

# Osteonecrosis Induced by Antiresorptive and Antiangiogenic Drugs in the Jaw

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## Abstract

ONMRM is a rare disease that attacks the soft and hard tissues of the oral cavity. The importance of this collection of information lies in providing a source of consultation necessary for the prevention, diagnosis, and treatment in the presence of Medication-Related Osteonecrosis in the Jaws (ONMRM). ONMRM treatments depend on various variables such as age, sex, comorbidities, disease status, ONJ stage, and symptoms. The protocol was considered in accordance with the Cochrane standards for systematic reviews. The search criteria complied with the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA) guidelines. A total of 378 were reviewed and 68 studies were included in the review. Preventing ONJ should be a priority in patients receiving treatment with antiresorptive and antiangiogenic drugs, carefully considering oral hygiene with a prior review by a dentist and hygienist before starting therapy with these drugs. Although there is a lack of clarity concerning the functioning and interaction of antiresorptive and antiangiogenic drugs with the jaws, doubts arise about the pathophysiology of this condition as well as the course of ONJ.

**Keywords:** jaw osteonecrosis; antiresorptives; antiangiogenic.

## 1. Introduction

Drug-related osteonecrosis of the jaw is a rare disease that attacks the soft and hard tissues of the oral cavity, a condition that is unknown to doctors and dentists. The importance of this collection of information lies in providing a source of consultation necessary for the prevention, diagnosis and treatment of the presence of Medication-Related Osteonecrosis in the Maxillae (MRONJ). Its mismanagement leads to a deterioration in the maxillary bones since oral health problems are not corrected before prescribing antiresorptive and antiangiogenic drugs(1)(2) (3). Knowing the medications that cause osteonecrosis in the jaw will help prevent damage that can be generated in the jaw. (4) Osteonecrosis occurs in individuals undergoing dental extractions in which infections are evident. Bisphosphonates and denosumab are currently presented, which are of great relevance in the treatment of osteoporosis, the most commonly used bisphosphonates contain nitrogen (alendronate, risedronate, ibandronate and zoledronic acid), important(5) as it helps prevent bone wear. Bisphosphonates have effects that depend on their affinity for hydroxyapatite which helps to be taken up by osteoclasts for bone

remodeling. (6) Preventive care when administering anti-inflammatory and antiangiogenic drugs is important and control should be encouraged in the presence of bacterial plaque, rigor in the process of surgical interventions during the healing process and optimal care in the dental hygiene process.(7) Among the risk factors, to determine the pathologies it is important to perform a histopathological examination of the damage caused by "Osteonecrosis in the Maxillae Related to Medication" (ONMRM), in order to rule out differential diagnoses, radiography examination to determine the symptoms, osteoradionecrosis. The subsequent conditions are included in the differential diagnosis: periodontitis, osteomyelitis, sinusitis, osteoradionecrosis, and primary bone tumors or metastases. Over time, research has been done on a way to prevent and treat drug-related osteonecrosis of the jaw and no ideal method has been found to treat it. There are alternatives such as treatment with hyperbaric oxygen therapy as a complement to conventional therapy but there is not enough evidence to rule out or confirm a benefit of this. Your treatment also depends on the stage, the AAOMS (American Association of Oral Maxillofacial Surgery) and the JADA (The Journal of the American Dental Association) established treatment strategies for each stage. The following review will be carried

out due to the need to deepen the pathophysiology of osteonecrosis of the jaw, in order to know the drugs (8)(9)(10)(11)(8) that cause osteonecrosis in the jaw, recognizing the mechanism of antiresorptive and antiangiogenic drugs. In addition, exposing its contraindications in dental processes to identify prevention, diagnosis and treatment practices. For this reason, it is of great importance to disseminate the professionals and organizations that express their skills in the health area.

## 2. Misall

The protocol was designed in accordance with Cochrane standards for systematic reviews. The search criteria met the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews and meta-analyses of intervention trials.(12) Ethical approval of this study was not necessary because it was a systematic review of the accessible literature and individual patient data were not included.

We searched three electronic databases (PubMed, LILACS and Elsevier via ScienceDirect), and used Boolean terms and operators as follows: "(osteonecrosis mandibular) AND (osteonecrosis of the jaw induced by antiresorptive and antiangiogenic drugs) OR osteonecrosis of the jaw induced by antiresorptive and antiangiogenic drugs OR osteonecrosis of the jaw induced by antiresorptive and antiangiogenic drugs) AND (jaw jaw jaw)". The year of

publication was limited to the last 7 years, language and publication status were not limited, and there were also no limitations in terms of any particular study design, including randomised or non-randomised controlled trials, cohort studies and case reports, plus drug leaflets were reviewed, and drug leaflets and ONJ treatment guidelines. In addition, article references were also manually checked to identify other potentially relevant literature. We did not search for unpublished articles.

The exclusion criteria were: studies older than 7 years, conducted on animals, studies without statistical analysis.

We screened the full texts of potentially relevant studies to answer the research question. Studies that investigate the mechanism of antiresorptive and antiangiogenic drugs recognizing their contraindications in dental processes and facilitating the understanding of the pathophysiology of osteonecrosis of the jaw. In addition, articles that determine in practices for its prevention, diagnosis and treatment were sought.

A total of 378 articles were reviewed, 10 studies were excluded by duplication, 120 studies based on title, 165 based on the information found in the abstract and title and 15 after reading the articles in full text. Finally, 68 studies were included in the review. You can see the diagram flow in Figure 1.

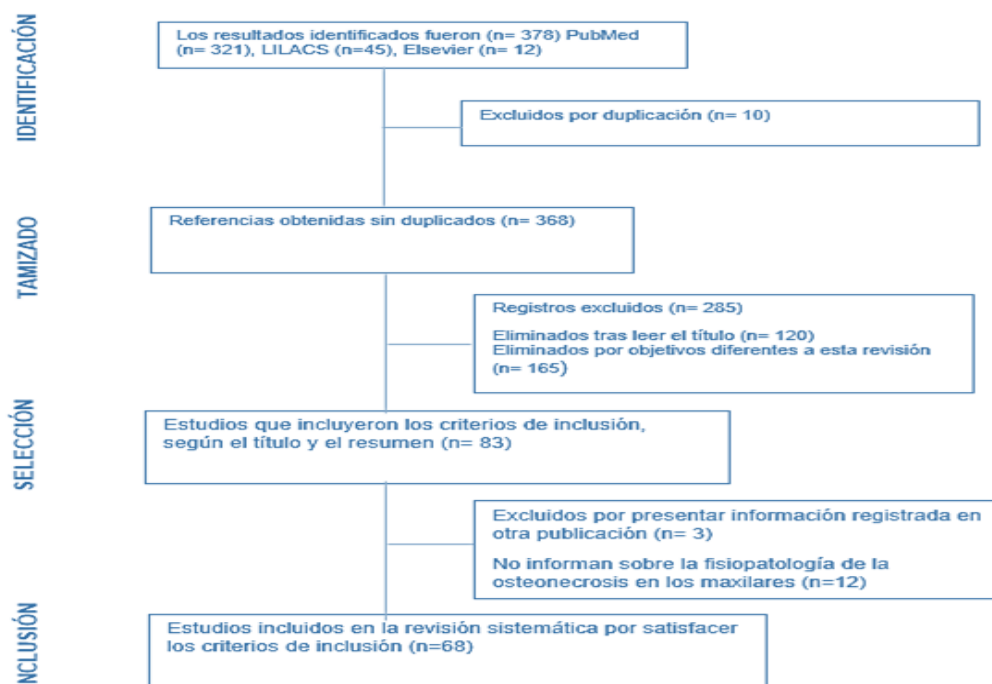


Fig 1: Flowchart of the systematic review conducted

## 3. Results

### Physiopathology of drug-induced osteonecrosis

Drug-induced osteonecrosis in the jaw is a little-known disease that occurs in people treated with antiresorptive and antiangiogenic drugs, as these affect bone physiology (8)(13) . In osteonecrosis of the jaw one or more parts of the bone in this

region die (suffering necrosis) there are bone fragments that can be seen exposed in the mouth are easily confused with broken teeth can affect the upper jaw (maxilla) and lower jaw (mandible) Figure 2(14) . The jaw turns out to be sensitive to drugs because it has a turnover rate up to 20 times higher than in other skeletal places. There are three hypotheses about (15)MRONJ that have explained its pathophysiology and they are; (a) the efficacy of the drug in preventing osteoclastic

bone resorption affecting bone remodeling, (b) by inhibition of angiogenesis in the endothelium, and (c) loss of balance between inflammation and infection. Drugs used as tyrosine kinase inhibitors and antiVEGF monoclonal antibodies that counteract the proliferation of maxillary cells, decreases the incorporation and exodus of human endothelial cells especially in the jaw. (16)It has been proposed that inflammation and infection are involved in ONJ (Mandibular Osteonecrosis). (17) There are bacteria that produce lipopolysaccharides, these incite the specific manufacture of cytokines, which increases the process of bone resorption. In addition, other bacteria directly regulate the production of the receptor that activates nuclear factor  $\kappa$ B ligand (RANKL) in human periodontal ligament cells, gingival fibroblasts and B cells (they are part of the immune system) that also incite bone resorption(18). Osteoclastogenesis is a process where the cells that act in bone resorption that are osteoclasts are produced by differentiation, here act the monocyte colony stimulating factor (M-CSF) and the activator of the NF $\kappa$ B ligand receptor (RANKL), if there is an imbalance in these processes and with the osteoblasts that are the bone formers pathologies such as osteopenia or osteolysis happen. After the extraction of a tooth, an inflammatory stage is initiated and the generated cavity is filled with blood, platelets and macrophages enter the fracture site and the secretion of inflammatory cytokines (growth mediators) such as interleukin 1 (IL-1) and IL-6, tumor necrosis factor alpha (TNF- $\alpha$ ), and prostaglandins (PGE2).(19)(20)

Osteoblasts (form bone), vascularization cannot be regenerated (8)(18) .

### Antiresorptive and antiangiogenic drugs

Bisphosphonates (BP) are the most widely used antiresorptive therapies, they act by binding the mineral component of bone and intrusive with the action of osteoclasts. Bisphosphonates containing nitrogen in the R2 side chain, also called first-generation BP, such as alendronate, act as inhibitors of farnesyl-pyrophosphate synthetase, which leads to inhibition of prenylation (addition of hydrophobic molecules to a protein) of many proteins that act in intracellular signaling for example the proteins Ras, Rab, nuclear lamellae, trimeric G protein subunits, protein kinases, and small GTP-binding proteins related to Ras, which are crucial for controlling the cellular activities of osteoclasts. N-BP has been shown to induce apoptosis in activated osteoclasts by inhibiting key enzymes, such as farnesyl pyrophosphate synthase (SPF) and geranylgeranyl pyrophosphate synthase, in the mevalonate pathway ( $\gamma$ (21)(22)Figure 3), which prevent complete post-translational prenylation of GTPases Ras, Rho (participates in the formation of actin tension fibers) and Rac (contribute to leukocyte migration). GTPases such as Ras, Rab, Rho and Rac are signaling proteins that regulate a myriad of cellular processes significant for function, morphology, cytoskeletal arrangement, membrane ripple, vesicle trafficking and apoptosis. Etidronate has the effect of expelling N-BPs that have accumulated in the bones. Clodronate has an anti-inflammatory effect by inhibiting phosphate transporters. These findings suggest that etidronate and clodronate may be useful in preventing and treating ONJ, but further clinical trials are needed to confirm this use. (21)(23)(24) Oral bisphosphonates are used for the treatment of osteoporosis, osteogenesis imperfecta, and Paget's disease. Data have shown that the use of bisphosphonates and RANKL inhibitors can effectively mitigate bone loss. In 2010, cases of osteonecrosis associated with a new drug, denosumab (DSB) began to be published, which is a human (non-chimeric) monoclonal IgG2 antibody against the nuclear factor activator receptor kappa-B (NF- $\kappa$ B) which blocks the activation of the RANK receptor both on the surface of osteoclast precursors and in osteoblasts inhibiting the formation of osteoclasts and their survival and function which decreases bone resorption, their risk of ONJ is similar to that of bisphosphonates. Denosumab (DSB) and zoledronic acid (ZA) may cause ONJ more often compared to pamidronate (PAM) and clodronate that are prescribed help prevent ONJ. Of the bisphosphonates, the most likely to cause MRONJ are aminobisphosphonates (N-BP), possibly because they are more potent than alkybiphosphonates. With pamidronate, alendronate and zoledronate being 10, 100 and 1000 times more potent than clodronate(25) (26)(27) (Table 1).(28)

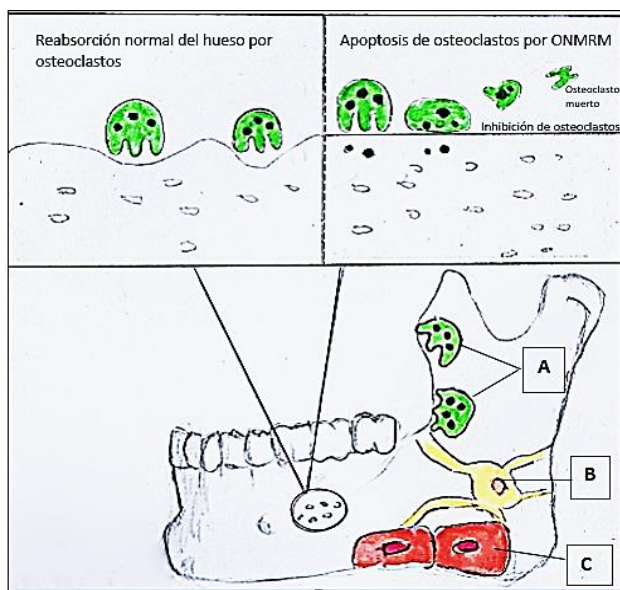


Figure 2: In bone remodeling, osteoclasts need to perform their function for osteoblasts and osteocytes to act. By not interacting correctly, apoptosis and therefore necrosis occur.

Mandibular osteonecrosis usually begins in the alveolar bone and then spreads to the jaw and is succeeded by apoptosis of A. osteoclasts (destroy bone), B. osteocytes (modulate signals) and C.

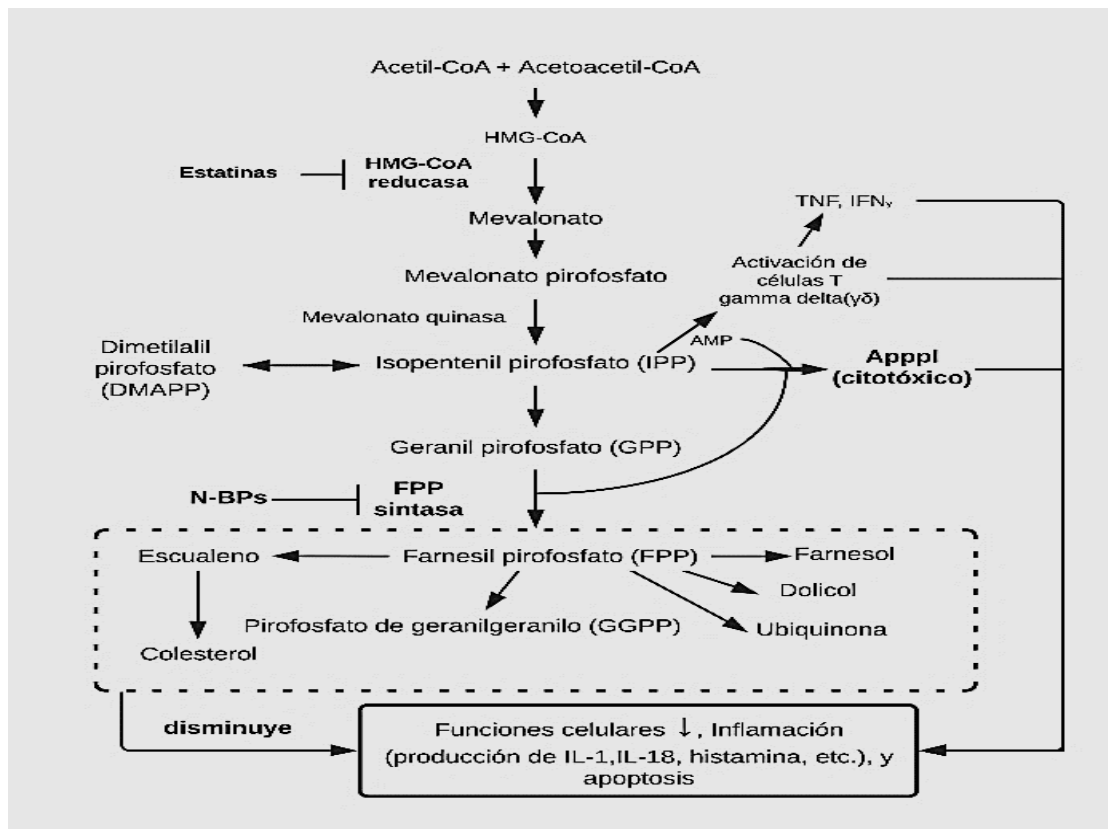


Figure 3: Inflammatory and/or cytotoxic effects of N-BP and the cholesterol biosynthesis pathway  
 N-BP inhibits FPP-synthase in the cholesterol biosynthesis pathway, which decreases cellular functions causing cytotoxicity and cell death in many cell types. Inhibition of FPP-synthase results in an increase in PPI (energy) that can activate a population of T cells. Statins (drugs used to lower cholesterol) inhibit 3-hydroxy-3-methylglutaryl (HMG)-CoA-reductase. N-BP induce apoptosis in activated osteoclasts by inhibiting key enzymes, such as farnesyl pyrophosphate synthase (SPF) and geranylgeranyl pyrophosphate synthase, in the mevalonate pathway decreasing cellular functions causing inflammation and eventually cell death (24)(23).

The antiangiogenic drug inhibits the proper development of new blood vessels. Angiogenesis requires the integration of vascular endothelial growth factor molecules into endothelial cell scavengers. This arrangement generates new blood in the growth of vessels. (29) (30) When it is inferred in the development of vascular endothelial cells by a reduction in proliferation increases the risk of apoptosis, decreased formation of capillary-like tubules and avascular necrosis. Sunitinib (31)(Figure 4) may cause osteonecrosis of the jaw after oral surgery without prior bisphosphonate exposure. The first report associated with bevacizumab was first known in 2008 mentioning cases recorded with this mandibular pathology. In addition, bevacizumab is involved in the integrity of the microvessels in the jaw which causes severe damage in regeneration of any microtrauma of the oral cavity(32) (Table 1). (33) Ziv-aflibercept delays the healing time of wounds, accompanied by bleeding or infection in the case of the oral area specifically exposed bone at the mandibular level. With increased risk in patients with periodontal conditions, dentoalveolar and mandibular surgery or places with concomitant prosthesis. (34)(35)(36) Zaltrap® is also used (Table 1). Sorafenib (Figure 4) (Table 1) in the oral cavity prolonged use causes neoplastic thrombosis of the portal branch, presents as gingival lesion, since there is bone exposure causes a mandibular infection and

osteonecrosis of the jaw(37). Axitinib and pazopanib are drugs involved in blocking the tyrosine kinase molecule (Table 1). Pazopanib decreases blood clotting activity in surgical procedures, so in the oral cavity it has a high rate of bleeding gums, inflammation due to platelet imbalance. Before starting treatment, the doctor should be informed if you have had surgery in the last 7 days(38) (39)(40).

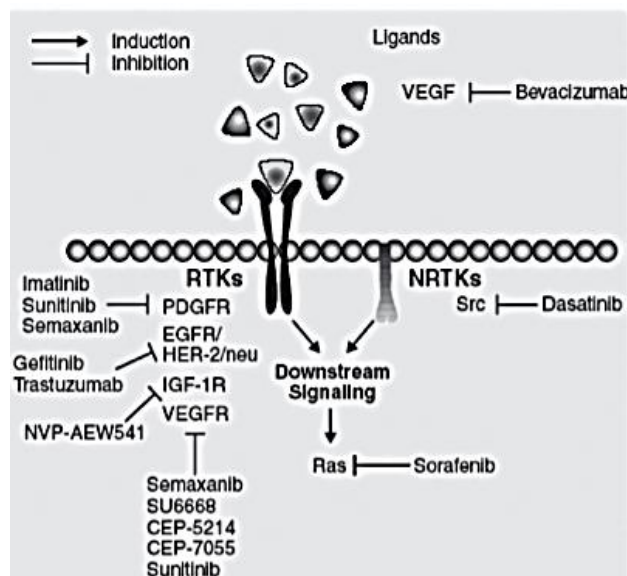


Figure 4: Receptors with protein-kinase activity and inhibitory drugs, structure.(68)

Medicament	Mechanism of action	Disease in which it is used
Alendronate	Inhibition of SPF	Treatment and prevention of osteoporosis
Bevacizumab	Inhibition of angiogenesis by blocking the action of VEGF	Metastatic colorectal carcinoma. Glioblastoma. Metastatic NSCLC. Metastatic renal carcinoma
Cabozantinib	Tyrosine kinase inhibition of VEGFR, MET, RET	Metastatic medullary thyroid carcinoma
Clodronato	action on osteoblasts modifying their physiology and damaging their repair capacity and alters macrophages and influences the migration and phagocytosis of THP-1 cells	Treatment and prevention of osteoporosis
Denosumab	Inhibition of bone remodeling by RANKL blockade	Osteoporosis. Prevention of ERE. Hypercalcemia due to cancer
Etidronato	Inhibition of SPF	Enf. De Paget
Everolimus	mTOR inhibition	Liver and kidney transplant. Hormone receptors positive for breast cancer. Metastatic renal cell carcinoma
Ibandronato	Inhibition of SPF	Treatment and prevention of osteoporosis
Pamidronato	Inhibition of SPF	Prevention of ERE. Hypercalcemia due to cancer. Paget's disease
Risedronato	Inhibition of SPF	Treatment and prevention of osteoporosis.
Sorafenib	Tyrosine kinase inhibition of VEGFR, PDGFR, FLT3, c-kit	Metastatic hepatic carcinoma. Metastatic renal cell carcinoma
Sunitinib	Tyrosine kinase inhibition of VEGFR, PDGFR, FLT3, c-kit	Metastatic renal cell carcinoma Neuroendocrine tumors
Temsirolimus	mTOR inhibition	Metastatic renal cell carcinoma
Tiludronato	Inhibition of osteoclastic activity reducing enzymatic and transport processes involved in bone resorption.	Enf. De Paget
Zoledronato	Inhibition of SPF	Osteoporosis. Prevention of ERE. Cancer hypercalcemia Paget's disease
Ziv-aflibercept (zaltrap®)	It is a recombinant human vascular endothelial growth factor (VEGF) receptor	It has been used to cure individuals with several serious tumors, colon cancer.
Axitinib and Pazopanib	Blockade of the tyrosine kinase molecule	Treatment in kidney cancer.

SPF = farnesyl pyrophosphate synthase; IV = intravenous; ERE = skeletal related events; RANKL = receptor activator for nuclear factor κ B ligand; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet-derived growth factor receptor; FLT3 = FMS-like tyrosine kinase 3; mTOR = mammalian target of rapamycin; MET = met proto-oncogene, receptor tyrosine kinase; RET = ret proto-oncogene. THP-1= is a cell line that corresponds to a line of human monocytes derived from acute lymphocytic leukemia and J774A cells.1 which is a macrophage cell line; NSCLC= non-small cell lung cancer.  
Modified from .(26)(28)(41)(24)(32)(33)(36)

### 4. Prevention and Diagnosis

Mandibular osteonecrosis sometimes does not present oral ulcerations, its diagnosis can be

complemented with dental x-rays that could be used for prognosis (Table 2). (42) Table s on the diagnosis and prevention of osteonecrosis of the jaw is presented below (Table 3 and Table 4).

Stadiums	Bone	Pain	infection	Other effects
Stage 0	no exposure	Asymptomatic	absent	None
Stage 1	exposed	Asymptomatic	absent	None
Stage 2	exposed	Symptomatic	present	Purulent drainage and erythema
Stage 3	exposed	symptomatic	Present	Extension beyond the alveolus, which can cause fracture

Table 2 NMO has a classification system for osteonecrosis of the jaw in 4 stages, according to the function of four criteria to be considered: bone, pain, infection and other diverse effects (69)

Diagnosis of Osteonecrosis of The Jaw		
	USE	JAW DETECTION
CT (computed tomography) scan	It allows panoramic visualization of the lower jaw, detects areas of cortical erosion with adjacent sclerotic bone, periosteal proliferation, extent of necrosis, bone sequestration demonstrate the presence of fistulas towards the sinuses and nostrils (43).	Detect complications such as bleeding from the floor of the mouth caused by injury to mandibular nutritious vessels during the placement of dental implants at the level of the duct that with antiresorptive and antiangiogenic drugs can spread to osteonecrosis (44).
Orthopantomography or panoramic radiography	It can be observed in depth characteristics such as diffuse sclerosis, poor healing of tooth extraction sites	show sclerosis in the alveolar margin with cortical enlargement, in the study narrowing of the dental canal will be observed(45).
Bone scan	shows hyperuptake of the affected area compatible with an infectious inflammatory process detailing early changes in bone (46).	to get a three-dimensional map at the bone level detailing its microcracks, observing the quantity and quality of the bone.
Axial tomography	computerized that helps detect maxillary sinus opacification and oroantral communication.	Diagnosis of osteonecrosis by bisphosphonates of the hemimandibula at the level of the teeth with the exact location of the maxilla to diagnose a possible oroantral fistula. prevents healing and generates bone necrosis (47)

Table 4. Methods of prevention of drug-induced osteonecrosis of the jaw .(48)(49)(50) (51)(52)		
PREVENTION OF OSTEONECROSIS		
STRATEGY	METHOD	ADVANTAGES
Blood test	Afinds out the biochemical marker, the concentration of carboxy-terminal telopeptide of type I collagen (CTX). Thenormal mean value of CTX is around 400 pg/ml, if CTX levels are equal to or greater than 150 pg/ml, the risk of necrosis in relation to surgical procedures is assumed to be minimal.	It deduces the period in which the medication must be mitigated to achieve higher levels of bone turnover and thus reduce the contingency of suffering from ONJ after oral extraction or surgery, and it is important to check the oral cavity and monitor oral hygiene before any treatment.
Revisiting the oral cavity before treatment	In case of presenting implants, perform the root canal treatment one year before the administration of antiangiogenic and antiresorptive drugs, control oral hygiene, in the case of using removable prostheses and the mucosa should be checked so that it does not induce wounds.	It prevents treatment with wounds in the oral cavity, and produces infection and therefore causes osteonecrosis in the jaws.
Delay therapy with antiresorptive and antiangiogenic drugs (At least 3 months after surgery or wait a period of 14-21 days)	The initiation of bisphosphonate therapy should be delayed until the extraction site has healthy mucosa. Mitigar procedures that involve the manipulation of the bone and periosteal detachment, in non-restorable pieces remove the crown, in roots an endodontic treatment, do not use implants, perform extractions only in necessary cases	Increased chance of avoiding severe ulcerations

### 5. TreatMent

MRONJ treatments depend on several variables such as age, sex, disease status, stage of ONJ, comorbidities, and symptoms. Currently worldwide, two approaches have been considered in clinical practice: (a) conservative non-surgical procedures and (b) surgical procedures. These two approaches are often used in combination either at the same time or because of insufficiency. The conservative

procedure involves maintaining good oral hygiene (home self-care and regular professional dental care). Non-surgical treatments include: hyperbaric oxygen therapy; low-intensity laser therapy; teriparatide; ozone; pentoxifylline; and tocopherol (53)(54)(55)(56) (Table 5). An expert panel has recommended the treatment strategies mentioned in Table 6 by the American Association of Oral and Maxillofacial Surgeons (AAOMS) endorsing symptomatic treatment only when necessary for all stages of MRONJ. (57)

Table 5: Treatment of Osteonecrosis of the Jaw	
Medical ozone (O3) in the treatment of patients with ONJ	Your derivatives for treatment + Hyperbaric oxygen (HBO)
O3 aids bone injury by oxidative preconditioning, stimulating or preserving endogenous antioxidant systems, and blocking the xanthine/xanthine oxidase pathway for the generation of reactive oxygen species.(58)	<ul style="list-style-type: none"> <li>✓ It is used as an adjunct to surgery and antibiotics in the treatment of ONJ as it decreases:                             <ul style="list-style-type: none"> <li>✓ edema</li> <li>✓ inflammation</li> </ul> </li> <li>✓ Increases microbial death.</li> </ul>

Table 5: treatment of osteonecrosis of the jaw La teriparatida (pth)	
It is a genetically modified analago of human parathyroid hormone. PTH can reverse the antiresorptive effects of bisphosphonates by stimulating osteoblast activity and viability and improving metabolic activity and osteoclast count, it is possible that the use of this drug will improve fracture healing in patients with ONJ (59).	PTH can reverse the antiresorptive effects of bisphosphonates by stimulating The activity and viability of osteoblasts improving metabolic activity and the number of osteoclasts the use of this medication may improve fracture healing in patients with ONJ (59).
Pentoxifylline.	
It is a methylxanthine derivative that has been used for the treatment of several peripheral vascular diseases, this drug is known to reduce blood viscosity, promote fibrinolysis and improve erythrocyte compliance (60).	Tocopherols are a class of organic chemical compounds consisting of several methylated phenols, these compounds produce antioxidant effects that protect cell membranes from lipid peroxidation and are known to partially inhibit transforming growth factor beta-1 (TGF-b1).(61)
Surgical treatment options for the management of MRONJ range from conservative (e.g., bone debridement, sequestectomy) to aggressive such as surgical resections and jaw bone reconstruction, when necessary, i.e., if MRONJ results in persistent symptoms or affects functionality despite initial conservative treatment. Aggressive surgical intervention is not recommended for asymptomatic bone exposure. Before aggressive surgery, the multidisciplinary care team and patient should discuss the risks and benefits. (56)(57)(62)	

Table 6: Treatment Strategies by Onmrm Stage	
Stages of ONMRM*	Treatment strategy +
At risk: no apparent necrotic bone in patients who have been treated with oral or intravenous bone-modifying agents	No treatment is indicated. Patient education and reduction of modifiable risk factors.
Increased risk: no clinical evidence of necrotic bone, but with nonspecific clinical findings, radiographic changes, and symptoms.	Systemic management, including the use of analgesics, and close scrutiny and monitoring. Refer to a dental specialist and follow up every 8 weeks with the communication of the status of the lesion to the oncologist. Patient education and reduction of modifiable risk factors.
Stage 1: Exposed and necrotic bone, or catheterized bone fistulas, in patients who are asymptomatic and have no evidence of infection.	Antibacterial mouthwash (chlorhexidine mouthwashes). Clinical follow-up every 8 weeks by the dental specialist with communication of the status of the lesion to the oncologist. Patient education and reduction of modifiable risk factors.
Stage 2: exposed and necrotic bone or catheterized bone fistulas associated with infection, evidenced by pain and erythema in the region of exposed bone with or without purulent drainage.	Systemic treatment with oral antibiotics and topical antibacterial rinse (chlorhexidine 0.12%). Pain control. Debridement to relieve soft tissue irritation and infection control. Clinical follow-up every 8 weeks by dental specialist with communication of the status of the lesion to the oncologist. Patient education and reduction of modifiable risk factors.
Stage 3: exposed and necrotic bone or catheterized bony fistula in patients with pain, infection, and one or more of the following signs: exposed, necrotic bone extending beyond the region of the alveolar bone (i.e., lower border and branch in the mandibular maxillary sinus and zygomatic in the maxilla) resulting in pathological fracture, extraoral fistula, bucosinusal communication, oronasal communication, or osteolysis extending to the lower edge of the jaw or breast floor.	Symptomatic treatment with oral antibiotics and topical antibacterial rinse. Pain control. Surgical debridement or resection for long-term palliation of infection and pain. Clinical follow-up every 8 weeks by dental specialist with communication of the status of the lesion to the oncologist. Patient education and reduction of modifiable risk factors.
Abbreviation: MRON, drug-related osteonecrosis of the jaw. *Exposed or probably exposed bone in the maxillofacial region without resolution for more than 8 weeks in patients who were treated with an antiresorptive or antiangiogenic agent and who have not received radiation therapy to the jaws. +Regardless of the stage of the disease, the mobile segments of bone sequestration (dead bone) should be removed without exposing the unaffected bone. Extraction of symptomatic teeth within the exposed necrotic bone should be considered, as extraction is unlikely to exacerbate the established necrotic process. Amended from: (57) (63).	

## 6. Discussion

According to the authors, Shibahara and Yuan agree that the jaw is more prone to infections compared to the bones of other parts of the human body, due to its anatomical and physiological particularities; an example is that the remodeling of the jaw is stimulated by the teeth through the process of chewing and its great capacity for turnover.(15)(64) Ayala, Aghaloo, Katsarelis state that of the three hypotheses about MRONJ that have explained its pathophysiology. Tooth extraction is generally the most common inciting event associated with ON M RM by the loss of balance between inflammation and infection since there are bacteria that intervene and damage the molecular processes of bone formation and that are part of the immune system.

Since(16)(17)(18) periodontal disease together with the action of drugs causes the bone to undergo oxidative stress, generating endotoxemia and favoring the release of mediators of inflammation and growth factors, which contributes to the production of both cellular and molecular toxicity which leads to local necrosis and abscesses or bacteria such as *Actinomyces*(65)(20). Zhang, et al. confirm that unfortunately, the use of antiresorptive and antiangiogenic drugs along with risk factors affecting the mucosal immune system, and bacterial infection, contribute to the occurrence of MRONJ(66). It is currently known that MRONJ has multifactorial etiology, without reaching something conclusive, but it is evident that being treated with these drugs influences the risk of the presentation of the signs and symptoms of this pathology in patients. Theauthors Cortés, Foncea, Rajcovich, Costantino

and Sá that for the prevention and diagnosis of ONJ the most used studies are computed tomography and magnetic resonance because they help in early diagnosis and establish the true extent of osteonecrosis(8)(9)(43)(44)(47).

Finally, there are alternatives such as treatment with hyperbaric oxygen therapy (HBOT) as a complement to conventional therapy, as well as Re and Lin mention that HBOT is an effective treatment in dental medicine since it facilitates the healing process and accelerates the patient's recovery. Despite the possible complications that can arise, it has several benefits. HBOT often works well along with other treatments. (58)(67)

## 7. Conclusion

Preventing ONJ should be a priority in patients receiving treatment with antiresorptive and antiangiogenic medications, carefully considering oral hygiene with a prior review by a dentist and hygienist before starting therapy with these medications, followed by regular self-monitoring and dental follow-up. If a tooth extraction or other surgery is needed in the oral cavity, it must be completed and wait for the healing time before starting therapy. A limitation of the review of this condition is that studies continue to be conducted, based on this information can direct the field of research to the pathophysiology of this condition in addition to the course of NMO and its way of responding to treatment are largely unknown and, in such a way, Clinical judgment should guide the individual treatment approach.

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