

## **Bisphosphonate Associated Osteonecrosis of the Jaw: A Bibliographical Review**

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### **Abstract**

**Aim of the Work:** to describe the function of bisphosphonates, investigate osteonecrosis of the jaws caused by drugs and the related therapeutic options, comparing pros and cons of each.

**Methods:** Reviewed of the literature and information on databases such as Pubmed, Embase and Scielo. Particular consideration was given to articles with objectives similar to this paper.

**Results:** Most authors, according to the cases analysed, use an either a medical or surgical approach, or both. Other complementary therapies to standard treatments are also reported.

**Conclusions:** The pathological picture can improve and, in some cases, completely heal through a careful choice of the most suitable treatment for the patient and the severity of the case. In most cases, a conservative approach is required along with a surgical strategy.

**Keywords:** *Osteonecrosis, Bisphosphonates, Jaw's Osteonecrosis, Osteonecrosis Treatments*

### **Abbreviations**

IV: Intravenously; MRONJ: Medication-Related Osteonecrosis of the Jaw; AAOMS: American Association of Oral and Maxillofacial Surgeons; HBO: Hyperbaric Oxygen; OT: Ozone Therapy; PRP: Autologous Platelet-Rich Plasma; LIL: Low-Intensity Laser

### **Introduction**

Numerous researches were carried out to stop the resorption capacity of osteoclasts and thus be able to treat the various bone pathologies of bone-mineral metabolism (osteoporosis, rheumatoid arthritis, Paget's disease, multiple myeloma and bone metastases) [1]. Around the 1960s, drugs called bisphosphonates began to be used. [2].

Bisphosphonates are drugs that act at the bone level, in an anti-resorptive manner, unite with hydroxyapatite, specifically block the activity of osteoclasts and inhibit mineral dispersion. Bisphosphonates can remain adhered to the bone surface for a long period, which is why their effects can persist even if the patient stops taking them. [3-4].

Bisphosphonates are now the standard in the treatment and prevention of bone complications.

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There are mainly two ways of taking such drugs: intravenously (i.v.) and orally. Intravenous bisphosphonates are more powerful than oral bisphosphonates and are generally used to treat bone metastases of malignant tumours. These medicines can improve patients' quality of life by increasing bone strength and mineral density and reducing the risk of fracture [5].

Medication-related osteonecrosis of the jaw (MRONJ) is one of the harmful effects of bisphosphonate treatment, and its pathophysiology and related treatments still remain unclear [6-7].

### MRONJ is defined according to the following criteria

- Current or previous treatment with anti-resorptive drugs or anti-angiogenic agents,
- Exposed bone or bone that can be probed through an intra or extraoral fistula in the jaws lasting more than eight weeks,
- Absence within the history of head and neck radiotherapy or metastasis of the jaw bones [7-8].

Around the affected area there is an inflamed area, purulent secretions and pain. Furthermore, if the necrosis is in an advanced stage, the patient may feel tingling and hypersensitivity. However, these clinical signs can remain silent for many months or years [9-11].

Given the great variety of clinical signs of MRONJ, some scholars proposed some classifications, the first was Ruggiero., *et al.*

Stage 1: Exposed bone with necrosis. Asymptomatic patient. There are no infections.

Stage 2: Exposed bone with necrosis. Pain, bone and soft tissue infection.

Stage 3: Exposed bone with necrosis. Pain and infection. Presence of extraoral fractures and/or fistulas and/or radiographic evidence of osteolysis up to the lower margin of the mandible.

Later this classification was changed by Bagan Sebastian, who introduced two levels in stage 2: levels A and B [12].

Stage 2 A: Exposed bone with necrosis or oral fistula without bone exposure, patient reports pain and infection of soft bone/tissue. It is kept under control with conservative treatment.

Stage 2 B: Exposed bone with necrosis or oral fistula without bone exposure, patient reports pain and infection of soft bone/tissue. Conservative treatment alone does not prevent the progression of necrosis/infection.

The latest classification was circulated by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014. This classification, like the others, describes different stages of evolution of the disease, introducing two more stages: "patients at risk" and "0".

Although stage 0 is a much-debated point of staging, many authors consider it extremely important for the early diagnosis of the disease [7-12].

Patients at risk have no exposed necrotic bone, but have previously been treated with i.v. bisphosphonates, or oral anti-resorptive or anti-angiogenic drugs.

In stage 0 there are no clinical signs of necrotic bone, but there are symptoms such as: odontalgia, pain in the jaw that radiates to the TMJ area, sinus pain with inflammation and enlargement of the maxillary sinus walls, sensorineural changes.

Other clinical symptoms are idiopathic tooth mobility, periapical or periodontal fistula. The radiographic features associated with stage 0 are as follows: bone resorption not attributable to chronic periodontal disease, changes in trabecular bone density, poor bone formation in areas of extraction, areas of osteosclerosis, larger periodontal ligament due to thickening of the lamina dura, sclerosis and reduction of the periodontal space [13-14].

In stage 1, patients present bone exposure or fistula, without symptoms or infections, radiographic features of stage 0 may be present. In stage 2, subjects exhibit the same clinical signs as stage 1, are symptomatic, and may have radiographic features of stage 0. In stage 3, there is bone exposure, necrosis, fistula, infection and at least one of the following clinical signs: necrotic bone in the alveolar area or even beyond this area, pathological fracture, extraoral fistula, oro-sinus or oro-nasal communication, osteolysis up to the lower edge of the mandible or sinus floor [12-15].

The pathogenesis of MRONJ seems to be multifactorial and to explain the causes it is essential to focus on bone exposure and its preferential place: the jaw [10-11].

In the jaw affected by the disease, there is an excessive suppression of bone turnover, infection and inflammation of the area, inhibition of angiogenesis, damage to soft tissues, damage to the immune system and microfractures.

All these factors, together with a certain genetic predisposition, contribute to the onset of the disease [8-12].

There are also risk factors in the development of MRONJ that can be systemic or local. In particular, the local factors are: dental prosthesis, oral surgery (extractions), periodontal pathologies, dental or gingival abscesses, local anatomical factors (thin mucosa, mandibular tori, palatine tori, mylohyoid crest) [9-12].

There are several methods of radiological diagnosis: orthopantomography, computed tomography, magnetic resonance, scintigraphy [16].

Panoramic radiographs can show radiolucent areas of osteolysis and radiopaque areas of osteosclerosis, bone sequestrers, hard lamina loss, and enlargement of the periodontal ligament space.

Computed tomography shows more clearly the destruction of cortical bone in the buccal-lingual area. If the osteonecrotic lesions are not detectable radiographically, an early diagnosis following the AAOMS classification is very useful [17].

Prevention is essential for MRONJ, considering that the treatment of this pathology is very complex and there is no universally approved protocol.

Communication between doctor, patient and dentist is the basis of good prevention [18].

The dentist will subject the patient to a complete oral examination and will carry out all the necessary treatments before the patient begins therapy.

In the first six months of taking bisphosphonate, the bone is still healthy and with normal bone renewal capacity, which is why in this first phase it is possible to carry out any invasive but necessary operations [19-20].

Risk factor control is the best approach to MRONJ prevention. Dental prophylaxis, the control of caries and the periodontal state have the aim of minimizing pathogenic bacteria in the oral cavity and controlling their entry, reducing the development of serious diseases or recognizing them in a timely manner, being able to cure them immediately [22-23].

### Materials and Methods

A literature review was carried out using the Pubmed, Embase, Scielo databases. Publications in English, Spanish and Italian were selected, in particular, 38 scientific articles.

In each database a search strategy was used by topics and keywords such as: “osteonecrosis por bifosfonatos”, “Bisphosphonates”, “Jaw’s osteonecrosis”, “Osteonecrosis treatments”. Most of the selected articles have been published in the past five years.

#### **The articles were then evaluated based on inclusion and exclusion criteria, including**

- Articles with similar objectives to this review, especially those that emphasized the functions of bisphosphonates, their action in the body and the development of MRONJ with the related therapeutic options.
- Consistency of the article with the topic of the revision.
- Reproducible materials and methods.
- Adequate patient sample and follow up.
- Clinical cases, animal studies, retrospective and prospective studies, systematic reviews, meta-analyses, articles with documented images to be able to visually analyse osteonecrosis lesions.

### Results and Discussion

Nowadays the treatment of MRONJ is a very controversial topic, there are different opinions according to the clinical cases.

However, there are objectives in common to all types of therapeutic approaches, such as: controlling the infection of hard and soft tissues, eliminating pain, avoiding the progression of lesions, promoting tissue healing and preventing the onset of new areas of necrosis.

In this paper we examine the multiple treatment strategies proposed by the authors of the analysed articles.

Some authors support and apply essentially conservative treatment to different types of patients, despite having some doubts about the effectiveness of a drug holiday.

Furthermore, if on the one hand all the authors confirm the effectiveness of antibiotics and antiseptics and therefore of the so-called conservative approach, on the other hand five of them (J. Gutiérrez [25], R. Filefel y cols [6], Danny Hadaya y cols [26], Louise Dunphy y cols [27], Noam Yarom y cols [13] limit the use of the conservative strategy to the early stages of MRONJ or in cases where the patient’s pathological picture does not allow surgery. Therefore, the five authors prefer a less conservative approach in the presence of osteonecrosis refractory to medical treatment or in cases of necrosis in advanced stages.

Another type of approach applied in different cases is surgical therapy. The most commonly used surgical procedures are flaps for bone exposure, sequestrectomy, resection of injured bone portions, flaps for closing the oro-antral communications and mandibular reconstructions.

Some authors state that in most cases the surgical approach relieves symptoms or completely cures bone necrosis. Beth-Tasdogan NH., *et al.* [28] prefers a surgical approach as little invasive as possible (sequestrectomy, debridement) to facilitate tissue healing. Authors

such as Ruggiero L., *et al.* [29] and Cesar A. Migliorati., *et al.* [7] recommend the application of the surgical method even in the early stages of MRONJ. However, Díaz R. J., *et al.* [30] and An J. G., *et al.* [31] pay particular attention to the potential risk factors of a possible invasive operation, such as the possibility of extending the lesion to healthy areas.

In summary, all the authors mentioned above prefer a more or less invasive surgical approach, but do not eliminate the use of medical treatment. In fact, the authors believe that surgery is superior to less invasive treatments, but always preceded or followed by conservative treatment.

In addition to medical and surgical treatment, the selected articles report other therapies complementary to standard treatments.

An alternative is teriparatide, a recombinant form of the parotid hormone, which can increase bone density by stimulating osteoblasts. Other therapeutic options are hyperbaric oxygen (HBO), ozone therapy (OT), autologous platelet-rich plasma (PRP) and low-intensity laser (LIL) [32-34].

Most authors recognize the usefulness of the various complementary therapies, which can give a better outcome than the main conservative or surgical therapies alone [28].

### Conclusions

- Bisphosphonates are drugs used to treat diseases of bone-mineral metabolism thanks to their anti-resorptive action. These medicines slow down the reabsorption of osteoclasts and join hydroxyapatite for a very long period, and the effects on the body can persist even when the patient interrupts the treatment.
- A secondary effect associated with bisphosphonates is the osteonecrosis of the jaw (MRONJ).
- Drug-induced osteonecrosis of the jaws presents pain and local oral symptoms similar to many other pathologies. In order to distinguish MRONJ from other pathologies it is essential to analyse the specific clinical signs. In addition, the patient who develops MRONJ is usually being treated, or has been, with anti-resorptive drugs.
- It is essential that the patient who will be treated with bisphosphonates undergoes a complete check-up of the oral cavity. Prophylaxis can prevent the onset of any pathologies.
- Therapeutic approaches are manifold and there is no standard therapy.

The conservative method is a non-invasive treatment that is applied starting from the early stages of the disease, it can include antibiotics, antiseptics and bisphosphonate suspension (drug holiday). Surgical therapy includes less invasive operations such as sequestrectomy and debridement but also more complex operations such as resection of necrotic bone portions, closure of the oro-antral communications and mandibular reconstruction.

The medical approach is always necessary, however, in some cases, it must be accompanied by surgery to lead to complete recovery from the disease.

Indeed, the combination of medical and surgical therapy could become the gold standard in the treatment of MRONJ.

Complementary therapies are another important part of the treatment. Among them, teriparatide and laser are the two options to be considered to improve pain, inflammation and tissue scarring, which can lead to a favourable prognosis of the clinical picture.

Finally, despite the various therapeutic options available, the choice of a conservative approach together with a surgical strategy, with the help of complementary treatments, can improve the pathological picture and in many cases can lead to complete recovery from the disease.

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