Osteonecrosis of the Jaw Caused by Denosumab in Treatment-Naïve and Pre-Treatment with Zoledronic Acid Groups: A Time-to-Onset Study Using the Japanese Adverse Drug Event Report (JADER) Database

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Abstract

Background Medication-related osteonecrosis of the jaw is a serious adverse event associated with bone-modifying agents, such as injectable bisphosphonate (zoledronic acid) and the anti-receptor activator of nuclear factor-κB ligand antibody (denosumab).

Objective This study aims to evaluate and compare the time-to-onset profile for medication-related osteonecrosis of the jaw associated with denosumab between treatment-naïve (naïve group) and pre-treatment with zoledronic acid (post-zoledronic acid group) patients using the Japanese Adverse Drug Event Report database.

Methods Medication-related osteonecrosis of the jaw was defined according to the Medical Dictionary for Regulatory Activities. The medication-related osteonecrosis of the jaw onset profiles were evaluated using the Weibull shape parameter and the log-rank test.

Results The Japanese Adverse Drug Event Report database contains 632,409 reports published between April 2004 and March 2020. In the time-to-onset analysis, after extracting the combinations with complete information for the treatment start date and the medication-related osteonecrosis of the jaw onset date, 272 reports of the naïve group and 86 reports of the post-zoledronic acid group were analyzed. The median onset in the naïve and post-zoledronic acid groups was 487.0 (25–75%: 274.0–690.8) and 305.5 (25–75%: 158.3–508.5) days, respectively. Medication-related osteonecrosis of the jaw occurred earlier in the post-zoledronic acid group than in the naïve group, and the log-rank test demonstrated a significant difference in their time transitions ($p < 0.0001$).

Conclusions The results indicated a risk of medication-related osteonecrosis of the jaw in naïve and post-zoledronic acid groups and a shorter onset time in the latter than in the former. Thus, healthcare professionals should take the early risk of medication-related osteonecrosis of the jaw into account when switching patients from zoledronic acid to denosumab treatment.

Key Points

We investigated the risk of medication-related osteonecrosis of the jaw (MRONJ) associated with denosumab in the naïve group and in pre-treatment with zoledronic acid (post-ZA) group.

Our study suggests that statistically, the onset time of MRONJ associated with denosumab is earlier in the post-ZA group than in the naïve group.

Healthcare professionals should particularly be aware of the increasing risk of MRONJ by denosumab, which occurs earlier in the post-ZA group.
1 Introduction

Bone metastases are frequently caused by various types of cancers, including prostate and advanced breast cancers, and are associated with a risk of developing complications such as fractures [1–3]. Bone metastases can lead to pain, pathologic fractures, and a decreased quality of life. In patients with bone metastases and tumor-associated hypercalcemia, bone-modifying agents, such as injectable bisphosphonate (BP) [zoledronic acid (ZA)] and the anti-receptor activator of nuclear factor-κB ligand antibody (denosumab), are used to prevent and treat skeletal-related events as they reduce skeletal complications remarkably [4–6]. Zoledronic acid has a high affinity for bone hydroxyapatite and specifically inhibits osteoclastic bone resorption. The effects of ZA on bone are long lasting as it has a long half-life [7, 8], whereas the half-life of denosumab is approximately 1 month [9, 10]. Denosumab is a human immunoglobulin G2 monoclonal antibody [9] that binds to the receptor activator of the nuclear factor-κB ligand with high affinity and specifically inhibits its action, suppressing osteoclast formation [11]. Denosumab is more effective than ZA for treating skeletal complications [4–6]. However, denosumab causes jawbone necrosis, which is similar to BP-related osteonecrosis of the jaw as reported by Marx in 2003 [12]. Similarly, bone-modifying agents can cause medication-related osteonecrosis of the jaw (MRONJ), which causes severe jaw pain and swelling, and reduces the quality of life [13–15]. The increased use of bone-modifying agents has led to an escalation in the number of MRONJ cases. Therefore, information on the risk of developing MRONJ with the use of denosumab and ZA is essential for healthcare professionals to enable early detection and take necessary preventive measures.

In cases where the therapeutic effects of intravenously administered ZA are insufficient for the treatment of bone metastases, the treatment regimen is switched to the subcutaneous administration of denosumab. However, this replacement therapy might not be as effective [14] and can increase the risk of MRONJ [15–17]. This was evidenced in our previous study using retrospective data from a single institution, where denosumab use in the pre-treatment with zoledronic acid (post-ZA group) was found to significantly increase the risk of MRONJ in patients with bone metastases as compared with that by ZA [17]. The risk differences of MRONJ associated with the administration of denosumab in the treatment-naïve (naïve group) and post-ZA groups indicate that this problem has not been clinically resolved.

Spontaneous reporting systems can play an essential role in the pharmacovigilance assessments of adverse events (AEs) that are observed during short-term clinical trials [18] and have previously identified several reports in which MRONJ was caused by BP or denosumab [19–22]. Further, we have previously reported the association between BP and MRONJ and evaluated the time to onset of MRONJ induced by BP using the Japanese Adverse Drug Event Report (JADER) database, developed by the Pharmaceuticals and Medical Devices Agency (PMDA) of the Japanese regulatory authority [22]. Zhang et al. utilized the Food and Drug Administration Adverse Event Reporting System and found that the risk of MRONJ associated with denosumab and ZA for the treatment of skeletal-related events was higher than that associated with osteoporosis [21].

The incidence profile for MRONJ associated with denosumab in the naïve and post-ZA groups is unclear, and there are relatively fewer reports on how ZA affects the onset time of MRONJ caused by denosumab. The present study aims to evaluate the time-to-onset profile of MRONJ associated with denosumab, based on the presence or absence of ZA pre-treatment.

2 Materials and Methods

2.1 Data Source

Japanese Adverse Drug Event Report data from April 2004 to March 2020 are available online on the PMDA website (https://www.pmda.go.jp). The PMDA is open to the public for “information on case reports with suspected AEs” as JADER with the entity relationship diagram protects personal information. The database consists of four data tables: patient demographic information, such as sex, age, and reporting year (demo); drug information, such as generic and brand names, the purpose of administration, the dose administered, association with AEs, and the start and end dates of administration (drug); information on AEs, such as outcome and onset date (rec); and medical history (hist). Each table contains an identification number anonymized by the PMDA. We integrated a relational database based on the four tables using the identification number as the key code with the FileMaker Pro 18 Advanced software (FileMaker, Santa Clara, CA, USA). The “drug” file includes the role codes assigned to each drug: “suspected,” “concomitant,” or “interacting.” In this study, we analyzed records coded as “suspected.”

2.2 Patient Selection

In Japan, two brands of denosumab are commercially available: Ranmark® (Daichi Sankyo Co. Ltd., Chuo-ku, Tokyo, Japan), which is used to treat advanced cancer with bone metastases at a dosage of 120 mg every 4 weeks [23], and Pralia® (Daichi Sankyo Co. Ltd., Chuo-ku, Tokyo, Japan), which is used to treat osteoporosis at a dosage of 60 mg every 6 months [24]. In USA and Europe, two brands of
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Denosumab are commercially available: Xgeva® (Amgen Manufacturing Ltd., a subsidiary of Amgen Inc., Thousand Oaks, CA, USA) at a dosage of 120 mg every 4 weeks [25] and Prolia® (Amgen Manufacturing Ltd) at a dosage of 60 mg every 6 months [26]. In this study, we focused on Ranmark®. We extracted reports from the drug table where the “brand name,” “dosage,” and “purpose of administration” were “Ranmark®,” “120 mg administration dose,” and “cancer, bone metastases, bone lesion, any cancer, or plasma cell myeloma,” respectively. We defined the post-ZA group based on the following conditions: (1) the presence of both selected denosumab coded as “suspected” and ZA in the drug table; (2) start dates for the ZA and denosumab administrations are provided; (3) the start date of denosumab was later than that of ZA; (4) the onset date of MRONJ was entered; and (5) the onset date of MRONJ was later than the start date of the denosumab administration (Fig. 1). Moreover, we defined the naïve group as a situation that met the following conditions: (1) ZA was not administered before and after denosumab administration; (2) denosumab was coded as “suspected”; and (3) the onset date of MRONJ was entered (Figs. 1 and 2). We excluded reports that did not have the onset date of MRONJ and the start date of the prescription for the time-to-onset analysis.

The AEs in the JADER database were defined based on the Medical Dictionary for Regulatory Activities/Japanese (https://www.meddra.org/how-to-use/support-documentation/japanese) version 22.1. For the extraction of cases from the JADER database, the preferred term for osteonecrosis of the jaw (preferred term code: 10064658) was used.

2.3 Statistical Analysis

The medians of the data, quartiles, and the Weibull shape parameter (WSP) were used in evaluations of the time-to-onset data for MRONJ. The WSP test was used for the statistical analysis of the time-to-onset data that described the non-constant incidence rates of the AEs [22, 27, 28]. The MRONJ onset profiles of the post-ZA group were compared with those of the naïve group using median duration, quartiles, and WSPs. The duration between the date of the first administration of denosumab and the date of the onset of MRONJ was calculated (Fig. 1). The WSP-α and WSP-β determine the scale and shape of the distribution function, respectively. The hazard function for WSP increases over time if $\beta > 1$ (wear-out failure type), decreases if $\beta < 1$ (initial failure type), and remains constant if $\beta = 1$ (random failure type), where it reduces to an exponential distribution [27].

Additionally, the time-to-onset profiles for MRONJ induced by the naïve and post-ZA groups were compared using the Kaplan–Meier method with the log-rank test. The difference was considered significant at $p < 0.05$. Statistical analyses were performed using JMP 11.2 (SAS Institute Inc., Cary, NC, USA).

3 Results

The JADER database contains 632,409 reports published between April 2004 and March 2020. We identified 3732 reports of denosumab administered, out of which 797 cases were reported as MRONJ. The number of reports curated with the brand name (Ranmark®), dosage, and purpose of administration was 491 (Fig. 2). The number of reports for cancer, bone metastases, bone lesion, any cancer, and plasma cell myeloma were 0, 775, 34, 168, and 46, respectively.

In the time-to-onset analysis, after extracting the combinations that have complete information for the date of starting treatment and the date of MRONJ onset, 272 reports of the naïve group and 86 reports of the post-ZA group were analyzed. The median onset of the naïve and post-ZA groups were 487.0 (25–75%: 274.0–690.8) and 305.5 (25–75%: 158.3–508.5) days, respectively. The WSP-β values for the naïve and post-ZA groups were 1.51 (95% confidence interval 1.38–1.66) and 1.004 (95% confidence interval 0.85–1.17), respectively (Table 1).

We generated Kaplan–Meier curves for the onset time of MRONJ using data from both the groups (Fig. 3). Medication-related osteonecrosis of the jaw occurred earlier in the post-ZA group than in the naïve group, and the log-rank test demonstrated a significant difference in their time transitions ($p < 0.0001$).
Discussion

The results of this study suggest that statistically, the onset time of MRONJ associated with denosumab in the pre-treatment with ZA group is earlier than that in the treatment-naive with ZA group. Several studies have reported that the risk of MRONJ caused by ZA or denosumab increases with time [29, 30]. Medication-related osteonecrosis of the jaw was found to occur earlier in patients who switched from BPs to denosumab than in patients who remained taking BPs [31, 32]. Loyson et al. reported a slightly higher and early risk of MRONJ in patients switching from BPs to denosumab than in those taking BPs alone [31]. Our results are complementary to those of previous reports. The post-ZA group has a median onset time of MRONJ of approximately 6 months earlier than the naive group. This information

4 Discussion

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| Table 1 Time-to-onset analysis of medication-related osteonecrosis of the jaw |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | Case | Median (25–75%) (day) | Scale parameter, α (95% confidence interval) | Shape parameter, β (95% confidence interval) |
| Naïve group     | 272  | 487.0 (274.0–690.8)     | 595.2 (547.4–646.2)                  | 1.51 (1.38–1.66)       |
| Post-ZA group   | 86   | 305.5 (158.3–508.5)     | 439.0 (348.6–549.0)                  | 1.004 (0.85–1.17)      |

ZA zoledronic acid

Fig. 2 Flowchart of data analysis. JADER Japanese Adverse Drug Event Report, ZA zoledronic acid, MRONJ medication-related osteonecrosis of the jaw

△ Adis
may also provide an “early warning” that could help detect MRONJ. Based on these outcomes, we suggest that clinicians, including dentists, should be aware of the history of ZA administration in patients prior to administering denosumab.

As BPs have a long half-life and high affinity for hydroxyapatite of the bone [7], the risk of MRONJ on switching from ZA to denosumab may increase owing to the residual effects of ZA. Osteoclast inhibition in patients who switched from BPs to denosumab could be stronger when using agents from both classes sequentially, and the incidence of MRONJ may be higher in such patients. Our results indicate that the incidence of MRONJ in the naïve group increased over time, while the lower limit of the 95% confidence interval of WSP-β in the post-ZA group was 1. The incidence of MRONJ was anticipated to increase over the exposure time of denosumab or ZA [29]. Hence, we interpreted that the post-ZA group had previously been exposed to ZA, owing to accumulation in the bone, and MRONJ in the post-ZA group had an earlier onset than that in the naïve group. It might be possible that the WSP of the naïve group was >1 (wear-out failure type), whereas that of the post-ZA group was 1 (random failure type). An objection will undoubtedly be raised that it is a simple WSP comparison; however, we believe this might be an important observation in the interpretation of our results.

The results obtained from the spontaneous reporting systems should be interpreted cautiously owing to their potential limitations. Spontaneous reporting systems use insufficient information regarding patient background, under-reporting or over-reporting, confounding factors, and no control population or reference group [33].

There might be a risk of selection bias when MRONJ with a missing start date and onset data are excluded in the time-to-onset analysis. Because the rates of the missing date were different between two groups [30.6% (120/392 reports for the naïve group), 13.1% (13/99 reports for the post-ZA group)] (Fig. 2), there might be the possibility of misclassification. The use of a sensitivity analysis, including MRONJ cases with a missing date, to evaluate the effect of selection bias would be a practical approach [34, 35]. In time-to-onset studies with long observation periods, it is known that various unknown factors are more likely to influence the occurrence of the event of interest [27]. As the observation period for this study is 1 year or longer, attention should be paid to the presence of factors other than denosumab that affect MRONJ. Conducting a detailed study will continue to be of interest in the future. Furthermore, as there was no information on dental consultation, periodontal disease, denture use, alcohol, tobacco use, oral infections, or invasion, such as tooth extraction, in the JADER database, we could not evaluate these risk factors. Further studies are thus required to better elucidate these points.

5 Conclusions

Despite the limitations inherent to spontaneous reporting systems, we found that the onset time of MRONJ by denosumab was earlier in ZA pre-treatment patients than in the naïve patients. We demonstrated that the effect of ZA pre-treatment on denosumab and MRONJ cannot be ignored. Therefore, clinicians must be cautious about prescribing drugs when treating bone disorders, such as bone metastases, as a lack of critical investigation may increase the risk of MRONJ in patients.

Declarations

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Conflicts of interest/Competing interests SH is an employee of Kaneichi Pharmaceutical Co. Ltd. The other authors have no conflicts of interest to declare.

Ethics approval Ethics approval was not sought because this was an observational study without any research subjects. All results were obtained from data openly available online from the website of the PMDA (http://www.pmda.go.jp). All data from the JADER database were fully anonymized by the regulatory authority before we accessed them.

Consent to participate Our research does not fall within the purview of any of the following laws and guidelines: "Clinical Trials Act (Act No. 16 of April 14, 2017)", "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Law number: Act No. 145 of 1960, Last Version: Amendment of Act
Author contributions SH, HI, and MN contributed to the overall concept and design of the study. SH, HI, and MN wrote the main manuscript text. SH, RS, MU, and YY carried out the data extraction and statistical analysis. MT, KM, WW, and KO contributed to the data validation process. NM, TH, and KI revised the article critically for important intellectual content. All authors have reviewed the manuscript.

Availability of data and material All data generated or analyzed during this study are included in this published article and its supplementary information files.

Code availability Not applicable.

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