ORIGINAL ARTICLE

Prevalence of Medication-Related Osteonecrosis of the Jaw in Osteoporotic Patients Treated with Antiresorptive Drugs at Pranangklao Tertiary Care Hospital in Nonthaburi Province, Thailand

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Background: Medication-related osteonecrosis of the jaw (MRONJ) could disturb the quality of life of the patients. In Thailand, published data reporting the prevalence of MRONJ is scarce.

Objective: To analyze the current situation regarding the occurrence of osteonecrosis of the jaw in osteoporotic patients taking antiresorptive drugs at Pranangklao Hospital in Nonthaburi Province, Thailand.

Materials and Methods: Data regarding osteoporotic patients received antiresorptive drugs were collected retrospectively from the electronic medical records between January 2014 and June 2020. Data were analyzed using descriptive statistics.

Results: The hospital database revealed that there were 1,188 patients that received antiresorptive drugs during the specified period. One thousand twenty-nine (86.62%) were prescribed with only one antiresorptive drug. Alendronate was the main drug among the four medications prescribed, which was used by 592 patients (49.83%). Mean antiresorptive drug exposure time was 1.52 years (SD 1.54) and median was 0.85 years. Among 49 patients who had tooth extraction after receiving oral bisphosphonate, two MRONJ cases were reported. Therefore, the prevalence of MRONJ among the 1,188 patients receiving antiresorptive drugs in the present study was 0.17%, and the prevalence of MRONJ among the 677 obtaining oral bisphosphonates was 0.295%. About 89% had comorbid diseases. The most common comorbid diseases were hypertension, followed by dyslipidemia, and diabetes mellitus. Furthermore, 17% had a history of corticosteroid drug administration.

Conclusion: MRONJ cases were found in osteoporotic patients receiving oral bisphosphonates. The prevalence of MRONJ and contributing factors gave information essential for managing this unwanted condition.

Keywords: Medication related osteonecrosis of the jaw; Prevalence; Osteoporosis; Comorbidity; Corticosteroid

Received 12 September 2022 | Revised 20 February 2023 | Accepted 24 March 2023

J Med Assoc Thai 2023;106(4):341-8

Website: http://www.jmatonline.com

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse effect, which involves the progressive destruction of the bone in the mandible or maxilla. The main factor of this adverse effect is the medications that are used for the treatment of osteoporosis and cancer metastasis to the bone. The drugs include bisphosphonates and RANK-L inhibitors[1]. The first time this unwanted condition was reported was in 2003[2]. The medical term of MRONJ was first used in the special committee appointed by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014[3].

MRONJ is associated with significant morbidity and adversely affects quality of life[4-6]. Treatment of MRONJ is challenging. An effective and appropriate therapy that improves the outcome remains to be identified. The median time to resolve osteonecrotic symptoms may be up to 12 months and depends on the specific therapeutic intervention[7]. There

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How to cite this article:

Settavanit C, Kettratad-Pruksapong M, Raksamani N, Patntirapong S. Prevalence of Medication-Related Osteonecrosis of the Jaw in Osteoporotic Patients Treated with Antiresorptive Drugs at Pranangklao Tertiary Care Hospital in Nonthaburi Province, Thailand. J Med Assoc Thai 2023;106:341-8.

DOI: 10.35755/jmedassocthai.2023.04.13832

are no universally accepted treatment protocols for MRONJ. In the absence of a defined treatment algorithm for MRONJ, there is a generally accepted approach for curative therapy, controlling associated infection, palliation of symptoms, and quality of life improvement. Treatment strategies range from conservative non-operative therapies to early surgical intervention. The extent of surgery also varies and depends upon the stages of disease[8].

Although incidence of MRONJ regarding antiresorptive drugs is low, management of MRONJ is generally difficult and these drugs were prescribed more widely. Occasionally, the medical comorbidities could contribute to the development of MRONJ[9-11]. Recent study from Japan reports that the prevalence of MRONJ in osteoporotic patients receiving antiresorptive drug is 0.06%[12]. However, data regarding MRONJ and the risk factors in Thailand has not been reported. Therefore, the authors aimed to explore the prevalence of MRONJ and detail the information of the possible factors as the present study baseline and situation analysis. The present study is the first report in Thailand and the data are intended to improve how the hospital should prevent and manage this adverse effect.

Materials and Methods

Study design and participants

The present study was a retrospective and descriptive study. The study was approved by the Ethics Committee of Thammasat University and Pranangklao Hospital (COA No. 049/2563 and EC 18/2563), and according to the declaration of Helsinki, the Belmont report, CIOMS guidelines and ICH-GCP. The register-based data were collected from Pranangklao Hospital in Nonthaburi Province. The census method was employed to analyze the electronic medical record of 1,224 osteoporotic patients who received antiresorptive drugs at Pranangklao Hospital between January 2014 and June 2020, a six years and six months period.

The inclusion criteria were electronic medical records of the patients aged equal to or over 60 years since the prevalence of osteoporosis in the age group 60 to 64 in Thai women was as high as 39.4% and increases by age. Furthermore, the antiresorptive drug was the drug of choice to treat osteoporosis in these patients[13,14]. The data of patients who passed away between January 2014 and June 2020 or patients who moved to other hospitals were also included. Thirty-five patients aged less than 60 years old and one patient who received bisphosphonate for treatment of cancer were excluded. Therefore, records of 1,188 were analyzed (Figure 1).

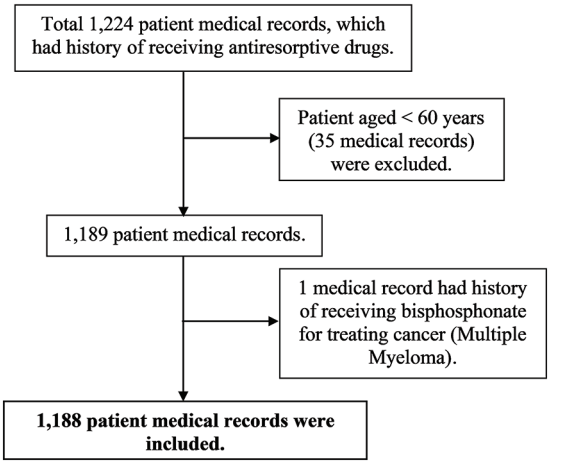

Figure 1. Diagram of register-based population.

Data extraction

All available data were extracted by one researcher. The data included age, gender, type of drug prescribed, method of drug prescribed, duration of drug used, dose of drug used, steroid used, comorbidities, and dental treatment. MRONJ was also recorded. MRONJ is defined by the AAOMS criteria in 2022[1] and consisted of three characteristics, 1) current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications, 2) exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for longer than eight weeks, and 3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

Statistical analysis

Descriptive statistics were used to analyze data including frequency, distribution, median, mean ± standard deviation (SD). Data were analyzed by a single researcher using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

General information of the extracted data

One thousand two hundred twenty-four patients were prescribed with antiresorptive drugs. Following criteria of the present study, 35 patients were excluded due to age and one patient used antiresorptive drug for treating a multiple myeloma cancer. Therefore, 1,188 medical records were included and analyzed

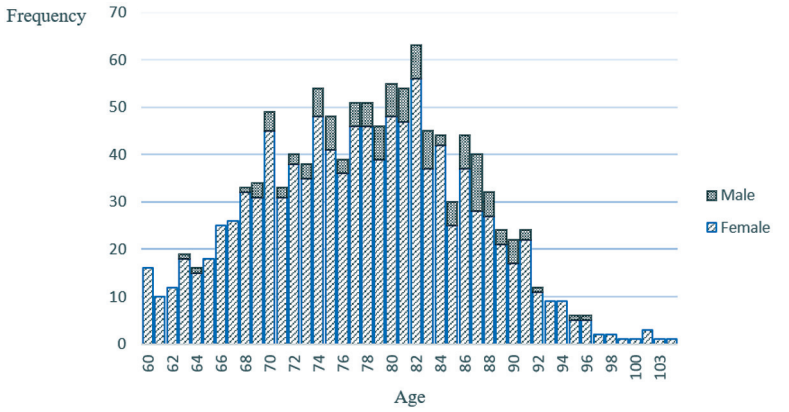

Figure 2. Histogram of aged population.

Table 1. Type and duration of antiresorptive drug

Type	Brand name	Prescription	Route	n (%)	Number of patients categorized by duration (year)						
					<1	1 to 2	2 to 3	3 to 4	4 to 5	5 to 6	6 to 7
1 drug											
Alendronate	Fosamax®/Sandoz®	70 mg/week	Oral	592 (49.83)	385	92	47	39	19	5	5
RANK-L inhibitors	Prolia®	60 mg/mL/6 months	SC	230 (19.36)	142	43	28	8	4	5	0
Ibandronate	Ostex®	3 mg/3 mL/3 months	IV	122 (10.27)	56	17	13	14	14	8	0
Risedronate	Actonel®	35 mg/week	Oral	85 (7.16)	59	11	6	3	5	1	0
Switch 2 drugs											
Alendronate, RANK-L inhibitors				60 (5.05)	4	16	13	11	10	6	0
Risedronate, RANK-L inhibitors				24 (2.02)	1	1	6	7	5	4	0
Ibandronate, RANK-L inhibitors				23 (1.94)	5	5	6	4	2	1	0
Risedronate, Alendronate				20 (1.69)	0	4	3	5	3	5	0
Alendronate, Ibandronate				13 (1.09)	3	1	1	2	2	4	0
Switch 3 drugs											
Risedronate, Alendronate, RANK-L inhibitors				13 (1.09)	0	0	0	4	2	7	0
Alendronate, Ibandronate, RANK-L inhibitors				5 (0.42)	0	0	2	0	1	2	0
Switch 4 drugs											
Risedronate, Alendronate, Ibandronate, RANK-L inhibitors				1 (0.08)	0	0	0	0	1	0	0

SC=subcutaneous; IV=intravenous

(Figure 1). The mean age was 77.9±8.42 for the group with 77.6±8.53 for 1,065 female patients and 80.8±6.60 for the 123 male patients. The distribution of patient age is shown in Figure 2.

Type and duration of antiresorptive drugs

Two types of antiresorptive drug were used, bisphosphonates and RANK-L inhibitors. Bisphosphonates prescribed by orthopedists included Alendronate, Risedronate, and Ibandronate. Detailed information of these drugs is shown in Table 1. Out of 1,188 patients, 1,029 (86.62%) were prescribed with only one drug. The most prescription drug was Alendronate, followed by RANK-L inhibitors, Ibandronate, and Risedronate, respectively. About 13.4% of the patients were discontinued from the original prescription and switched to other antiresorptive drugs (Table 1).

Overall, the mean duration of antiresorptive drug exposure was 1.52±1.54 years (median of 0.85 year). In the group that was prescribed with only one drug, the mean duration of bisphosphonate exposure was 1.26±1.41 years (median of 0.56 year), while the mean duration of RANK-L inhibitors was 1.25±1.1 years (median of 0.72 year). In the groups that were prescribed with more than one antiresorptive drug,

Table 2. Comorbid diseases

Comorbid diseases	Total n=1,188; n (%)
Hypertension	866 (72.90)
Dyslipidemia	576 (48.48)
Diabetes mellitus	371 (31.23)
Chronic kidney disease	197 (16.58)
Anemia	72 (6.06)
Rheumatoid arthritis	16 (1.35)
Malignant neoplasm of breast	12 (1.01)
Malignant neoplasm of cervix uteri	6 (0.51)
Malignant neoplasm of colon	6 (0.51)
Thalassemia	5 (0.42)
Bullous pemphigoid	3 (0.25)
Malignant neoplasm of prostate	3 (0.25)
Myelodysplastic syndrome	3 (0.25)
SLE	3 (0.25)
HIV	2 (0.17)
Malignant neoplasm of bladder	2 (0.17)
Progressive systemic sclerosis	2 (0.17)
Acute myeloid leukemia	1 (0.08)
Diffuse large B-cell lymphoma	1 (0.08)
Discoid lupus erythematosus	1 (0.08)
Idiopathic thrombocytopenia purpura	1 (0.08)
Malignant neoplasm of larynx	1 (0.08)
Malignant neoplasm of lung	1 (0.08)
Malignant neoplasm of parotid gland	1 (0.08)
Malignant neoplasm of sigmoid junction	1 (0.08)
Multiple myeloma	1 (0.08)
Non-hodgkin lymphoma	1 (0.08)

SLE=systemic lupus erythematosus; HIV=human immunodeficiency virus

the mean duration of drug exposure was 3.23±1.576 years with a median of 3.24 years. Six hundred fifty-five patients (55.13%), received antiresorptive drug for less than one year and 121 patients (10.19%) obtained the drugs for equal to or greater than four years. Detailed information of antiresorptive drug exposure is shown in Table 1.

Comorbid diseases

One thousand forty-seven patients (88.82%) had comorbid diseases, while 140 patients (11.87%) had no history of comorbid disease. The most common comorbid disease was hypertension in 866 patients or 72.90%, followed by dyslipidemia in 576 patients or 48.48%, and diabetes mellitus in 371 patients or 31.23%. At a lesser extent, other diseases implicated with MRONJ were anemia in 72 patients or 6.06%, autoimmune disease in 26 patients or 2.19%, and cancer in 37 patients or 3.11% (Table 2).

Table 3. Number of patients who had corticosteroid medication

Antiresorptive drugs	Number of patients using corticosteroid (n=1,188); n (%)
Only 1 drug	
Alendronate	101 (8.50)
RANK-L inhibitors	43 (3.62)
Ibandronate	18 (1.52)
Risedronate	14 (1.18)
Switch 2 drugs	
Alendronate, RANK-L inhibitors	7 (0.59)
Risedronate, RANK-L inhibitors	6 (0.51)
Alendronate, Ibandronate	5 (0.42)
Ibandronate, RANK-L inhibitors	5 (0.42)
Risedronate, Alendronate	1 (0.08)
Switch 3 drugs	
Risedronate, Alendronate, RANK-L inhibitors	1 (0.08)
Alendronate, Ibandronate, RANK-L inhibitors	1 (0.08)
Switch 4 drugs	
Risedronate, Alendronate, Ibandronate, RANK-L inhibitors	0 (0.00)

Corticosteroid medication

Two hundred two patients (17%) had a history of corticosteroid drug administration. Corticosteroid drugs prescribed consisted of Prednisolone tab 5 mg, Dexamethasone tab 4 mg, Dexamethasone injection 4 mg/mL, Triamcinolone injection 10 mg/mL, Triamcinolone injection 40 mg/mL, Fluorescein sodium injection 500 mg in 5 mL, and Hydrocortisone injection 100 mg/mL. One hundred one patients (8.50%) received Alendronate, which was mostly prescribed with corticosteroid (Table 3).

MRONJ development and prevalence

In the present study, 49 patients had tooth extraction. Extraction has been known as an inciting factor that can cause MRONJ. Two patients developed MRONJ after tooth extraction. The prevalence of MRONJ related to antiresorptive drugs and oral bisphosphonates was 0.17% (2 of 1,188 patients) and 0.295% (2 of 677 patients), respectively. Detail of MRONJ cases was as follows.

These two cases were older than 74 years old. Both cases received oral bisphosphonates, which were Risedronate and Alendronate for less than three years. Oral bisphosphonates were prescribed for osteoporosis treatment. There was no history of corticosteroid drug administration. Patient comorbid diseases and drug information are shown in Table 4. In the first case, the extracted tooth was diagnosed

Table 4. Detail of 2 MRONJ cases

Case No.	Gender	Age (year)	Antiresorptive drug	Location	Duration of received drug (year)	Prescription	Predisposing factor/ triggering factor	Comorbid diseases	Corticosteroid used
1	Female	74	Risedronate	Upper left first molar	2.76	35 mg/week	Extraction, wearing ill-fitting denture after extraction	Diabetes mellitus, hypertension, dyslipidemia	No
2	Female	81	Alendronate	Lower right canine	2.32	70 mg/week	Extraction, periodontal disease	Anemia, diabetes mellitus, hypertension, dyslipidemia	No

with vertical root fracture. The extraction procedure was complicated. Furthermore, this patient wore a metallic removable partial denture, which was ill-fitting even after tooth extraction. In the second case, the tooth was extracted because of periodontal disease. Two weeks after extraction, the wound still showed sign of non-healing socket and had bone sequestrum. Then both cases were referred to Oral and maxillofacial surgeon for diagnosis and treatment. The wounds were curette, suture, and irrigated with normal saline. Amoxycillin and 0.12% Chlorhexidine mouthwash were prescribed. Patients were followed up every one to two weeks. The wounds remained non-healing for more than eight weeks. Treatment time for each case was 5.2 and 4.5 months, respectively.

Discussion

The prevalence of MRONJ in patients receiving bisphosphonate ranges from 0.02% to 0.1%[1,15-17]. Among osteoporosis patients, the risk of MRONJ is 0% to 0.02%. The risk of MRONJ increases when obtaining bisphosphonates[18-23]. In the 2022, AAOMS(1) showed that in the patients exposed to oral bisphosphonates, MRONJ risk was estimated to be 0.05% or less and patients should be informed about the risk of MROMJ when they have tooth extraction, which is 0% to 0.15%. The present study illustrated that the prevalence of MRONJ among all patients receiving antiresorptive drugs and only on oral bisphosphonates was 0.17% and 0.295%, respectively. However, patients who were on IV bisphosphonate and RANK-L inhibitors in the present study had no report of MRONJ, which might stem from a small number of patients. Dental examination and dental treatment prior to commencement medication could play a role in the difference of prevalence in these studies[9,24,25]. Previous study had addressed dental examination, treatment, and routine dental screening before prescribing antiresorptive drugs as a guideline for management in osteoporotic patient[15].

Duration of antiresorptive medication is a risk factor of MRONJ. Hallmer et al.[21] illustrated that mean duration of oral bisphosphonates before developing MRONJ was 5.8 years. The U.S. Food and Drug Administration (FDA)[23] informs that the patient who receives oral bisphosphonate between 2 and 2.9 years has a prevalence of MRONJ at 0.05%. The value increases remarkably when patients receive this medication for more than four years. In the present study, two patients developed MRONJ. The duration of oral bisphosphonate medication was 2.76 and 2.32 years. The time to onset of MRONJ in the present study was shorter than the mean duration. It is possible that these cases had other inciting factors.

All 1,047 osteoporotic patients in the present study had systemic comorbidity. In the two cases that developed MRONJ, one case had diabetes mellitus and the other case had diabetes mellitus and anemia. Diabetes mellitus has been shown to associate to MRONJ[26,27]. Patients with diabetes mellitus has higher correlation to MRONJ compared with individuals without this condition[28]. Diabetes mellitus could promote MRONJ possibly through several mechanisms including microvascular ischemia of the bone, endothelial cell dysfunction and apoptosis, decreased bone turnover and remodeling, and increased apoptosis of osteoblasts and osteocytes[29]. Thus, wound healing is delayed after dental surgery or trauma[30]. Anemia is also reported to increase the risk of MRONJ with the odd ratio of 14.599[31]. The level of hemoglobin less than 10 g/dL is associated with increasing risk of MRONJ[32]. However, the pathogenesis in these cases is unclear.

Osteonecrosis of the jaw can occur spontaneously. Extraction is a potential triggering factor. In patients exposed to oral bisphosphonate, the risk of MRONJ development increases to 0.5% after extraction[33]. However, Soutome et al.[34] study reported that extraction was not a factor, but the underlying infection of tooth was a factor to increase risk of MRONJ. Study from Tsao et al.[35] reported that

periodontitis was significantly associated with MRONJ. Furthermore, one site of pocket depth at least 4 mm had adjusted odd ratio of 12.3 when compared with control case. Furthermore, removable denture wearing is reported as a risk factor[9,36]. Additionally, other studies reported other factors such as corticosteroid drug, smoking, and antiangiogenic drug[37-39]. One patient who developed MRONJ wore improper denture after extraction. Because the denture was ill-fitting, it could distribute excessive pressure to the underlying soft tissue, interfering with the healing process. Hence, wearing denture for at least the first two weeks after dental extraction should be avoided. The denture base should be examined, relined with soft material, or replaced to improve fitting denture to minimize risk of MRONJ[40]. It is superlative that patients should be informed about this risk before starting bisphosphonates. Furthermore, the removable denture should be thoroughly examined and adjusted for the areas of oral mucosal trauma. There are factors related to MRONJ. This information is essential for healthcare workers when managing osteoporosis patients and treating MRONJ cases. In Addition, oral health maintenance and dental prophylaxis before commencement with antiresorptive medication must be provided to the patients to reduce MRONJ prevalence.

The authors acknowledge that the present study has limitation. The data in the present study was from one hospital. Thus, the present study cannot represent MRONJ situation in Thailand. In the future, more data should be collected and analyzed from the other areas in Thailand.

Conclusion

The present study provided information of the prevalence of MRONJ case in one tertiary care hospital in Thailand. The prevalence of MRONJ in osteoporotic patients obtaining antiresorptive drugs was 0.17%. Furthermore, detailed information of comorbidities and corticosteroid usage of these patients are included.

What is already known on this topic?

The prevalence of MRONJ is known and helps planning treatment between orthodontist and dentist to reduce the risk of MRONJ.

What this study adds?

This is a new study that illustrated the prevalence of MRONJ in Thailand.

Acknowledgement

The authors would like to thank the Department of Gerodontology, Faculty of Dentistry, Thammasat University and Pranangklao Hospital for supporting the present study.

Conflicts of interest

The authors declare no conflict of interest and the present study was not supported by any research grants or other sources.

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