

Article

What Do Prescribers of Bone Modifying Agents Know about Medication-Related Osteonecrosis of the Jaw? Is Current Prevention Enough?

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Abstract: Osteonecrosis of the jaw represents interference by external and internal factors in the natural bone remodeling system. Numerous bone remodeling agents (BMAs), such as bisphosphonates, denosumab, and tyrosine kinase inhibitors, can lead to medication-related osteonecrosis of the jaw (MRONJ). This is a serious condition that occurs as a side-effect of treatment in patients with osteoporosis or malignancies. Antiresorptive drugs are medications that target osteoclasts with the aim of preventing bone resorption and are used to treat osteoporosis, osteopenia, and a variety of other conditions, such as Paget's disease. They are also used in cancer patients with active bone metastases where antiresorptive treatment is used for the prevention of skeletal complications. Poor dental health, infections, and especially dental surgery are the primary causes of MRONJ, while other risk factors, such as smoking, alcohol abuse, and diabetes mellitus, can also influence its development. Prevention is the key component of management, and thus awareness of the risk factors among prescribers is very important. The aim of our study was to evaluate current knowledge about MRONJ among BMA prescribers in an academic hospital and their awareness about oral health and dental check-ups. By using a custom-designed questionnaire addressed to general and internal medical practitioners, endocrinologists, rheumatologists, and oncologists as an instrument for collecting data, we tried to identify trends in BMA prescription among different specialists and their recommended preventative measures, with the aim of creating new strategies to prevent the occurrence of MRONJ. The survey revealed a low awareness among physicians of the potential risk factors and underlined the need for a concerted effort to improve patient management. In this sense, a multidisciplinary team approach that includes the patient, the drug prescriber, the dentist, and the oral surgeon could significantly improve the quality of life of patients with MRONJ.

Keywords: osteonecrosis of the jaw; medication-related osteonecrosis of the jaw; bisphosphonate-related osteonecrosis of the jaw; dentistry; oral health; multidisciplinary approach



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1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a serious condition that occurs as a side-effect of treatment in patients with osteoporosis or malignancies. Antiresorptive drugs are medications that target osteoclasts with the aim of preventing bone resorption and are used to treat osteoporosis, osteopenia, and a variety of other osteopathies, such as Paget's disease. They are also used in the treatment of cancer patients with active bone metastases where antiresorptive treatment is used for the prevention of skeletal complications.

Osteonecrosis of the jaw related to bisphosphonates has been reported since the 2000s [1] and has been proven to negatively affect quality of life, causing significant morbid-

ity in affected patients. After denosumab was approved for the treatment of osteoporosis and metastatic bone diseases, cases of osteonecrosis of the jaw were identified and defined as denosumab-related osteonecrosis of the jaw [2,3]. Another drug related to the appearance of osteonecrosis is sunitinib, a multi-targeted tyrosine kinase receptor inhibitor with a potent antitumor effect that is used in second- and first-line chemotherapy in renal cell carcinoma [4,5]. The current definition of MRONJ summarizes osteonecrosis of the jaw resulting from bisphosphonates, denosumab, and antiangiogenic drugs, such as bevacizumab, sunitinib, and aflibercept, or other bone modifying agents (BMAs). Eating disorders, pain, and local erythema are usually the initial symptoms of MRONJ, with signs specific to a local infection appearing later and evidence of purulent secretion, with or without drainage fistula, and denuded bone as further possible occurrences. Other signs include sensory disorders, deformities of the jaw, and even pathological fractures of the jaw, especially at the mandibular level, and the appearance of maxillary oroantral communications, where the denuded bone size can vary from a few millimeters to a few centimeters in size.

The diagnosis of MRONJ requires that all of the characteristics listed in Table 1 be present.

Table 1. Definition and staging of MRONJ [6].

Definition	
(a)	Current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications
(b)	Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks
(c)	No history of radiation therapy to the jaw or metastatic disease to the jaw
Staging	
Stage 0.	Non-specific symptoms or clinical and radiographic findings, with no clinical evidence of necrotic bone
Stage 1.	Symptomatic patients with exposed and necrotic bone, or fistula that probes to the bone, with no evidence of infection/inflammation
Stage 2.	Exposed and necrotic bone, or fistula that probes to the bone, with evidence of infection/inflammation
Stage 3.	Exposed and necrotic bone, or fistulae that probes to the bone, with evidence of infection, and one or more of the following: • Exposed necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla); • Pathologic fracture; • Extraoral fistula; • Oroantral/oral–nasal communication; • Osteolysis extending to the inferior border of the mandible or sinus floor

The optimal treatment of MRONJ is still debated and, depending on the clinical stage of the disease, general steps are recommended, such as local hygiene with antiseptic solutions, local and general antibiotic treatment, pain control, and local surgical interventions with curettage or classical sequestrectomy. The currently recommended staging of the disease is also presented in Table 1. Modern approaches, such as piezo surgery or laser treatments, are still under investigation; however, the one thing generally acknowledged is that prevention is the most important step of treatment. Hyperbaric oxygen therapy can also improve the local healing process, and epithelization is an essential step in the management of osteonecrosis, but the costs of these treatments are still impediments.

Due to the difficulty of treating patients with MRONJ, primary prevention is the most effective management approach and awareness of the risk factors among prescribers of drugs associated with the disease is paramount for patient safety.

The aim of our study was to investigate awareness of MRONJ among BMA prescribers, their current prescribing practices, and the preventative measures currently used by different specialties for patients prescribed BMAs. The goals of our study were to evaluate current knowledge about MRONJ caused by different BMAs through a survey performed in an academic hospital in order to evaluate current gaps in knowledge with the aim of improving the quality of care and life of MRONJ patients.

2. Materials and Methods

An online survey was performed using a purposely developed questionnaire that was sent to all medical practitioners who prescribed antiresorptive treatment in our institution, which is an academic hospital and a tertiary center, using their institutional or personal email addresses. The survey included physicians from different fields, such as general medicine, internal medicine, endocrinology, rheumatology, and oncology. The questionnaire allowed the respondents to maintain their anonymity, though one disadvantage of an anonymous questionnaire is the fact that interviewees may not be entirely honest in their responses. The practitioners surveyed were of different experience levels, both junior and senior. The survey aimed at identifying awareness of the disease and risk factors, prescribing practices, and current preventative measures used. The initial section of the questionnaire gathered the respondents' demographic data, the second included questions regarding the main indications and common forms of BMAs prescribed and oral side effects of bisphosphonates and other bone modifying agents, while the last section contained questions regarding the dental management of patients with MRONJ. A model of the questionnaire is presented in Table 2.

Table 2. Model of the questionnaire used.

Questions	Possible Answers
Sex	
Age	
Current job	Urban/rural Private practice/public health care
Medical field	Endocrinology Rheumatology Oncology General practitioner Internal medicine Oral and maxillofacial Surgeon
Professional Degree	Senior doctor Specialist doctor Resident doctor
Level of experience	<5 years 5–10 years >10 years
Do you prescribe or have you ever prescribed medication for?	Osteoporosis Osteopenia Paget's disease Multiple myeloma Prophylaxis of bone metastases Imperfect osteogenesis
What drugs do you prescribe for these bone pathologies?	Oral bisphosphonates i.v. bisphosphonates Denosumab Parathormone Teriparatide Tyrosine Kinazis Others

Table 2. Cont.

Questions	Possible Answers
What specific bone modifying agents do you prescribe?	Pamidronate (Aredia®) Risedronate (Actonel®) Ibandronate (Bonviva®) Teriparatide (Forsteo®) Alendronate (Fosamax®) Denosumab (Prolia®) Sunitinib (Sutent®) Zolendronate (Zometa®) Tiludronate (Skelid®) Etidronat (Didronel®) Others
Do you recommend a dental check-up for patients before initialing BMA treatment?	Yes No
Are you aware of the side effects that may occur frequently following anti-resorptive treatments?	Nausea, vomiting, diarrhea Headache Dyspnea Kidney disease Musculoskeletal pain Osteonecrosis of the jaw Others
Do you know the definition/term Medication-induced Osteonecrosis of the jaw?	Yes No
Which definition is more familiar to you?	Bisphosphonate-related osteonecrosis of the jaw (BRONJ) Medication-related osteonecrosis of the jaw (MRONJ) Antiresorptive drug related osteonecrosis of the jaw (ARONJ)
How many patients with MRONJ have you ever managed?	5–1 10–5 >10
What type of management options did you recommend?	Sending the patient to OMF Surgeon Stopping the anti-resorptive treatment Prescribing antibiotics Recommending Hyperbaric oxygen therapy Applying blood growth factors
For patients with MRONJ, for which drug do you recommend a temporary withdrawal	Oral bisphosphonates I.v. bisphosphonates Denosumab Parathormone Teriparatide Tyrosine Kinazis Others
What is the usual drug withdrawal period recommended?	<3 months >3 months
Which dental procedure do you recommend drug withdrawal for?	Dental cleaning Dental filling Dental extraction Dental Implant insertion

The answers were gathered and later compiled and analyzed. Statistical analysis included elements of descriptive statistics included in the tables, which are presented as frequencies and percentages, and elements of inferential statistics. The chi-squared test was applied to determine the associations between qualitative variables. The threshold of significance chosen for the p -value was 0.05, and the statistical analysis was performed using the demo version GraphPad utility and the EpiInfo version 7 trial utility.

3. Results

For our study, we identified 90 BMA prescribers in our hospital. Out of these, 14 were excluded due to the lack of a valid email address or to their not being available for response

during the time of the study, resulting in 76 possible participants. A total of 55 BMA prescribers from different medical fields considered relevant to our purpose, including rheumatologists, oncologists, endocrinologists, and general practitioners, answered our questionnaire, which constituted a response rate of 72% and an attainability rate of 61%. Most responders were female (77%), and the average age of the responders was 40 years old. Most were endocrinologists (45%) and senior physicians (37%), and experience of prescribing BMAs was relatively well-distributed. The composition of the physician cohort is presented in Table 3.

Table 3. Survey respondents' characteristics.

Respondent Characteristics	Number (%)
Specialty	
Endocrinology	25 (46%)
General practitioner	11 (20%)
Oncology	9 (16%)
Rheumatology	10 (18%)
Professional status	
Senior physician	20 (37%)
Specialist	24 (43%)
Resident	11 (20%)
Experience prescribing BMA	
<5 years	22 (40%)
5–10 years	14 (25%)
10 years	19 (35%)

The physicians usually prescribed BMAs for osteoporosis (83%) and osteopenia (67%), with bone metastases presenting as a less frequent indication for treatment (20%), followed by osteogenesis imperfecta (18%) and Paget's disease (15%). The most common BMAs prescribed were oral bisphosphonates (96%), followed by i.v. preparations (56%), with less than half using denosumab (42%) and teriparatide (35%) or other treatment options. The most commonly used medications for these patients were both second- and third-generation bisphosphonates, such as alendronate (Fosamax®) and ibandronate (Bonviva®), with other preparations being used far less frequently, such as denosumab (Prolia®) and teriparatide (Forsteo®), while sunitinib (Sutent®) was prescribed by even fewer physicians. The complete prescribing practices of the respondents are presented in Table 4.

Current knowledge of the definition of MRONJ was very prevalent in our responders (91%), regardless of specialty, although most prescribers preferred the previous notion of bisphosphonate-related osteonecrosis of the jaw (BRONJ) to MRONJ or antiresorptive drug-related osteonecrosis of the jaw (ARONJ)—70% vs. 17% and 13%, respectively. Most of the physicians surveyed had encountered patients with MRONJ, with an average of 62%, but there were differences related to their fields of practice, with all oncologists having encountered this complication, 60% of endocrinologists and rheumatologists, and only 36% of general practitioners.

Regarding prevention practices, most physicians recommended a dental check-up prior to initiating treatment with bisphosphonates (65%), but not when prescribing denosumab (47%), teriparatide (29%), or tyrosine kinase inhibitors (31%). This recommendation was not influenced by physician specialty regarding bisphosphonates, with no significant differences reported between different specialties ($p = 0.273$), or denosumab ($p = 0.347$); however, general practitioners were more likely to recommend it to patients when initiating teriparatide ($p = 0.032$) or tyrosine kinase inhibitors ($p = 0.015$). A summary of recommendations and comparisons between physicians are presented in Table 5.

Table 4. Survey respondents' prescribing practices.

Prescribing Practices	Number (%)
Indication for BMA	
Osteopenia	37 (67%)
Osteoporosis	46 (84%)
Osteogenesis imperfecta	10 (18%)
Paget's disease	8 (15%)
Bone metastasis	11 (20%)
Myeloma	2 (4%)
Type of BMA prescribed	
Oral bisphosphonates	53 (96%)
I.v. bisphosphonates	31 (56%)
Denosumab	23 (42%)
Tyrosine kinase inhibitors	4 (7%)
PTH	19 (35%)
Teriparatide	19 (35%)
Others	2 (4%)
Specific BMA prescribed	
Pamidronate (Aredia®)	1 (2%)
Risedronate (Actonel®)	3 (5%)
Ibandronate (Bonviva®)	32 (58%)
Teriparatide (Forsteo®)	14 (25%)
Alendronate (Fosamax®)	44 (80%)
Denosumab (Prolia®)	16 (29%)
Sunitinib (Sutent®)	5 (9%)
Zoledronate (Zometa®)	11 (20%)
Others	1 (2%)

Table 5. Recommendations for dental check-ups before BMA initiation and comparisons between specialties. Significant differences are marked with *.

Recommendation for Dental Check-Ups before Initiating BMA	Bisphosphonates	Denosumab	Teriparatide	Tyrosine Kinase Inhibitors
Specialty				
Endocrinology	17 (68%)	13 (52%)	5 (20%)	3 (12%)
General practitioner	6 (55%)	7 (64%)	7 (64%)	7 (64%)
Oncology	8 (89%)	3 (33%)	1 (11%)	4 (44%)
Rheumatology	5 (50%)	3 (30%)	3 (30%)	3 (30%)
Overall	36 (65%)	26 (47%)	16 (29%)	17 (31%)
<i>p</i> -value for comparisons	0.273	0.347	0.032 *	0.015 *

Patients who required dental treatment while on BMA therapy were more likely to be recommended temporary withdrawal of the drug only when using bisphosphonates (55%) but not when using any other BMA. This practice varied among different specialties, with general practitioners and oncologists being significantly more likely to apply this preventative measure for patients on bisphosphonates ($p = 0.041$) and tyrosine kinase inhibitors ($p < 0.001$) and only general practitioners for patients on teriparatide ($p = 0.025$). Table 6 presents the results of the survey regarding recommendations for drug withdrawal before dental treatments in patients with MRONJ.

Table 6. Recommendations for discontinuation of BMAs before dental treatment and comparisons between specialties. Significant differences are marked with *.

Recommendation for Discontinuation of BMA before Dental Treatment	Bisphosphonates	Denosumab	Teriparatide	Tyrosine Kinase Inhibitors
Specialty				
Endocrinology	10 (40%)	6 (24%)	2 (8%)	1 (4%)
General practitioner	9 (82%)	7 (64%)	6 (55%)	7 (64%)
Oncology	7 (78%)	5 (56%)	3 (33%)	6 (67%)
Rheumatology	4 (40%)	3 (30%)	3 (30%)	3 (30%)
Overall	30 (55%)	26 (47%)	14 (25%)	17 (31%)
<i>p</i> -value for comparisons	0.041 *	0.086	0.025 *	<0.001 *

4. Discussion

The study sought to draw attention to the side effects of BMA treatment in the oromaxillofacial region. Unfortunately, in addition to the positive effects of BMA therapy used in the treatment of osteoporosis or bone metastases, the side effects remain a topic worthy of consideration.

Osteonecrosis of the jaw (ONJ) is a process of bone degradation that occurs through the action of several internal and external factors on bone tissue. During the last two decades, a strong correlation between BMA and ONJ has been reported. The correlation between dosing and the pathophysiological mechanisms of osteonecrosis due to BMA has not yet been established. One theory is related to the effect of BMA in inhibiting osteoclast differentiation and increasing apoptosis, due to the fact that the differentiation of osteoclasts has an important role in bone healing and remodeling. Another theory is related to local bacterial inflammation and infection, because periapical or periodontal pathology usually presents at the time of extraction alongside evidence of bacteriological factors, especially from the *Actinomyces* group, at the necrotic zone of the jawbone. [6] Medications such as bisphosphonates [1], denosumab [2,3], and sunitinib [4,5] have been implicated in the occurrence of MRONJ. This shows that different classes of drugs can cause MRONJ and that other agents from the same drug class should also be investigated in more controlled prospective studies aimed at assessing the risk of ONJ associated with these agents.

Among these, the bisphosphonates are most frequently involved in a condition also known as BRONJ, due to their use as a gold-standard therapy for osteoporosis, where they increase bone mineral density and decrease the risk of spine and hip fracture, and for preventing the skeletal manifestation of bone metastases. Currently, they are used both in oral and i.v. forms, and in our study more than 96% of our prescribers were still using these agents. Bisphosphonates have been shown to be beneficial in suppressing bone remodeling that helps slow bone loss in patients with osteoporosis. However, the danger posed by osteonecrosis has caused researchers to lose some of their enthusiasm for this class of drugs, and new treatment options have yet to be developed. Special attention should be paid to denosumab, which has been gaining more widespread use lately. In our study, almost 30% of prescribers, especially endocrinologists, were prescribing denosumab for osteoporosis with good results in patients with renal dysfunction. Compliance with this treatment has increased because of the biannual administration of denosumab, although more frequent administration, including monthly administration, can be used, which increases the risk of MRONJ. Prescribers should always advise patients to inform their dentist if they are using bisphosphonates or other BMAs before any dental treatment is performed.

In our study, there was a significant negative correlation between the use of tyrosine kinase inhibitors and teriparatide and the recommendation of a prior dental status check. In a systematic review of ONJ associated with sunitinib published by Vallina et al., 91% of patients received sunitinib at a dose of 50 mg/day for 1 to 36 months before the occurrence of ONJ. Due to this fact, attention should be given to those cases in which bisphosphonates and sunitinib are combined [4].

Unfortunately, only 17% of prescribers were familiar with the definition of MRONJ, and the BRONJ term is still preferred. Continuing medical education should increase knowledge about BMA therapy and the risk of developing MRONJ, not only after bisphosphonate use, because new treatments involving the antiangiogenic activity of the targeted agents can inhibit bone remodeling and delay the healing of tissues and thus enhance the development of ONJ [4].

Risk factors for the development of MRONJ are dental surgery, trauma, and poor oral hygiene with periodontal disease. Therefore, a dental check-up before initializing BMA treatment should be mandatory, good oral health should be ensured, and invasive treatments should be performed before any BMA initiation. Local development is primarily influenced by the drug administered, the pathology for which bisphosphonates are administered, the intravenous or oral route of administration, the dose administered, and the duration of treatment. A higher incidence is seen in patients with bone metastases receiving high doses of intravenous bisphosphonates over long periods [6].

Once initiated, treatment of MRONJ becomes a challenge. The decrease in quality of life for these patients is important, with eating and speaking disorders and toothbrushing difficulties being very common because of local pain. Non-surgical treatment of ONJ aims, firstly, to improve quality of life by improving symptoms and, secondly, to stop the progression of the disease. The treatment is influenced by the stage of the disease and can vary from simple conservative measures, such as clinical and radiological follow-up, oral hygiene with antiseptic solutions, local and general antibiotic treatment, symptomatic treatment, including pain control, or, in advanced stages, minimally invasive surgery [7] to remove sharp bone edges, or, in some cases, major surgery with partial maxillectomy or mandibular resection [8]. In addition, treatment is influenced by the type of BMA, as evidenced by the review conducted by Bermudez-Bejarano [7] which differentiates ONJ caused by oral bisphosphonates, where conservative treatment, clinical and radiological follow-up, minimally invasive surgical treatment, and adjuvant therapies are recommended, and i.v. bisphosphonates, where local conservative treatment, clinical and radiological follow-up, minimally invasive surgical treatment, but no adjuvant therapies are the most favorable approach [7].

Patient dental follow-up should also include an imaging screening by X-ray, where osteolysis, bone sclerosis, bone cortical erosion, bone sequestration, and the persistence of post-extraction unhealed alveoli with no bone formation may be observed, making imaging examinations essential in the early diagnosis of osteonecrosis. In advanced stages, pathological fractures and osteolysis can extend to the inferior border of the mandible or sinus floor; also, for the identification of early stages, measuring bone density can be recommended. A simple panoramic X-ray, which is commonly used by dentists, can indicate some of the initial signs, but after that, for more accurate information regarding the dimension of the lesion, cone beam computer tomography or magnetic resonance imaging are preferred.

A systematic review to answer the question of whether drug withdrawal at the time of tooth extraction or dentoalveolar surgery is necessary to prevent the development of MRONJ was conducted [9]. As previously mentioned, drug withdrawal is commonly used and the prescribers involved in our study tended to stop the administration of BMA before dental treatment mostly for bisphosphonates, rather than other BMAs, even though there currently is no evidence of benefit for this intervention and there are no studies that directly compare discontinuation with continuation of bisphosphonates or other BMAs. The effect of drug stoppage is still debated because of the different pharmacokinetics of BMAs. Temporary discontinuation of denosumab could be favorable due to denosumab's short half-life but unfavorable for i.v. bisphosphonates with a longer half-life [9], and drug interruptions should be continued for at least four months to prevent poor prognosis after surgery [10]. Our study reinforces the idea that insufficient information is available regarding the ideal period for a drug holiday pre-operatively or post-operatively and regarding which kind of dental intervention should indicate this preventative measure.

When allowed, such medication interruptions would ideally come to an end once the soft tissue has healed, and each case should be assessed separately.

Due to the multifactorial etiology of MRONJ, we recommend a multidisciplinary approach for these patients which should mandatorily include the dentist. The value of educating medical professionals about this issue and keeping current with new knowledge is immeasurable. Prescribers must be aware of MRONJ in order to properly assess the risks associated with prescribing medications associated with the condition and increase focus on necessary preventative measures. Before initiating BMA treatment, a dental check-up should be performed, any oral disease should be treated, and a good oral status should be obtained, with subsequent regular dental follow-ups necessary. It is clear that the dentist plays a crucial role in MRONJ prevention by evaluating local risk factors in patients who are undergoing BMA therapy. Patients receiving these medications should also be advised to pay closer attention to oral care and report any symptoms or signs of ONJ. Although treatment of the condition improves symptoms, curing ONJ is a difficult goal to achieve in most patients using the current methods available.

The patient should be informed regarding the risk of developing MRONJ, clear information regarding factors risk must be delivered, and the patient should be advised to maintain very good oral health to prevent the appearance of ONJ. Poor patient knowledge or comprehension of preventative measures is a significant barrier to MRONJ prevention. Improvement of oral hygiene by a preventive dental check-up must be performed. In addition, imaging examinations for these patients using X-rays should be included as screening measures, with simple panoramic X-ray or cone beam computed tomography use for the attainment of more accurate information.

Although the results of the study are very useful, there are some inherent limitations. Due to its single-center nature, our results are difficult to generalize, though they can create a snapshot of the current knowledge and practices of physicians prescribing BMAs for patients with MRONJ at an academic-hospital level in our region. Furthermore, a higher number of responders would have improved the generalizability of the results; as participation was voluntary, the number of respondents was limited.

5. Conclusions

BMA prescribers of different specialties, including rheumatology, oncology, endocrinology, and general medicine, have relatively good awareness of MRONJ and of the drugs associated with this condition. Most physicians recommend a dental check-up prior to initiating treatment with bisphosphonates, but this practice is less prevalent for other BMAs. Patients who required dental treatment while receiving BMA therapy were more likely to be recommended a temporary withdrawal of the drug only when using bisphosphonates, not when using any other BMAs. When providing dental care to patients with osteoporosis or bone metastases, dentists and physicians must work together to assess patient drug history and general health. Attention should be paid to newer BMAs, such as denosumab and sunitinib, and not only to classic agents, such as bisphosphonates. Health care professionals should improve communication and clear guidelines to prevent MRONJ should be introduced while ONJ and new angiogenetic therapies are still being researched.

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