Original paper

Analysis of potential risk factors for the development of medication-related osteonecrosis of the jaw

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Abstract

Background. Medication-related osteonecrosis of the jaw (MRONJ) is an undesirable consequence of the action of drugs, involving the exposure of bones in a patient not exposed to ionizing radiation in the head and neck area. The occurrence of MRONJ is associated with therapy with anti-resorptive drugs (bisphosphonates), receptor activator of nuclear factor-kappa B ligand (RANKL) drugs, e.g., denosumab, and anti-angiogenic drugs that are vascular endothelial growth factor (VEGF) inhibitors.

Objectives. The aim of the present study was to identify risk factors for the development of MRONJ.

Material and methods. The medical records of patients hospitalized in the years 2015–2022 in the Department of Maxillofacial Surgery of the Ludwik Rydygier Specialist Hospital in Krakow and the Clinical Department of Maxillofacial Surgery of University Hospital in Krakow, Poland, were retrospectively analyzed. The study included patients treated for MRONJ in the maxilla and/or the mandible with a history of past bisphosphonate therapy. Patients with symptoms of osteonecrosis after radiotherapy of the head and neck region were excluded from the study. The patients' demographic data, comorbidities, the initial disease treated with bisphosphonates, the route of drug administration, the type of causative dental surgery, the area of necrosis, and the MRONJ class according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria were analyzed.

Results. The investigated group consisted of 29 females and 14 males. Common comorbidities were anemia, diabetes mellitus (DM) and hypertension. Bisphosphonates were used in 30 patients (69.8%) treated for cancer, in 10 patients (23.3%) treated for osteoporosis and in 2 patients (4.7%) treated for osteopenia. In the majority of cases ($n = 19$; 44.2%), bisphosphonates were administrated intravenously. Medication-related osteonecrosis of the jaw was diagnosed in the mandible in 25 cases (58.1%) and in 18 (41.9%) – in the maxilla. In 14 patients (32.6%), necrosis was initiated by a dental procedure, most often tooth extraction.

Conclusions. Risk factors for the development of MRONJ in patients treated with bisphosphonates include the intravenous route of drug administration, past intraoral surgery, female gender, and senior age.

Keywords: therapy, diagnosis, risk factors, MRONJ, bisphosphonate-associated osteonecrosis of the jaws

Highlights

- Preventing medication-related osteonecrosis of the jaw (MRONJ) involves educating both patients and dentists about the risks and proper management strategies, especially when performing intraoral procedures.
- Before initiating bisphosphonate therapy, it is essential to conduct a thorough oral cavity examination to identify and eliminate any potential sources of inflammation or infection.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an undesirable consequence of the action of drugs, involving the exposure of bones in a patient not exposed to ionizing radiation in the head and neck area.[1] It is associated with significant local pain, the mobility or loss of the teeth, paresthesia, and the presence of intra- and/or extraoral fistulas with oozing purulent contents. Medication-related osteonecrosis of the jaw often leads to a significant reduction in the quality of life (QoL) and the disfigurement of the patient.[2]

The occurrence of MRONJ is associated with therapy with anti-resorptive drugs (bisphosphonates), receptor activator of nuclear factor-kappa B ligand (RANKL) drugs, e.g., denosumab, and anti-angiogenic drugs that are vascular endothelial growth factor (VEGF) inhibitors.[3,4]

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), the following criteria are used to diagnose MRONJ: current or past treatment with anti-resorptive or anti-angiogenic drugs; visible bone exposure, or the possibility of the intra- or extraoral probing of the jaw bones through a cutaneous or mucosal fistula for a period longer than 8 weeks; no history of radiotherapy to the jaw area; and no cancer metastases to this area.[4]

The AAOMS more specifically distinguishes 4 stages of MRONJ[4]:

– stage 0 – non-specific clinical symptoms, i.e., jaw pain and osteonecrosis, without the exposure of the jaw;
– stage I – exposed/necrotic bone in patients without symptoms of infection;
– stage II – exposed/necrotic bone associated with infection, presenting with pain and erythema in the area of the exposed bone, with or without a purulent exudate;
– stage III – exposed/necrotic bone in patients with pain, infection, and one or more of the following: a pathological fracture; an extraoral fistula; or osteolysis extending to the floor of the sinus.

At the molecular level, the mechanism of bone destruction in MRONJ is related to an imbalance in the RANK/RANKL/OPG (receptor activator of nuclear factor-kappa B/receptor activator of nuclear factor-kappa B ligand/osteoprotegerin) system. The ratio of RANKL to OPG plays an important role in initiating and maintaining osteoclastogenesis, and thus in regulating bone resorption, which is crucial for bone remodeling.[5] Factors that play a vital role in the pathomechanism of MRONJ include the inhibition of bone resorption and remodeling, the inhibition of angiogenesis, and vitamin D deficiency. Also immune system dysfunctions, e.g., those connected with diabetes mellitus (DM) linked to obesity, as well as genetic predispositions, might lead to MRONJ.[1,5] Mechanical and thermal injuries should also be taken into consideration.[6] Local, intraoral risk factors for MRONJ include areas of thinned oral mucosa over bone exostoses or an atrophic mandible, the presence of periodontal disease as additional local inflammation, and poor oral hygiene.[7–9]

The objective of this cohort observational study was to identify risk factors for the development of MRONJ.

Materials and methods

The medical records of patients hospitalized in the years 2015–2022 in the Department of Maxillofacial Surgery of the Ludwik Rydygier Specialist Hospital in Krakow and the Clinical Department of Maxillofacial Surgery of University Hospital in Krakow, Poland, were retrospectively analyzed. The study included patients treated for MRONJ in the maxilla and/or the mandible with a history of past bisphosphonate therapy. Patients with symptoms of osteonecrosis after radiotherapy of the head and neck region were excluded from the study.

The analyzed data was as follows: the patients' demographics (gender, age, the place of residence, education); comorbidities (anemia, DM, hypertension, other); the initial disease treated with bisphosphonates; the route of drug administration; the type of causative dental surgery; the area of necrosis; the MRONJ class according to the AAOMS criteria; and the bacterial cultures taken from the necrotized tissues. The analysis of data regarding the treatment used for MRONJ included surgical methods, pharmacotherapy, antibiotic therapy, anti-inflammatory drugs, and supportive treatment.

The relationship between the location of MRONJ and the place of the performed dental surgery, the relationship between the MRONJ stage and the route of administration of bisphosphonates, and the relationships between the MRONJ stage and parameters such as gender, age,

the place of residence, education, the nature of work, the initial reason for using drugs, the presence of comorbidities, and the performed dental procedure as a direct cause of MRONJ were examined.

Statistical analysis

Statistical analysis was performed using the R software, v. 4.2.1 (https://www.r-project.org). The analysis of qualitative variables (i.e., not expressed in numbers) was performed by calculating the number and percentage of occurrences of each value. The comparison of qualitative variables in groups was performed using the χ^2 test (with Yates correction for 2×2 tables) or Fisher's exact test, where low expected numbers appeared in the tables. A significance level of 0.05 was adopted in the analysis. Therefore, all *p*-values below 0.05 were interpreted as indicating significant relationships.

Results

A total of 43 patients hospitalized in both centers met the inclusion criteria for the study. Female subjects were predominant (n = 29; 67.4%), and the largest group were patients over 70 years of age (n = 22; 51.2%), living in cities with over 500,000 inhabitants (n = 16; 37.2%), with vocational education (n = 13; 30.2%). Detailed data is presented in Table 1.

The most common comorbidities in the studied group of patients were anemia (n = 34; 79.1%), DM (n = 17; 39.5%) and hypertension (n = 13; 30.2%).

Bisphosphonates were used in 30 patients (69.8%) in the course of cancer treatment (breast and prostate cancer), while 10 patients (23.3%) were treated for osteoporosis, 2 (4.7%) for osteopenia, and for one patient (2.3%) there was no data. It is also worth noting that male subjects were treated for osteoporosis much less frequently (9 subjects vs. 1 subject; 20.9% vs. 2.3%). The reasons for administering bisphosphonates by patient gender are shown in Fig. 1.

Bisphosphonates were most often administered intravenously – in 19 patients (44.2%). The oral route of administration was used in 11 patients (25.6%). The medical records of 13 patients (30.2%) did not include information on the route of drug administration.

In the studied group of patients, MRONJ was diagnosed in the mandible in 25 subjects (58.1%), and in the maxilla, in 18 cases (41.9%) (Table 2). The most frequently diagnosed stage of necrosis according to the AAMOS classification was stage 0 in 18 subjects (41.9%), followed by stage II in 16 subjects (37.2%). Detailed data is presented in Table 3.

Medication-related osteonecrosis of the jaw developed without an identifiable local cause in 29 cases (67.4%), in contrast to 14 patients (32.6%) whose necrosis was initiated by a dental procedure, most often tooth extraction.

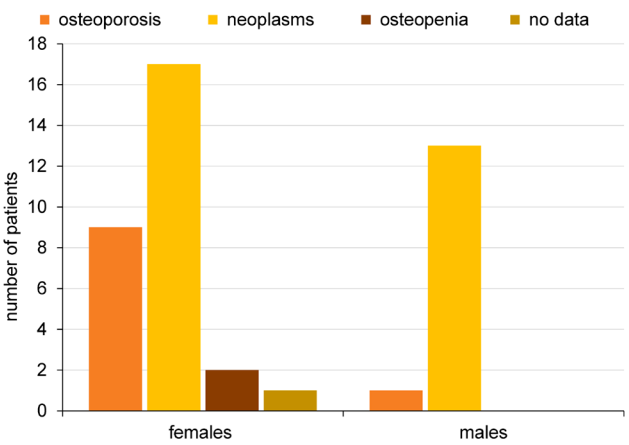

Fig. 1. Reasons for administering bisphosphonates in female and male subjects

Table 1. Demographic structure of the studied group of patients (N = 43)

Parameter		*n* (%)
Gender	F	29 (67.4)
	M	14 (32.6)
Age [years]	<60	6 (14.0)
	60–70	15 (34.9)
	>70	22 (51.2)
Place of residence	village	7 (16.3)
	city with up to 50 thousand inhabitants	10 (23.3)
	city with 50–500 thousand inhabitants	10 (23.3)
	city with over 500 thosand inhabitants	16 (37.2)
Education	primary	6 (14.0)
	vocational	13 (30.2)
	secondary	12 (27.9)
	higher	11 (25.6)
	no data	1 (2.3)

F – female; M – male.

Table 2. Incidence of medication-related osteonecrosis of the jaw (MRONJ) in the maxilla and the mandible

Location of MRONJ	After dental surgery	No identifiable local cause	Total
Maxilla	9 (20.9)	9 (20.9)	18 (41.9)
Mandible	5 (11.6)	20 (46.5)	25 (58.1)

Data presented as number (percentage) (*n* (%)).

Table 3. Staging of medication-related necrosis of the jaw (MRONJ) according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) classification

Stage of MRONJ	*n* (%)
0	18 (41.9)
I	2 (4.7)
II	16 (37.2)
III	6 (14.0)
No data	1 (2.3)

Detailed data is presented in Table 4. Following dental procedures, necrotic lesions appeared at the surgical site. Detailed data regarding the location of MRONJ developing after dental surgery is presented in Table 5.

The patients underwent surgical and non-surgical treatment for MRONJ. The most common surgical methods were sequestrectomy in 28 cases (65.1%), and the segmental resection of the maxilla or the mandible in 17 patients (39.5%).

The results of microbiological tests conducted on the material collected from the patients showed the presence of Gram-positive bacteria, such as *Staphylococcus aureus* and *Streptococcus mitis*, as well as Gram-negative ones – *Klebisiella oxytoca*, *Escherichia coli* and *Pseudomonas aeruginosa*.

The most commonly identified bacterium was *Escherichia coli*, found mainly in male patients over 70 years old and females over 60 years old. The prevalence of bacteria highly adapted to anaerobic conditions was observed. The isolated microorganisms represented flora typical for healthcare-associated infections in our hospital environment.

Pharmacological treatment included antibiotic therapy, possibly targeted, and anti-inflammatory drugs. The most frequently used antibiotics and drugs included augumentin, amoksiklav, clindamycin, cipronex, and the chemotherapy drug metronidazole. The treatment process was also supported by hyperbaric oxygen therapy.

It was found that when bisphosphonates were administered orally, the most common type of necrosis was stage II, whereas in the case of intravenous administration it was stage 0. This relationship was statistically significant ($p = 0.048$) (Table 6). There were no statistically significant relationships between the MRONJ stage and parameters such as gender, age, the place of residence, education, the nature of work, the initial reason for using drugs, the presence of comorbidities, and the performed dental surgery as a direct cause of MRONJ. The stage of MRONJ did not depend on its location (the maxilla vs. the mandible).

Table 4. Causes of medication-related necrosis of the jaw (MRONJ)

Cause of MRONJ		*n* (%)
Drug treatment, with no identifiable local cause		29 (67.4)
Dental procedure	extraction	13 (30.2)
	periodontal treatment	1 (2.3)

Table 5. Relationship between the location of medication-related necrosis of the jaw (MRONJ) and prior dental surgery

Location of MRONJ caused by dental procedures	Place of the performed procedure	*n* (%)	*p*-value
Maxilla	lateral segment	7 (16.3)	<0.001*
	anterior segment	2 (4.7)	
Mandible	lateral segment	4 (9.3)	
	anterior segment	1 (2.3)	

*statistically significant.

Table 6. Relationship between the medication-related osteonecrosis of the jaw (MRONJ) stage and the route of administration of bisphosphonates

Stage of MRONJ	Route of administration of bisphosphonates			*p*-value
	oral ($n = 11$)	intravenous ($n = 19$)	no data ($n = 12$)**	
0 ($n = 18$)	3 (27.3)	11 (57.9)	4 (33.3)	0.048*
I ($n = 2$)	0 (0.0)	2 (10.5)	0 (0.0)	
II ($n = 16$)	8 (72.7))	3 (15.8)	5 (41.7)	
III ($n = 6$)	0 (0.0)	3 (15.8)	3 (25.0)	

Data presented as *n* (%).
*statistically significant; ** one chart contained no data on the progress of MRONJ.

Discussion

In the analyzed group of patients, MRONJ most often occurred in female subjects, which is consistent with the results of studies conducted by other authors.[10,11] According to Lira[12] and Jeong et al.,[13] MRONJ most often appears in the 7th decade of life. In our own material, the age of the patients was higher, and MRONJ was diagnosed mainly in the 8th decade of life.

In the study group, no statistically significant relationship between comorbidities and the incidence of MRONJ was observed, although anemia and DM were the most commonly encountered comorbidities. This discrepancy with regard to other studies, which stress the importance of comorbidities, might be caused by a relatively small sample size in our study. Further analysis of this issue is necessary. Magremanne et al. included hematological disorders (sickle cell anemia, β-thalassemia, coagulation disorders, etc.), metabolic disorders (DM, hypercholesterolemia, hyperlipidemia, Cushing's disease, etc.), rheumatological disorders (disseminated lupus erythematosus, rheumatoid arthritis, etc.), exogenous factors (alcohol, tobacco), and infectious factors (viral, bacterial, fungal) among the systemic factors affecting the development of MRONJ in patients taking bisphosphonates.[14] Gavaldá and Bagan also emphasized in their work the influence of comorbidities, such as DM, anemia or rheumatoid arthritis, and the patient's habits (smoking, drinking alcohol) on the occurrence of MRONJ.[15] Anastasilakis et al., stressed the importance of DM, rheumatoid arthritis, smoking, drinking alcohol, obesity, anemia, and HIV infection as systemic risk factors for MRONJ.[1]

In our study, bisphosphonates were administered mainly during the course of oncological (multiple myeloma, breast cancer and prostate cancer) treatment, which is consistent with the observations of other authors.[3,16–19] The remaining cases of bisphosphonate therapy referred to osteoporosis and osteopenia.

In their retrospective work, Farrugia et al. analyzed the impact of new-generation bisphosphonates – zolendronate, pamidronate and alendronate – on the development of MRONJ.[20] Of the 23 patients diagnosed with MRONJ, 18 subjects were treated with the intravenous form

of a drug.[20] Lira also noted in his paper that the highest percentage of MRONJ occurred as a result of the intravenous use of bisphosphonates.[12] Gavaldá and Bagan included the route and duration of drug administration during the course of the underlying disease as systemic risk factors for the development of MRONJ.[15] Similar results were obtained in the present study. It is noteworthy that with the intravenous administration of bisphosphonates, type I necrosis developed statistically significantly more often. No similar relationship was found in the available literature.

Our research showed a slightly higher incidence of MRONJ in the mandible than in the maxilla. This result is consistent with those obtained by Migliorati et al.,[3] Bamias et al.[16] and Saad et al.[21] Bamias et al. found that in a studied group of 17 subjects, necrosis developed in the mandible in 14 cases and in the maxilla – in 3 cases.[16]

Patients at dental offices are at increased risk of developing medication-related necrosis. It has been shown that MRONJ may be a consequence of a previously performed dental procedure, e.g. tooth extraction, implant surgery, a periodontal procedure, endodontic treatment, trauma caused by a denture plate, or a hygienization procedure.[1] Research conducted in Sweden by Hallmer et al. on the causes of MRONJ indicates that the most common factor predisposing to the development of osteonecrosis is tooth extraction, followed by a periodontal procedure and an injury caused by a denture plate.[22,23] Similarly, Lira[12] and McGowan et al.[24] identified tooth extraction as the main factor causing MRONJ. This is consistent with the results of our own research.

In the available reports, the incidence of spontaneous necrosis varies from 2.2% to 60%.[25,26] Although the definition of spontaneous MRONJ is fairly clear (no previous dental problems, injury or therapy), it is possible that in some cases, the patients are not aware of painless, necrotic, exposed bone.[27] Among our patients, a high percentage (67.4%) of spontaneous necrosis was observed, which differs from the results presented by other authors.[20,23] In our opinion, that may have been caused by micro-injuries in the oral cavity, previously unnoticed by the patients.

Current knowledge about the treatment of MRONJ is presented in a diagram prepared by the authors (Fig. 2). Surgical treatment is preferred; Vassiliou et al. recommend such treatment in stages III and IV of necrosis, while implementing conservative treatment in stages I and II.[28] Other methods include laser surgery, which supports the repair process by stimulating the growth of lymphatic and blood vessels.[16] Hyperbaric oxygen therapy and ozone therapy are also used in complementary treatment.[17,29] In our study, all patients with MRONJ underwent surgical treatment, regardless of the stage of necrosis.

Hallmer's research on the bacterial flora of necrotic bone in the course of MRONJ showed the presence of *Porphyromonas* spp., *Lactobacillus* spp., *Tonarella* spp., *Prevotella* spp., *Actinomyces* spp., *Treponema* spp., *Streptococcus* spp., and *Fusobacterium* spp.[22] In turn,

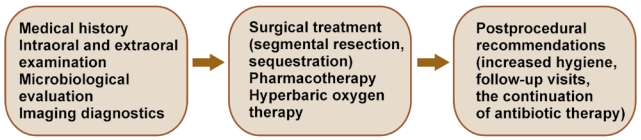

Fig. 2. Treatment regimen in the group of patients described in the article

Zirk et al.,[18] Cerrato et al.[30] and Micheletti et al.[31] identified biofilms containing *Streptococcus* spp., *Prevotella* spp., *Actinomyces* spp., *Veillonella* spp., and *Parvimonas micra* in the cultures from the tissues collected from patients with MRONJ. Ewald et al. showed the presence of *Actinomyces* spp., *E. coli*, *Veionella parvula*, *Enterobacter* spp., *Lactobacillus* spp., *Neiseria* spp., *Enterococcus* spp., *Eikenella* spp., and *Fusobacterium* spp.[32]

Our microbiological evaluations of the necrotic tissue in the patients with MRONJ revealed the presence of bacteria typical for hospital-acquired infections, such as *E. coli* and *P. aeruginosa*. That was probably related to the prolonged therapy, multiple hospitalizations and immunological condition of the patients, especially those receiving oncological treatment.

The obvious limitations of our study are a small sample size, as well as the retrospective character of this research. These factors limit the generalizability of our findings.

Conclusions

Risk factors for the development of MRONJ in patients treated with bisphosphonates include the intravenous route of drug administration, past intraoral surgery, female gender, and senior age

The prevention of MRONJ requires the education of both patients and the dentists performing basic intraoral procedures. The decision to start therapy with bisphosphonates should also be preceded by a thorough examination of the oral cavity and the elimination of potential foci that may lead to the development of osteonecrosis of the jaw in the future.

Ethics approval and consent to participate

The study received approval from the Bioethics Committee of the Jagiellonian University, Krakow, Poland (approval No.: 1072.6120.33.2022).

Data availability

The datasets supporting the findings of the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

Not applicable.

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