5-Year Retrospective Cohort Study on Medication-Related Osteonecrosis of the Jaw Following Romosozumab Treatment in Osteoporosis Patients

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ABSTRACT

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Purpose

Osteoporosis treatments are classified into bone resorption inhibitors and bone formation stimulators. Bone resorption inhibitors include bisphosphonate (BP), denosumab (Dmab), and selective estrogen receptor modulators (SERM), while bone formation stimulators include parathyroid hormone (PTH) preparations and Wnt signaling regulators such as romosozumab. Romosozumab, a sclerostin inhibitor approved in 2019, activates Wnt signaling, promoting bone formation and inhibiting resorption. It increases bone density through a dual mechanism. MRONJ has been reported with romosozumab; AAOMS added it to MRONJ-related drugs in 2022. Risk is similar to alendronate. MRONJ cases were reported in romosozumab trials. Romosozumab was approved in Korea in 2019 and covered by insurance from 2020. Coverage is limited to specific osteoporosis patients and restricted to 12 lifetime doses. Due to rising use, long-term effects and MRONJ risk require further study. The purpose of this study is to analyze cases of MRONJ occurring in osteoporosis patients receiving Evenity (romosozumab, Amgen Inc. and UCB, Thousand Oaks, CA, and Brussels, Belgium) treatment at the Endocrinology Department of Severance Hospital (In Seoul) and undergoing invasive dental treatment at the Department of Advanced General Dentistry or the Department of Oral and Maxillofacial Surgery of Yonsei University Dental Hospital (In Seoul), and to analyze the factors influencing the occurrence of MRONJ.

Body

In this study, patients who were diagnosed with osteoporosis and treated with romosozumab at the Department of Endocrinology, Severance Hospital, between June 1, 2019, and May 31, 2024, and who underwent tooth extraction and implant treatment at Yonsei University Dental Hospital were included. A total of 130 patients (273 teeth) were included in the final analysis, while 24 patients (32 teeth) were excluded due to insufficient electronic medical records (EMR).

Independent variables were categorized into demographic, medical, and dental characteristics. Demographic information included sex, age, and systemic diseases (e.g., hypertension, diabetes, cardiovascular diseases, and cancer). Medical data included osteoporosis medications such as Alendronate, Dmab, PTH, and romosozumab, both before and after dental treatment. The use of romosozumab was tracked based on the frequency, duration, and timing of administration. Dental data included detailed information on extractions or implants, the cause of extraction (caries, fracture, periodontitis), location, and reconstruction. Occurrence of MRONJ, date of diagnosis, location, history of osteoporosis medication administration, symptoms, type of treatment, and treatment outcomes were recorded.

Among 130 osteoporosis patients treated with romosozumab, MRONJ occurred in 3 patients (2.2%). In all three cases, MRONJ had occurred or was diagnosed before the initiation of romosozumab treatment, and all patients had a history of bisphosphonate or denosumab therapy. Patients with MRONJ had histories of switching from bisphosphonates to denosumab and long-term use of antiresorptive agents. All MRONJ patients underwent invasive dental procedures during or around the romosozumab treatment period. Many patients included in the study also had histories of hypertension and cardiovascular disease.

Conclusions

In this study, cases of MRONJ were analyzed in patients diagnosed with osteoporosis who were treated with romosozumab and underwent invasive dental procedures. All three MRONJ cases occurred in patients with a history of long-term use of antiresorptive agents such as BP or Dmab prior to receiving romosozumab. No cases were identified in which romosozumab alone was the direct cause of MRONJ. These findings suggest that a combination of prior treatment history and invasive dental procedures are more closely associated with MRONJ onset. These findings suggest that the onset of MRONJ is more closely associated with a history of prior antiresorptive treatment and invasive dental procedures, rather than romosozumab alone.

Therefore, the likelihood that romosozumab by itself induces MRONJ appears to be low. This highlights the importance of thoroughly evaluating patients' medication history and oral health status before initiating treatment.

In the future, long-term and prospective studies will be necessary to determine the independent effects of romosozumab on MRONJ and to identify related risk factors during dental treatment.

Key words : **Romosozumab, osteoporosis, medication-related osteonecrosis of the jaw**

1. Introduction

Osteoporosis treatments can be broadly classified into bone resorption inhibitors and bone formation stimulators. Bone resorption inhibitors include bisphosphonate (BP), denosumab (Dmab), and selective estrogen receptor modulators (SERM), while bone formation stimulators include parathyroid hormone (PTH) preparations and Wnt signaling regulators such as romosozumab.

However, cases of osteonecrosis of the jaw have been reported in relation to the use of BP, which was subsequently identified as Bisphosphonate-related osteonecrosis of the jaw (BRONJ)[1, 2]. Research continued into BP, and cases of osteonecrosis were reported with other drugs, such as Dmab and imatinib, which are vascular endothelial growth factor inhibitors[3, 4]. As a result, the American Association of Oral and Maxillofacial Surgeons (AAOMS) committee renamed the term BRONJ to medication-related osteonecrosis of the jaw (MRONJ)[5]. The definition of MRONJ is as follows: 1) History of treatment with anti-resorptive or anti-angiogenic agents; 2) Exposure of bone in the maxillofacial area or bone that can be probed through an oral or external fistula for more than 8 weeks; 3) No history of radiation therapy to the jaw or no clear metastatic disease in the jaw[5]. However, the exact cause of MRONJ has not been determined. Drug factors such as the type of medication and duration of treatment are known to influence its occurrence, while systemic factors such as old age, smoking, hypertension, corticosteroid therapy, or comorbidities like diabetes, and local factors like periodontal disease, abscesses, oral infections, tooth extraction, implant placement, and invasive dental procedures are also risk factors for MRONJ[5]. Therefore, it is necessary to evaluate and consider MRONJ in relation to the use of bone resorption inhibitors, including BP and Dmab. As more anti-resorptive and anti-angiogenic drugs are developed, the risk of MRONJ will likely increase. In 2022, AAOMS included romosozumab, a new monoclonal antibody, as a drug associated with MRONJ in addition to BP and Dmab[6].

Romosozumab is the first sclerostin inhibitor approved by the Food and Drug Administration (FDA) in 2019, used for the treatment of osteoporosis in postmenopausal women at high risk of fractures[7]. This drug inhibits sclerostin, a protein that activates the Wnt/β-catenin signaling pathway. When the Wnt pathway is activated, the differentiation and activity of osteoblasts are increased, leading to enhanced bone formation with the promotion of bone matrix protein expression[8, 9]. Simultaneously, it temporarily inhibits bone resorption, effectively increasing bone density. Sclerostin typically blocks the Wnt pathway and inhibits bone formation, but romosozumab blocks this action, restoring normal bone metabolic balance. As a result, romosozumab is considered an effective osteoporosis treatment because it promotes bone formation and inhibits bone resorption simultaneously[10]. That is, romosozumab increases bone mineral density and plays an effective role in the treatment of bone diseases such as osteoporosis through its dual mechanism of action that promotes bone formation while inhibiting bone resorption[11, 12].

However, there are precautions when using romosozumab. It has been reported that romosozumab may increase the risk of cardiovascular diseases. Therefore, it should be avoided in patients with a history of myocardial infarction or stroke within the past year, and it should be used cautiously in patients at high risk of cardiovascular disease. Additionally, romosozumab may decrease blood calcium levels. Patients with hypocalcemia should normalize their calcium levels before treatment, and adequate intake of calcium and vitamin D should be ensured during treatment. romosozumab is administered as an injection, and some patients may experience acute allergic reactions, urticaria, and angioedema after the injection. Therefore, patients should be closely monitored after the first injection of romosozumab. Like BP and Dmab, romosozumab has been reported to carry the risk of MRONJ[13, 14]. According to the AAOMS 2022 position statement, the risk of MRONJ in patients exposed to BP is estimated to be 0.03% to 0.05%, which is similar to the risk associated with Alendronate (0.5%). romosozumab is also considered to have the potential to cause MRONJ due to its dual action of promoting bone formation while inhibiting bone resorption[6]. However, since

romosozumab is a recently introduced drug, additional studies are required to estimate the relationship and risk of MRONJ. Moreover, patients receiving romosozumab should be aware of the risk of MRONJ when undergoing dental treatments. In the phase 3 osteoporosis study of romosozumab, two cases of osteonecrosis of the jaw (ONJ) were reported in osteoporosis patients treated with romosozumab[13, 14]. In one case, ONJ occurred 12 months after romosozumab treatment, and in another, ONJ occurred after tooth extraction followed by a bone marrow infection in the jaw, and subsequent administration of Dmab after 12 months of romosozumab treatment. Such case reports suggest that romosozumab may influence the occurrence of MRONJ, and the risk may increase, especially when dental procedures are involved.

Romosozumab was approved by the Korean Ministry of Food and Drug Safety on May 31, 2019, and the health insurance coverage started on December 1, 2020[15]. The coverage applies to patients who have not responded to or are unable to use existing BP agents, and "ineffective cases" refer to those who experience new fractures despite at least one year of adequate treatment. Additionally, to be eligible for health insurance coverage, the following three conditions must be met: 1) postmenopausal women aged 65 or older; 2) T-score of -2.5 SD or lower in the lumbar spine or femur; 3) at least two osteoporotic fractures have occurred[16]. Patients who meet these three conditions can receive romosozumab under the health insurance system up to 12 times with a 1-month interval between doses during their lifetime. Afterward, based on the results of bone mineral density tests, the treatment may be switched to bone resorption inhibitors (such as oral Alendronate or injectable Dmab), and additional treatment for up to 12 months may be possible[16]. The frequency of romosozumab administration is expected to increase continuously. However, since romosozumab is a new osteoporosis treatment, there is insufficient research on its long-term clinical effects and safety. Especially since MRONJ cases continue to be reported with long-term use of existing osteoporosis treatments (BP, Dmab), further research is needed on the long-term effects of romosozumab and its potential for MRONJ occurrence.

The purpose of this study is to analyze cases of MRONJ occurring in osteoporosis patients receiving romosozumab (Evenity® Inj. Pre-filled Syringe, AMGEN, Seoul, Korea) treatment at the Endocrinology Department of Severance Hospital (In Seoul) and undergoing invasive dental treatment at the Department of Advanced General Dentistry or the Department of Oral and Maxillofacial Surgery of Yonsei University Dental Hospital (In Seoul), and to analyze the factors influencing the occurrence of MRONJ.

2. Materials and Methods

2.1. Study design

This retrospective study was conducted using the Severance Clinical Research Analysis Portal (SCRAP 2.0) of Yonsei University Health System. SCRAP 2.0 is a clinical data system designed to retrieve information from EMR and the order communication system, enabling the extraction of data such as diagnoses and prescriptions.

2.2. Ethical considerations

This study protocol was approved by the Institutional Review Board (IRB) of Yonsei University Dental Hospital (approval number: 2-2024-0085). As this was a retrospective study with de-identified personal data, the requirement for written informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.3. Inclusion/exclusion criteria

A total of 130 patients were screened for this study. These patients were diagnosed with osteoporosis and treated with romosozumab at the Department of Endocrinology, Severance Hospital (In Seoul) between June 1, 2019, and May 31, 2024, and subsequently underwent invasive dental procedures at the Department of Advanced General Dentistry or the Department of Oral and Maxillofacial Surgery, Yonsei University Dental Hospital (In Seoul).

Inclusion criteria were as follows: (1) adults aged 19 years or older; (2) patients diagnosed with osteoporosis and treated with romosozumab who received dental treatment—such as tooth extraction or implant placement for teeth with poor prognosis due to caries, periodontitis, or

impaction—at either the Department of Advanced General Dentistry or the Department of Oral and Maxillofacial Surgery at Yonsei University Dental Hospital (In Seoul).

Exclusion criteria included: (1) patients with incomplete or inaccurate EMR; (2) patients who did not undergo extraction or implant-related dental treatment before or after romosozumab administration; (3) patients without a history of romosozumab administration; (4) patients who received romosozumab or invasive dental treatment at another institution, making accurate assessment difficult; and (5) patients deemed unsuitable for study participation by the researchers.

Of these, a total of 23 patients (30 teeth) were excluded due to not receiving treatment after prescription (Patients n=16), absence of electronic medical records (Patients n=6), and limited access to chart records (Patients n=1) (Figure 1).

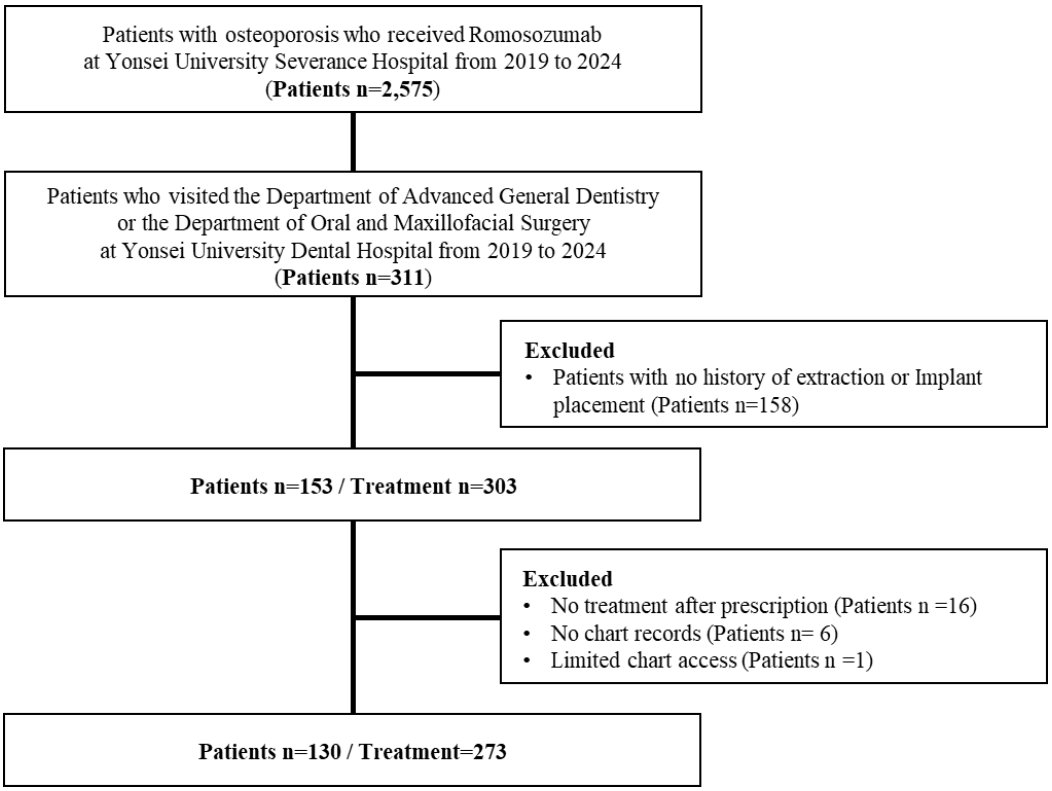

Figure 1. Study flowchart

2.4. Variables

The variables used in this study were categorized into demographic, medical, and dental characteristics.

2.4.1. Demographic information

Demographic characteristics included the patient's sex, age, and major systemic diseases. Systemic conditions were categorized as hypertension, diabetes, other cardiovascular diseases, and cancer. For patients with cancer, solid cancer and blood cancer.

2.4.2. Medication information

The medication characteristics included information on osteoporosis medications. Prior to romosozumab administration, patients had been treated with various osteoporosis drugs, including Alendronate, Risedronate, Ibandronate, Zoledronate, Pamidronate, Dmab, PTH, Raloxifene, and Bazedoxifene. After undergoing dental treatment, patients received medications such as Alendronate, Risedronate, Ibandronate, Zoledronate, Pamidronate, Dmab, PTH, Raloxifene, Bazedoxifene, and Romosozumab. Regarding romosozumab, the number of administrations and total duration of use were recorded. In addition, patients were categorized and analyzed based on the timing of romosozumab administration in relation to the invasive dental procedures.

2.4.3. Dental information

Dental characteristics included the type and detailed information of dental treatments received by the patients. The types of dental treatment were classified as either extraction or implant placement. Reasons for tooth extraction were categorized as caries, crack, fracture, periodontitis, or root rest. Additionally, data were collected on the location of extractions or

implants (maxillary anterior, maxillary posterior, mandibular anterior, and mandibular posterior), tooth number, date of extraction, date of implant placement, and whether post-extraction site reconstruction was performed (no reconstruction, denture, or implant). The evaluation of MRONJ focused on the occurrence and diagnosis date of MRONJ, and in cases where MRONJ was present, additional information was collected, including the location of the lesion, history of prior medication use, clinical symptoms, treatment methods for MRONJ, and clinical outcomes.

2.5. Statistical analysis

Descriptive statistics were used to present patient demographics, medication histories, and dental treatment characteristics. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using means and standard deviations (SD). All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic and clinical characteristics

A total of 130 patients with osteoporosis who were treated with romosozumab were included in this study. The mean age of the patients was 69.37 ± 12.42 years. Among them, 47 patients (36.4%) were younger than 65 years, while 83 patients (63.8%) were 65 years or older. The majority of the study population were female (86.9%, n = 113), and male patients accounted for 13.1% (n = 17).

Regarding past medical history (PMHx), hypertension was the most common comorbidity, observed in 60 patients (46.2%). This was followed by cardiovascular disease in 35 patients (26.9%), diabetes in 22 patients (16.9%), and cancer in 16 patients (12.3%). Among those with cancer, 14 patients (10.8%) had solid tumors, and 2 patients (1.5%) had hematologic malignancies(Table 1).

Table 1. Demographics and clinical characteristics of osteoporosis patients treated with romosozumab

Characteristics	Patient (n=130)
Age, (year; mean ± SD)	69.37 ± 12.42
< 65 years	47 (36.4)
≥ 65 years	83 (63.8)
Sex	
Female	113 (86.9)
Male	17 (13.1)
PMHx	
Hypertension	60 (46.2)
Cardiovascular disease	35 (26.9)
Diabetes	22 (16.9)
Cancer	16 (12.3)
Solid tumors	14 (10.8)
Hematologic malignancy	2 (1.5)

Values are n (%) as indicated.
[a] The PMHx has duplicate values.

3.2. History of osteoporosis medications prior to romosozumab administration

Table 2 shows the history of osteoporosis medication use prior to the administration of romosozumab. Among the 33 patients who had used BP, 14 patients (51.9%) received the medication orally, with a mean duration of 12.89 ± 9.81 months, while 13 patients (48.1%) received it intravenously, with a mean duration of 20.64 ± 25.66 months. Of these, 6 patients later received a subsequent osteoporosis medication before starting romosozumab: 5 patients (83.3%) who had initially taken oral BP and 1 patient (16.7%) who had received intravenous BP. The mean durations for the subsequent treatments were 16.2 ± 10.32 months and 23 ± 17.76 months, respectively.

Among the 35 patients who had been treated with Dmab, the vast majority (n = 33, 25.4%) received it via subcutaneous injection, with a mean treatment duration of 34.54 ± 22.91 months. Only 2 of these patients (1.5%) were administered a subsequent osteoporosis medication prior to romosozumab, with a mean duration of 27 ± 38.18 months.

All 16 patients (12.3%) who had been treated with PTH received it subcutaneously, with a mean duration of 10.93 ± 12.94 months. No subsequent osteoporosis medications were recorded for these patients prior to romosozumab initiation.

Among the 25 patients who had used SERM, 19 (14.6%) received the medication orally for a mean duration of 21 ± 22.33 months. Six of these patients (4.6%) were treated with a subsequent osteoporosis drug before starting romosozumab, with a mean duration of 5.66 ± 6.25 months(Table 2).

Table 2. History of osteoporosis medication use prior to romosozumab administration

Drug Class	Route	Initial Medication[a], n (%)	Mean Duration (months ± SD)	Subsequent Medication[b], n (%)	Mean Duration (months ± SD)
Bisphosphonate (n=33)	PO	14 (51.9)	12.89 ± 9.81	5 (83.3)	16.2 ± 10.32
	IV	13 (48.1)	20.64 ± 25.66	1 (16.7)	23 ± 17.76
Denosumab (n=35)	SC	33 (25.4)	34.54 ± 22.91	2 (1.5)	27 ± 38.18
Parathyroid hormone (n=16)	SC	16 (12.3)	10.93 ± 12.94	N/A	N/A
Selective estrogen receptor modulator (n=25)	PO	19 (14.6)	21 ± 22.33	6 (4.6)	5.66 ± 6.25

[a] Initial Medication refers to the first osteoporosis drug administered prior to romosozumab.
[b] Subsequent Medication refers to any additional osteoporosis drug administered before romosozumab initiation, following a switch from the initial medication.
Abbreviations : PO = per oral; IV = intravenous; SC = subcutaneous; SD = standard deviation.

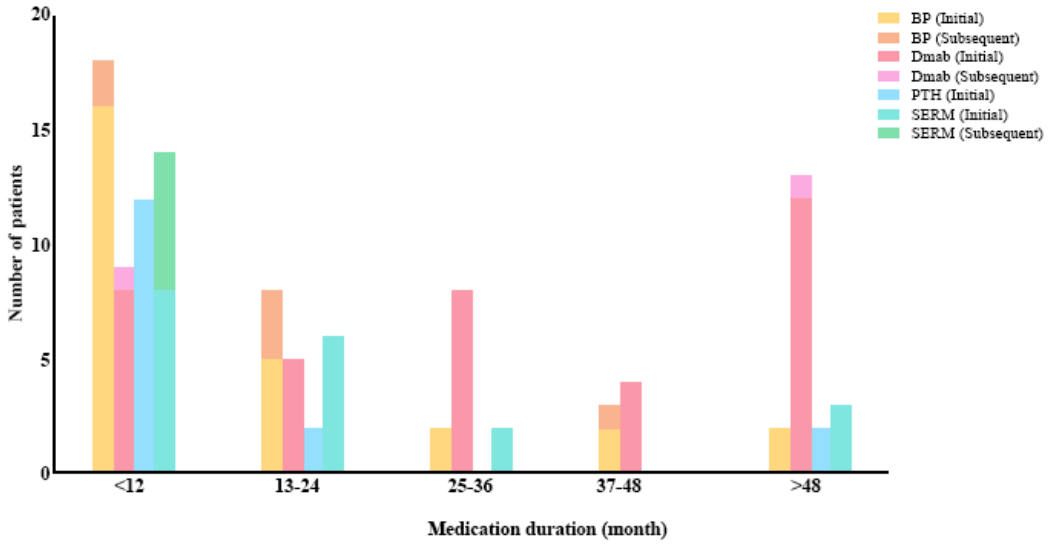

Figure 2. Duration of osteoporosis medications prior to romosozumab use

Patients are categorized by the duration of medication use (0–12, 13–24, 25–36, 37–48, and >48 months). Each bar is subdivided into initial and subsequent use.

3.3. Dental treatment characteristics

Table 3 presents the dental characteristics of osteoporosis patients treated with romosozumab, based on a total of 273 teeth. Regarding the type of dental treatment, tooth extraction alone was performed in 217 cases (79.5%), while implant placement after tooth extraction was conducted in 56 cases (20.5%).

As for the reasons for tooth extraction, dental caries was the most common cause, accounting for 113 cases (41.4%), followed by periodontitis in 69 cases (25.3%), root rest in 66 cases (24.2%), fracture in 17 cases (6.2%), crack in 5 cases (1.8%), and implant failure in 3 cases (1.1%).

In terms of extraction site, 39 teeth (14.3%) were located in the maxillary anterior region and 112 teeth (41%) in the maxillary posterior region. In the mandible, 28 teeth (10.3%) were in the anterior region and 94 teeth (34.4%) in the posterior region.

Among the teeth that were only extracted, most did not undergo reconstructive treatment (n = 194, 89.4%). Dentures were used in 22 cases (10.1%), and implant placement was performed in 1 case (0.5%).

Regarding the occurrence of MRONJ, it was absent in 267 teeth (97.8%) and present in 6 teeth (2.2%). All MRONJ cases occurred before the administration of romosozumab (100%), and no cases were reported after romosozumab initiation(Table 3).

Table 3. Dental characteristics of osteoporosis patients treated with romosozumab

Characteristics	Teeth (n=273)
Type of dental treatment	
Tooth extraction only	217 (79.5)
Implant placement after tooth extraction	56 (20.5)
Reason for extraction	
Dental caries	113 (41.4)
Periodontitis	69 (25.3)
Root rest	66 (24.2)
Fracture	17 (6.2)
Crack	5 (1.8)
Implant failure	3 (1.1)
Location	
Maxillary	
Anterior	39 (14.3)
Posterior	112 (41)
Mandible	
Anterior	28 (10.3)
Posterior	94 (34.4)
Reconstructive treatment (only extracted)	
No reconstruction treatment	194 (89.4)
Denture	22 (10.1)
Implant	1 (0.5)
Occurrence of MRONJ	
Absent	267 (97.8)
Present	6 (2.2)
Before romosozumab administration	6 (100)
After romosozumab administration	N/A

Values are n (%) as indicated.
Abbreviations : MRONJ = medication-related osteonecrosis of the jaw.

3.4. Romosozumab administration pattern.

Table 4 presents the timing and duration of romosozumab administration among 130 patients. Romosozumab was administered before dental treatment in 52 patients (40.0%) and after dental treatment in 78 patients (60.0%).

With respect to treatment duration, 27 patients (20.8%) received romosozumab for 3 months or less, 15 patients (11.5%) for 4 to 7 months, 84 patients (64.6%) for 8 to 12 months, and 4 patients (3.1%) for 13 months or longer. The mean duration of romosozumab administration was 8.62 ± 6.12 months, and the average number of administrations was 9.75 ± 4.46(Table 4).

Table 4. Timing and duration of romosozumab administration

Characteristics	Patient (n=130)
Timing of administration	
Pre-treatment	52 (40.0)
Post-treatment	78 (60.0)
Duration of administration	
≤ 3 months	27 (20.8)
4-7 months	15 (11.5)
8-12 months	84 (64.6)
≥ 13 months	4 (3.1)
Administration period (month ± SD)	8.62 ± 6.12
Number of administrations (mean ± SD)	9.75 ± 4.46

Values are n (%), mean ± SD as indicated.

3.5. Osteoporosis medications following dental treatment

Table 5 describes the status and types of osteoporosis medication use after dental treatment according to the timing of romosozumab administration in a total of 129 patients. Among patients who received romosozumab before dental treatment (n = 52), 2 patients (3.8%) were administered BP with a mean duration of 1.5 ± 2.12 months, 12 patients (23.1%) received Dmab for 3.58 ± 5.28 months, and no patients received PTH. Additionally, 7 patients (13.5%) used SERM for 10.28 ± 10.09 months, and 6 patients (11.5%) continued romosozumab for a mean duration of 4 ± 3.52 months.

For patients who started romosozumab after dental treatment (n = 78), 2 patients (2.6%) received BP immediately after dental treatment followed by romosozumab, with a mean administration period of 6 ± 8.48 months. Similarly, 16 patients (20.5%) were given Dmab immediately after dental treatment followed by romosozumab, with a mean duration of 5.25 ± 8.37 months. Additionally, 5 patients (6.4%) received PTH for 3 ± 3.93 months, and another 5 patients (6.4%) received SERM for 4.8 ± 5.01 months. Romosozumab was administered to 38 patients (48.7%) for a mean duration of 5.35 ± 4.84 months(Table 5).

Table 5. Status and types of osteoporosis medication use after dental treatment according to the timing of romosozumab administration

Medication Type	Total (n=130)	
	Administered n (%)	Mean Administration period (months ± SD)
Pre-treatment (n=52)		
BP	2 (3.8)	1.5 ± 2.12
Dmab	12 (23.1)	3.58 ± 5.28
PTH	N/A	N/A
SERM	7 (13.5)	10.28 ± 10.09
Romosozumab	6 (11.5)	4 ± 3.52
Post-treatment (n=78)		
[a] BP	2 (2.6)	6 ± 8.48
[b] Dmab	16 (20.5)	5.25 ± 8.37
PTH	5 (6.4)	3 ± 3.93
SERM	5 (6.4)	4.8 ± 5.01
Romosozumab	38 (48.7)	5.35 ± 4.84

Abbreviations : BP = bisphosphonate, Dmab = denosumab, PTH = Parathyroid Hormone , SERM = Selective Estrogen Receptor Modulators.

[a] BP ; bisphosphonate was administered immediately after dental treatment followed by romosozumab.

[b] Dmab ; Denosumab was administered immediately after dental treatment, followed by romosozumab.

3.6. MRONJ occurrence summary

Table 6 summarizes three clinical cases of MRONJ occurrence in osteoporosis patients treated with romosozumab.

MRONJ Case 1 was a 76-year-old male with osteoporosis and diabetes. His prior osteoporosis medications included BP taken orally for 1 year, followed by PTH for 4 months, and then Dmab for 1 month. He received romosozumab 3 times over 2 months after dental treatment. The MRONJ lesions were located on the right anterior mandibular teeth. The patient exhibited necrotic bone exposure and was treated with necrotic bone removal. His condition was maintained.

MRONJ Case 2 involved an 80-year-old male with osteoporosis and diabetes. His osteoporosis treatment history included BP for an unknown duration followed by Dmab for 4 years. Romosozumab was administered 7 times over 4 months after dental treatment. MRONJ affected in both the left and right posterior mandibular teeth. The patient developed osteomyelitis and was treated with tooth extraction. His condition was maintained.

MRONJ Case 3 described a 73-year-old female with osteoporosis and uterine cancer. She had taken BP orally for 2 years, followed by Dmab for 5 years. Romosozumab was administered 12 times over 11 months post-treatment. The lesion was located in the right maxillary molar area, presenting as peri-implant mucositis. Implant removal was performed, and her condition was maintained(Table 6).

Table 6. Clinical summary of MRONJ in Osteoporosis patients treated with romosozumab

Case	Age	Sex	Comorbidities	Prior osteoporosis medication	Romosozumab use	Location	Symptoms	Treatment	Outcome
1	76	Male	Osteoporosis Diabetes	BP (PO, 1 year) → PTH (4 months) → Dmab (1 month)	3 times, 2 months (Post-treatment)	#41i, #43i (Mandible, Right)	Necrotic bone exposure	Necrotic bone removal	Maintained
2	80	Male	Osteoporosis Diabetes	BP (Unknown duration) → Dmab (4 years)	7 times, 4 months (Post-treatment)	#16, #36, #46 (Mandible, Left and Right)	Osteomyelitis	Tooth extraction	Maintained
3	73	Female	Osteoporosis Uterine cancer	BP (PO, 2 years) → Dmab (5 years)	12 times, 11 months (Post-treatment)	#17 (Maxilla, Right)	Peri-implant mucositis	Implant placement	Maintained

Abbreviations : BP = bisphosphonate; Dmab = denosumab; PTH = parathyroid hormone; MRONJ = medication-related osteonecrosis of the jaw; PO = per oral.

3.7. MRONJ case descriptions

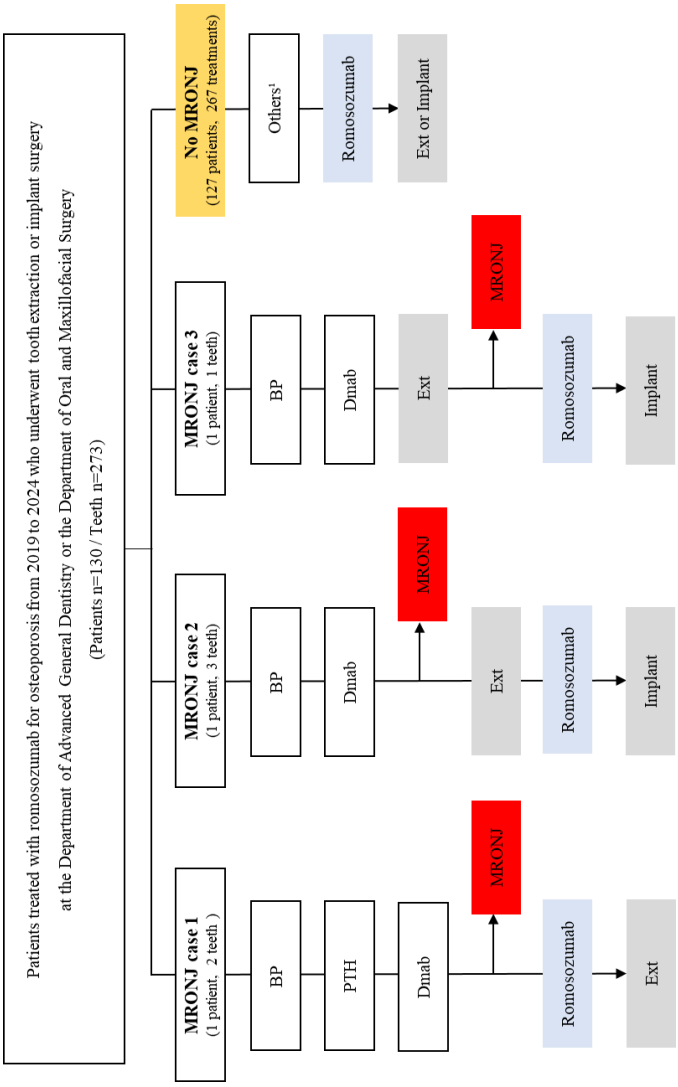

Figure 3. MRONJ occurrence flow chart

[1] refers to osteoporosis medications, including BP, Dmab, PTH, and SERM, administered prior to the initiation of romosozumab. Abbreviations : BP = bisphosphonate, Dmab = denosumab, PTH= parathyroid hormone, SERM = Selective Estrogen Receptor Modulators,
MRONJ = medication-related osteonecrosis of the jaw, Ext=extraction

3.7.1. MRONJ Case 1.

A 76-year-old male patient with a medical history of osteoporosis and diabetes mellitus had previously received osteoporosis treatment with a single dose of BP Fosamax plus D (alendronate, cholecalciferol, Merck & Co., Inc., USA) on September, 2016. He was later administered a single dose of Prolia (denosumab, Amgen Inc., USA) on February, 2023. Subsequently, he began Evenity therapy, receiving three doses between April and June, 2023.

The patient initially presented to the clinic in January 2023 with symptoms of pain and swelling in the anterior mandible. A panoramic radiograph revealed suspected lesions consistent with MRONJ at the implant sites in the right central and canine regions of the mandible. In April 2023, a consultation was requested by the prosthodontic department to the oral and maxillofacial surgery department, where MRONJ was provisionally diagnosed in the same areas. In May 2023, the neurosurgery consultation was completed, confirming no contraindications for further dental treatment. Later in May 2023, necrotic bone in the right anterior mandibular region was removed using forceps. At a follow-up visit in September 2023, the patient received local dressing at the same implant sites, and a treatment plan was established for the extraction of the right anterior and premolar maxillary teeth due to retained root fragments. Extractions were carried out in October 2023, followed by a postoperative check-up later that month. The patient's final follow-up visit was in November 2023 (Figure 4).

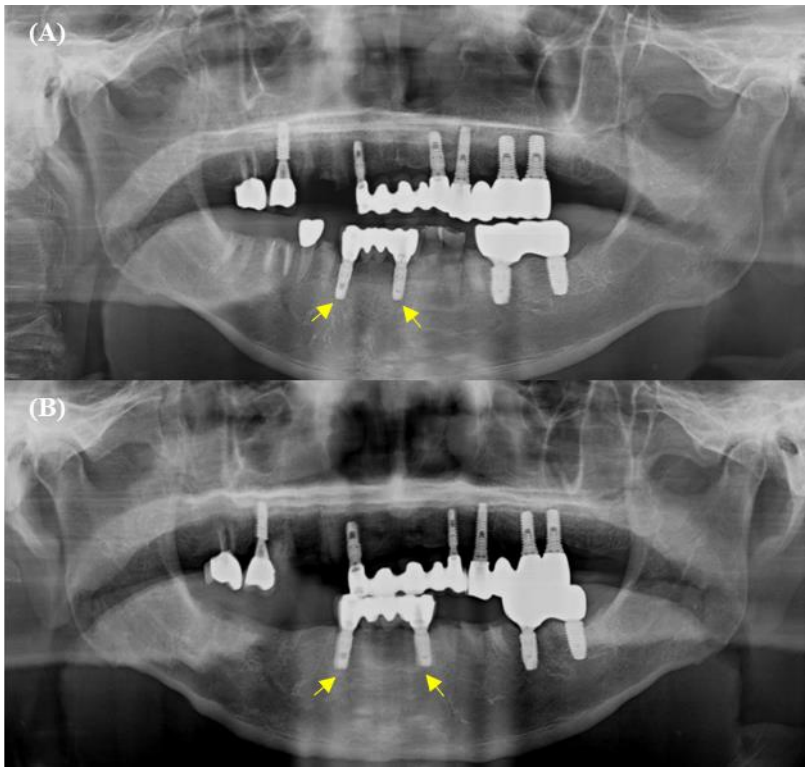

Figure 4. MRONJ case 1; (A) Panoramic radiograph taken at the initial visit, showing a MRONJ lesions around implants in the right anterior mandibular region. (B) Panoramic radiograph showing follow-up findings in the same area. Yellow arrows indicate areas of MRONJ lesions.

3.7.2. MRONJ Case 2.

An 80-year-old male patient with a history of diabetes was reported to have received BP medication beginning approximately 4–5 years ago; however, the exact date and name of the medication are unknown. From November 2016 to March 2021, he received 28 doses of Prolia at six-month intervals for the treatment of osteoporosis. Subsequently, he received a total of 7 doses of Evenity from May 2024 to September 2024.

The patient first visited the clinic in October 2021 and was diagnosed with MRONJ in the area of the left posterior mandibular teeth. He did not return for follow-up until January 2024, at which time additional MRONJ lesions were diagnosed in the right posterior maxillary region and the right posterior mandibular region. The right posterior maxillary tooth was extracted in January 2024. In March, signs of inflammation were noted in the area of the left posterior mandibular teeth, and in June 2024, the first-stage implant surgery was performed in the region of the right posterior maxilla. Following the implant surgery, bone exposure was observed in the right posterior maxillary region. The left posterior mandibular tooth was extracted in September 2024. Due to persistent inflammation, sequestrectomy of the mandible was performed in December 2024 in the region of the left posterior mandible. In January 2025, necrotic bone in the region of the left posterior mandibular teeth was removed, and the second-stage implant surgery for the right posterior maxilla was completed. The prosthetic restoration of the implant in the right posterior maxillary region was finalized in January 2025 (Figure 5).

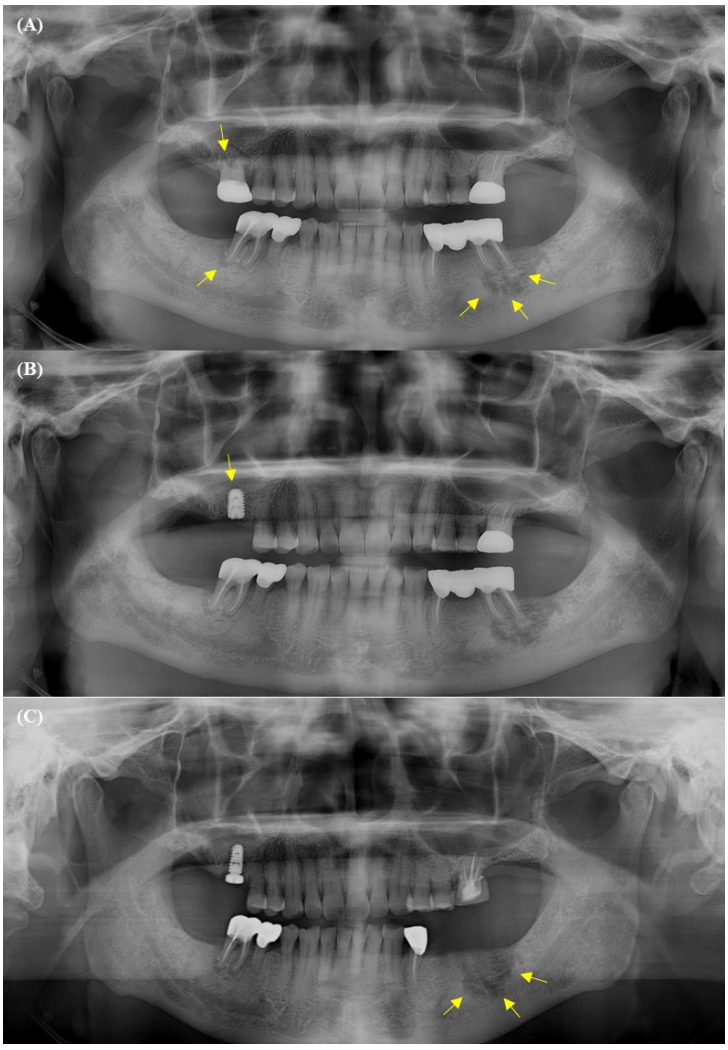

Figure 5. MRONJ case 2; (A) Panoramic radiograph taken at the initial visit, showing periodontitis in the right posterior maxillary region and MRONJ lesions in the right posterior maxilla, left posterior mandible, and right posterior mandible. (B) Panoramic radiograph following first-stage implant surgery in the right posterior maxillary region. (C) Panoramic radiograph following sequestrectomy in the left posterior mandibular region. Yellow arrows indicate areas of MRONJ lesions.

3.7.3. MRONJ Case 3.

A 73-year-old female patient with a history of osteoporosis and uterine cancer received a total of eight doses of Actonel (risedronate sodium, Sanofi, France), a BP, from February 2014 to February 2016. She was subsequently treated with Prolia a total of 12 times between August 2017 and March 2023. Treatment with Evenity began in September 2023 and continued through August 2024, with a total of 12 doses administered.

In June 2023, the patient was diagnosed with MRONJ in the right posterior maxillary region. A first-stage implant surgery was performed in October 2023. In January 2024, a second-stage implant surgery in the right posterior maxillary region was carried out along with a simple extraction of a left anterior mandibular tooth. From January to April 2024, prosthetic restoration of the implant in the right posterior maxilla was completed in the prosthodontics department. In June 2024, the patient was diagnosed with peri-implant mucositis at the right posterior maxillary implant site. A flap elevation and surgical debridement were performed. On the same day, first-stage implant surgeries were performed in the left anterior mandibular region and the left posterior maxillary region. However, in June 2024, bone dehiscence and pus discharge were observed at the implant site in the left anterior mandible, and explantation was performed. In September 2024, the patient complained of pain and extraoral swelling in the left posterior mandibular region, and recurrence of odontogenic origin was diagnosed. The left posterior mandibular tooth was extracted on the same day. Finally, in December 2024, first-stage implant surgeries were performed in the left posterior mandibular region and the left anterior mandibular region (Figure 6).

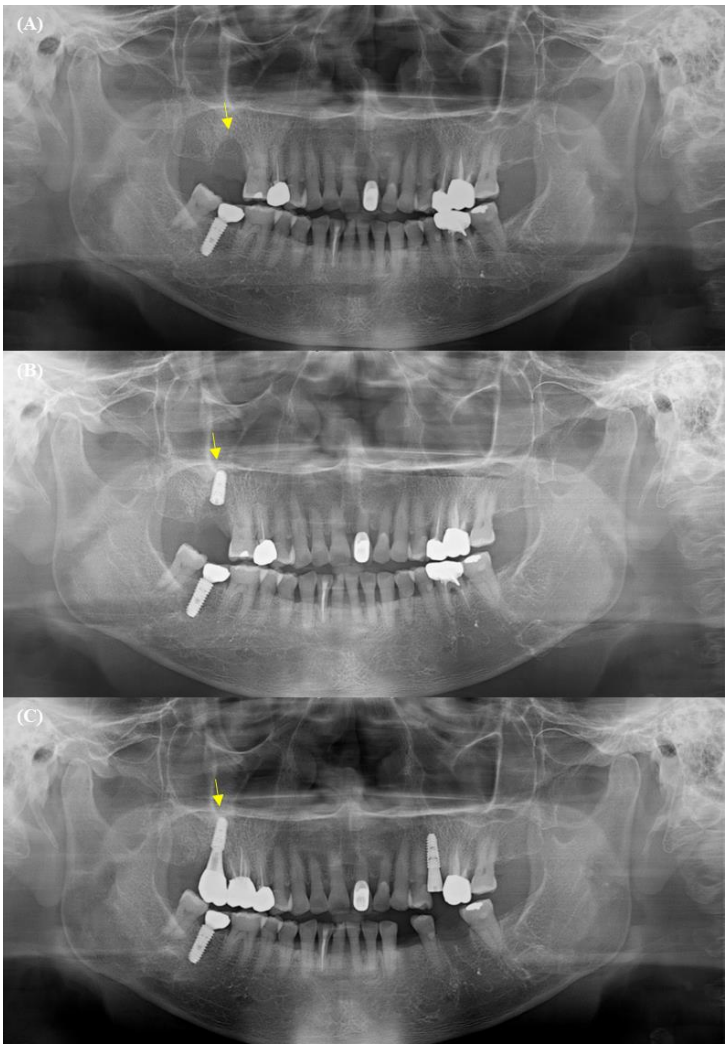

Figure 6. MRONJ case 3; (A) Panoramic radiograph taken at the initial visit, showing an MRONJ lesion in the right posterior maxillary region, (B) Panoramic radiograph following first-stage implant surgery in the right posterior maxillary region, (C) Panoramic follow-up radiograph of the right posterior maxillary region. Yellow arrows indicate areas of MRONJ lesions.

4. Discussion

This study investigated the occurrence and clinical characteristics of MRONJ in osteoporosis patients who were diagnosed and treated with romosozumab at the Department of Endocrinology of Severance Hospital, and who underwent invasive dental procedures at the Department of Advanced General Dentistry or the Department of Oral and Maxillofacial Surgery of Yonsei University Dental Hospital. In this study, MRONJ was confirmed in 3 out of 130 osteoporosis patients (2.2%) who received romosozumab treatment and underwent invasive dental procedures before or after the administration of romosozumab. However, in all three cases, the MRONJ lesions either occurred or were diagnosed before the initiation of romosozumab treatment. All three cases had a history of BP or Dmab use, suggesting that cumulative exposure to previous antiresorptive agents may have been a contributing factor. romosozumab is an osteoanabolic agent that inhibits sclerostin and activates the Wnt signaling pathway, mechanistically different from conventional antiresorptive agents. Therefore, it remains unclear whether romosozumab is independently associated with the onset or progression of MRONJ.

Several studies have reported the possibility of MRONJ occurrence during romosozumab administration[13, 14]. According to a study by Soon Hye Yang, a phase 3 randomized controlled trial evaluating the efficacy and safety of romosozumab in osteoporosis treatment reported one case of MRONJ[17, 18]. Overall, the incidence was very low (approximately 0.1–0.2%). However, in this study, the incidence of MRONJ was 2.2%, significantly higher than that reported in previous clinical trials. Several factors may account for this discrepancy. First, this study included patients with pre-existing MRONJ lesions before romosozumab administration and allowed invasive dental procedures during treatment. In contrast, clinical

trials minimized dental interventions, which could be a major reason for the higher MRONJ incidence in this study. Second, although romosozumab has a dual mechanism of action different from existing antiresorptive agents, its independent association with MRONJ has not been clearly established. However, considering its effects on bone metabolism, the possibility of MRONJ occurrence cannot be completely excluded. Everts-Graber et al. reported that the incidence of MRONJ during Dmab administration was 28.3 cases per 10,000 persons, compared to 4.5 cases per 10,000 persons for BP. Notably, patients who switched from BP to Dmab had a higher risk of MRONJ[19, 20]. Similar trends have been observed in other studies. Everts-Graber et al. (2022) reported an MRONJ incidence of 28.3 cases per 10,000 persons with Dmab use, compared to 4.5 cases with BP use. Furthermore, patients who transitioned from BP to Dmab had a higher MRONJ incidence and more complex clinical courses than those treated with BP alone[21]. Several studies have reported MRONJ incidence rates ranging from 1.3% to 5.8% in such patients, along with poor surgical outcomes. In particular, these patients required more extensive surgical interventions than those treated with BP or Dmab alone. Boquete-Castro et al. emphasized that Dmab-related MRONJ showed a more aggressive clinical course and worse prognosis than BP-related cases. All MRONJ patients in this study had a history of BP or Dmab use, highlighting the importance of cumulative antiresorptive exposure[22].

In this study, a total of three MRONJ cases were reported. Among them, two patients (Case 2 and Case 3) had cumulative antiresorptive treatment durations exceeding 4 to 7 years before romosozumab administration. These cases involved long-term Dmab administration (4–5 years) after BP treatment. This finding aligns with previous studies suggesting that prolonged use of antiresorptive agents, especially Dmab, increases the risk of MRONJ[23-25].

In Case 1, MRONJ developed after a relatively short treatment duration (approximately 1.5 years). However, this patient had a sequential history of BP, PTH, and Dmab exposure. Romosozumab was administered afterward, but MRONJ was diagnosed before the initiation of romosozumab, making it unlikely that the drug was a direct cause. This case demonstrates that MRONJ can occur even with short-term exposure to multiple osteoporosis medications. In cases involving implant surgery during romosozumab treatment (Cases 2 and 3), the causal relationship between the administration of romosozumab and the onset of MRONJ was unclear. However, it cannot be excluded that surgical procedures during treatment may have contributed to the aggravation or recurrence of MRONJ. This suggests that a more cautious approach is necessary when performing oral surgery during romosozumab treatment due to the potential risk of MRONJ.

ONJ has been reported during romosozumab treatment. Yasser El Miedany suggested that patients suspected of having or diagnosed with ONJ should be treated by dental or oral surgery specialists with expertise in the condition. He also recommended carefully considering whether to continue treatment based on the patient's condition and suggested temporary discontinuation of the drug if necessary[26]. These findings indicate that MRONJ occurrence is more closely related to previous cumulative antiresorptive therapy than to romosozumab itself and further emphasize that long-term Dmab therapy may be a significant risk factor. Therefore, when planning romosozumab treatment, it is essential to consider the patient's history of osteoporosis therapy and conduct a preemptive assessment and management of oral health.

Romosozumab has been evaluated as a useful treatment for high-risk osteoporosis patients due to its bone-forming effects. However, there is still controversy regarding its cardiovascular safety. Some clinical studies have reported a higher incidence of major cardiovascular events

in the romosozumab group. For example, there was a trend toward increased myocardial infarction and stroke in the romosozumab group compared to the placebo group, leading to recommendations for cautious use in patients with a history of cardiovascular disease. In this study, many patients had comorbidities such as hypertension and cardiovascular disease[27, 28]. These underlying conditions could affect drug responsiveness and the likelihood of adverse effects, suggesting that an integrated treatment plan considering the patient's overall health is necessary, not just osteoporosis management[29].

This study was a retrospective analysis conducted at a single institution, which may limit the generalizability of the findings. Since romosozumab was approved by the U.S. FDA in 2019 and has been reimbursable in Korea only since December 2020, long-term usage data remains limited. According to the reimbursement criteria in Korea, romosozumab can be prescribed only to postmenopausal women over the age of 65 with a T-score below -2.5 and at least two osteoporotic fractures. Therefore, patients under 65 or male patients received romosozumab as an out-of-pocket treatment. This introduced heterogeneity among study participants, which could affect the interpretation of the results. As such, it was difficult to directly compare MRONJ incidence between patients treated exclusively with romosozumab and those with prior antiresorptive therapy.

To clearly determine the association between romosozumab administration and MRONJ occurrence during invasive dental procedures, long-term prospective studies are needed. Future research should focus on how various drug histories and the duration of romosozumab use affect the risk of MRONJ. Such studies are expected to improve identification of MRONJ risk factors and contribute to establishing appropriate dental treatment plans for patients receiving romosozumab therapy.

5. Conclusion

This study analyzed cases of MRONJ that occurred in patients diagnosed with osteoporosis and treated with romosozumab who underwent invasive dental procedures. The results showed that all three cases of MRONJ occurred in patients with a history of long-term use of existing antiresorptive agents such as BP or Dmab prior to romosozumab administration. These findings suggest that cumulative exposure to prior antiresorptive agents may have a greater impact on the development of MRONJ than the effect of romosozumab alone. In particular, this study did not identify any cases where romosozumab itself was the direct cause of MRONJ. Rather, it suggests that the combined factors of previous treatment history and invasive dental procedures are more closely associated with the development of MRONJ. These results imply that the likelihood of romosozumab alone causing MRONJ is low and emphasize the importance of prior assessment of the patient's medication history and oral health condition. In the future, long-term and prospective studies will be needed to clarify the independent effect of romosozumab and its causal relationship with MRONJ, and to identify related risk factors during dental treatment.

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Abstract in Korean

골다공증 환자에서 로모소주맙 치료 후 발생한 약물 관련 악골괴사에 대한 5 년 후향적 코호트 연구

서론

골다공증 치료제는 골흡수 억제제와 골형성제로 분류된다. 골흡수 억제제에는 비스포스포네이트, 데노수맙, 선택적 에스트로겐 수용체 조절제(SERM)이 있으며, 부갑상선 호르몬 제제 (PTH)와 Wnt 신호 경로 조절제인 로모소주맙이 있다. 2019년 FDA 승인을 받은 로모소주맙은 스클레로스틴을 억제하여 Wnt 신호전달을 활성화시켜 골 형성을 촉진하고 골 흡수를 억제한다. 이중 작용 기전을 통해 뼈 밀도를 증가시킨다. 로모소주맙과 관련된 MRONJ 사례가 보고되었고, AAOMS는 2022년 로모소주맙을 MRONJ 관련 약물 목록에 추가하였다. MRONJ 발생 위험은 알렌드로네이트와 비슷하다고 보고되었다. 로모소주맙 임상 시험에서 MRONJ 사례가 보고되었으며, 로모소주맙 치료 후, 특히 치과 시술 후 MRONJ 사례가 보고되었다. 또한 로모소주맙은 2019년 한국에서 승인되어 2020년부터 보험 적용을 받기 시작하였다. 건강보험 급여 적용은 특정 골다공증 환자로 제한되며, 최대 12회 투여로 제한된다. 따라서 로모소주맙 사용 증가에 따라 장기적인 효과와 MRONJ 위험에 대한 추가 연구가 필요하다. 이 연구의 목적은 2019년 6월 1일부터 2024년 5월31일까지 세브란스병원 내분비내과에서 로모소주맙 치료를 받은 골다공증 환자들이 연세대학교 치과병원에서 침습적인 치과 치료를 받으면서 발생한 MRONJ 사례를 후향적으로 분석하는 것을 목표로 하였다.

본론

본 연구에서는 2019년 6월 1일부터 2024년 5월 31일까지 세브란스병원 내분비내과에서 골다공증 진단을 받고 로모소주맙으로 치료받았으며, 연세대학교 치과병원 통합치의학과 또는 구강악안면외과에서 발치 및 임플란트 수술을 받은 환자를 대상으로 하였다. 로모소주맙 치료를 받은 골다공증 환자 130명 중 3명(2.2%)에서 MRONJ가 발생하였다. 그러나 세 사례 모두 로모소주맙 투여 이전에 MRONJ가 발생하거나 진단되었으며, 이들 환자는 모두 비스포스포네이트 또는 데노수맙 치료 병력이 있었다. 이는 MRONJ 발생에 있어 누적된 항흡수제 노출이 주요한 위험요인임을 시사한다. 로모소주맙은 골형성 촉진 작용을 하는 약물로, 항흡수제와는 작용 기전이 다르지만 MRONJ와의 독립적인 연관성은 아직 명확하지 않다. 본 연구에서의 MRONJ 발생률(2.2%)이다. 이는 기존 MRONJ 병변이 있던 환자 포함 및 치료 중 침습적 치과 처치 허용 등 연구 설계의 차이에 기인한 것으로 보인다. 특히 비스포스포네이트에서 데노수맙으로의 전환 및 장기간의 항흡수제 사용은 MRONJ 발생률과 예후 악화에 영향을 줄 수 있는 중요한 요인으로 나타났다. 로모소주맙 치료 중 시행된 치과 수술과 MRONJ 진행 사이의 직접적인 인과관계는 명확하지 않으나, 외과적 처치가 병변 악화 또는 재발에 기여했을 가능성은 배제할 수 없다.

또한 로모소주맙은 효과적인 골다공증 치료제이나, 일부 임상 연구에서 심혈관계 부작용 가능성이 제기된 바 있다. 본 연구 대상자 중에도 고혈압 및 심혈관 질환 병력을 가진 환자가 다수 포함되어 있었으며, 이는 약물 반응성과 부작용 발생 가능성에 영향을 줄 수 있다. 연구의 설계적 한계(후향적 분석, 단일기관 연구, 대상자 이질성 등)로 인해 로모소주맙 단독 사용과 MRONJ 간의 명확한 인과성을 규명하기는 어려웠다. 향후에는 로모소주맙과 MRONJ 간의 관련성을 보다 명확히 밝히기 위한 장기적 전향적 연구가 필요하다.

결론

본 연구에서는 골다공증 진단을 받고 로모소주맙 치료를 받은 환자에서 침습적 치과 치료를 받은 환자들에서 발생한 MRONJ 증례를 분석하였다. 연구 결과, 세 건의 MRONJ 사례 모두 로모소주맙 투여 전 비스포스포네이트 또는 데노수맙 등 기존 항흡수제를 장기간 사용한 병력이 있는 환자에서 발생하였다. 이러한 결과는 로모소주맙의 단독 약물의 효과보다 기존 항흡수제 노출의 누적이 MRONJ 발생에 더 큰 영향을 미칠 수 있음을 시사한다. 특히, 본 연구에서는 로모소주맙 약물 자체가 MRONJ 발생의 직접적인 원인이 된 사례는 확인되지 않았으며, 오히려, 기존 치료 이력과 침습적 치과 치료 등의 복합적인 요인이 MRONJ 발병에 더 밀접하게 연관되어 있음을 시사한다. 이러한 결과는 로모소주맙이 단독으로 MRONJ 를 유발할 가능성은 낮다는 점을 시사하며, 환자의 약물 복용이력과 구강상태에 대한 사전 평가의 중요성을 강조한다. 향후에는 로모소주맙의 독립적인 효과와 MRONJ 간의 명확한 인과관계를 규명하고, 치과 치료 중 관련 위험 요인을 파악하기 위해서는 장기적이고 전향적인 연구가 필요하다.

핵심되는 말 : 로모소주맙, 골다공증, 약물관련악골괴사