

## RESEARCH ARTICLE

# Medication-related Osteonecrosis of the Jaws: A Prospective Cross-sectional Study in a Moroccan Population

Chaimae Mahad <sup>a,\*</sup>, Abdellatif Benider <sup>c</sup>, Ihsane Ben. Yahya <sup>b</sup>

<sup>a</sup> Oral Medicine and Oral Surgery, CCTD CHU Ibn Rochd, FMDC Casablanca, Morocco

<sup>b</sup> Faculty of Dental Medicine of the University Mohammed VI of Health and Sciences, Morocco

<sup>c</sup> Oncology Center CHU Ibn Rochd, Casablanca, Morocco

## Abstract

**Introduction:** The surgical dentistry department of the CCTD in Casablanca is increasingly receiving cases of medication-related osteonecrosis of the jaws (MRONJ); however, there is a lack of epidemiological data in the department concerning aspects of these conditions. Therefore we proposed to conduct a descriptive cross-sectional study, the main objective of which is to draw up the epidemiological profile of cases of MRONJ in the Oral Surgical department and in the Oncology Department of the Ibn Rochd University Hospital in Casablanca.

**Methods:** A descriptive cross-sectional prevalence study, lasting 2 years, was carried out in the surgical dentistry department of the CCTD and in the oncology department of the Ibn Rochd University Hospital in Casablanca. All patients on bisphosphonates or with a history of bisphosphonate treatment were included in the study. Data was collected on the basis of an anonymous self-administered questionnaire after obtaining the patient's consent. Statistical analysis was performed using SPSS version 22 software.

**Results:** Our study population included 25 patients receiving BP treatment. The average age was 55 years old. 88% of patients were women. 64% of patients were receiving Zoledronic acid intravenously. MRONJ was diagnosed in 40% of the patients in our study. Mandibular localization was found in 70% of cases. 55.6% of patients had undergone dental extractions without preparation. Practitioners took a conservative approach to the treatment of MRONJ in 60% of patients.

**Conclusion:** Several factors can promote or trigger the occurrence of MRONJ. They are both related to treatment with BP and to the patient. Given the frequency, the difficulty of management and the often reserved prognosis of this pathology, prevention and follow-up must occupy an important place in the management of patients.

**Keywords:** Osteonecrosis of the jaws, Bisphosphonates, Diagnosis, Management

## 1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is defined by direct bone exposure in the maxillofacial region or via intra- or extra-oral fistula, persistent for more than eight weeks, in the absence of history of head and neck radiotherapy or metastatic involvement of the jaw [1,2].

Bisphosphonates (BP) are synthetic analogs of pyrophosphates with a strong affinity for hydroxyapatite crystals. They have a half-life of up to 12 years. Discovered in the 1960s, BP were primarily prescribed to inhibit the activity of osteoclasts. Historically, the first BP (Etidronate) was approved by the Food and Drug Administration (FDA) in 1977. Bisphosphonates have multiple actions, they inhibit osteoclastogenesis

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\* Corresponding author.  
E-mail address: [mahadchaimae.1991@gmail.com](mailto:mahadchaimae.1991@gmail.com) (C. Mahad).

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and induce osteoclast apoptosis. They also have an anti-angiogenic, anti-inflammatory action by inhibiting cytokines and a specific anti-tumor action, by targeting the Epidermal Growth Factor receptor (EGFR). There are two categories of BP with a different mode of action, the first generation amine-free bisphosphonates (clodronate, etidronate, tiludronate, etc.) and aminobisphosphonates (pamidronate, risedronate, alendronate, ibandronate, zoledronate, etc.) which represent the second and third generation of BP. They are characterized by the presence of a nitrogen atom on their side chain with a potency in vitro much greater than the others. BP are indicated in malignant pathology in the prevention of bone complications (pathological fractures, spinal cord compression, etc.) and in the treatment of hypercalcaemia or in benign bone pathologies (osteoporosis, Paget's disease). They are administered intravenously or orally. The prevalence of osteonecrosis of the jaws (ONJ) depends on the route of administration, the first cases were described by Marx and 2003, and since then the increase has been constant [3,4].

The Oral Surgical department of the Casablanca Dental Consultation and Treatment Center receives more and more cases of MRONJ and due to the lack of epidemiological data in our department concerning aspects of these conditions, we proposed to conduct a descriptive cross-sectional study, the main objective of which is to draw up the epidemiological profile of cases of MRONJ induced by BP in the Oral Surgical department and in the Oncology Department of the Ibn Rochd University Hospital in Casablanca.

## 2. Methods

**Study design:** We conducted a prospective cross-sectional study during a period of 2 years, from 2018 to 2020.

A preliminary survey was carried out before starting the main survey. The aim was to familiarize the interviewer with the clues used in the survey and to make changes to the questionnaire if necessary. At the end of the pre-survey, the questionnaire was validated and no changes were reported.

**Study population:** the target population was patients consulting the Oral Surgical department of the Casablanca Dental Consultation and Treatment Center, as well as those consulting or followed up in

the department of Oncology at the Ibn Rochd University Hospital in Casablanca. All patients on bisphosphonates or with a history of bisphosphonate treatment were included in our study. On the other hand, patients irradiated to the orofacial sphere were excluded from the study.

**Data collection:** Data was collected on the basis of an anonymous self-administered questionnaire made up of 23 questions divided into 5 sections: The first on the identification of the patient, the second on the general condition and lifestyle, the third on report with the reason for prescribing bisphosphonates, the 4th concerning the molecule administered and the last devoted to the characteristics of the attack by osteonecrosis (in our study, we used the 2009 AAOMS classification to determine the stage of ONJ).

**Course of the study:** the survey was conducted by a single interviewer (resident in the oral surgery department). According to the standard procedure, the investigator presented himself to the patient with the form, explained the procedure to him (nature of the study, its objectives, and the conditions of participation) then proceeded to collect the data after obtaining the patient's consent.

**Statistical analysis:** Data analysis was performed using SPSS version 22 software.

### 2.1. Ethical considerations

We conducted a descriptive study, the authorization of the ethics committee was not necessary, however an informed consent was obtained by all the patients included in the study.

## 3. Results

Our study population included 25 patients receiving BP treatment. The average age was 55 years old. 88% of patients were women. BP treatment was indicated in 40% of cases for breast cancer metastases. 64% of patients were receiving Zoledronic acid intravenously. 40% of patients developed MRONJ which was diagnosed at stage 2 in 40% and stage 3 in 50% with a mandibular location in 70% of cases. Furthermore 55.6% of patients had undergone dental extractions without preparation. Regarding patient care, practitioners took a conservative approach to the treatment of MRONJ in 60% of patients and a medical-surgical approach in 20%.

Variables	Number	%
Gender:		
Male	3	12%
Female	22	88%
General pathology under medical treatment:		
High blood pressure	3	12%
High blood pressure/anemia	1	4%
High blood pressure/ hyperlipidemia/uterine cancer	1	4%
Diabetes	2	8%
Hypothyroidism	1	4%
Rheumatoid arthritis	1	4%
Immunodeficiency	1	4%
No pathology	15	60%
Indication of BP:		
Breast cancer	10	40%
Prostate cancer	2	8%
Chronic leukemia	2	8%
Multiple myeloma	1	4%
Osteogenesis imperfecta	2	8%
Osteoporosis	8	32%
Molecule administered:		
Ibandronic acid	1	4%
Alendronic acid	8	32%
Zoledronic acid	16	64%
Route of administration:		
Oral route	9	36%
Intravenous	16	64%
Frequency of administration:		
Once/week	8	32%
Once/month	7	28%
1time/3 months	8	32%
1time/4 months	1	4%
1time/8 months	1	4%
Duration of BP treatment:		
1 month	1	4%
3 months	1	4%
4 months	1	4%
6 months	3	12%
8 months	3	12%
12 months	4	16%
14 months	1	4%
18 months	2	8%
24 months	5	20%
30 months	1	4%
5 years	1	4%
7 years	2	8%
Prevalence of ONJ	10	40%
Oral risk factors:		
Poor hygiene	2	22.2%
Extraction with preparation	2	22.2%
Extraction without preparation	5	55.6%
ONJ's site:		
Maxilla	2	20%
Mandible	7	70%
Both	1	10%
Stages (AAOMS):		
Stage 1	1	10%
Stage 2	4	40%
Stage 3	5	50%
Date of onset of ONJ:		
2 months	1	10%

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Variables	Number	%
3 months	1	10%
8 months	2	20%
10 months	1	10%
12 months	4	40%
3 years	1	10%
Management:		
Medical treatment	6	60%
Surgical treatment (non-radical)	1	10%
Medical/surgical Traitement (non-radical)	2	20%
None (monotoring)	1	10%
Medical treatment:		
ATB/Antiseptic	7	87.5%
ATB/Analgesic/Antiseptic	1	12.5%

#### 4. Discussion

ONJ was diagnosed in 40% of the patients in our study. In the literature, the prevalence reported by studies is variable. It depends on the type of BP and the route of administration used as well as the duration of treatment. Not all BP carries the same risk of developing ONJ. Almost all ONJ occur with amino-BP [4]. All patients treated with BP in our study received second and third generation BP. The intensity of bone effects linked to the presence of nitrogen function could explain the involvement of second and third generation BP in the occurrence of ONJ. Third generation BPs (Risenedronate, Ibandronate, Zoledronate) have methylation of the amine group, which makes them 10 to 20 times more potent than second generation BPs [5]. In our study, the majority of patients (64%) were treated with Zoledronic acid. In studies by K. Vahntsevanos, K. Zervas et al., The authors found a significant increased risk of developing ONJ with the use of Zoledronic acid [2,6]. According to the American Society of Clinical Oncology, Zoledronic acid is one of the most potent bone resorption inhibitors, associated with a high incidence of ONJ. In addition to its potent antiresorbent action, Zoledronate also has an anti-angiogenic effect which may constitute an important etiopathogenic co-factor for the development of ONJ [4].

The prevalence of ONJ is different depending on the route of administration used. The frequency of ONJ during oral BP treatments varies greatly depending on the studies. It varies between 0.001 and 0.1% [7,8]. Intravenous (IV) bisphosphonates are more often involved in the development of ONJ than those taken by orally. In our study 64% of patients received IV BP. ONJ induced by IV BP, for malignancies, is estimated to be between 1 and 10% [9]. In 2002 the United States government identified a total of four million patients with ONJs induced by Zoledronic acid [10]. In France,

the Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM) reported an incidence of ONJ varying between 0.8 and 12% in patients treated for malignant disease by IV BP [11]. Some studies have reported significantly higher incidences of up to 28% [4].

In our study, the duration of treatment with bisphosphonates was between 1 month and 7 years. The risk of developing ONJ goes from 1% after 12 months of treatment to 11% after 48 months. On the other hand, the bone lifetime of BP is around 10 years, due to a very strong affinity for bone tissue by binding to hydroxyapatite crystals, and prolonged use of these drugs can lead to its accumulation in the skeleton. The risk of occurrence of ONJ is therefore proportional to the cumulative dose and increases with the duration of exposure. The American Dental Association (ADA) and AAOMS confirm this increased risk related to dose and duration of exposure. In patients treated with IV amino-BP, the risk of occurrence increases significantly after 2 years [3,4].

Poor oral hygiene, infectious dental or periodontal focus, trauma and dental treatment exposing the jaws (dental extractions, surgery periodontal or implant) have also been demonstrated to be risk factors for the development of ONJ. The presence of a solution of continuity of the mucosa promotes contamination, from the oral flora, of the bone in the process of necrosis, which leads to the appearance and extension of the necrosis process [12]. According to AAOMS, the risk of ONJ is multiplied on average by seven in the event of dental surgeries [13]. The average time between performing an invasive oral treatment and the onset of ONJ is 6.6 months. Several studies have shown that surgery is the trigger for ONJ [14–16]. In our study, 90% of patients had a local risk factor, 22.2% had poor oral hygiene and 55.6% had received dental extractions without preparation. For Bamias et al., 88% of patients with ONJ had undergone dental extractions in the 12 months preceding the discovery of ONJ [17]. However, avulsion may make visible the underlying necrotic bone already present at an initial stage, which may be the cause of the indication for extraction. In 14%–20% of cases, ONJ occurs spontaneously, indeed 10% of patients reported spontaneous onset of ONJ in our study.

The onset of ONJ is more common in the mandible than the maxilla. In our study, mandibular localization was found in 70% of cases against 20% in the maxilla. Similar results have been reported in the literature. Khan et al., reported a higher incidence in the mandible (65–73%) compared to the

maxilla [18]. Delamarre et al., reported a mandibular localization in 59% of cases and maxillary in 27% [9].

The diagnosis of ONJ is based on the correlation of clinical and radiological signs. There are several classifications of bisphosphonate related osteonecrosis of the jaw. In 2007 AAOMS established an ONJ classification with 3 stages. This classification was updated in 2009 and 2014 by adding new stages [14,19].

In our study, most patients had ONJ diagnosed at stage 2 (40%) and 3 (50%). This can be explained by the delay in consultation. Indeed, 40% of patients consulted 12 months after the onset of ONJ. In a prospective study conducted by Stockmann et al. on 50 patients receiving IV BP, 23 patients presented ONJ at stage 2 and 14 at stage 3. In another study by Barrier et al., 7 patients were at stage 2, 4 at stage 3 and only one patient at stage 1 [20]. Most authors have also relied on this classification. Petra Rugani et al., James S. Goodwin et al. and T. Shintani used the latest AAOMS classification as a benchmark to determine the incidence and stage of ONJ [21–23].

The management of ONJ is multidisciplinary. The goal is to control pain, prevent further bone complications, and preserve quality of life. There is currently no international consensus regarding therapeutic strategies for ONJ. Most scientific societies use the AAOMS classification to determine which treatment strategies to adopt.

A conservative approach is often recommended for stages 0–2 [24–26], aimed at reducing pain, infection of soft and bone tissue, and minimizing progression of necrosis. It is based on patient education with maintenance of good oral hygiene, as well as the prescription of antiseptic mouthwashes, suitable analgesics in case of pain and antibiotic therapy in the presence of suppuration (Amoxicillin, Phenoxyethylpenicillin or Penicillin V, Amoxicillin-Clavulanic Acid or Clindamycin, with or without Metronidazole) for at least 7–14 days. Superficial local debridement may be necessary to remove soft tissue irritation and to remove any mobile bone sequestration [3,19]. In our department, practitioners opted for a conservative approach in 60% of patients with the prescription of medical treatment based on antibiotics (ATB) and antiseptics for 87.5% of patients. Surgical treatment is most often indicated for advanced stages (stage 3), or in case of failure of the conservative treatment. Removal of necrotic bone, which is a chronic irritant, allows the site to heal. In severe forms, radical surgery may be indicated, combining segmental resection and reconstruction using a microvascularized bone flap (fibula) or regional tissue flap. Recent studies have shown encouraging cure

rates with Teriparatide (recombinant parathyroid hormone (PTH)). Other adjuvant experimental treatments have been proposed such as ozone therapy, the use of Pentoxifylline and Tocopherol in combination with the usual antibiotics or the addition of plasma rich in platelets, in an attempt to improve treatment, by stimulating cell proliferation and the tissue repair process [3].

## 5. Conclusion

The prevention of the occurrence of MRONJ plays an important role in the management of patients, given the frequency, the difficulty of management and the often reserved prognosis of this pathology. It requires close collaboration between the attending physician (oncologist, rheumatologist, hematologist) and the dental surgeon.

## 6. Limitations of the study

- The study was conducted during the COVID pandemic
- Contact was made with the rheumatology department, but given the circumstances of the COVID-19 pandemic, the consultation was carried out remotely by rheumatologists, which prevented us from carrying out our investigation within the department.

## Conflict of interest

The authors declare that there is no conflict of interest.

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