



ORIGINAL ARTICLE

Medication-related osteonecrosis of the jaw after dental clearance: Prevalence in an oncology center



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KEYWORDS

MRONJ;
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alendronate;
oral bisphosphonates;
denosumab

Abstract Objective: Medication-related osteonecrosis of the jaw (MRONJ), a complication of bisphosphonate therapy, has significant morbidity. This study aimed to determine the prevalence of MRONJ and compare its risks among patients who received antiresorptive or antiangiogenic therapy in King Fahad Medical City.

Study design: In this retrospective study, the sample comprised data of all patients referred for dental treatment before antiresorptive and antiangiogenic therapy between 2008 and 2018. All patients were classified as at risk or having stage 0, stage 1, stage 2, or stage 3 MRONJ.

Results: The sample comprised 622 patients, including 358 (249 IV route, 34 oral route, and 75 subcutaneous route) who fulfilled the inclusion criteria and 25 in stage ≥ 0 . Greater risk was observed in the intravenous group (8.82%) than in the oral and subcutaneous groups (2.94% and 2.67%, respectively). The overall prevalence rate was 6%. Patients with no history of dentoalveolar surgery had an MRONJ rate of 1.03%, whereas patients who underwent dentoalveolar surgery > 3 weeks before a lower MRONJ rate of 0.96%. Patients who underwent dentoalveolar surgery < 3 weeks before starting medication, and those who underwent surgery after starting the medication had higher MRONJ rates (21.42%, and 35.85%, respectively). The risk of spontaneously developing MRONJ was low.

Conclusion: Risk of developing MRONJ was found to be higher when dentoalveolar procedures performed within 3 week before starting antiresorptive medications.

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Abbreviations: MRONJ, Medication-related osteonecrosis of the jaw

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1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a rare disease with significant morbidity. It was first described in 2003 as a complication of bisphosphonate therapy (RE Marx, 2003). As reports of this disease increased, it was given the nomenclature “bisphosphonate-related osteonecrosis of the jaw,” a term later changed by the American Association of Oral and Maxillofacial Surgeons (AAOMS)

Special Committee in 2014 to “medication-related osteonecrosis of the jaw” (MRONJ) when denosumab, antiresorptives, and antiangiogenic therapies were also reported to be associated with this condition (Ruggiero et al., 2009; Ruggiero et al., 2014). The disease is defined as exposed bone in the maxillofacial region that has persisted for >8 weeks in patients with current or previous treatment with an antiresorptive or antiangiogenic agent and no history of radiation therapy to the jaws or apparent metastatic disease to the jaws. The exact etiology remains debatable; however, many theories attempt to explain the disease and its exclusive relation to the jaws, attributing it to altered bone remodeling, jaw-related inflammation or infection, altered immunity, soft tissue toxicity, and angiogenesis inhibition (Bamias et al., 2005; Roelofs et al., 2006; Reid, Bolland, and Grey 2007; Chang, Hakam, and McCauley 2018). The most common finding is that it follows trauma to the jaws, in cases of reduced bone healing ability, resulting in bony necrosis, and patients frequently present with pain, fistulae, exposed necrotic bone, purulence, or a pathologic fracture in advanced cases (Khan et al., 2015). Some studies implicated numerous families of non-antiresorptive medications, including tyrosine kinase inhibitors, monoclonal antibodies, fusion proteins, mTOR inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants as risk factors for MRONJ (Fusco et al., 2016; Nicolatou-Galitis et al., 2019; King, Tanna, and Patel 2019; Sacco et al., 2020). Yet, AAOMS believes that identifying a single medication as the etiologic agent for MRONJ seems unlikely in case reports or mini-case series. More substantial evidence will be required to measure the risk of MRONJ associated with non-antiresorptive agents (Ruggiero et al., 2022). MRONJ is staged according to AAOMS into: at risk, received intravenous or oral antiresorptive or antiangiogenic therapy but with no symptoms or necrotic bone; stage 0, non-specific clinical findings, radiographic changes, and symptoms with no clinical evidence of necrotic bone; stage 1, exposed and necrotic bone or fistulae that probe into the bone in an asymptomatic patient; stage 2, pain and erythema in the area of exposed and necrotic bone or fistulae probing into the bone; or stage 3, exposed and necrotic bone or fistulae probing into the bone with pain, evidence of infection, and at least one of the following: exposed and necrotic bone extending beyond the alveolar bone resulting in a pathologic fracture, extraoral fistula, oronasal communication, or osteolysis extending to the inferior border of the mandible or floor of the maxillary sinus (Ruggiero et al., 2014; Ruggiero et al., 2022).

The prevalence ranges from 0.2% to 6.7% among patients receiving intravenous bisphosphonates (Vahtsevanos et al., 2009; Mauri et al., 2009; Chiang et al., 2013; Van den Wyngaert et al., 2013; Raje et al., 2018), whereas it ranges from 0.004% to 0.2% in patients receiving oral bisphosphonates (Lo et al., 2010). The prevalence of MRONJ with denosumab, an antiresorptive agent, ranges from 0.7% to 3% (Scagliotti et al., 2012; Qi et al., 2014; Raje et al., 2018). The present study aims to determine the prevalence and compare the risks of MRONJ among patients receiving antiresorptive or antiangiogenic therapy in King Fahad Medical City.

2. Materials and methods

This was a retrospective study based on the data collected from King Fahad Medical City. Before initiating treatment, the hospital protocol mandates dental clearance which includes a complete dental checkup, caries and periodontal disease control, root canal treatments and retreatments, and extraction of all teeth with questionable restorability or the possibility of requiring extraction later, and all data of dental clearance patients are entered into an electronic database. Patients were maintained on routine dental checkups and hygiene visits after starting the medication. Routine visits include a full oral checkup, suspicious inflammation or exposure documentation, and diagnosis according to the AAOMS position paper (Ruggiero et al., 2014).

The study population included 629 patients who were referred for dental clearance before antiresorptive and/or antiangiogenic therapy at King Fahad Medical City between 2008 and 2018. Of this sample, 358 patients met the eligibility criteria: Any patient who referred for dental clearance before antiresorptive and/or antiangiogenic therapy and received this medication and had documented follow-up. Patients who didn't received the medication at our institution or didn't have a documented follow up were excluded. Information were collected from the medical records. The electronic database for dental clearance patients was reviewed retrospectively, included the demography, medical diagnosis, medication, route of administration, starting date of medication, periodontal status, history of dentoalveolar surgery, highest MRONJ stage, area covered by MRONJ, and follow-up. The diagnosis and staging of MRONJ were based on the AAOMS position paper. The study protocol was approved by the Institutional Review Board at King Fahad Medical City, and it was granted an exemption in writing.

2.1. Predictors of MRONJ

Logistic regression was used to evaluate each predictor's impact on MRONJ rates in patients when modeled simultaneously. The results of the full model are shown in Table 3. The history of dentoalveolar surgery after starting medication was the single largest predictor. Patients with a history of dentoalveolar surgery were significantly more likely to have MRONJ than those without ($P = 0.0004$ and $P < 0.0001$ for patients who underwent surgery before and after medication, respectively). Patients who underwent dentoalveolar surgery < 3 weeks before starting the medication were 22 times more likely to have MRONJ and those who underwent surgery after the medication start were 62 times more likely to have MRONJ than patients with no history of surgery, with all other variables remaining constant. The type of medication and medical diagnosis were both nonsignificant at a significance level of 0.05, but had $P < 0.1$, indicating insufficient evidence that the rate of MRONJ was affected by these variables. The odds ratio (OR) of patients on medications different from zoledronic acid was 0.308, indicating that patients not taking zoledronic acid had a lower rate of MRONJ than those taking it.

Similarly, patients with osteoporosis-related diseases had an OR of 0.232, indicating that the rate of MRONJ among these patients was approximately four times less than that

among patients with cancer. The P values for medication and medical diagnosis were 0.089 and 0.079, respectively. While the proportions of patients with MRONJ differed according to these variables, the counts were small, reducing the estimator's precision.

The model's pseudo- R^2 , comparing the full model's log likelihood to that of a null model, was 0.406. This indicated that the independent variables explain 40.6% of the total variance. The area under the receiver operating characteristic curve was 0.9092, indicating the model's relatively high accuracy in predicting MRONJ occurrences based on the selected predictor variables.

3. Results

Data from 358 patients on various types of medications were collected. The medical diagnosis and type of medication prescribed were recorded, including other information related to oral status and surgery. The occurrence of MRONJ was observed in each patient and was used as the dependent variable for this analysis. Of the observed patients, 25 had MRONJ and 333 did not have MRONJ.

3.1. Patient population

Of the 358 patients (average age, 55.78 years), 64 (17.9%) were men and 294 (82.1%) were women. The majority of patients were prescribed zoledronic acid ($n = 236$; 65.9%), with the remaining patients prescribed other types of medications. The intravenous route was used to deliver medication in 249 (69.5%) patients, oral route in 34 (9.5%), and subcutaneous route in 75 (20.9%). While 80 (22.3%) patients had no history of dentoalveolar surgery after starting medication, 211 (58.9%) underwent dentoalveolar surgery > 3 weeks before starting medication, 14 patients (3.91%) underwent dentoalveolar surgery < 3 weeks before starting medication, and 53 (14.8%) underwent surgery after starting the medication (Table 1). Three weeks were chosen based on the literature and experience of osteoradionecrosis (Ruggiero et al., 2014).

3.2. Indicators of MRONJ

Before modeling MRONJ occurrence based on relevant covariates, Fisher's exact tests were used to evaluate the relationship between dependent and independent variables at a significance level of 0.05. The null hypothesis for each test stated that MRONJ diagnosis for a patient had no statistical difference among the levels of a category (for example, males vs females). Tests with P values < 0.05 indicated statistical evidence to reject the null hypothesis. The contingency table representing the number of patients with and without MRONJ within each predictor variable level is shown in Table 2.

Among all patients, the rates of MRONJ diagnosis in men and women were 20.0% and 17.7%, respectively ($\chi^2 = 0.082$; $P = 0.786$), indicating no significant statistical difference based on sex. Patients diagnosed with cancer had 8.64% occurrence of MRONJ compared with 2.89% in patients diagnosed with osteoporosis ($\chi^2 = 2.195$; $P = 0.188$), indicating no statistical difference among patients diagnosed with different diseases. Patients prescribed zoledronic acid had a 9.32% occurrence of the disease, nearly four times that of patients prescribed

Table 1 Patient demographics and characteristics ($n = 358$).

Sex	
Male	64 (17.9)
Female	294 (82.1)
Age	
< 26 years	23 (6.4)
26–35 years	13 (3.6)
36–45 years	36 (10.1)
46–55 years	74 (20.6)
56–65 years	127 (35.5)
> 65 years	85 (23.7)
MRONJ	
Yes	25 (6.9)
Maxilla	12 (3.4)
Mandible	10 (2.8)
Both	3 (0.8)
No	333 (93)
Medication	
Zoledronic acid	236 (65.9)
Neridronic acid	1 (0.3)
Alendronate	32 (8.9)
Denosumab	75 (20.9)
Pamidronate	2 (0.6)
Bevacizumab	12 (3.3)
Medical diagnosis	
Cancer	236 (65.9)
Multiple myeloma	46 (17.8)
Osteoporosis-related diseases	76 (21.2)
Route	
Intravenous	249 (69.5)
Oral	34 (9.5)
Subcutaneous	75 (20.9)
History of dentoalveolar surgery	
No history	80 (22.3)
Surgery > 3 weeks before starting medication	211 (58.9)
Surgery < 3 weeks before starting medication	14 (3.9)
Surgery after starting medication	53 (14.8)

Values are presented as n (%).

MRONJ, medication-related osteonecrosis of the jaw.

other medications (2.46%). This resulted in a P value of 0.015 ($\chi^2 = 5.832$), signifying that the proportion of patients with MRONJ significantly depended on the type of medication. Patients administered with medication through the intravenous, oral, and subcutaneous routes were diagnosed with MRONJ at 8.82%, 2.94%, and 2.67%, respectively ($\chi^2 = 4.322$; $P = 0.094$). Among patients with no history of dentoalveolar surgery, the rate of MRONJ was 1.25%, whereas patients who underwent dentoalveolar surgery > 3 weeks before starting medication had a lower MRONJ rate of 0.96%. Patients who underwent dentoalveolar surgery < 3 weeks before starting medication, and those who underwent surgery after starting the medication had higher MRONJ rates (21.42%, and 35.85%, respectively); $\chi^2 = 88.357$, $P < 0.0001$).

4. Discussion

The prevalence of MRONJ in this study was within the average range reported in the literature, which is higher with the intravenous route of administration. The prevalence ranges

Table 2 Contingency table of patients with and without MRONJ according to each predictor variable.

	With MRONJ	Without MRONJ
Sex		
Male	5	59
Female	20	274
Diagnosis		
Cancer	23	266
Osteoporosis	2	76
Medication		
Zoledronic acid	22	214
Alendronate	1	31
Denosumab	2	73
Route		
Intravenous	22	227
Oral	1	33
Subcutaneous	2	73
History of dentoalveolar surgery		
No history	1	79
Surgery > 3 weeks before starting medication	2	209
Surgery < 3 weeks before starting medication	3	11
Surgery after starting medication	19	34

MRONJ, medication-related osteonecrosis of the jaw.

Table 3 Full multivariate logistic regression model for the occurrence of MRONJ.

Variable	Estimate	Standard error	Odds ratio	P value
Intercept	-4.134	0.590	-	< 0.0001
Non-zoledronic acid	-1.176	0.692	0.308	0.089
Osteoporosis	-1.458	0.831	0.232	0.079
Surgery < 3 weeks before starting medication	3.092	0.882	22.033	0.0004
Surgery after starting medication	4.133	0.662	62.423	< 0.0001

MRONJ, medication-related osteonecrosis of the jaw.

from 0.2% to 6.7% among patients receiving intravenous bisphosphonates, (Vahtsevanos et al., 2009; Mauri et al., 2009; Chiang et al., 2013; Van den Wyngaert et al., 2013; Rajee et al., 2018) whereas it ranges from 0.004% to 0.2% in patients receiving oral bisphosphonates (Lo et al., 2010). The prevalence for denosumab ranges from 0.7% to 3% (Scagliotti et al., 2012; Qi et al., 2014; Rajee et al., 2018). The literature has limited information regarding the anatomic risk factors of MRONJ (Dodson 2015; Ruggiero et al., 2014). Among the MRONJ patients in this study, the sites of occurrence were in the maxilla (12 cases, 48%), mandible (10 cases, 40%), and both jaws (3 cases, 12%). In a study by Saad et al. (Saad et al., 2012), MRONJ was more likely to appear in the mandible (73%) than in the maxilla (22.5%) and can appear in both jaws (4.5%). The aim of this study was to report the incidence of MRONJ in patients receiving antiresorptive or antiangiogenic medications at a large oncology center in Saudi Arabia. Limited data are available on the prevalence of MRONJ in Saudi

Arabia: only one article was found in the literature, describing a study conducted in 2011 in Riyadh City, which showed 0% prevalence among the sample of 88 subjects in the study (Alzoman, 2011).

The overall prevalence of MRONJ in our study was 6.9%. The prevalence was higher in the intravenous group (8.82%) than in the oral and subcutaneous groups (2.94% and 2.67%, respectively). History of dentoalveolar surgery was the largest predictor of MRONJ, those who underwent dentoalveolar surgery < 3 weeks before medication initiation were 22 times more likely to have MRONJ, whereas patients who underwent dentoalveolar surgery after starting medication were 62 times more likely to have MRONJ than patients with no history of surgery, and the disease occurred at the same area of the surgery.

This study has several limitations. The study's small sample size was managed during modeling. Owing to limited data, a significance level of 0.1 was used to reduce the number of variables during modeling, including the magnitude of the dentoalveolar surgery (i.e., number of extractions). Thus, the patient's medication, history of dentoalveolar surgery, and medication route were considered. Another potential limitation is the number of evaluators, as multiple evaluators can affect accuracy. However, all staff members were familiar with the AAOMS guidelines for diagnosis and staging, and the final stage was reached through consensus among the staff and the senior author. The patients followed a regular follow-up protocol, and the data were collected in an electronic database as part of the hospital's protocol.

Since it was discovered, MRONJ has had a relatively low level of evidence and a challenging disease frequency estimation (Diniz-Freitas et al., 2019; Dodson 2015). In their bibliometric analysis of the 100 most-cited studies of MRONJ, Diniz-Freitas et al. (Dodson 2015) found a generally low evidence level and lack of randomized clinical trials. With the relatively low level of evidence, in many situations, they are the best available evidence in clinical practice, as a randomized study is difficult to conduct in some situations (Ahmad et al., 2015).

The duration between the last dental surgery and starting medication can be affected by many factors, most notably disease status. The findings of this study support previous research on the strong relationship between the history of dentoalveolar surgery and the development of MRONJ (Kyrgidis et al., 2008; Vahtsevanos et al., 2009; Fehm et al., 2009; Saad et al., 2012). Previous published recommendations regarding the duration between dentoalveolar surgery and the start of medication that may cause MRONJ were based on the literature and experience of osteoradionecrosis (Ruggiero et al., 2014). Based on this, the patients were grouped into four categories according to their history of dentoalveolar surgery: the first group had no history of dentoalveolar surgery, the second group had history of surgical intervention at least 3 weeks before the start of the medication; the third group included patients who had surgery < 3 weeks before starting medication but no surgery after starting medication; and the fourth group included patients who underwent surgery after the start of the medication. Our results show that the risk of MRONJ increased significantly if the medication was initiated within 3 weeks from the last dentoalveolar surgery. The results of this study should be interpreted with caution, as future research should further explore the implications of the timeframe

between the dentoalveolar procedure and the medication initiation, to better understand the risk more clearly and minimize this duration.

Spontaneous occurrence of MRONJ with no related dental surgery was noted in three patients in this study. Two of these patients used dentures, which could predispose to the development of MRONJ. In previous reports, patients who used dentures had a twofold higher risk of developing ONJ (Kyrgidis et al., 2008; Vahtsevanos et al., 2009). The defect in the mucosal healing in these patients can open the communication to the bone and lead to ONJ (Landesberg et al., 2008). The third patient had a chronic dental infection in a remaining root managed conservatively with root canal treatment and root retention and ended up with exposure and diagnosis of MRONJ.

CRedit authorship contribution statement

Saad Hajeri: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Yasir Alturkistany:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Presentation

No.

Statement of Clinical Relevance

Risk of developing MRONJ was found highest when dentoalveolar procedures were done less than 3 weeks before the start of antiresorptive and/or antiangiogenic therapy, an interval of more than 3 weeks is suggested to allow healing and reduce the risk of developing MRONJ.

IRB approval

The study granted an exemption in writing by the Institutional Review Board at King Fahad Medical City.

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