, monoclonal antibody for cancer, corticosteroid, tyrosine kinase inhibitor, mammalian target of rapamycin inhibitor, aromatase inhibitor, cyclin-dependent kinase 4/6 inhibitor, immunomodulator, microtubule inhibitor, selective estrogen receptor modulator, sclerostin monoclonal antibody, estrogen receptor antagonist, and cytotoxic drug. Bisphosphonate, RANKL inhibitor, and radiotherapy drug exhibited higher risk than other classes with higher ROR or EIC 95% CI lower limit. Females had higher MRONJ incidence than males, and the mean age was 67.33 ± 11.71 yr. Compared with previous research, this study identified more drug classes and more novel medications with positive MRONJ signals that warrant further attention.

Keywords: medication-related osteonecrosis of the jaw, FDA Adverse Event Reporting System (FAERS), pharmacovigilance, signal detection, osteonecrosis of the jaw, exposed bone in jaw

Lay Summary

Medication-related osteonecrosis of the jaw (MRONJ) is a rare and serious adverse drug reaction during metastatic cancer or osteoporosis treatment. Given that novel drugs constantly emerge in the anticancer therapeutic and osteoporosis fields, the causative drugs of MRONJ need to be tracked continuously.

Our study explored the causative drug trend of MRONJ according to data from a longer time span (2010-2023), analyzed MRONJ cases in the Food and Drug Administration Adverse Event Reporting System database more comprehensively, and identified 30 suspect drugs with positive MRONJ signals that warrant further attention.

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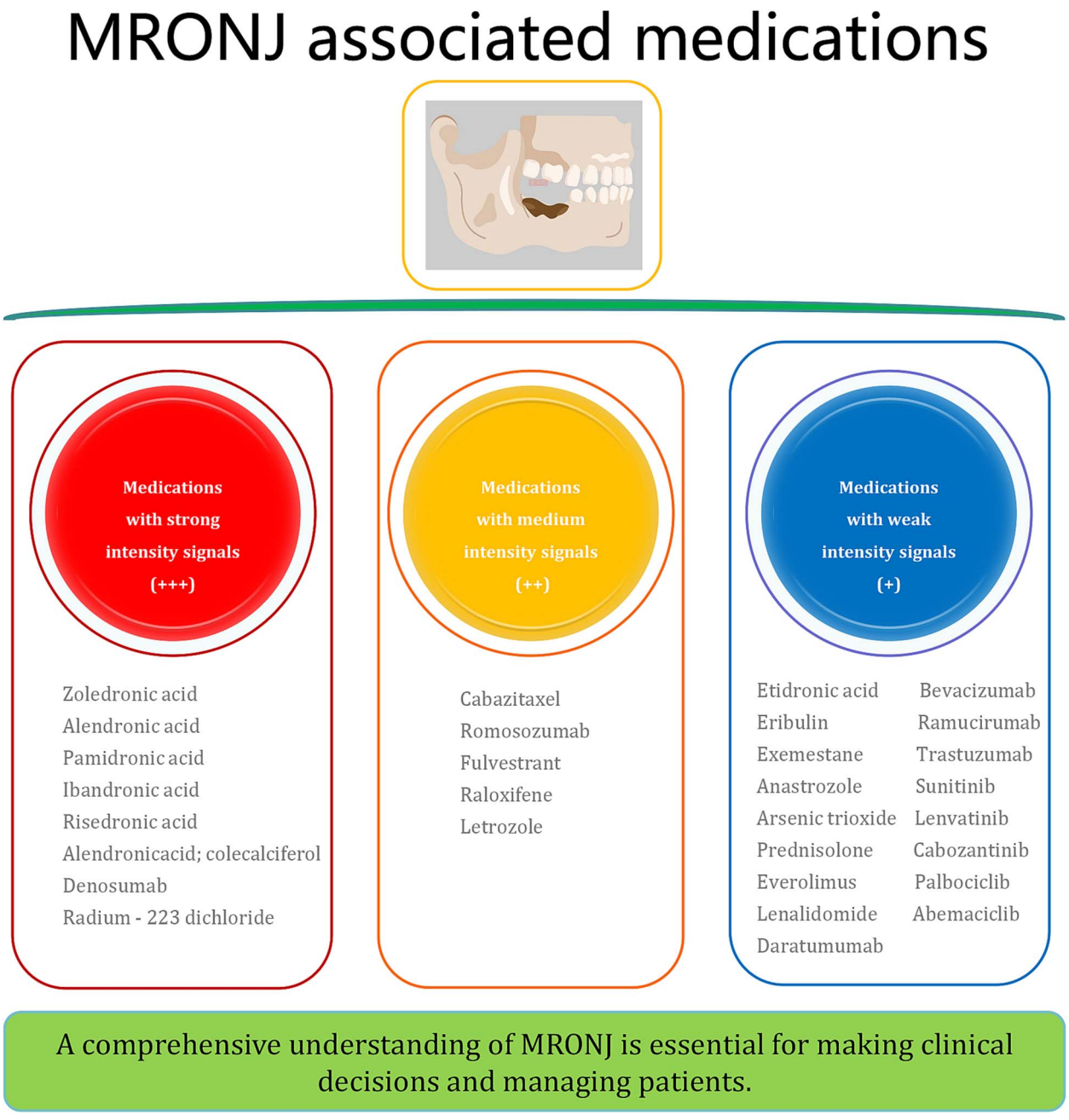
Graphical Abstract



Introduction

Osteonecrosis of the jaw (ONJ) can be divided into 3 types: spontaneous ONJ, osteoradionecrosis of the jaw, and medication-related osteonecrosis of the jaw (MRONJ). MRONJ is a relatively uncommon but potentially serious complication in patients treated for cancer or osteoporosis. In 2022, the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined MRONJ as the following criteria: current or previous treatment with antiresorptive monotherapy or combined with immune modulators or antiangiogenic medications; exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for over 8 wk; and no history of radiation therapy or metastatic disease to the jaws.[1] According to both clinical and particularly preclinical animal studies, AAOMS proposes 5 hypotheses regarding MRONJ pathophysiology: bone remodeling inhibition, inflammation or infection, angiogenesis inhibition, innate or acquired immune dysfunction, and genetic predisposition.[1] Traditionally, MRONJ was considered to be caused by 3 main classes of medications: bisphosphonates (BPs), RANKL inhibitors, and antiangiogenic medications. In recent studies using the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database, some additional and unexpected classes of medications associated with MRONJ were identified constantly beyond antiresorptive agents; some

of them are the mammalian target of rapamycin (m-TOR) inhibitors, cyclin-dependent kinase (CDK) 4/6 inhibitors, corticosteroids, tyrosine kinase inhibitors, monoclonal antibodies, aromatase inhibitors, microtubule inhibitors, and immunomodulators.[2–6]

Three blinded active-controlled phase III trials reported that MRONJ occurred in 1.6% of patients receiving zoledronic acid or denosumab therapies for bone metastases secondary to solid tumors or myeloma, and over one-third of them were healed.[7] Considering the continuous emergence of novel antitumor medications in the market, as a rare and serious adverse drug reaction (ADR) in metastatic cancer and osteoporosis, MRONJ has recently gained increasing attention. Tracking the dynamic changes of the suspected drugs of MRONJ continuously and disseminating pharmacovigilance information to relevant healthcare professionals are crucial. Necessary reminders can facilitate timely detection of MRONJ and decrease damage in post-marketing time.

While prior studies have analyzed MRONJ by stages (2010-2014 and 2015-2021), utilizing the public database FAERS,[2,3] the analysis results of continuous data collection from a longer period of time can be more conducive in identifying the pharmaco-epidemiological trend of MRONJ and probably disclosing some differences comparing with segmented data retrieval. Hence, using previous research results, this study aimed to analyze MRONJ in FAERS database within an expanded time frame from 2010 to 2023 more comprehensively and explore the trend of suspected drugs related to ONJ more objectively.

Materials and methods

Data

Given that exposed bone in the jaw is the main symptom of ONJ, our search strategy was as follows. First, we chose "Osteonecrosis of the jaw (10064658)" and "Exposed bone in jaw (10071014)" as preferred terms for ADR, basing on Medical Dictionary for Regulatory Activities (MedDRA), which was established in March 2010. Second, considering that the FAERS database has a significant degree of duplication among reported cases, our study removed duplicate case reports. Lastly, to exclude the interference of combined medications, we selected the primary suspect drug as the searching condition. The FAERS database was queried from the first quarter (Q1) of 2010 through the last quarter (Q4) of 2023 using 3 searching conditions mentioned above. This study is non-interventional, and ethical approval is not required.

Statistical analysis

In the disproportionality analysis for screening MRONJ signals in the FAERS database, the signal data-mining algorithm adopted the reporting odds ratio (ROR) method and the Bayesian confidence propagation neural network (BCPNN) method. ROR and its 95% CI for each primary suspect drug were calculated as previously reported. Positive signals for the ROR method were required to meet the following criteria: the number of reports ≥ 3 and the lower limit of the 95% CI of the ROR > 1.[8,9] The BCPNN method was used to distinguish the signal level and calculate the expected information component (EIC) and its 95% CI for the primary suspect drug. Signal generation was required to satisfy the following conditions: EIC 95% CI lower limit (IC-2SD) > 0 and the criterion of signal intensity wherein IC-2SD ≤ 0 indicated no signal [−], $0 <$ IC-2SD ≤ 1.5 indicated a weak intensity signal (+), $1.5 <$ IC-2SD ≤ 3.0 indicated a medium intensity signal (++), and IC-2SD > 3.0 indicated a strong intensity signal (+++).[9]

Finally, the data were comprehensively summarized and discussed across various aspects of MRONJ, including the analysis of characteristics such as age, sex, continent, outcome distribution, and annual report numbers of MRONJ cases, as well as the occupational distribution of MRONJ reporters. Additionally, the indications, median medication time (MMT), and signal intensity levels for the primary suspect drugs were summarized. Figure 1 presents a flowchart of the abovementioned details.

Results

By December 2023, we found 17 307 196 cases of ADR in the FAERS database after removing 3 448 437 duplicate reports. Finally, we obtained 22 845 MRONJ cases in 2010-2023 using strict data curation, including the primary suspect drug and preferred term codes (10064658 and 10071014) as the searching condition. Using the ROR and BCPNN methods, we screened 30 primary suspect drugs, and their different signal intensity levels are presented using a forest map.

Characteristics of MRONJ cases

Figure 2 presents the characteristics of MRONJ cases reported in the FAERS database from 2010 to 2023. Figure 2A illustrates the distribution of cases by sex, while Figure 2B depicts the age distribution of MRONJ patients over the same period. More than 2000 MRONJ cases were reported in 2014 and from 2016 to 2018. Subsequently, the number of MRONJ cases dropped dramatically. Among them, 60.3% (13 779/22 845) were females, 29.6% (6766/22 845) were males, and 10.1% (2300/22 845) had unknown sex information. The mean age was 67.33 ± 11.71 yr, with 29.8% (6801/22 845), 2.3% (535/22 845), 15.8% (3616/22 845), 33.9% (7736/22 845), and 18.2% (4157/22 845) for unclear and below 18, 18-45, 46-60, 61-75, and above 75 yr, respectively.

Figure 2C and D illustrate the continent distribution of the reporting countries and the occupation distribution of reporters, respectively. In terms of the report number, Europe, North America, and Asia were the top 3 continents, with their total proportion of reports exceeding 95.5%. Top 5 countries were the United States (6813, 29.8%), Japan (3474, 15.2%), Germany (1999, 8.7%), France (1174, 5.1%), and England (896, 3.9%). Major occupations included physicians, other health professionals, consumers, and pharmacists, accounting for more than 96% of the total.

Figure 2E illustrates the trends in the annual report numbers of MRONJ cases for the top 6 primary suspect drugs. Six suspect drugs had more than 400 reported MRONJ cases from 2010 through 2023. Denosumab had the highest number of MRONJ cases (7750), followed by zoledronic acid (7184), alendronic acid (2495), pamidronic acid (883), ibandronic acid (491), and lenalidomide (437), with their combined reports accounted for 84% of the total. Figure 2F illustrates the outcome distribution of MRONJ cases, with severe cases accounting for more than 99.13% (22 648 out of 22 845) of the total. This category includes instances of hospitalization, disability, required interventions, other severe outcomes, and death, among others.

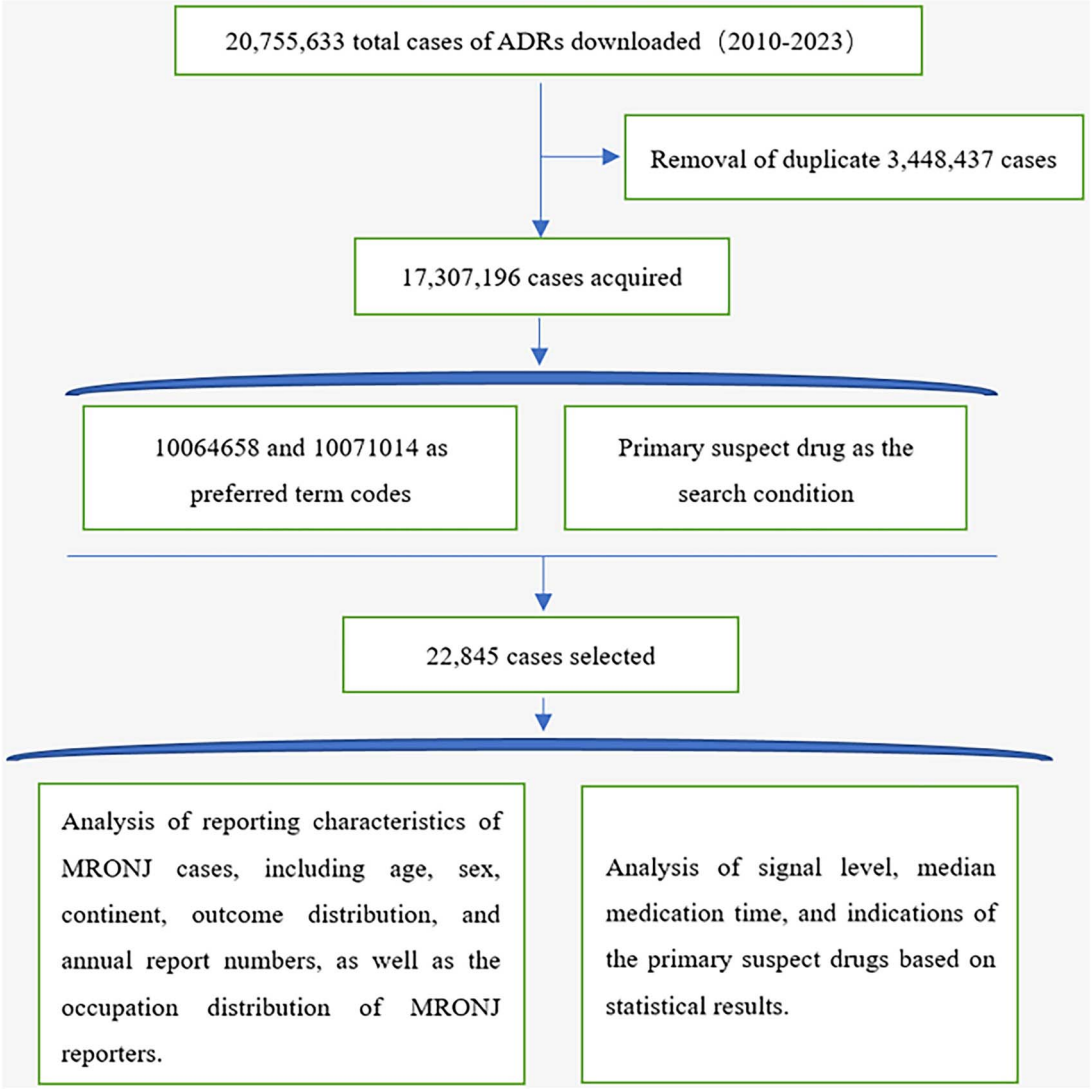


Figure 1. Flowchart illustrating the research method and the inclusion and exclusion criteria.

Statistical analysis of primary suspect drugs and medication time

A total of 15 classes including 30 primary suspect drugs demonstrated positive signals of MRONJ by ROR and BCPNN methods from 2010 to 2023, with their reporting cases accounting for more than 91% of the total. Table 1 summarizes the medications reported for these MRONJ cases and their statistical analysis results as well as the reporting number for each of the suspect drugs. The 15 drug classes involved BPs, RANKL inhibitor, radiotherapy drug, monoclonal antibody (mAb) for cancer, corticosteroid, tyrosine kinase inhibitor (TKI), mammalian target of rapamycin (m-TOR) inhibitor, aromatase inhibitor, CDK 4/6 inhibitor, immunomodulator, microtubule inhibitor, selective estrogen receptor modulator, sclerostin monoclonal antibody, estrogen receptor antagonist, and cytotoxic drug.

According to the BCPNN methods,[9] the signal intensity of each suspect drug was distinguished in terms of the EIC and its IC-2SD. Out of 30 primary suspect drugs, 8 had strong intensity signals (+++) and showed relatively high risks, with IC-2SD values greater than 3. First, zoledronic acid had an EIC of 6.02 and a quantity proportion of 31.4%. Second, the RANKL inhibitor denosumab had an EIC of 5.72 and a quantity proportion of 33.9%. The BPs involved were as follows: alendronic acid (EIC, 4.15; quantity proportion, 10.9%), pamidronic acid (5.19, 3.9%), ibandronic acid (4.27, 2.1%), risedronic acid (3.99, 1.0%), and alendronic acid plus colecalciferol (4.05, 0.3%). Lastly, the radiotherapy drug radium-223 dichloride had an EIC of 3.57 and a quantity proportion of 0.3%. As for the medium intensity signals, 5 drugs, namely, microtubule inhibitor (cabazitaxel), sclerostin monoclonal antibody (romosozumab), estrogen receptor antagonist (fulvestrant), selective estrogen receptor modulator (raloxifene), and aromatase inhibitor (letrozole), were involved. Moreover, 17 suspect drugs had weak positive signals. Table 1 further elaborates the aforementioned information, including a comprehensive statistical analysis of all suspected medications associated with MRONJ. Figure 3 presents a more direct comparison of the EIC 95% CI for the 3 groups of suspected medications with varying signal intensities.

To elucidate the relationship between the treatment duration of suspected drugs and the ONJ, we calculated the

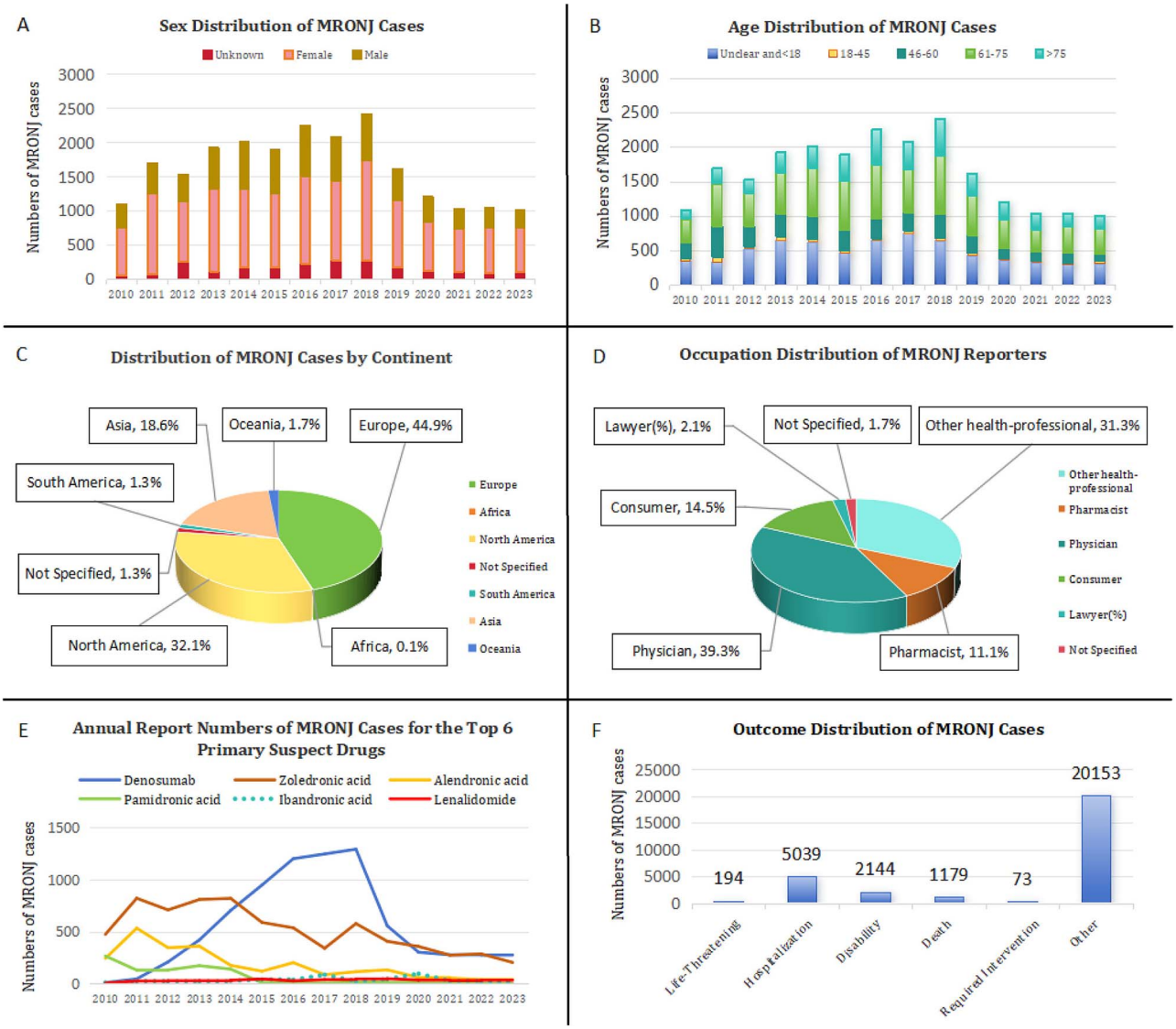


Figure 2. Characteristics of medication-related osteonecrosis of the jaw (MRONJ) cases from 2010 to 2023 in FDA Adverse Event Reporting System.

MMT of each suspect drug, with the reports with incomplete information of medication time being removed (Table 1). The MMTs of BPs, raloxifene, lenalidomide, denosumab, letrozole, trastuzumab, and anastrozole were over 1 yr. The MMT of the preparation of alendronic acid containing cholecalciferol was longer than that of alendronic acid monotherapy. The MMTs of suspect drugs ranged from 37.0 to 2784.5 d.

Indication distribution of primary suspect drugs

Among the 22 845 patients with MRONJ, over 48% received medications for skeletal-related events (SREs), with or without bone metastases; 26.59% for osteoporosis treatment or prevention, with or without fracture; and 23.43% for unknown or not specified cases related to MRONJ. Patients with indications for both SREs and osteoporosis were not included in this analysis, considering the use of the preferred indication as the searching condition. Among MRONJ cases using these drugs for SREs prevention or treatment, 19.26% had bone neoplasm or metastatic bone cancer, 9.79% had breast cancer, 8.55% had myeloma or hematologic tumor, 7.88% had urinary system cancer, 1.94% had other or unknown cancer types, 1.34% had immune diseases or prophylaxis, 0.86% had lung cancer, and 0.36% had digestive system cancer. Table 2 presents all the details about the distribution of indications and involved medications.

Discussion

While the condition of primary suspect drug and the removal of duplicate cases led to overall fewer identified cases of MRONJ, using the primary suspect drug and the preferred term codes (10064658 and 10071014) as the searching conditions made our goal clearer and more targeted. Although unable to imply incidence from our data because of the nature of the FAERS database, our study provided more valuable and detailed information on MRONJ according to a longer time span in the FAERS database, identifying more drug classes than the prior studies.[2,3] The ROR and BCPNN methods, which are commonly employed for FAERS data analysis, were both utilized in this study to compare and contrast their

Table 1. Distribution of primary suspect drugs in medication-related osteonecrosis of the jaw cases and the statistical analysis results reported in FDA Adverse Event Reporting System.

			BCPNN		
Medication	N	ROR (95%CI)	EIC (95%CI)	SI	MMT (IQR) (d)
Bisphosphonate					
Zoledronic acid	7184	102.91 (100.20-105.69)	6.02 (6.00-6.07)	+++	495.0 (274.0-789.8)
Alendronic acid	2495	20.00 (19.20-20.83)	4.15 (4.09-4.21)	+++	549.0 (280.0-949.0)
Pamidronic acid	883	40.16 (37.70-42.77)	5.19 (5.10-5.28)	+++	551.5 (227.8-1042.8)
Ibandronic acid	491	20.55 (18.86-22.40)	4.27 (4.14-4.39)	+++	551.0 (293.3-949.3)
Risedronic acid	239	17.16 (15.16-19.42)	3.99 (3.81-4.17)	+++	639.0 (398.0-1050.3)
Alendronicacid; colecalciferol	61	22.34 (17.39-28.70)	4.05 (3.68-4.41)	+++	644.0 (216.3-906.8)
Etidronic acid	4	15.20 (6.30-36.03)	2.17 (0.99-3.35)	+	2784.5 (2166.3-3398.8)
RANKL inhibitor					
Denosumab	7750	79.38 (77.26-81.56)	5.72 (5.68-5.76)	+++	457.0 (228.0-776.0)
Radiotherapy drug					
Radium-223 dichloride	70	14.21 (11.25-17.95)	3.57 (3.23-3.92)	+++	70.0 (34.5-141.5)
Microtubule inhibitor					
Eribulin	9	2.74 (1.43-5.27)	1.22 (0.31-2.14)	+	37.0 (24.0-49.0)
Cabazitaxel	18	7.33 (4.61-11.65)	2.46 (1.79-3.12)	++	91.5 (38.5-115.0)
Sclerostin monoclonal antibody					
Romosozumab	37	5.69 (4.12-7.86)	2.34 (1.87-2.81)	++	153.0 (84.0-346.0)
Estrogen receptor antagonist					
Fulvestrant	81	5.51 (4.43-6.85)	2.38 (2.06-2.70)	++	245.0 (126.0-397.0)
Selective estrogen receptor modulator					
Raloxifene	38	4.31 (3.13-5.93)	1.99 (1.52-2.45)	++	928.0 (280.8-1530.3)
Aromatase inhibitor					
Letrozole	141	4.06 (3.45-4.79)	1.98 (1.74-2.22)	++	397.0 (84.0-755.0)
Exemestane	23	2.35 (1.56-3.54)	1.15 (0.56-1.74)	+	230.0 (71.5-564.0)
Anastrozole	40	1.73 (1.27-2.37)	0.77 (0.32-1.22)	+	845.0 (435.0-845.0)
Cytotoxic drug					
Arsenic trioxide	10	4.89 (2.63-9.10)	1.85 (0.98-2.72)	+	58.0 (—)
Corticosteroid					
Prednisolone	118	2.61 (2.19-3.12)	1.36 (1.10-1.62)	+	328.0 (191.5-438.0)
mAb for cancer treatment					
Bevacizumab	129	1.40 (1.18-1.66)	0.48 (0.22-0.73)	+	199.5 (108.8-403.5)
Ramucirumab	11	3.21 (1.78-5.80)	1.44 (0.60-2.27)	+	380.0 (280.0-480.0)
Trastuzumab	61	1.42 (1.11-1.82)	0.49 (0.13-0.86)	+	486.0 (480.0-643.0)
Daratumumab	20	1.69 (1.09-2.62)	0.71 (0.08-1.34)	+	103.0 (13.5-191.0)
Tyrosine kinase inhibitor					
Sunitinib	118	1.87 (1.57-2.23)	0.89 (0.63-1.15)	+	190.5 (66.8-369.8)
Lenvatinib	54	2.07 (1.58-2.70)	1.02 (0.63-1.41)	+	122.0 (80.5-334.0)
Cabozantinib	74	1.45 (1.15-1.82)	0.52 (0.19-0.86)	+	151.0 (42.0-293.0)
m-TOR inhibitor					
Everolimus	134	2.37 (2.01-2.78)	1.22 (0.98-1.46)	+	142.0 (27.0-429.8)
Immunomodulator					
Lenalidomide	437	1.38 (1.25-1.51)	0.45 (0.31-0.59)	+	426.0 (171.3-734.3)
CDK 4/6 inhibitor					
Palbociclib	144	1.29 (1.10-1.52)	0.36 (0.12-0.60)	+	224.0 (70.0-578.0)
Abemaciclib	17	1.81 (1.13-2.92)	0.79 (0.11-1.47)	+	220.0 (133.0-245.0)

Abbreviations: BCPNN, Bayesian confidence propagation neural network; CDK, cyclin-dependent kinase; EIC, expected information component; IQR, interquartile range; mAb, monoclonal antibody; MMT, median medication time; m-TOR, mammalian target of rapamycin; N, number; ROR, reporting odds ratio; SI, signal intensity: weak intensity signal (+), medium intensity signal (++), and strong intensity signal (+++); "—", incomplete data.

respective results, thereby augmenting the persuasiveness of the conclusion. After statistical processing, 15 class containing 30 drugs were identified with different MRONJ signal intensity levels.

According to the results, since 2018, the number of reported MRONJ cases has been decreasing, probably because the release of consensus guidelines and position papers increased healthcare professionals' awareness on MRONJ and promoted dental screening and the institution of appropriate measures before and during the use of antiresorptive drugs and other suspected drugs in patients at risk for developing MRONJ. Therefore, pharmacovigilance analysis such as this study could be a valuable reference for clinicians, reminding them to be vigilant to MRONJ prevention when encountering patients exposed to specific medications in clinical settings.

Risk comparison of MRONJ from demographics and indications

Regarding the sex distribution of MRONJ cases, females were more than males; the number of females with MRONJ was twice as that of males, consistent with the previous studies.[2,3,10] Contributing to the high prevalence of MRONJ among females was that they have a higher incidence of osteoporosis and bone metastases from breast cancer requiring treatment with antiresorptive medications than males. Age distribution showed that more than 50% were over 60 yr old.

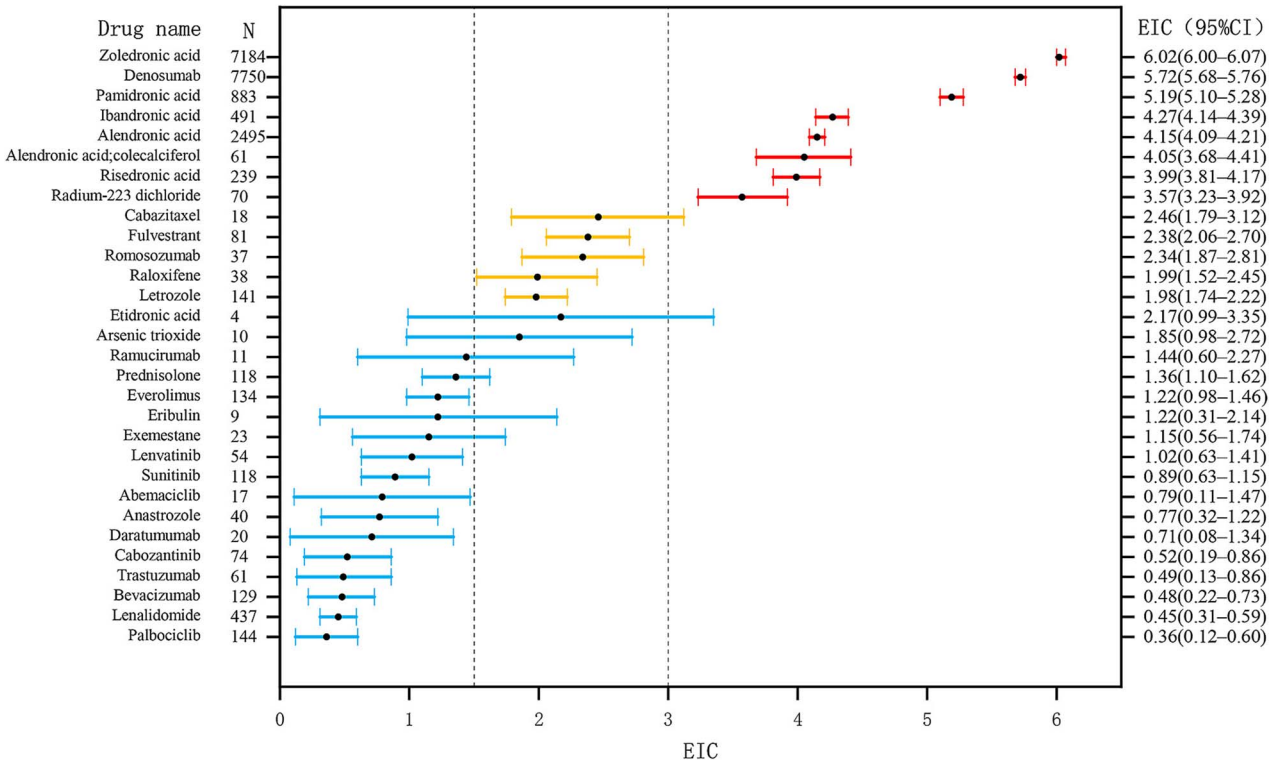


Figure 3. Expected information component (EIC) and its 95% CI for each suspect drug and their signal intensity. Note: 0 < IC-2SD ≤ 1.5 indicated a weak intensity signal (+), 1.5 < IC-2SD ≤ 3.0 indicated a medium intensity signal (++), and IC-2SD > 3.0 indicated a strong intensity signal (+++).

Table 2. Distribution of indication and the involved medications documented in FDA Adverse Event Reporting System.

Indications	Involved medications	Number	%
Not specified or unknown	All medications	5352	24.43
Treatment or prevention of osteoporotic fracture	Romosozumab, denosumab, alendronic acid: (colecalciferol), raloxifene, risedronic acid, romosozumab, pamidronic acid, ibandronic acid, zoledronic acid, etidronic acid	6074	26.59
Bone neoplasm or bone cancer metastatic	Bevacizumab, radium-223 dichloride, denosumab, lenalidomide, pamidronic acid, ibandronic acid, zoledronic acid, cabazitaxel, daratumumab	4400	19.26
Breast cancer	Abemaciclib, palbociclib, fulvestrant, bevacizumab, denosumab, letrozole, trastuzumab, ibandronic acid, zoledronic acid, anastrozole, eribulin, exemestane, everolimus	2236	9.79
Myeloma or other hematologic tumor	Bevacizumab, denosumab, pamidronic acid, ibandronic acid, zoledronic acid, arsenic trioxide	1954	8.55
Urinary system cancer	Bevacizumab, radium-223 dichloride, denosumab, cabozantinib, cabazitaxel, pamidronic acid, zoledronic acid, everolimus, sunitinib, lenvatinib	1800	7.88
Other cancer or adjuvant therapy	Bevacizumab, denosumab, zoledronic, lenvatinib acidprednisolone, zoledronic acid, everolimus, lenvatinib	444	1.94
Immune diseases or Prophylaxis	Denosumab, prednisolone, ibandronic acid, zoledronic acid, everolimus	307	1.34
Lung cancer	Bevacizumab, denosumab, ramucirumab, zoledronic acid	196	0.86
Digestive system cancer	Bevacizumab, ramucirumab	82	0.36

Generally, the prevalence of cancer and osteoporosis is higher in people over 60 yr old than in younger people.

Risk for MRONJ in a malignant setting is higher than that in osteoporosis or immune-related setting in our study, as demonstrated from the indication distribution of suspected drugs in Table 2. The number of patients with MRONJ being treated for cancer was nearly twice as many as those being treated for osteoporosis. The reason may be that patients with malignant tumors usually need larger and more frequent dosages of antiresorptive medications than those with osteoporosis. Common MRONJ-related tumors include bone neoplasm or metastatic bone cancer, breast cancer, myeloma or hematologic tumor, and prostate cancer. The appearance of chronic autoimmune disease should not be surprising, given that immune system dysfunction is one of the theories explaining MRONJ occurrence as a causative factor and that autoimmune diseases often accompany osteoporosis. In this regard, our study is consistent with previous reports.[10–13]

Bacterial, viral, or fungal infections, trauma, smoking, steroids, immunocompromised host, autoimmune diseases, and chemotherapy are linked to jaw necrosis. Thus, MRONJ

is multifactorial in nature, prone to patients with cancer particularly having used antiresorptive medications, combining other suspected drugs with similar mechanisms of action and other comorbidities; all the abovementioned contributing factors should to be considered when needed.[1,12,13]

Mechanisms of MRONJ caused by various suspected medications

Antiresorptive and radiotherapy medications

In this study, antiresorptive medications, including BPs and denosumab, were the major medications associated with ONJ and had a relatively higher ROR and EIC values, consistent with the results of previous studies.[1–3] Interestingly, radium-223 dichloride is another medication with a strong intensity signal along with antiresorptive medications. The pathophysiology of MRONJ induced by antiresorptive medications involves bone remodeling inhibition and angiogenesis inhibition. Animal studies can verify the importance of bone remodeling in the process of recovering from MRONJ by BP or denosumab withdrawal.[14,15] Antiresorptive agents can diminish the arteriole and venule network areas and disrupt the subclinical vasculature organization around experimental periodontitis in animals.[16] Additionally, zoledronic acid had an in vivo antiangiogenic property through a significant and long-lasting reduction in serum VEGF levels.[17] Regarding the pathophysiology of radium-223 dichloride related to ONJ, possibly, this drug preferentially incorporates into a newly formed bone matrix within the osteoblastic metastatic lesions, thereby inducing DNA double-strand breaks and leading to cell death including the osteoblasts and osteoclasts nearby via high-energy alpha particles, as well as inhibiting bone remodeling.[18] The 7 antiresorptive medications and radium-223 dichloride strongly correlated with ONJ in our study, with their IC-2SD > 3.0 when using the BCPNN method,[9] as demonstrated in Table 1 and Figure 3.

CDK 4/6 inhibitor, microtubule inhibitor, and cytotoxic drug

The cyclin D1: CDK 4/6 axis has a role in breast cancer by overexpressing cyclin D1 and dysregulating CDK. CDK 4/6 inhibitors can block the progression of cell cycle from G1 to S phase by inhibiting the kinase activity, thereby hindering cancer cell proliferation.[19,20] CDK4/6 inhibitors with endocrine therapy can significantly improve the progression-free survival of patients with breast cancer that is positive for hormone receptor (HR+) and negative for human epidermal growth factor receptor 2 (HER2).[21] ONJ related to CDK4/6 inhibitors have also been reported recently.[5,22] In our study, 161 ONJ cases associated with CDK4/6 inhibitors, involving palbociclib (144) and abemaciclib (17). Both drugs showed weak intensity positive signals; these drugs were marketed in 2015 and 2018, respectively. Indications of CDK4/6 inhibitors for the treatment of breast cancer accounted for 98% in our study.

In this study, 2 novel anti-microtubule drugs, namely, cabazitaxel and eribulin, were found to be associated with ONJ; the former is used for treating prostate cancer, with a medium intensity signal in BCPNN analyses, whereas the latter is often used for treating breast cancer, with a weak intensity positive signal. In this regard, our study differs from a previous study, which found that traditional microtubule inhibitors such as paclitaxel and docetaxel are related to ONJ.[3] This discrepancy may be explained by the fact that different results originated from different searching conditions during different time periods. Although ONJ has been related to arsenic trioxide in previous studies,[23,24] our study demonstrated that it is another novel cancer medication associated with ONJ, considering that it has not appeared in systematic studies.

The mechanism of ONJ associated with CDK4/6 inhibitor and microtubule inhibitor as well as cytotoxic drug may be as follows. First, they can interrupt the normal cell cycle of oral mucosal cells and impair its barrier function, which, in turn, make the mandible and maxillary more susceptible to the bacterium in multiple oral diseases, including periodontal disease and periradicular lesions. Second, their cytostatic or cytotoxic effect can increase oral mucositis and bone exposure, contributing to avascular necrosis or osteonecrosis.

mAb for cancer treatment, TKIs, immunomodulator, and m-TOR inhibitor

This study identified 4 mAbs for cancer treatment and 3 TKIs associated with ONJ with weak intensity positive signals. The mAbs bevacizumab, ramucirumab, trastuzumab, and the CD38-targeted antibody daratumumab target proteins and genes on cancer cells or cells involved in tumor growth and spread by reducing or disrupting the blood supply to the tumor, thereby reducing tumor growth.[25] Tyrosine kinases are enzymes that aid in modulating growth factor signaling and can result in increased cell growth and proliferation, promoting tumor metastasis. TKIs can inhibit tyrosine kinase activity and block the molecules that are overexpressed by tumor cells.[25] VEGF receptor is one of the acting targets of TKIs. VEGF participates in regulating osteoclast function, as well as their differentiation and survival. VEGF receptor inhibition by TKIs can inhibit bone remodeling. Bone remodeling inhibition and angiogenesis inhibition of mABs and TKIs are key mechanisms in MRONJ development.[1,25]

The signal of m-TOR inhibitor everolimus is reportedly linked to the VEGF pathway. VEGF is essential for bone healing; the main mechanism of ONJ induced by everolimus may be its antiangiogenic effect, which results in bone healing impairment.[26,27]

Daratumumab and lenalidomide are used for treating multiple myeloma and other hematopoietic malignancies. Lenalidomide, a thalidomide analog, has immunomodulatory, antiangiogenic, and antitumor effects. CD38 is highly expressed on the surface of multiple myeloma cells. Daratumumab is a humanized IgG1κ monoclonal antibody that binds to CD38 and inhibits the growth of CD38-expressing tumor cells. The addition of daratumumab to lenalidomide and dexamethasone can significantly lengthen progression-free survival among patients with relapsed or refractory multiple myeloma. The most frequent adverse reactions of daratumumab plus lenalidomide were infusion-related reactions and a higher rate of neutropenia than the control therapy.[28] Thus, innate or acquired immune dysfunction, secondary infection, and angiogenesis inhibition may be the mechanisms of ONJ associated with lenalidomide and daratumumab.

Sclerostin monoclonal antibody

Romosozumab is a new monoclonal antibody with a dual effect of increasing bone formation and decreasing bone resorption; it binds to and inhibits sclerostin, a key protein in bone remodeling. Alendronate following romosozumab treatment is thought to be better than alendronate alone in lowering risk of fracture in postmenopausal women

with osteoporosis.[29] Romosozumab had a medium intensity MRONJ signal (++) in our study. The impact on bone remodeling may be the key of proposed theory for romosozumad-related ONJ.

Selective estrogen receptor modulator, estrogen receptor antagonist, aromatase inhibitor, and corticosteroid

Raloxifene, fulvestrant, and letrozole are 3 medications that can affect hormone levels in vivo, with medium intensity MRONJ signals (++) and higher ROR in our study (Table 1 and Figure 3).

Raloxifene is a second-generation selective estrogen receptor modulator used for osteoporosis in postmenopausal women, whereas letrozole and fulvestrant are used for breast cancer by inhibiting aromatase or antagonizing estrogen receptor, respectively. The link between raloxifene and MRONJ may be its regulating bone homeostasis by negatively modulating the osteoclasts and positively affecting the osteoblast.[30]

Osteoclast and osteoblast activities, including differentiation, recruitment, and activation, can be influenced by many factors, among which the estrogen level and long-term corticosteroid therapy are the 2 major medication factors influencing osteoporosis development.[31] The causal relationship between ONJ and estrogen receptor antagonists as well as aromatase inhibitor may be explained by the notion that they can reduce estrogen level or interrupt the protective effect of estrogen on bone formation and theoretically have a negative regulatory effect on bone formation. Corticosteroids are part of the adjunctive therapy for malignancy and are commonly prescribed in rheumatoid arthritis and other immune-related diseases; its weak correlation with ONJ in our study may be because of the fact that glucocorticoids can induce osteocyte apoptosis,[32] especially in long-term cases such as patients with autoimmune disease, or cases using high doses in oncology, consistent with prior studies; hence, prior or current corticosteroid exposure is another risk factor to consider.[3,12,33]

Discovery and limitations

A total of 12 novel drugs related to ONJ were discovered in our study: romosozumab, cabazitaxel, eribulin, arsenic trioxide, raloxifene, exemestane, anastrozole, ramucirumab, trastuzumab, lenvatinib, abemaciclib, and daratumumab. Among them, romosozumab, cabazitaxel, and raloxifene showed medium intensity signals with ONJ. Although these drugs were not mentioned in previous systematic studies,[2,3] they indeed can more or less affect the bone remodeling process, lower the VEGF level or inhibit angiogenesis, block the cell cycle, lower the estrogen level, and exert directly cytotoxic effects in vivo. In our study, over 60% indications were malignant tumors. Patients with malignant tumors are often treated with combined medications with different mechanisms individually. This situation makes the specific medication that triggers MRONJ difficult to identify, and in most cases, a mixed mechanism of action is likely. The MMTs of suspect drugs were all over 1 mo; the longest MMT was more than 7 yr, indicating that MRONJ may be dose- and time-related.

This study has some limitations. First, MRONJ is likely to be related to the administration route, total dose, or utilization intensity.[34,35] Confounding factors such as tumor burden, radiotherapy, or bone metastasis progression may also increase the risk of MRONJ. However, the abovementioned specific information on primary suspected drugs in the FAERS remains incomplete. Thus, the total dose or utilization intensity of drugs cannot be calculated exactly, and detailed subgroup analysis is limited. Second, adverse events in the FAERS are voluntary, and only MRONJ cases reported to the system can be identified; thus, the true incidence rates of MRONJ cannot be estimated because of the nature of the FAERS database. Third, given that multiple drugs are often used in the same patient with malignant tumors and when the culprit drug is more than 1 and the primary suspect drug was used as the searching condition, the synergistic effect of drug combination is likely to be ignored, and interference factors cannot be ruled out.

Conclusion

Our study identified 15 drug classes including 30 drug varieties with different MRONJ intensity signals. Owing to the frequent combination of novel antitumor drugs with antiresorptive drugs and other chemotherapy drugs in patients with cancer, drugs with different mechanisms of action can lead or contribute to MRONJ deterioration. Given the continuous introduction of novel drugs and the widespread use of drugs with antiangiogenic properties and multitarget mechanisms in the field of cancer treatment, as well as the multifactorial nature of MRONJ, dentists and other related healthcare professionals must have a comprehensive understanding and correct recognition of MRONJ, taking into account the patient's disease type and stage, pharmacological effects and frequency of medication used, oral health status, and lifestyle habits. Having comprehensive information and rich experience in multidisciplinary collaboration helps them identify which patients are at risk for MRONJ in time and scientifically manage patients with this ADR.

Author contributions

Yuhao Zhong (Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing—original draft, Writing—review & editing), Wei Dai (Data curation, Methodology, Software, Visualization), Lin Yin (Data curation, Investigation, Software), Guomin Wu (Conceptualization, Methodology, Supervision, Validation, Writing—review & editing), and Xiaoying Wang (Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing—review & editing)

Yuhao Zhong and Wei Dai are co-first authors.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Data availability

The datasets analyzed for this study can be found in the Food and Drug Administration Adverse Event Reporting System with open access,

and downloaded as quarterly data (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) into the SAS 9.4 software for data cleaning and analysis. The generated data can be requested from the corresponding author.

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