ORIGINAL ARTICLE

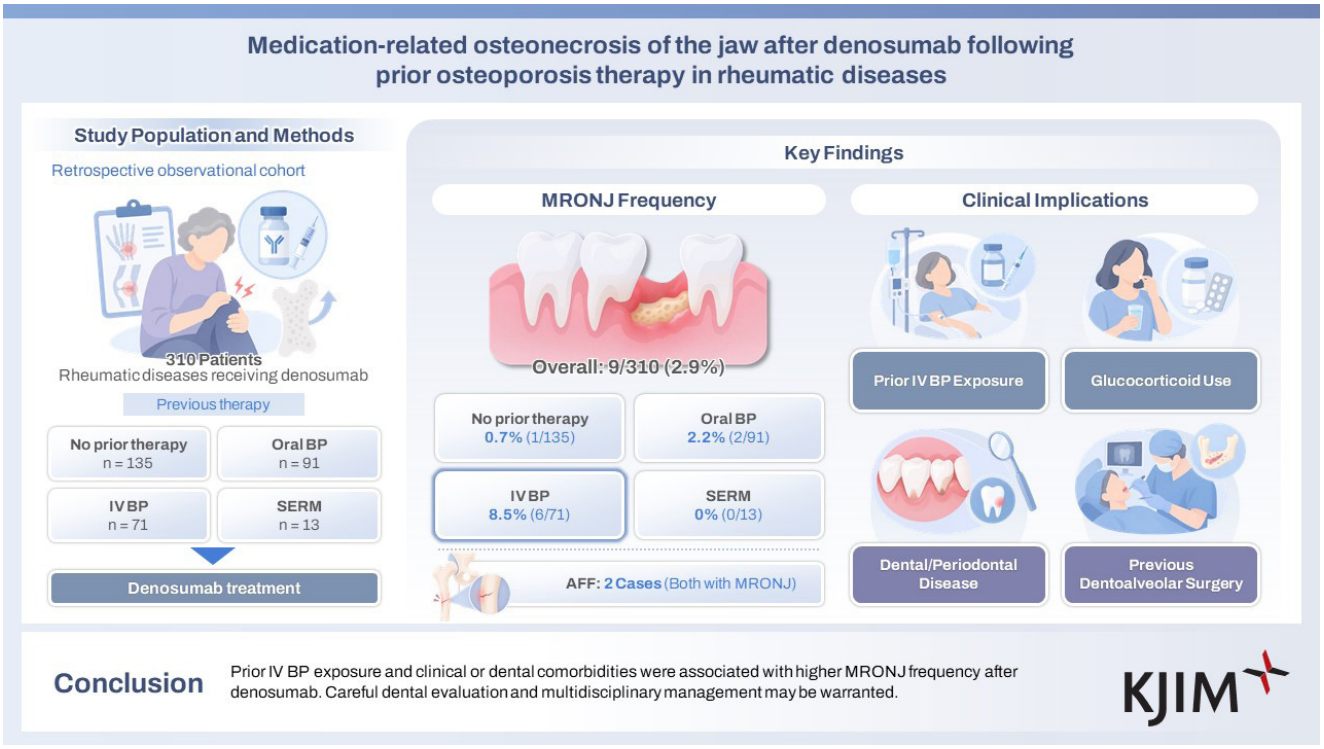
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KJIM

Medication-related osteonecrosis of the jaw after denosumab following prior osteoporosis therapy in rheumatic diseases

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Background/Aims: Patients with rheumatic diseases frequently require long-term osteoporosis treatment, and sequential antiresorptive therapy is commonly used. However, data on medication-related osteonecrosis of the jaw (MRONJ) following the transition from bisphosphonates (BPs) to denosumab remain limited.

Methods: We retrospectively reviewed 310 patients with rheumatic diseases treated with denosumab between 2015 and 2022 at a tertiary referral center. The patients were classified according to prior osteoporosis therapy as none, oral BP, intravenous BP (IV BP), or selective estrogen receptor modulators (SERMs). The incidence of MRONJ and atypical femoral fractures (AFFs) was evaluated, and the factors associated with MRONJ were explored using multivariate logistic regression analysis.

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Results: Nine patients (2.9%) developed MRONJ: 8.5% in the IV BP group, 2.2% in the oral BP group, and 0.7% in the no prior therapy group. No cases occurred in the SERM group. MRONJ occurred more frequently in patients with prior IV BP exposure, long-term glucocorticoid use, rheumatoid arthritis, polymyalgia rheumatica, and dental comorbidities. Two patients developed AFFs, both of whom had MRONJ. Due to the limited number of events, the estimates should be interpreted with caution.

Conclusions: Prior IV BP exposure and clinical or dental comorbidities were associated with a higher frequency of MRONJ after transition to denosumab in patients with rheumatic diseases. Given the retrospective design and small number of events, these findings should be considered exploratory and hypothesis-generating. Careful dental evaluation and multidisciplinary management are warranted when planning sequential osteoporosis therapies.

Keywords: Bisphosphonate-associated osteonecrosis of the jaw; Denosumab; Bisphosphonate; Rheumatoid arthritis; Osteoporosis

INTRODUCTION

Patients with rheumatic diseases are at an increased risk of both osteoporosis and medication-related osteonecrosis of the jaw (MRONJ) due to factors such as advanced age, postmenopausal status, chronic inflammation, long-term use of glucocorticoids (GCs), bisphosphonates (BPs), and disease-modifying antirheumatic drugs (DMARDs), and the unique nature of the disease [1]. Considering the need for the long-term treatment of osteoporosis, clear treatment guidelines are essential. However, data on the clinical characteristics of MRONJ and factors potentially associated with its occurrence in patients with rheumatic diseases, particularly in those receiving denosumab after prior BP therapy, are limited.

The annual incidence of MRONJ in the population with bone metabolism is approximately 10 cases per 1 million people [2]. The prevalence of MRONJ varies according to the duration and type of treatment as follows: 1–5% for intravenous BP (IV BP) therapy, 0.001–0.01% for oral BP, and 0.04% for patients with osteoporosis treated with denosumab [3,4]. No cases of MRONJ have been reported in patients using selective estrogen receptor modulators (SERMs).

MRONJ is a serious complication of antiresorptive therapy, especially after the long-term use of BPs [5,6]. Recently, denosumab, a RANKL inhibitor with a different mechanism of action, has emerged as an alternative treatment option [7]. As rheumatic diseases are lifelong conditions that require management [8], investigating the long-term safety and efficacy of osteoporosis treatment is important. Denosumab offers benefits in the field of rheumatology, including reduced drug burden and ease of dosing and administration [9]. Fracture risk and bone loss can be mitigated by denosumab in patients previously treated with BPs [10,11].

Another concern is the risk of atypical femoral fractures (AFFs). Some studies reported an increased risk of AFFs with long-term BP use [12], whereas others reported a lower risk in patients treated with BPs, denosumab, or both [13].

This study aimed to evaluate the incidence and clinical characteristics of MRONJ and AFF in patients with rheumatic diseases receiving denosumab after prior osteoporosis treatment, and to explore factors potentially associated with their occurrence. In this retrospective single-center study, we sought to provide real-world data on MRONJ and AFFs in patients with rheumatic diseases.

METHODS

Study design and participants

This retrospective observational cohort study was conducted at the Kyung Hee University Hospital (Seoul, Republic of Korea). Patients with rheumatic diseases who initiated denosumab therapy for osteoporosis between April 2015 and March 2022 were included in this study. A total of 310 patients were identified from the electronic medical records. Diagnoses included rheumatoid arthritis (RA) (n = 124), osteoarthritis (OA) (n = 100), and other connective tissue diseases (n = 86). The patients were categorized according to prior osteoporosis treatment as follows: no prior therapy (n = 135), oral BPs (n = 91), IV BPs (n = 71), or SERMs (n = 13).

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Data collection

Demographic and clinical data, including age, sex, menopausal status, body mass index (BMI), smoking history, comorbidities, GC use (including duration), disease status, prior osteoporosis therapies, and dental comorbidities, were extracted from electronic medical records. The cumulative duration of anti-resorptive therapy (combined duration of BP and denosumab use) was calculated for each patient.

Bone density and biochemical markers

Bone mineral density (BMD) was evaluated using T-scores measured in the lumbar spine and femoral neck. Bone turnover markers, including the C-terminal telopeptide of type 1 collagen (CTX) and osteocalcin, were measured at baseline and at 6-month intervals where available. These values were obtained from routine clinical tests. The assay types may have varied across the study period (April 2015 to March 2024), and not all patients had complete bone marker data. Therefore, the results were interpreted descriptively.

Diagnosis of MRONJ and AFF

MRONJ was diagnosed according to the 2022 criteria of the American Association of Oral and Maxillofacial Surgeons. Two board-certified oral and maxillofacial surgeons independently confirmed the diagnoses. Patients with findings consistent with chronic periodontitis or dental abscesses unrelated to antiresorptive therapy and those without exposed bone were excluded. The term "drug holiday" was avoided, and treatment intervals were recorded.

AFFs were identified based on the radiographic findings and clinical symptoms. The diagnosis was confirmed by musculoskeletal radiologists and orthopedic consultants.

Follow-up duration

Patients were followed up from the initiation of denosumab therapy until treatment discontinuation, development of MRONJ or AFF, loss to follow-up, death, or the study endpoint (March 2024), whichever occurred first. The average duration of denosumab therapy was 36 months (range, 12–60 months).

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki (2013 revision) and was approved by the Institutional Review Board of the Kyung Hee University Hospital (IRB No. 2024-07-055). The requirement for informed consent was waived due to the retrospective nature of the study.

Statistical analyses

Categorical variables were compared using the chi-squared or Fisher's exact tests, and continuous variables were compared using the Kruskal–Wallis and Wilcoxon rank-sum tests. Univariate and multivariate Firth's penalized logistic regression analyses were performed to explore the factors potentially associated with MRONJ and AFFs. Multivariate analyses were considered exploratory and were interpreted with caution owing to the limited number of MRONJ events. The multivariate models were adjusted for age, sex, menopausal status, smoking status, and BMI. All tests were two-sided, with statistical significance defined as p values ≤ 0.05. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study cohort

Among the 310 patients with rheumatic diseases who received denosumab, 124 had RA, 100 had OA, and 86 had other connective tissue diseases. Prior osteoporosis therapy included no prior treatment (n = 135; 43.5%), oral BPs (n = 91; 29.3%), IV BPs (n = 71; 22.9%), and SERMs (n = 13; 4.2%) (Fig. 1). The median age was 68 years (range, 36–95 years); 64.2% were aged ≥ 65 years, and 89.4% were female. The mean duration of denosumab therapy was 36 ± 12 months (range, 12–60 months). Lumbar spine T-scores differed significantly among the groups at Time 2 (p = 0.009) and Time 3 (p = 0.016), with lower values observed in the IV BP group (Table 1).

In patients who switched from IV BP to denosumab, lumbar spine T-scores showed slower improvement over the observation period than in the other groups (p = 0.0376). The oral BP group showed the largest mean improvement, although the overall between-group differences in the femoral neck T-score changes were not statistically significant (p = 0.6420).

Bone turnover marker data (CTX and osteocalcin) were available for a subset of patients. The delta CTX values did not differ significantly between the groups (p = 0.7413) but showed substantial variability. Delta osteocalcin values were

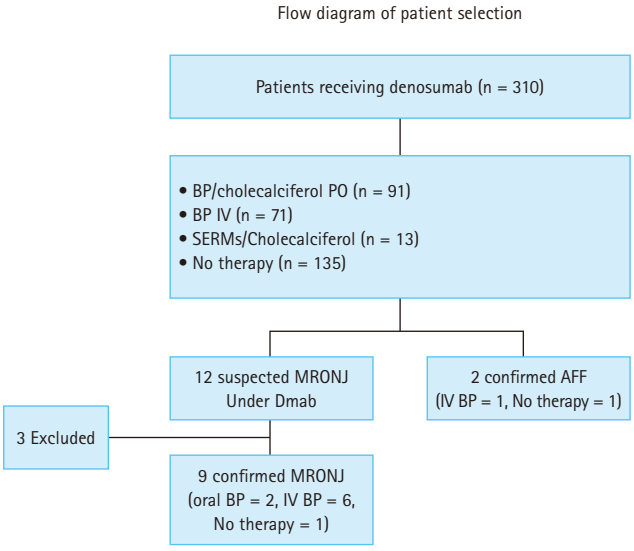


Figure 1. Study cohort and distribution of prior osteoporosis therapy before denosumab initiation. Patients were categorized into four groups: no prior therapy, oral bisphosphonates (BPs), intravenous bisphosphonates (IV BPs), and selective estrogen receptor modulators (SERMs). The numbers of patients and subsequent cases of medication-related osteonecrosis of the jaw (MRONJ) are shown. This figure is intended to illustrate the cohort distribution; MRONJ frequencies should be interpreted cautiously because of the small number of events and the retrospective study design. AFF, atypical femoral fracture.

relatively stable in the SERM group but tended to decline in the IV BP group (p = 0.0284). Owing to inconsistent availability and changes in assay methods over the 9-year period, these results should be interpreted descriptively (Fig. 2).

Description of MRONJ cases and risk of MRONJ

Nine patients (2.9%; eight females and one male) developed MRONJ during denosumab treatment. The proportion was higher in the prior IV BP group (6/71, 8.5%) than in the oral BP group (2/91, 2.2%) and the no prior therapy group (1/135, 0.7%), whereas no MRONJ cases occurred in the SERM group. All patients with MRONJ were aged ≥ 70 years. The duration of antiresorptive therapy before MRONJ onset ranged from 1 to 6 years, and the interval between BP discontinuation and denosumab initiation varied from 2 months to 6 years. Eight of the nine patients had RA, and one had polymyalgia rheumatica. Dental comorbidities, including periodontal disease, denture-related pressure, and previous dentoalveolar surgery, were common in these patients (Table 2). Most patients received conventional synthetic DMARDs, including methotrexate, combined with leflunomide or hydroxychloroquine.

Table 1. Patient characteristics by previous treatment with denosumab (n = 310)

Baseline characteristics	All patients (n = 310)	No prior treatment (n = 135)	Oral BP (n = 91)	IV BP (n = 71)	SERM (n = 13)	p value[a]
Age (yr)	68 (14)	68 (13)	70 (17)	69 (14)	70 (11)	0.339[c]
< 65	111 (35.8)	50 (37.0)	34 (37.3)	24 (33.8)	3 (23.1)	0.750
≥ 65	199 (64.2)	85 (63.0)	57 (62.6)	47 (66.2)	10 (76.9)	
Gender						
Male	33 (10.6)	26 (19.3)	7 (7.7)	0 (0)	0 (0)	< 0.001
Female	277 (89.4)	109 (80.7)	84 (92.3)	71 (100)	13 (100)	
Menopausal	271 (87.4)	106 (78.5)	83 (91.2)	69 (97.2)	13 (100)	< 0.001
Smoking history						
Never smoker	289 (93.2)	121 (89.6)	88 (96.7)	67 (94.4)	13 (100)	0.188[b]
Ex-/current smoker	21 (6.8)	14 (10.4)	3 (3.3)	4 (5.6)	0 (0)	
BMI (kg/m^2)	22.9 (4.8)	23.2 (4.7)	23.1 (4.6)	22 (5.5)	24 (2.7)	0.360[c]
< 20	63 (20.3)	25 (18.5)	18 (19.8)	20 (28.2)	0 (0)	0.098
≥ 20	247 (79.7)	110 (81.5)	73 (80.2)	51 (71.8)	13 (100)	
Duration of medication (mo)	38 (39)	.	37 (39)	38.5 (41)	.	0.361[c]
Administering vitamin D	221 (71.3)	100 (74.1)	59 (64.8)	52 (73.2)	10 (76.9)	0.441
Duration of glucocorticoids use (mo)	3 (42)	2 (22)	9 (45)	2 (47)	0 (107)	0.605[c]
Treatment with glucocorticoids	184 (59.4)	84 (62.2)	55 (60.4)	37 (52.1)	8 (61.5)	0.557
Co-morbidity factors						

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Table 1. Continued

Baseline characteristics	All patients (n = 310)	No prior treatment (n = 135)	Oral BP (n = 91)	IV BP (n = 71)	SERM (n = 13)	*p* value[a]
Hypertension	169 (54.5)	75 (55.6)	49 (53.8)	35 (49.3)	10 (76.9)	0.322
Diabetes	71 (22.9)	35 (25.9)	23 (25.3)	12 (16.9)	1 (7.7)	0.247
Liver disease	18 (5.8)	10 (7.4)	5 (5.5)	3 (4.2)	0 (0)	0.765[b]
Cardiovascular disease	21 (6.8)	9 (6.7)	3 (3.3)	8 (11.3)	1 (7.7)	0.212[b]
Cerebral infarction	9 (2.9)	7 (5.2)	2 (2.2)	0 (0)	0 (0)	0.218[b]
Chronic kidney disease	21 (6.8)	17 (12.6)	2 (2.2)	2 (2.8)	0 (0)	0.007[b]
Cancer	12 (3.9)	5 (3.7)	5 (5.5)	1 (1.4)	1 (7.7)	0.348[b]
GERD	16 (5.2)	10 (7.4)	3 (3.3)	3 (4.2)	0 (0)	0.520[b]
Disease status						
Rheumatoid arthritis	124 (40)	53 (39.3)	38 (41.8)	24 (33.8)	9 (69.2)	0.116
Psoriatic arthritis	3 (1)	1 (0.7)	1 (1.1)	1 (1.4)	0 (0)	> 0.999[b]
Osteoarthritis	100 (32.3)	34 (25.2)	29 (31.9)	34 (47.9)	3 (23.1)	0.469
Systemic lupus erythematosus	20 (6.5)	12 (8.9)	5 (5.5)	3 (4.2)	0 (0)	0.567[b]
Ankylosing spondylitis	5 (1.6)	1 (0.7)	3 (3.3)	1 (1.4)	0 (0)	0.503[b]
Behcet's disease	13 (4.2)	9 (6.7)	3 (3.3)	1 (1.4)	0 (0)	0.348[b]
Polymyositis/Dermatomyositis	9 (2.9)	6 (4.4)	3 (3.3)	0 (0)	0 (0)	0.304[b]
Systemic sclerosis	8 (2.6)	3 (2.2)	3 (3.3)	2 (2.8)	0 (0)	0.930[b]
Gout	4 (1.3)	3 (2.2)	1 (1.1)	0 (0)	0 (0)	0.643[b]
Polymyalgia rheumatica	6 (1.9)	3 (2.2)	0 (0)	3 (4.2)	0 (0)	0.218[b]
Sjogren's syndrome	10 (3.2)	5 (3.7)	2 (2.2)	2 (2.8)	1 (7.7)	0.573[b]
SAPHO syndrome	1 (0.3)	0 (0)	1 (1.1)	0 (0)	0 (0)	0.565[b]
MCTD	1 (0.3)	0 (0)	1 (1.1)	0 (0)	0 (0)	0.565[b]
ANCA associated vasculitis	6 (1.9)	5 (3.7)	1 (1.1)	0 (0)	0 (0)	0.331[b]
Lumbar spine median (T-score) (mo)						
Time1	-2.6 (1)	-2.6 (1.2)	-2.5 (0.8)	-2.7 (0.9)	-2.6 (1.4)	0.167[c]
Time2	-2.4 (1.1)	-2.3 (1)	-2.3 (0.9)	-2.8 (1)	-1.9 (1.2)	0.009[c]
Time3	-2.4 (0.9)	-2.4 (0.7)	-2 (0.9)	-2.9 (1)	-2.1 (0.5)	0.016[c]
Femoral neck median (T-score) (mo)						
Time1	-2.3 (1.1)	-2.2 (1.1)	-2.4 (1.1)	-2.5 (1.1)	-2.5 (1)	0.408[c]
Time2	-2.3 (1)	-2.1 (1.2)	-2.3 (0.9)	-2.4 (0.9)	-2.6 (0.9)	0.061[c]
Time3	-2.2 (1.2)	-1.9 (1.4)	-2.2 (1.1)	-2.4 (0.8)	-2.6 (0.7)	0.223[c]

The data are presented as number (%) of patients or median (interquartile range), unless otherwise indicated.
BP, bisphosphonate; Oral BP, oral bisphosphonates; IV BP, intravenous bisphosphonates; SERM, selective estrogen receptor modulator; BMI, body mass index; GERD, gastroesophageal reflux disease; SAPHO syndrome, synovitis-acne-pustulosis-hyperostosis-and osteomyelitis syndrome; MCTD, mixed connective tissue disease; ANCA, antineutrophil cytoplasmic antibody.
[a]Chi-square test, [b]Fisher's exact test, [c]Kruskal–Wallis test.

A reduction in CTX levels after antiresorptive treatment is generally considered a marker of treatment response. CTX levels are expected to decrease by approximately 20–60% from baseline after treatment initiation, although the degree of reduction varies according to the drug type and patient characteristics [14].

In several MRONJ cases, CTX levels increased after switching from IV BP to denosumab. However, because the bone

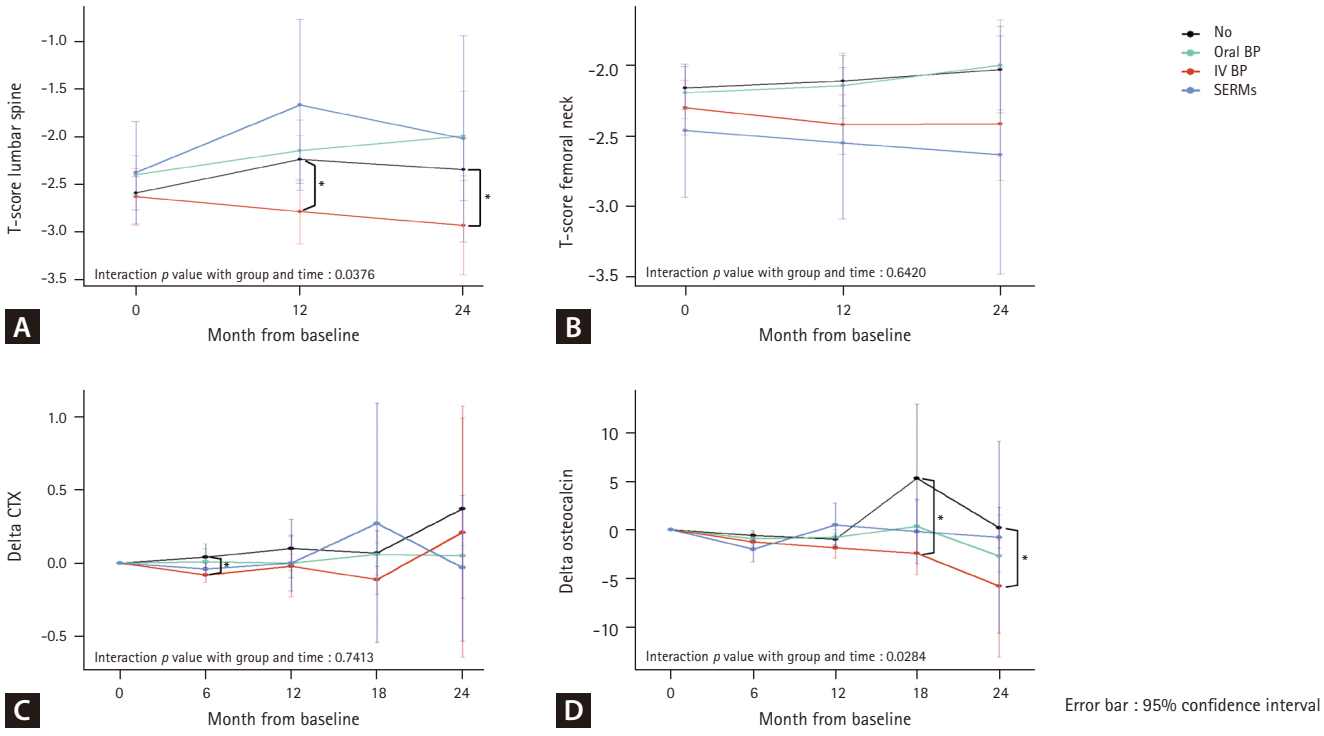


Figure 2. Changes in bone mineral density and bone turnover markers according to prior osteoporosis treatment. (A) Lumbar spine T-score, (B) femoral neck T-score, (C) delta CTX, and (D) delta osteocalcin over time after denosumab initiation. Error bars indicate 95% confidence intervals. BP, bisphosphonate; IV BP, intravenous bisphosphonate; SERM, selective estrogen receptor modulator; CTX, cross-linked C-telopeptide.

marker data were incomplete, assay methods varied over the study period, and sampling times were not standardized, these observations should be interpreted descriptively.

In univariate analysis, several variables were associated with MRONJ, including age > 65 years, longer GC use, prior IV BP therapy, preexisting dental or periodontal disease, denture pressure, implant-related disease, history of dentoalveolar surgery, and lower baseline femoral neck T-scores (Table 3). In the exploratory multivariate logistic regression analysis adjusted for demographic factors, prior IV BP therapy, GC exposure (both treatment and duration), preexisting dental or periodontal disease, and a history of dentoalveolar surgery remained associated with higher odds of MRONJ. However, because of the limited number of events, the resulting estimates showed wide confidence intervals (e.g., prior IV BP: odds ratio, 24.88; 95% confidence interval, 2.49–248.76), and these findings should be interpreted with caution and regarded as exploratory.

AFF on sequential antiresorptive treatment

Two patients in this cohort were diagnosed with AFFs. Both patients had RA, were receiving DMARDs and GCs, and each experienced unilateral AFFs. One patient was male and had received denosumab at the time of diagnosis, whereas the other had previously received IV BPs. Both patients had concurrent MRONJ (Table 4).

Patient no. 5 was diagnosed with an AFF after a relatively short duration of IV BP therapy, whereas Patient no. 9 had received no prior antiresorptive treatment before starting denosumab. Both patients met the criteria for a very high fracture risk according to the 2020 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines. This classification was based on factors such as a recent fracture within 12 months, fracture while on approved osteoporosis therapy, multiple prior fractures, long-term GC or immunosuppressant use, very low T-score (< –3.0), high fall risk, and a ≥ 20% fracture probability by FRAX scores [15].

Given the very small number of AFF events, no statistical analysis was performed, and these observations should be interpreted descriptively.

The coexistence of AFFs and MRONJ in these high-risk pa-

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Table 2. Clinical details of patients with medication-related osteonecrosis of the jaw (MRONJ) (n = 9)

Patient no.	Age	Gender	Disease status	Use of csDMARDs	Causative events	Previous therapy	Duration of glucocorticoid (yr)	Duration of BP therapy (yr)	CTX-mean percentage change from baseline	Osteocalcin levels at the time of ONJ diagnosis (5–25 ng/mL)
1	79	Female	RA	MTX, leflunomide	Periapical abscess	Oral BP	12	4	18.8% decrease	1.16
2	79	Female	RA	MTX	Dental extraction	Oral BP	8	5	22.3% decrease	2.13
3	85	Female	RA	MTX, leflunomide	Implant-related disease	IV BP	6	3	12.9% decrease	2.73
4	85	Female	RA	MTX, HCQ	Periapical abscess	IV BP	6	3	25.3% decrease	2.90
5	77	Female	RA	MTX, leflunomide	Periapical abscess	IV BP	17	2	11.3% increase	1.89
6	73	Female	PMR	-	Implant-related disease	IV BP	7	5	37.2% decrease	1.14
7	73	Female	RA	MTX, HCQ	Dental extraction	IV BP	4	1	11.1% increase	2.60
8	71	Female	RA	MTX, leflunomide	Denture irritation	IV BP	9	6	10.5% decrease	0.98
9	86	Male	RA	MTX, tacrolimus	Denture irritation	None	2	-	62.6% decrease	4.28

RA, rheumatoid arthritis; PMR, polymyalgia rheumatica; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; HCQ, hydroxychloroquine; Oral BP, oral bisphosphonates; IV BP, intravenous bisphosphonates; CTX, crosslinked C-telopeptide.

tients highlights the importance of careful clinical monitoring of patients receiving antiresorptive therapy.

DISCUSSION

This study examined the clinical characteristics of MRONJ and AFFs in patients with rheumatic diseases who received denosumab after prior osteoporosis treatment. Patients with rheumatic diseases often exhibit reduced BMD and elevated FRAX scores compared with the general population, placing them at an increased risk of osteoporotic fractures and requiring long-term antiresorptive therapy [16]. In our study, owing to the insurance coverage criteria in Korea during the study period, as well as the medication burden and physical limitations faced by patients with rheumatic diseases, IV BP was frequently considered the first-line treatment for osteoporosis. When IV BP was ineffective or the fracture risk remained high, alternative treatments such as denosumab were commonly used. Current osteoporosis guidelines support the use of denosumab, romosozumab, and parathyroid hormone (PTH)/PTHrP analogs in patients with a high or very high fracture risk, particularly when additional treatment beyond BPs is required [17,18]. However, owing to reimbursement restrictions in Korea, the use of anabolic agents is limited, and denosumab is often prescribed after prior antiresorptive therapy in patients requiring additional osteoporosis treatment.

In this cohort, the proportion of patients with MRONJ was higher in those with a history of IV BP use and long-term GC treatment. These observations are consistent with prior reports of increased MRONJ risk in patients with prior IV BP exposure [19]; however, given the retrospective nature of this study and potential confounding by indication, these associations should be interpreted with caution. Patients with a very high fracture risk, as determined by FRAX scores, and those with inflammatory diseases are more likely to develop AFFs and MRONJ when receiving antiresorptive treatment. Several epidemiological studies have reported an increased risk of subtrochanteric and femoral shaft fractures after long-term BP use [20-22]. However, in our study, AFFs occurred despite the relatively short duration of BP use, suggesting that factors other than cumulative BP exposure may have contributed to AFFs.

Several clinical characteristics, including advanced age, prior IV BP exposure, long-term GC use, inflammatory dis-

Table 3. Exploratory analysis of clinical factors associated with medication-related osteonecrosis of the jaw (MRONJ)

Risk factors	Univariate analysis		Multivariable analysis*	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (≥ 65)	1.11 (1.04–1.20)	0.004	adj.	.
Female sex	0.68 (0.11–4.12)	0.678	adj.	.
Menopausal	0.83 (0.14–4.95)	0.836	adj.	.
Smoking	2.42 (0.39–15.10)	0.343	adj.	.
BMI (≥ 20)	0.77 (0.18–3.33)	0.724	adj.	.
Duration of antiresorptive therapy (mo)	1.01 (0.95–1.08)	0.738	1.00 (0.94–1.07)	> 0.999
Treatment with glucocorticoids	13.7 (0.78–240.14)	0.073	18.15 (1.31–252.54)	0.031
Duration of glucocorticoid use (mo)	1.02 (1.01–1.02)	0.001	1.02 (1.01–1.03)	0.001
Prior osteoporosis treatment				
Oral BP	2.51 (0.32–19.47)	0.380	5.13 (0.55–47.74)	0.151
IV BP	8.90 (1.46–54.24)	0.018	24.88 (2.49–248.76)	0.006
SERM	3.32 (0.12–94.19)	0.482	4.08 (0.10–171.76)	0.461
Dental comorbidities				
Pre-existing dental or periodontal disease	61.10 (3.05–∞)	0.007	4.64 (2.01–70.34)	< 0.001
Denture pressure	367.86 (13.57–∞)	< 0.001	.	.
Implant-related disease	858.48 (22.72–∞)	< 0.001	.	.
Dentoalveolar surgery	111.96 (4.94–∞)	0.003	18.27 (1.52–110.86)	< 0.001
T-score lumbar spine				
Baseline lumbar spine T-score	0.88 (0.44–1.74)	0.707	0.89 (0.47–1.67)	0.711
T-score femoral neck				
Baseline femoral neck T-score	0.37 (0.16–0.85)	0.019	0.48 (0.20–1.16)	0.103

The data are presented as number (%) of patients or median (interquartile range), unless otherwise indicated.
Exploratory multivariable Firth's penalized logistic regression adjusted for age, sex, menopausal status, smoking status, and body mass index.
BP, bisphosphonate; Oral BP, oral bisphosphonates; IV BP, intravenous bisphosphonates; SERM, selective estrogen receptor modulator; OR, odds ratio; CI, confidence interval.
*Exploratory multivariable Firth's penalized logistic regression adjusted for age, sex, menopausal status, smoking status, and body mass index.

eases, preexisting dental conditions, and previous dentoalveolar surgery, were more frequently observed in patients with MRONJ in this cohort. Exploratory regression analysis suggested a possible association between prior IV BP therapy and MRONJ occurrence. However, these findings should be interpreted cautiously because of the limited number of events and retrospective design. Prolonged skeletal retention of BPs and their incorporation into mineralized bone may contribute to the persistent susceptibility to MRONJ, even after switching to denosumab [23-28]. Among patients who received denosumab after prior IV BP therapy, the higher frequency of MRONJ may reflect greater cumulative antiresorptive exposure resulting from sustained treatment adherence before switching therapy. Slower improvement in the lumbar spine T-score in the IV BP-to-denosumab group may also be related to the effects of residual BPs on bone remodeling. The CTX level, a marker of bone resorption, is generally expected to decrease by 20–60% from baseline after the initiation of antiresorptive therapy [14], although the extent varies depending on the drug type and patient condition. In some MRONJ cases, the CTX levels increased after switching from IV BP to denosumab. Fluctuating CTX levels in this group may reflect delayed or variable treatment responses; however, the interpretation is limited by incomplete bone marker data, assay variability, and non-standardized sampling. Long-term GC exposure was more frequent-

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Table 4. Clinical details of RA patients with ONJ and AFF (n = 2)

Patient no.	Age	Gender	Comorbidity	Use of steroid	Use of DMARDs	Previous therapy	Duration from anti-osteoporosis treatment administration to occurance of AFF (yr)	Duration of glucocorticoid use (yr)	Initial BMD L1-4	FRAX probability	Recent fracture (within 12 mo)
5	77	Female	HTN	Yes	MTX, leflunomide	IV BP	1.8	16.8	-3.3	50%	Vertebral compression fx
9	86	Male	HTN, cardiovascular disease	Yes	MTX, tacrolimus	-	-	2.1	-3.5	28%	Multiple right rib 6-8 Fx, Compression fracture, L2 and L3

RA, rheumatoid arthritis; ONJ, osteonecrosis of the jaw; DMARDs, disease-modifying antirheumatic drugs; AFF, atypical femoral fracture; BMD, bone mineral density; FRAX, fracture risk assessment tool; HTN, hypertension; MTX, methotrexate; IV BP, intravenous bisphosphonates.

ly observed among patients with MRONJ. GCs can impair bone regeneration and healing, and their immunosuppressive effects may delay recovery from oral infections. Most MRONJ cases occurred in patients with RA, and inflammatory diseases, together with long-term GC exposure, may contribute to impaired bone remodeling and wound healing. However, disease-specific subgroup analyses were not performed because the limited number of events precluded meaningful statistical inferences. Therefore, these findings should be considered exploratory and interpreted with caution. Inflammatory diseases influence bone turnover, and long-term GC use may amplify this effect, which is consistent with previous findings that DMARD use increases the risk of osteoporosis and fractures [29]. Oral health-related factors, including preexisting dental and periodontal disease, alveolar bone surgery, and denture pressure, were also more frequently observed among patients with MRONJ, supporting previous reports emphasizing the importance of dental health in MRONJ prevention [30-32]. Preventive dental care and regular follow-ups before and during BP therapy are important strategies to reduce the risk of MRONJ.

In summary, our findings suggest that prior IV BP exposure, GC use, inflammatory diseases, and poor oral health are associated with the occurrence of MRONJ in patients with rheumatic diseases receiving denosumab after prior osteoporosis treatment. However, because of the retrospective design, heterogeneous study population, limited number of MRONJ events, and lack of a non-denosumab control group, these findings should be considered exploratory and hypothesis-generating rather than confirmatory. Most MRONJ cases occurred in patients with RA; however, disease-specific subgroup analyses were not performed because the small number of events precluded meaningful statistical inference. Larger prospective studies are warranted to further characterize the clinical features of MRONJ and AFFs and to clarify the potential factors associated with these complications in patients with rheumatic diseases.

This retrospective study suggests that prior IV BP exposure, long-term GC use, inflammatory diseases, advanced age, and poor oral health may be associated with the occurrence of MRONJ in patients with rheumatic diseases receiving denosumab after prior osteoporosis treatment. Although AFFs are rare, their coexistence with MRONJ in two patients highlights the importance of careful clinical monitoring.

Given the limited number of MRONJ and AFF cases, the heterogeneous study population, and the retrospective sin-

gle-center design, these findings should be interpreted with caution and regarded as exploratory and hypothesis-generating rather than confirmatory. Nonetheless, our findings emphasize the importance of comprehensive dental evaluation and multidisciplinary care in patients receiving long-term antiresorptive therapy. Larger prospective studies are warranted to further characterize the clinical features and potential factors associated with MRONJ and AFF in this high-risk population.

KEY MESSAGE

1. Medication-related osteonecrosis of the jaw (MRONJ) occurred in 2.9% of patients with rheumatic diseases receiving denosumab, with a higher frequency in those previously treated with intravenous bisphosphonates.
2. Prior intravenous bisphosphonate exposure, glucocorticoid use, and dental comorbidities were associated with higher odds of MRONJ, although these findings should be interpreted cautiously because of the small number of events.
3. Careful dental evaluation and multidisciplinary monitoring are warranted when sequential antiresorptive therapy is planned in patients with rheumatic diseases.

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