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Medication-related osteonecrosis of the jaw (MRONJ)

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Summary

Introduction: Medication-related osteonecrosis of the jaw, formerly known as bisphosphonate-associated osteonecrosis of the jaw, is a syndrome first described in 2003. Prescription drugs such as bisphosphonates, denosumab and anti-angiogenic agents, including monoclonal antibodies, have been implicated in the development of medication-related osteonecrosis of the jaw (MRONJ). **Purpose:** The aim of this research was to investigate drugs related to osteonecrosis of the jaw. **Method:** This were a quantitative, cross-sectional descriptive study, using a search of scientific databases to collect information on the drugs associated with the development of drug-related osteonecrosis of the jaw. **Result:** Bisphosphonates have been associated with the development of osteonecrosis of the jaw, as they inhibit osteoclastic activity by altering bone remodeling. Denosumab was introduced as a more effective alternative to bisphosphonates; however, it has also been linked to the production of osteonecrosis of the jaw, as this drug induces a sustained decrease in bone turnover. **Conclusions:** Osteonecrosis of the jaw has been linked to some drugs, which include bisphosphonates, especially zoledronic acid. Another drug that has been implicated in osteonecrosis of the jaw is denosumab, which is used for the treatment of osteoporosis and metastatic bone disease.

Keywords: Bisphosphonate–associated osteonecrosis of the jaw; osteonecrosis; maxilla; mandible; drug effects; pharmaceutical preparation.

Resumen

Osteonecrosis de la mandíbula relacionada con medicamentos (ONMRM)

Introducción: La osteonecrosis de la mandíbula relacionada con la medicación, anteriormente conocida como osteonecrosis de la mandíbula asociada a los bisfosfonatos, es un síndrome descrito por primera vez en 2003. Medicamentos recetados como los bisfosfonatos, denosumab y agentes antiangiogénicos, incluidos los anticuerpos monoclonales, han sido implicados en el desarrollo de la osteonecrosis de la mandíbula relacionada con la medicación (MRONJ, por sus siglas en inglés). **Propósito:** El objetivo de esta investigación fue investigar los medicamentos relacionados con la osteonecrosis de la mandíbula. **Método:** Este fue un estudio descriptivo cuantitativo, transversal, utilizando una búsqueda en bases de datos científicas para recopilar información sobre los medicamentos asociados con el desarrollo de la osteonecrosis de la mandíbula relacionada con la medicación. **Resultado:** Los bisfosfonatos han sido asociados con el desarrollo de osteonecrosis de la mandíbula, ya que inhiben la actividad osteoclástica al alterar la remodelación ósea. El denosumab fue introducido como una alternativa más efectiva a los bisfosfonatos; sin embargo, también ha sido relacionado con la producción de osteonecrosis de la mandíbula, ya que este medicamento induce una disminución sostenida en el recambio óseo. **Conclusiones:** La osteonecrosis de la mandíbula ha sido relacionada con algunos medicamentos, que incluyen los bisfosfonatos, especialmente el ácido zoledrónico. Otro medicamento que ha sido implicado en la osteonecrosis de la mandíbula es el denosumab, que se utiliza para el tratamiento de la osteoporosis y la enfermedad ósea metastásica.

Palabras clave: Osteonecrosis de la mandíbula asociada a los bifosfonatos; osteonecrosis; maxilar; mandíbula; efectos de medicamentos; preparación farmacéutica.

Resumo

Osteonecrose da mandíbula relacionada a medicamentos (ONMRM)

Introdução: A osteonecrose da mandíbula relacionada a medicamentos, anteriormente conhecida como osteonecrose da mandíbula associada a bifosfonatos, é uma síndrome descrita pela primeira vez em 2003. Medicamentos prescritos como bifos-

fonatos, denosumabe e agentes antiangiogênicos, incluindo anticorpos monoclonais, têm sido implicados na desenvolvimento de osteonecrose da mandíbula relacionada a medicamentos (MRONJ, na sigla em inglês). **Objetivo:** O objetivo desta pesquisa foi investigar medicamentos relacionados à osteonecrose da mandíbula. **Método:** Este foi um estudo quantitativo, transversal e descritivo, utilizando uma busca em bases de dados científicas para coletar informações sobre medicamentos associados ao desenvolvimento de osteonecrose da mandíbula relacionada a medicamentos. **Resultado:** Os bifosfonatos têm sido associados ao desenvolvimento de osteonecrose da mandíbula, pois inibem a atividade osteoclástica alterando a remodelação óssea. O denosumab foi introduzido como uma alternativa mais eficaz aos bifosfonatos; No entanto, também tem sido relacionado com a produção de osteonecrose da mandíbula, uma vez que este medicamento induz uma diminuição sustentada da remodelação óssea. **Conclusões:** A osteonecrose da mandíbula tem sido associada a alguns medicamentos, incluindo os bifosfonatos, especialmente o ácido zoledrônico. Outro medicamento implicado na osteonecrose da mandíbula é o denosumabe, usado para tratar a osteoporose e doenças ósseas metastáticas.

Palavras-chave: Osteonecrose da mandíbula associada a bifosfonatos; osteonecrose; maxilar; mandíbula; efeitos de medicamentos; preparação farmacêutica.

Introduction

Drug-related osteonecrosis of the jaw, formerly known as bisphosphonate-associated osteonecrosis of the jaw, is a syndrome first described in 2003 by Marx; it is characterized by the exposure of necrotic bone in the maxilla or mandible and is, triggered by the performance of an intraoral surgical procedure at the same time that the patient is under medical treatment with antiresorptive drugs such as bisphosphonates [1, 2].

Since the publication of its discovery, 19 years have passed, during which little scientific information has generated misinformation and certain fears among patients and doctors or dentists. Drug-related osteonecrosis of the jaw is undoubtedly a serious disease that can lead to a radical change in the daily habits of the patient [3].

The Food and Drug Administration (FDA) approves the use of bisphosphonates for administration in postmenopausal women with osteoporosis, men with osteoporosis, and patients with glucocorticoid-induced osteoporosis, hypercalcemia of malignancy, Pagt's disease, malignancy with bone metastasis, giant cell tumors or fibrous dysplasia. However, it should be reported that the same association (FDA) does not approve the

use of these drugs for the treatment of osteogenesis imperfecta in children and adults as a prevention of glucocorticoid-induced osteoporosis [4-6].

Bisphosphonates are antiresorptive drugs, that regulate the bone metabolism of calcium (Ca) and phosphorus (P) by binding to the hydroxyapatite of the mineralized matrix, remaining in the skeleton for a prolonged period, and exerting antiresorptive activity. These drugs, in turn, are classified into two categories: those containing nitrogen, such as alendronate, risedronate, ibandronate, pamidronate and zoledronic acid, and those without nitrogen, such as etidronate disodium, clodronate disodium and tiludronate disodium [5, 7-9].

The mechanism of action of bisphosphonates is to inhibit bone resorption by binding to hydroxyapatite binding sites in bones, particularly in areas of active resorption. Those drugs that contain nitrogen will inhibit farnesyl diphosphate, which is important for promoting osteoclast binding to bone and, as a result, the osteoclast will become detached from the bone surface, which inhibits bone resorption. Non-nitrogen-containing drugs result in osteoclast apoptosis, which, in turn, leads to an overall decrease in bone degradation [7, 8, 10].

The efficacy of bisphosphonates is based on improving the bone mineral density in postmenopausal women with osteoporosis. Thus, alendronate reduces the risk of vertebral fractures by 50% and hip fractures and other non-vertebral fractures by 30%; risedronate reduces vertebral and non-vertebral fractures by 40%; zoledronic acid reduces vertebral fractures by 70% and hip fractures and other non-vertebral fractures by 35%; and ibandronate reduces vertebral fractures by 50%. It is important to point out that alendronate, risedronate and ibandronate are administered orally, while zoledronic acid and pamidronate are administered intravenously. Denosumab acts as an antiresorptive agent by inhibiting osteoclast function and bone resorption because it does not bind to bone, and its effects on bone remodeling mostly diminish within six months after the discontinuation of treatment. This drug is effective at reducing metastatic bone disease from solid tumors when administered monthly subcutaneously, as it significantly reduces the risk of vertebral, non-vertebral and hip fractures in patients with osteoporosis [8, 11-13].

Antiresorptive drug administration may cause adverse gastrointestinal effects, such as gastrointestinal reflux, esophagitis, esophageal/gastric ulcers and gastritis; intravenous infusion reactions, as they are associated with an acute phase reaction characterized by flu-like symptoms, fever, myalgia, arthralgia and headache; hypocalcemia, which is more common from intravenously administered bisphosphonates and in patients with a vitamin D deficiency, a deficient calcium intake or hypoparathyroidism; arthralgia

and myalgia; ocular conditions, such as uveitis, conjunctivitis and scleritis; atypical femur fractures due to a rare effect that generally affects the diaphysis or the subtrochanteric region of the femur; and osteonecrosis, since most cases occur in patients with multiple myeloma or breast cancer that are treated with high doses of intravenous bisphosphonates [14, 15].

Invasive dental procedures, dental trauma, periodontal disease, exodontia, exostoses and dental implants are important risk factors for the development of osteonecrosis in patients with osteoporosis, with a percentage of 0-0.15% for bisphosphonate and 1% for denosumab. In patients with a history of cancer after exodontia, the percentage is 1.6% - 14.8% when consuming bisphosphonates. Osteonecrosis of the jaw occurs three times more frequently in the lower jaw (75%) than in the upper jaw (25%) due to anatomical factors, while patients with breast cancer, multiple myeloma or prostate cancer have a higher risk of developing osteonecrosis [11, 16, 17].

Patients receiving chemotherapy or corticosteroids, older adults, and Caucasians are at a greater risk of developing osteonecrosis; in addition, genetic factors (such as CYP2C8 gene polymorphism in patients with multiple myeloma who receive treatment with zoledronic acid and pamidronate) and smoking are risk factors for the development of osteonecrosis with bisphosphonate therapy [18].

There are several hypotheses that can explain the pathophysiology of drug-associated osteonecrosis. Among them is the inhibition of bone remodeling, since antiresorptive drugs, including bisphosphonates and denosumab (DMB), have direct effects on the formation, differentiation or function of osteoclasts; inflammation or infection, since, although extraction is the main triggering event for osteonecrosis, most teeth that are extracted have periodontal disease or an infection; the inhibition of angiogenesis, since bisphosphonates and denosumab inhibit the angiogenesis that is normally seen in post-extraction alveolar healing, and they also reduce the arterial area, venous area and general vascularization of periodontal tissues; dysfunction of the innate and acquired immune systems, as patients with comorbidities such as diabetes and rheumatoid arthritis or an immunocompromised state have a significantly increased risk of drug-associated osteonecrosis, as confirmed in animal studies where chemotherapy, steroids and antirheumatic drugs combined with antiangiogenic and antiresorptive drugs increased the prevalence of drug-associated osteonecrosis; and, finally, genetic factors, since there are some polymorphisms that are associated with the development of osteonecrosis, with most of these polymorphisms being located in genes associated with bone turnover and collagen formation [11, 19-21].

The American Association of Oral and Maxillofacial Surgeons states that patients are considered to have drug-related osteonecrosis of the jaw if they have certain specific characteristics, as can be seen in Table 1 [7, 8].

There is also drug-related, or spontaneous, mandibular necrosis without a predisposing event, which represents the second most common group responsible for triggering mandibular osteonecrosis. Spontaneous medication-related osteonecrosis of the jaw (MRONJ) is related to certain anatomical sites such as the torus, exostosis, and mylohyoid ridges. On the other hand, a bony protrusion contradicts the term spontaneous, as it represents a higher risk of trauma [11-13].

Drug-associated osteonecrosis of the jaw occurs and is classified according to the conditions present, which is why it can be classified into four stages, as can be seen in Table 2 [22-24].

Table 1. Characteristics required to consider a patient to have drug-associated osteonecrosis of the mandible.

Characteristics to be considered according to AAOMS	Current or previous treatment with antiresorptive or anti-angiogenic agents.
	Exposed bone or bone that can be probed by an extrabuccal or intrabuccal fistula, that is located in the maxillofacial region, and that has been maintained for more than eight weeks.
	No history of radiation to the jaws or metastases in the jaws.

Table 2. Stages of drug-associated osteonecrosis of the mandible.

Stage 0	Absence of necrotic bone, without bone exposure, but with specific clinical or radiographic findings. - SYMPTOMS Odontalgia. Pain in the mandibula that may radiate to the TMJ. Sinus pain. - CLINICAL FINDINGS Tooth mobility due to chronic periodontal disease. Intraoral or extraoral inflammation. - RADIOLOGICAL FINDINGS Bone loss not attributable to chronic periodontal disease. Absence of new bone in the alveoli post-extraction. Regions of osteonecrosis involving alveolar bone.

(*Continued*)

Table 2. *Continuation.*

Stage 1	Bone exposure and necrotic bone tissue or fistula where bone can be explored by probing; asymptomatic patients with the absence of an infection.
Stage 2	Infection, pain and/or erythema with necrotic bone exposure or fistula when probing bone.
Stage 3	Extension of necrotic bone and infection beyond the alveolar ridge, pathological fracture or oral-antral/oral-nasal communication, or an extraoral fistula.

The management of patients on bisphosphonate therapy prior to oral surgery should be performed under a protocol that includes asking all patients about their current or past bisphosphonate use and mode of administration, because intravenous bisphosphonates have a longer half-life and therefore pose a greater risk of the patient developing osteonecrosis than oral bisphosphonates. Patients who have not yet begun bisphosphonate therapy should first be examined to determine whether they require surgical dental procedures prior to therapy. A comprehensive treatment should be performed to minimize the need for future dental treatment. For patients who have already started therapy, any elective procedures should be avoided, if possible, to avoid the risk of bisphosphonate-induced osteonecrosis of the jaw. Root canal therapy should be performed in lieu of tooth extraction when possible. Patients should be educated about the importance of good oral hygiene, regular dental checkups and the symptoms of osteonecrosis of the jaw so that the patient can report early if symptoms develop. Patients in whom extractions are unavoidable should first consult with the treating physician to discontinue bisphosphonate therapy temporarily. The patient should be maintained on a chlorhexidine mouth rinse twice daily for two months and should be followed up postoperatively for 2 months [16, 25].

The most important therapeutic method is the prevention of drug-related osteonecrosis of the jaw by performing dental extractions or surgical interventions prior to the administration of antiresorptive and anti-angiogenic drugs. Prolonged perioperative antibiotic prophylaxis, adequate wound closure, and atraumatic procedures are important during dental treatment, as they minimize the risk of drug-related osteonecrosis of the jaw [26-31].

Asymptomatic lesions can be treated with antibacterial mouth rinses and prolonged antibiotic therapy. In cases where the patient presents with less severe symptoms, they can be treated by the removal of necrotic bone tissue, the smoothing of sharp bony edges, adequate wound closure and postoperative antibiotics. Those with symptomatic lesions are treated using a surgical approach, which may include a partial mandibulectomy

followed by bridging with reconstruction plates or a reconstruction with vascularized bone grafting in compromised patients [32-34].

The C-terminal telopeptide cross-linking (CTX) assay is used as a monitoring method in patients undergoing antiresorptive therapy, using a biological index (pg/ml) to measure bone remodeling and resorption as a parameter of osteoclastic activity. As bone resorption proceeds, osteoclastic enzymes digest the organic bone matrix and release type I collagen products, which include C-terminal telopeptide fragments of type I collagen called CTX and structural rings called pyridinoline crosslinks. During normal bone metabolism, mature type 1 collagen is degraded, and small fragments pass into the blood and are excreted through the kidneys. As a control, it has been suggested to measure CTX before starting bisphosphonate therapy, since the level will be reduced by 60% at 6 weeks when using the conventional dose. Whenever there is more rapid bone turnover, the CTX level will be higher, as in Paget's disease, but if the bone resorption rate is low, the CTX will also be low. It has been established that CTX values below 100 pg/ml represent a high risk of OMIB, values between 100 and 150pg/ml represent a moderate risk and values above 150 pg/ml represent minimal or no risk. CTX has been used in medicine to measure the bone turnover in diseases such as osteoporosis and bone metastases in response to bisphosphonates and is used as a parameter to assess the efficacy of oral bisphosphonate therapy [35].

However, since the 2014 American Association of Oral and Maxillofacial Surgery (AAOMS) paper, there has been a move away from bone turnover markers, so there are no validated biomarkers for clinical decision making and a test cannot be considered as a tool to estimate the ONJ risk [11].

For the performance of a surgical procedure on a patient that has been administered denosumab, a dentoalveolar surgery should be performed 3-4 months after the last dose, when the level of osteoclast inhibition is decreasing, and then the dose should be restored 6-8 weeks after surgery [36, 37].

For the management of patients who have already developed osteonecrosis due to medication, a panoramic radiograph is recommended to determine the extent of the necrosis and the position of the sequestration or osteomyelitis. Microbial cultures of soft tissue inflammation or the associated purulent discharge should be performed to identify any superinfection and the appropriate antimicrobial therapy; any dental trauma should be avoided, as it may further delay wound healing, and it should also be properly classified so that the appropriate treatment can be performed [16, 38, 39].

The treating physician may consider the non-invasive management of osteonecrosis of the jaw, initially with the administration of FDA-approved pentoxifylline for the treat-

ment of peripheral arterial disease, such as ischemic heart disease, since pentoxifylline has a mechanism of action that improves the peripheral blood flow by increasing vasodilatation, reducing blood viscosity, improving the arrival of erythrocytes, inducing effects against tumor necrosis factor alpha, inhibiting inflammation and decreasing fibrosis [40, 41].

This research focuses on describing the medications that produce mandibular osteonecrosis and the way in which these medications act on the bone tissue of each person, since it is very important for the dentist to know the side effects of these medications in order to look for alternatives when performing dental treatments.

Methods

A quantitative, cross-sectional, descriptive study was conducted by searching scientific databases for information on drugs associated with the development of drug-related osteonecrosis of the jaw. A literature search was carried out in databases and documentaries such as Pubmed, Scielo and Google Scholar; Boolean operators such as "AND", "OR" and "NOT" were applied with the keywords "bisphosphonate-associated osteonecrosis of the jaws", "osteonecrosis", "maxilla", "mandible", "drug effects" and "pharmaceutical preparation". In the bibliographic search, 127 articles were found, to which some inclusion criteria were applied, including the following: published between 2006 and 2023 and related to drugs that cause osteonecrosis of the jaw. Some bibliographies were discarded using exclusion criteria such as articles published earlier than 2014 and publications that did not contribute significant information to our search. This resulted in 103 articles of interest to us, which were classified by their year of publication (Figure 1).

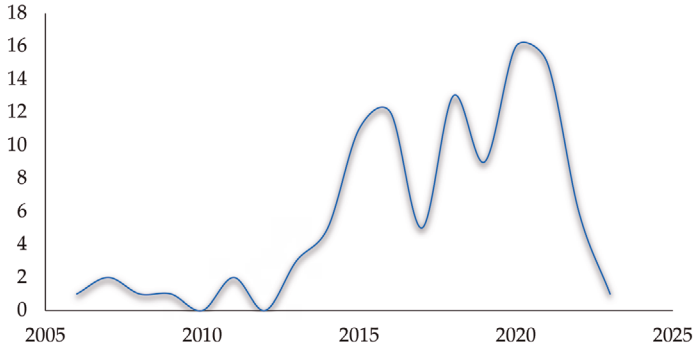

Figure 1. Analysis of study articles by year of publication.

Table 3. Other drugs associated with the production of osteonecrosis of the jaw other than the bisphosphonate family of drugs.

Group	Feature	Applications	Osteonecrosis	References
Denosumab	Introduced with the hope of decreasing the side effects of bisphosphonates; however, it has also been implicated in the production of osteonecrosis of the jaw. Suppresses bone resorption and osteoclast function. Alters bone turnover by directly altering osteoclasts. Its efficacy is similar to that of bisphosphonates. Strong blockade of osteoclastic activity may lead to maxillary and mandibular osteonecrosis. By blocking RANKL, it decreases the osteoblastic effect on osteoclasts and osteoclast progenitors and prevents their activation and differentiation, respectively. There is an increased risk of osteonecrosis of the jaw with denosumab compared to bisphosphonates. Decreases the resorption and destruction of bone tissue induced by tumor cells, thereby increasing the level of bone density and preventing future fractures. Enters the body subcutaneously or orally. Suppresses osteoclast formation by acting on preosteoclasts in the extracellular environment, as compared to bisphosphonates that act on active mature osteoclasts. Improves bone quality, strength, geometry and mineral density.	Used to combat osteoporosis and bone metastases. Prescribed in orthopedics, rheumatology and oncology. Prevents osteoclast-mediated bone resorption. Used for skeletal complications in metastatic bone lesions and to reduce vertebral and hip fractures in patients suffering from osteoporosis. Used for the treatment of multiple myeloma.	Yes	[42-73]

(*Continued*)

Table 3. *Continuation.*

Group	Feature	Applications	Osteonecrosis	References
Bevacizumab	Decreases the action of vascular endothelial development component inhibitors and causes a reduction in angiogenesis.	Used to combat the metastasis of solid tumors, osteoporosis and multiple myeloma. It has been used in several types of cancer.		[74-76]
Pembrolizumab + denosumab	PEMBROLIZUMAB: A humanized monoclonal antibody targeting the programmed cell death protein. Bone tissue is the third most recurrent site of metastasis for a wide range of solid tumors, including prostate cancer, breast cancer, lung cancer and myeloma. DENOSUMAB: Reduces osteoclast function, formation and survival as an anti-osteoclastogenic agent.	The standard treatment in people with metastatic non-small cell lung cancer, as it increases progression-free preservation and resistance in these patients. Prevents skeletal-related events in advanced solid tumors with bone metastases.	Yes	[77]
Lenvatinib	Interacts with receptor tyrosine kinases (RTKs) involved in vascular endothelial growth (e.g., VEGFR1, VEGFR2 and VEGFR3), as well as other RTKs, including fibroblast development component receptor alpha, platelet-derived development component receptor alpha, RET and KIT. These RTKs are responsible for pathogenic angiogenesis, cancer progression and tumor growth.	Given to fight thyroid cancer that has returned or metastasized to other parts of the body.	Yes	[78]
Tyrosine kinase inhibitors (sunitinib, rafenib, pazopanib, axitinib, imatinib and regorafenib)	Linked to the development of osteonecrosis of the jaw. Limits the function of tyrosine kinase via various receptors, such as the vascular endothelial growth factor receptor.	Intervenes in the function of the cell surface receptors, which are known to be abnormally active in tumors.	Yes	[76, 79]

(*Continued*)

Table 3. *Continuation.*

Group	Feature	Applications	Osteonecrosis	References
Monoclonal antibodies (rituximab, adalimumab, infliximab and romosozumab)	Reported to be possibly related to osteonecrosis of the jaw, along with denosumab and bevacizumab.	A rituximab injection (Rituxan) is used to fight pemphigus vulgaris. Adalimumab blocks the action of TNF (a substance in the body that causes inflammation). Infliximab is designed to bind to a chemical messenger in the body known as "tumor necrosis factor alpha". It is responsible for initiating the inflammatory process, occurring at increased levels in patients routinely treated with Remicade. Romosozumab increases bone formation and decreases bone breakdown.	Yes	[76]
mTOR inhibitors (everolimus and temsirolimus) and immunosuppressants (methotrexate and corticosteroids)	Linked to the development of osteonecrosis of the jaw; however, this event is extremely rare.	Given to combat rheumatoid arthritis, as a prophylaxis for transplant rejection and for the treatment of malignant diseases.	Yes	[76]
Imatinib	Works by blocking the action of the abnormal protein that tells cancer cells to multiply. This stops the spread of cancer cells.	Used to treat gastrointestinal stromal tumors, chronic myeloid leukemia and other cancers.	Yes	[76]

(*Continued*)

Table 3. *Continuation.*

Group	Feature	Applications	Osteonecrosis	References
Anti-angiogenic drugs	Anti-angiogenic drugs; i.e., they inhibit the formation of blood vessels.	Developed and supplied for various antineoplastic treatments (including treatments for ovarian cancer and glioblastoma, breast cancer, lung cancer, renal cancer and colorectal cancer).	Yes	[80]
Sunitinib	Blocks the growth of tumor cells. Intervenes in tumor cell division. Blocks the VEGF receptor, which is responsible for supplying blood to the tumor. Eliminates sources of nutrients to the tumor. Inhibits angiogenesis by preventing the formation of blood vessels.	Used for the treatment of gastrointestinal stromal cancer.	Yes	[71, 73, 77]
Everolimus	An immunosuppressive drug that inhibits the mTOR complex.	Used for advanced stages of kidney cancer, and also used to prevent rejection in transplants.	Yes	[72, 73]
Inhibitors of the mammalian target of rapamycin (mTOR)	A new therapy for the treatment of metastatic renal carcinoma.	Used for the treatment of metastatic renal carcinoma.	Yes	[80]
Aflibercept	Antiangiogenic drug with a different mechanism of action than bevacizumab, with the latter being a vascular endothelial growth factor receptor.	Used for the treatment of advanced colorectal cancer.	Yes	[73]
Thalidomide	This drug and its analogues (pomalidomide and lenalidomide) have an anti-angiogenic effect.	Used for treatment in patients with myeloma, who are largely receiving oral bisphosphonates and therefore at risk for MRONJ.	Yes	[73]

Table 4. Drugs related to osteonecrosis of the jaw according to the family to which they belong.

Group	Feature	Applications	Osteonecrosis	References
Bisphosphonates	Decreases bone turnover. Inhibits osteoclasts and disrupts normal bone healing. Strong inhibition of bone resorption may induce drug-associated osteonecrosis of the jaw. Induces apoptosis in osteoclasts. Increases bone density; inhibits osteoclastogenesis by interfering with prostaglandin and interleukin-6 secretion by osteoblasts. Reduces the risk of fractures and improves quality of life. Has been used as a tool to prevent and reduce bone complications caused by bone metastasis. Reduces bone resorption through intracellular effects. Believed to reduce osteolytic defects. Has a biological life of ten years. In osteoclastic resorption, bisphosphonates are internalized through pinocytosis in osteoclasts; the inhibition of the enzyme farnesyl-pyrophosphate synthase leads to reduced cellular activity, differentiation and apoptosis, depending on the dose of bisphosphonate applied. In the presence of these drugs, there is evidence of delayed healing after a surgical procedure. Drug-associated osteonecrosis of the jaw is the main side effect. Inhibits osteogenic cells, endothelial cells, human fibroblasts and macrophages, and decreases the viability of oral keratinocytes. Regulates the processing of phosphorus and calcium in bone tissue by binding to hydroxyapatite and reducing its resorption by osteoclasts.	Used to prevent osteoporosis and osteopenia and as a treatment for skeletal metastases (especially in lung cancer, breast cancer and prostate cancer), hypercalcemia associated with malignancies, osteogenesis imperfecta, Paget's disease and multiple myeloma. Used for the prevention of bone complications (pathological fractures or spinal cord compression). Helps prevent bone metastases from some types of carcinomas and multiple myeloma. As injectables, they are used to stabilize osteolysis of bone metastases from malignant tumors and improve malignancy-induced hypercalcemia, while oral bisphosphonates are mainly used to treat osteoporosis, and have also been reported to reduce the risk of fracture.	Yes	[44-49, 51, 52, 54-58, 60-64, 66, 68, 70-73, 76-78, 81-90]

(*Continued*)

Table 4. *Continuation.*

Group	Feature	Applications	Osteonecrosis	References
	The half-life of bisphosphonates in circulation is considerably short, ranging from thirty minutes to two hours; however, once incorporated into bone, they can persist for more than 10 years.			
Pamidronate and zoledronate	Have demonstrated characteristics of inducing apoptosis and the death of osteoclasts.	Used to treat elevated blood calcium concentrations, which can be attributed to certain types of cancer. Used for the treatment of bone metastases.	Yes	[91]
Intravenous bisphosphonates	Impedes the physiological activity of osteoclasts. Limits bone resorption.	This drug is used for hypercalcemia related to malignant diseases, and it is also used in the treatment of osteolytic lesions and skeletal complications in patients with osteoporosis and osteopathic cancer.	Yes	[92]
Zoledronic acid	Has a good affinity for hydroxyapatite in bone tissue and reduces osteoclastic bone resorption. Has shown greater potency than other bisphosphonates. The poor vascularization caused by the impact of antiresorptive drugs in inhibiting physiological bone tissue remodeling appears to be essential for the development of necrotic bone tissue. Produces soft tissue toxicity and inhibits angiogenesis and immune dysfunction. The decrease in the creation of new vascularization networks impairs reconstruction after surgery. Has a long half-life. IV doses per year of zoledronic acid have a greater effect on bone remodeling compared to oral antiresorptive drugs. Improves bone mineral density and decreases the prevalence of hip fractures, non-vertebral fractures and vertebral fractures.	Used in the treatment of bone metastases. An important option in the treatment of osteoporosis and as a supportive therapy for bone metastatic malignancies by controlling bone resorption.	Yes	[47, 93-99]

Results

Once the information had been analyzed, in Table 3 we describe the mechanism of action of these drugs on the bone and the way in which they affect and produce osteonecrosis, and in turn, in Table 4 we proceeded to classify the drugs related to osteonecrosis of the jaw according to the family to which they belonged.

Osteonecrosis of the jaw has been linked to certain drugs, with bisphosphonates being the most commonly linked to the production of osteonecrosis of the jaw, as these drugs inhibit osteoclastic activity by altering bone remodeling. Denosumab was introduced as a more effective alternative to bisphosphonates. By introducing this drug, it was hoped that it would reduce the side effects; however, it has also been linked to the production of osteonecrosis of the jaw, as this drug induces a sustained decrease in bone turnover. With less scientific evidence, other drugs have been shown to be involved in the production of osteonecrosis of the jaw, including: Lenvatinib, tyrosine kinase inhibitors, monoclonal antibodies, mTOR inhibitors and immunosuppressants, imatinib, sunitinib, everolimus, temsirolimus, antiangiogenic drugs (bevacizumab, aflibercept), mammalian target of rapamycin limiters, aflibercept and thalidomide. These drugs have been used to treat certain malignancies by acting as inhibitors of vascular tissue construction and impeding the differentiation cascade in angiogenesis.

Discussion

Based on the data collected, drug-associated osteonecrosis of the jaw is increasing due to the frequent use of bisphosphonates, and the AAOMS recommends prior drug restriction for three months before dental procedures. Considering the half-life of these drugs, when treatments with bisphosphonates are prescribed for prolonged periods of time, it is essential to maintain constant vigilance to rule out adverse effects. Once the drug enters the body, it penetrates directly into the bone, accumulating in areas of increased resorption. When osteoclasts begin to act in areas with bisphosphonates, they enter and inhibit their activity, promoting their apoptosis and producing antiresorptive effects, which can be used in a variety of clinical situations: tumor hypercalcemia, Paget's disease, osteogenesis imperfecta, bone metastasis and osteoporosis. Long-term treatment with bisphosphonates inhibits bone remodeling, which is essential for repairing physiologically occurring micro-injuries, causing them to persist and resulting in hypo-dynamic and avascular bones.

Walton *et al.* [100] mentioned in 2019 that there are significant differences in the clinical appearance of drug-related osteonecrosis of the jaw depending on the underly-

ing primary disease condition in less advanced cancer patients, along with a tendency towards the dentate areas of the mandible. Radiographic findings often increase in parallel with the clinical staging, but not unequivocally, confirming that imaging provides additional information on the bone disease burden that the current clinical staging system does not provide. Klingelhöffer *et al.* [101] demonstrated that, in alveolar bone dynamics, there is a greater range of bone remodeling when compared to the different bone tissues of the appendicular or axial human body, which explains the incidence of necrosis in the maxillary bones.

Matsuda *et al.* [102] conducted a multicenter observational study on drug-induced osteonecrosis of the jaw in patients with advanced cancer and myeloma in northwest Italy in 2020 and stated that the primary diseases were breast cancer (46%), prostate cancer (21%), multiple myeloma (19%) and other types of carcinomas (14%). In the same study, they mentioned that dental treatment prior to the administration of intravenous bisphosphonates helps to reduce the prevalence of drug-associated osteonecrosis of the jaw. Ogawa *et al.* [103] stated in 2021 that dental extraction and local hard and soft tissue trauma are the main factors and triggers for the development of maxillary and mandibular osteonecrosis, and that these triggers, in addition to antiresorptive or antiangiogenic treatments, are responsible for producing bone necrosis of the jaws. However, in some cases, it has not been possible to identify a relationship to a specific triggering event. Blus *et al.* [104] stated in 2016 that bone remodeling is significantly delayed in the presence of bisphosphonates and antiresorptive agents, as they suppress normal bone turnover. Therefore, in the presence of certain drugs, a delay in healing is observed after a surgical procedure that alters tissue homeostasis and bone remodeling. Such procedures are considered a precipitating or triggering event for osteonecrosis of the jaw. Dental extractions have been identified as the triggering factor in 60-87% of cases. To further reiterate this, a study on ONJ patients with bone neoplasms reported that tooth extractions are the main trigger in 73% of cases. In addition to wound healing complications such as bleeding, postoperative infection and postoperative pain, certain medications, when administered, can alter the physiological phases of healing, e.g., anti-angiogenic and antiresorptive agents. Therefore, in the field of dentistry/oral surgery, dental extractions and dentoalveolar surgical procedures should be well planned, especially in patients receiving bisphosphonates and other antiresorptive drugs.

Hallmer *et al.* [49] mentioned in 2020 that the pathophysiology of drug-associated osteonecrosis of the jaw is still debated, with related causes including infection, inflammation, the impairment of bone tissue remodeling and resorption, and the inhibition of angiogenesis. Related factors for the development of drug-associated osteonecrosis of the jaw include the length of time the patient is on antiresorptive therapy. Local fac-

tors include tooth extractions and periodontal and dentoalveolar surgeries. An investigation in southern Sweden showed that the prevalence of mandibular and maxillary osteonecrosis associated with intravenous bisphosphonates was 2.8%. Over the course of time and with the implementation of antiresorptive drugs and the introduction of denosumab treatment, it has become necessary to study the predisposing factors for the development of drug-associated osteonecrosis of the jaw. On the other hand, Ikesue *et al.* [91] mentioned in 2021 that various factors have been suggested as predisposing factors for the development of osteonecrosis, including the factor of drugs; however, the drugs that have been most associated with osteonecrosis of the jaw are zoledronic acid and denosumab, although their mechanisms of action are different. Zoledronic acid has a greater affinity for the hydroxyapatite in bone tissue, which is why this drug is used to combat bone metastasis. In contrast, denosumab is considered a humanized monoclonal antibody with a high affinity for the RANKL ligand of nuclear factor B (NFkB). Another characteristic that differentiates them is the time of the effect on the bone, since zoledronic acid has a greater effect on the bone than denosumab, which has a temporary effect on the bone.

Dupic *et al.* [66] stated in 2015 that bisphosphonates are drugs used to treat malignant diseases, to prevent pathological fractures and spinal cord compression and to treat hypercalcemia, as well as to treat benign diseases such as Paget's disease and osteoporosis. Bisphosphonates have been implicated in the production of osteonecrosis of the jaw, with a prevalence of between 0 and 27.5% and an estimated 7% when administered via the venous route. In oncology patients, the prevalence increases, ranging from 1 to 15%, and in the case of administration via the venous route, it may increase even more, depending on the type of cancer. Denosumab has also been implicated in the production of osteonecrosis of the jaw. Similarly, Wasserzug *et al.* [61] stated in 2017 that bisphosphonates are antiresorptive drugs and that they prevent the resorption of trabeculated bone tissue by osteoclasts, which will lead to increased bone density. The most important effect of bisphosphonates is drug-associated osteonecrosis of the jaw. Two very important predisposing factors for osteonecrosis of the jaw are the route of drug administration and the cumulative dose of the drug. Studies have shown that there is a higher incidence of osteonecrosis of the jaw when the drug is administered intravenously rather than orally (0.88 to 1.15% versus 0.01 to 0.04%), and the time in which patients presented with osteonecrosis of the jaw was shorter in those treated with intravenous bisphosphonates.

Maluf *et al.* [63] mentioned in their 2016 research that denosumab has a different mechanism of action to bisphosphonates, mentioning that bisphosphonates inter-

vene in mature, active osteoclasts while denosumab acts on osteoclasts by inhibiting RANKL, thus preventing their function, differentiation and formation, and above all, intervening in bone resorption. Among the most important side effects of bisphosphonates is osteonecrosis of the jaw, which has a prevalence ranging from 0.9 to 5%; osteonecrosis of the jaw associated with denosumab is similar to that associated with bisphosphonates, ranging from 1 to 2%. Similarly, Voss *et al.* [62] noted in 2017 that the prevalence of drug-induced osteonecrosis of the jaw ranges from 0.001 to 1% in drugs prescribed for the treatment of osteoporosis and up to 20% in patients undergoing treatment for malignant pathologies.

Conclusion

The drugs that are related to adverse effects such as osteonecrosis are mainly bisphosphonates, especially zoledronic acid. Another drug that has been linked to osteonecrosis of the jaw is denosumab, which is used for the treatment of osteoporosis and metastatic bone disease. With less scientific evidence, other drugs that are also associated with osteonecrosis of the jaw have been described, including: Lenvatinib, tyrosine kinase inhibitors, monoclonal antibodies, mTOR inhibitors and immunosuppressants, imatinib, sunitinib, everolimus, temsirolimus, anti-angiogenic drugs (bevacizumab, aflibercept), mammalian target of rapamycin inhibitors, aflibercept and thalidomide. The severity of bone pathology will depend on the route of administration (oral or parenteral) and the dose accumulated in the body. As this is an extremely important topic in the field of dentistry, it is essential to keep up-to-date and to be aware of the drugs that affect physiological bone turnover in the jaw.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. L. Dunphy, G. Salzano, B. Gerber, J. Graystone, Medication-related osteonecrosis (MRONJ) of the mandible and maxilla, *BMJ Case Reports*, **13**(1), e224455 (2020). Doi: https://doi.org/10.1136/bcr-2018-224455

2. M. Diniz-Freitas, J. Fernández-Feijoo, P.D. Dios, X. Pousa, J. Limeres, Denosumab-related osteonecrosis of the jaw following non-surgical periodontal therapy: A case report, *Journal of Clinical Periodontology*, **45**(5), 570-577 (2018). Doi: https://doi.org/10.1111/jcpe.12882

3. A. Matsumoto, M. Sasaki, R. Schmelzeisen, Y. Oyama, Y. Mori, P. Voss, Primary wound closure after tooth extraction for prevention of medication-related osteonecrosis of the jaw in patients under denosumab, *Clinical Oral Investigations*, **21**(1), 127-134 (2017). Doi: https://doi.org/10.1007/s00784-016-1762-y

4. J. Sunyecz, R. Derman, Update on the use of bisphosphonates in the management of postmenopausal osteoporosis by obstetricians-gynecologists, *Obstetrical & Gynecological Survey*, **62**(6), 407-416 (2007). Doi: https://doi.org/10.1097/01.ogx.0000266070.47052.52

5. A. Jaiman, D. Sabat, S. Arora, M.A. Hafez, We need a break: Bisphosphonates, *Journal of Clinical Orthopaedics and Trauma*, **4**(1), 11-14 (2013). Doi: https://doi.org/10.1016/j.jcot.2013.01.010

6. L. Chen, G. Wang, F. Zheng, H. Zhao, H. Li, Efficacy of bisphosphonates against osteoporosis in adult men: A meta-analysis of randomized controlled trials, *Osteoporosis International*, **26**(9), 2355-2363 (2015). Doi: https://doi.org/10.1007/s00198-015-3148-4

7. M. Drake, B. Clarke, S. Khosla, Bisphosphonates: Mechanism of action and role in clinical practice, *Mayo Clinic Proceedings*, **83**(9), 1032-1045 (2008). Doi: https://doi.org/10.4065/83.9.1032

8. A. Kuźnik, A. Październiok-Holewa, P. Jewula, N. Kuźnik, Bisphosphonates-much more than only drugs for bone diseases, *European Journal of Pharmacology*, **866**, 172773 (2020). Doi: https://doi.org/10.1016/j.ejphar.2019.172773

9. J. Klara, J. Lewandowska-Łańcucka, How efficient are alendronate-nano/biomaterial combinations for anti-osteoporosis therapy? An evidence-based review of the literature, *International Journal of Nanomedicine*, **17**, 6065-6094 (2022). Doi: https://doi.org/10.2147/IJN.S388430

10. S.A. Lozano-Calderon, M.W. Colman, K.A. Raskin, F.J. Hornicek, M. Gebhardt, Use of bisphosphonates in orthopedic surgery: Pearls and pitfalls, *Orthopedic Clinics of North America*, **45**(3), 403-416 (2014). Doi: https://doi.org/10.1016/j.ocl.2014.03.006

11. S.L. Ruggiero, T.B. Dodson, T. Aghaloo, E.R. Carlson, B.B. Ward, D. Kademani, American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws-2022 update, *Journal of Oral and Maxillofacial Surgery*, **80**(5), 920-943 (2022). Doi: https://doi.org/10.1016/j.joms.2022.02.008

12. K.N. Tu, J.D. Lie, C.K.V. Wan, M. Cameron, A.G. Austel, J.K. Nguyen, K. Van, D. Hyun, Osteoporosis: A review of treatment options, *P & T*, **43**(2), 92-104 (2018). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5768298/pdf/ptj4302092.pdf

13. S.R. Malwal, B. O'Dowd, X. Feng, P. Turhanen, C. Shin, J. Yao, B.K. Kim, N. Baig, T. Zhou, S. Bansal, *et al.*, Bisphosphonate-generated ATP-analogs inhibit cell signaling pathways, *Journal of the American Chemical Society*, **140**(24), 7568-7578 (2018). Doi: https://doi.org/10.1021/jacs.8b02363

14. S. Cremers, S. Papapoulos, Pharmacology of bisphosphonates, *Bone*, **49**(1), 42-49 (2011). Doi: https://doi.org/10.1016/j.bone.2011.01.014

15. K. Ganesan, A. Goyal, D. Roane, Bisphosphonate, StatPearls [Internet], National Library of Medicine, 2022. URL: https://pubmed.ncbi.nlm.nih.gov/29262103/

16. S. Kalra, V. Jain, Dental complications and management of patients on bisphosphonate therapy: A review article, *Journal of Oral Biology and Craniofacial Research*, **3**(1), 25-30 (2013). Doi: https://doi.org/10.1016/j.jobcr.2012.11.001

17. L. Arboleya, M. Alperi, S. Alonso, Efectos adversos de los bisfosfonatos, *Reumatología Clínica*, **7**(3), 189-197 (2011). Doi: https://doi.org/10.1016/j.reuma.2010.10.005

18. A. Izzotti, M. Menini, A. Pulliero, G. Dini, C. Cartiglia, P. Pera, D. Baldi, Biphosphonates-associated osteonecrosis of the jaw: The role of gene-environment interaction, *Journal of Preventive Medicine and Hygiene*, **54**(3), 138-145 (2013). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4718369/pdf/1121-2233-54-138.pdf

19. H. Bansal, Medication-related osteonecrosis of the jaw: An update, *National Journal of Maxillofacial Surgery*, **13**(1), 5-10 (2022). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9326203/pdf/NJMS-13-5.pdf

20. D. Rosella, P. Papi, R. Giardino, E. Cicalini, L. Piccoli, G. Pompa, Medication-related osteonecrosis of the jaw: Clinical and practical guidelines, *Journal of International Society of Preventive and Community Dentistry*, **6**(2), 97-104 (2016). Doi: https://doi.org/10.4103/2231-0762.178742

21. S. Kuehn, R. Scariot, M. Elsalanty, Medication-related osteonecrosis: Why the jawbone? *Dentistry Journal*, **11**(5), 109 (2023). Doi: https://doi.org/10.3390/dj11050109

22. L.D. Carbonare, M. Mottes, M.T. Valenti, Medication-related osteonecrosis of the jaw (MRONJ): Are antiresorptive drugs the main culprits or only accomplices? The triggering role of vitamin D deficiency, *Nutrients*, **13**(2), 561 (2021). Doi: https://doi.org/10.3390/nu13020561

23. T. Suzuki, R. Sekiya, Y. Hamada, M. Takahashi, K. Karakida, H. Sakamoto, Fatal bleeding in conjunction with mandibular medication-related osteonecrosis of the jaw (MRONJ), *The Bulletin of Tokyo Dental College*, **59**(1), 27-34 (2018). Doi: https://doi.org/10.2209/tdcpublication.2016-0052

24. L.-Y. Wei, S.-H. Kok, Y.-C. Lee, W.-Y. Chiu, J.-J. Wang, S.-J. Cheng, H.-H. Chang, J.-J. Lee, Prognosis of medication-related osteonecrosis of the jaws in metastatic prostate cancer patients, *Oral Diseases*, **28**(1), 182-192 (2022). Doi: https://doi.org/10.1111/odi.13737

25. C. Scully, C. Madrid, J. Bagan, Dental endosseous implants in patients on bisphosphonate therapy, *Implant Dentistry*, **15**(3), 212-218 (2006). Doi: https://doi.org/10.1097/01.id.0000236120.22719.02

26. G. Campisi, R. Mauceri, F. Bertoldo, V. Fusco, A. Bedogni, A pragmatic window of opportunity to minimise the risk of MRONJ development in individuals with osteoporosis on Denosumab therapy: A hypothesis, *Head & Face Medicine*, **17**, 25 (2021). Doi: https://doi.org/10.1186/s13005-021-00280-4

27. A. Yuan, A. Munz, S. Reinert, S. Hoefert, Histologic analysis of medication-related osteonecrosis of the jaw compared with antiresorptive-exposed bone and other infectious, inflammatory, and necrotic jaw diseases, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, **129**(2), 133-140 (2020). Doi: https://doi.org/10.1016/j.oooo.2019.08.018

28. T.B. Dodson, The frequency of medication-related osteonecrosis of the jaw and its associated risk factors, *Oral and Maxillofacial Surgery Clinics of North America*, **27**(4), 509-516 (2015). Doi: https://doi.org/10.1016/j.coms.2015.06.003

29. L. dos Santos-Ferreira, L.G. Abreu, C.B. Calderipe, M.D. Martins, L.F. Schuch, A.C.U. Vasconcelos, Is teriparatide therapy efective for medication-related osteonecrosis of the jaw? A systematic review and meta-analysis, *Osteoporosis International*, **32**(12), 2449-2459 (2021). Doi: https://doi.org/10.1007/s00198-021-06078-z

30. A. Muthukrishnan, L. Bijai, G. Ramalingam, Medication-related osteonecrosis of the jaw: a dentist's nightmare, *BMJ Case Reports*, **2016**, bcr2016214626 (2016). Doi: https://doi.org/10.1136/bcr-2016-214626

31. J.-H. Park, A.M. Alfafara, Y.L. Park, J.-H. Bae, S.-J. Kim, Medication-related osteonecrosis of the maxilla: Prognosis of oral surgery combined with endoscopic sinus surgery, *Oral Diseases*, **27**(4), 962-969 (2021). Doi: https://doi.org/10.1111/odi.13615

32. E. Yamachika, M. Matsubara, A. Ikeda, T. Matsumura, N. Moritani, S. Iida, Treatment of Osteonecrosis of the Jaw, *Journal of Craniofacial Surgery*, **26**(7), e575-e577 (2015). Doi: https://doi.org/10.1097/SCS.0000000000002127

33. F.-J. Rodriguez-Lozano, R.-E. Oñate-Sánchez, Treatment of osteonecrosis of the jaw related to bisphosphonates and other antiresorptive agents, *Medicina Oral, Patología Oral, Cirugía Bucal*, **21**(5), e595-e600 (2016). URL: http://www.medicinaoral.com/medoralfree01/aop/20980.pdf

34. P. Procacci, M. Albanese, L. Trevisiol, V. Favero, D. Bertossi, F. Lonardi, A. D'Agostino, E. Manfrin, P.F. Nocini, Medication related osteonecrosis of the posterior maxilla: Surgical treatment using a combined transnasal endoscopic and intraoral approach, our experience with seven consecutive patients, *Clinical Otolaryngology*, **43**(2), 685-691 (2018). Doi: https://doi.org/10.1111/coa.12999

35. H.C. Schwartz, American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 Update and CTX, *Journal of Oral and Maxillofacial Surgery*, **73**(3), 377 (2015). Doi: https://doi.org/10.1016/j.joms.2014.10.035

36. O. Di Fede, V. Panzarella, R. Mauceri, V. Fusco, A. Bedogni, L. Lo Muzio, SIPMO ONJ Board, G. Campisi, The dental management of patients at risk

of medication-related osteonecrosis of the jaw: New paradigm of primary prevention, *Biomed Research International*, **2018**, 2684924 (2018). Doi: https://doi.org/10.1155/2018/2684924

37. M. Kaczoruk-Wieremczuk, P. Adamska, Ł.J. Adamski, P. Wychowanski, B.A. Jereczek-Fossa, A. Starzynska, Oral surgery procedures in a patient with Hajdu-Cheney syndrome treated with Denosumab-A rare case report, *International Journal of Environmental Research and Public Health*, **18**(17), 9099 (2021). Doi: https://doi.org/10.3390/ijerph18179099

38. G. Ficarra, F. Beninati, Bisphosphonate-related osteonecrosis of the jaws: an update on clinical, pathological and management aspects, *Head and Neck Pathology*, **1**(2), 132-140 (2007). Doi: https://doi.org/10.1007/s12105-007-0033-2

39. H. Al Farii, S. Zhou, A. Albers, Management of osteomyelitis in sickle cell disease: Review article, *JAAOS: Global Research and Reviews*, **4**(9), e20.00002-e20.00010 (2020). Doi: https://doi.org/10.5435/JAAOSGlobal-D-20-00002

40. A.A. Owosho, C.L. Estilo, J.M. Huryn, S.K. Yom, Pentoxifylline and tocopherol in the management of cancer patients with medication-related osteonecrosis of the jaw: An observational retrospective study of initial case series, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, **122**(4), 455-459 (2016). Doi: https://doi.org/10.1016/j.oooo.2016.06.019

41. H. Squires, E. Simpson, Y. Meng, S. Harnan, J.W. Stevens, R. Wong, S. Thomas, J. Michaels, G. Stansby, A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease, *Health Technology Assessment*, **15**(40), 1-228 (2011). Doi: https://doi.org/10.3310/hta15400

42. P. Lorz-Ulloa, R. Varela-Guillén, La prueba CTX como evaluador de riesgo en el diagnóstico y tratamiento de osteonecrosis de los maxilares inducida por el uso de bifosfonatos, *ODOVTOS-International Journal of Dental Sciences*, **17**(1), 41-51 (2015). Doi: https://doi.org/10.15517/ijds.v0i0.22044

43. M.C. Cortés-Motta, R. Fernández-Grisales, Osteonecrosis de los maxilares: Fisiopatología, diagnóstico y tratamiento, *Revista CES: Odontología*, **29**(2), 65-77 (2016). URL: http://www.scielo.org.co/pdf/ceso/v29n2/v29n2a08.pdf

44. A. Baba, T.K. Goto, H. Ojiri, M. Takagiwa, C. Hiraga, M. Okamura, S. Hasegawa, Y. Okuyama, N. Ogino, H. Yamauchi, *et al.*, CT imaging features of antiresorptive agent-related osteonecrosis of the jaw/medication-related osteonecrosis of the jaws, *Dentomaxillofacial Radiology*, **47**(4), 20170323 (2018). Doi: https://doi.org/10.1259/dmfr.20170323

45. W.B. Williams, F. O'Ryan, Management of medication-related osteonecrosis of the jaw, *Oral and Maxillofacial Surgery Clinics of North America*, **27**(4), 517-525 (2015). Doi: https://doi.org/10.1016/j.coms.2015.06.007

46. N. Ohga, Y. Yamazaki, K. Tsuboi, Y. Kitagawa, Healing of osteonecrosis of the jaw (ONJ) after discontinuation of denosumab in a patient with bone metastases of colorectal cancer: A case report and hypothesis, *Quintessence International* (Berlin), **46**(7), 621-626 (2015). Doi: https://doi.org/10.3290/j.qi.a33528

47. N. Ohga, J. Sato, T. Asaka, M. Morimoto, Y. Yamazaki, Y. Kitagawa, Successful conservative treatment of jaw osteonecrosis caused by denosumab in patients with multiple bone metastasis, *Journal of Oral Science*, **60**(1), 159-162 (2018). Doi: https://doi.org/10.2334/josnusd.17-0027

48. B. Svejda, C. Muschitz, R. Gruber, C. Brandtner, C. Svejda, R.W. Gasser, G. Santler, H.P. Dimai, Positionspapier zur medikamentenassoziierten Osteonekrose des Kiefers (MRONJ), *Wiener Medizinische Wochenschrift*, **166**, 68-74 (2016). doi: https://doi.org/10.1007/s10354-016-0437-2

49. F. Hallmer, O. Bjarnadottir, B. Gotrick, P. Malmstrom, G. Andersson, Incidence of and risk factors for medication-related osteonecrosis of the jaw in women with breast cancer with bone metastasis: A population-based study, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, **130**(3), 252-257 (2020). Doi: https://doi.org/10.1016/j.oooo.2020.04.808

50. H. Ikesue, K. Doi, M. Morimoto, M. Hirabatake, N. Muroi, S. Yamamoto, T. Takenobu, T. Hashida, Switching from zoledronic acid to denosumab increases the risk for developing medication-related osteonecrosis of the jaw in patients with bone metastases, *Cancer Chemotherapy and Pharmacology*, **87**, 871-877 (2021). Doi: https://doi.org/10.1007/s00280-021-04262-w

51. S. Soutome, S. Hayashida, M. Funahara, Y. Sakamoto, Y. Kojima, S. Yanamoto, M. Umeda, Factors affecting development of medication-related osteonecrosis of the jaw in cancer patients receiving high-dose bisphosphonate or denosumab therapy: Is tooth extraction a risk factor? *PLoS One*, **13**(7), e0201343 (2018). Doi: https://doi.org/10.1371/journal.pone.0201343

52. J. Bagan, A. Peydró, J. Calvo, M. Leopoldo, Y. Jiménez, L. Bagan, Medication-related osteonecrosis of the jaw associated with bisphosphonates and denosumab in osteoporosis, *Oral Diseases*, **22**(4), 324-329 (2016). Doi: https://doi.org/10.1111/odi.12447

53. M. Badr, E. Kyriakidou, A. Atkins, S. Harrison, Aggressive denosumab-related jaw necrosis – A case series, *British Dental Journal*, **223**(1), 13-16 (2017). Doi: https://doi.org/10.1038/sj.bdj.2017.573

54. N. Ueda, C. Nakashima, K. Aoki, H. Shimotsuji, K. Nakaue, H. Yoshioka, S. Kurokawa, Y. Imai, T. Kirita, Does inflammatory dental disease affect the development of medication-related osteonecrosis of the jaw in patients using high-dose bone-modifying agents? *Clinical Oral Investigations*, **25**(5), 3087-3093 (2021). Doi: https://doi.org/10.1007/s00784-020-03632-7

55. M.A. Altay, A. Radu, S.E. Pack, N. Yıldırımyan, A. Flores-Hidalgo, D.A. Baur, F.A. Quereshy, Medication-related osteonecrosis of the jaw: An institution's experience, *CRANIO®: The Journal of Craniomandibular & Sleep Practice*, **38**(5), 333-341 (2020). Doi: https://doi.org/10.1080/08869634.2018.1528711

56. N. Adachi, Y. Ayukawa, N. Yasunami, A. Furuhashi, M. Imai, K. Sanda, I. Atsuta, K. Koyano, Preventive effect of fuvastatin on the development of medication-related osteonecrosis of the jaw, *Scientific Reports*, **10**(1), 5620 (2020). Doi: https://doi.org/10.1038/s41598-020-61724-6

57. R. Correia-Cavalcante, G. Tomasetti, Pentoxifylline and tocopherol protocol to treat medication-related osteonecrosis of the jaw: A systematic literature review, *Journal of Cranio-Maxillofacial Surgery*, **48**(11), 1080-1086 (2020). Doi: https://doi.org/10.1016/j.jcms.2020.09.008

58. O. Ristow, C. Gerngroß, M. Schwaiger, B. Hohlweg-Majert, V. Kehl, H. Jansen, L. Hahnefeld, S. Koerdt, S. Otto, C. Pautke, Effect of antiresorptive drugs on bony turnover in the jaw: Denosumab compared with bisphosphonates, *British Journal of Oral and Maxillofacial Surgery*, **52**, 308-313 (2014). Doi: https://doi.org/10.1016/j.bjoms.2014.01.021

59. Y. Myoken, Y. Fujita, K. Kawamoto, S. Toratani, Osteonecrosis of the jaw in a metastatic lung cancer patient with bone metastases undergoing pembrolizumab + denosumab combination therapy: Case report and literature review, *Oral Oncology*, **111**, 104874 (2020). Doi: https://doi.org/10.1016/j.oraloncology.2020.104874

60. T.M. You, K.-H. Lee, S.-H. Lee, W. Park, Denosumab-related osteonecrosis of the jaw: A case report and management based on pharmacokinetics, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, **120**(5), 548-553 (2015). Doi: https://doi.org/10.1016/j.oooo.2015.07.017

61. O. Wasserzug, I. Kaffe, T.S. Lazarovici, T. Weissman, R. Yahalom, D.M. Fliss, N. Yarom, Involvement of the maxillary sinus in bisphosphonate-related osteonecrosis of the jaw: Radiologic aspects, *American Journal of Rhinology & Allergy*, **31**(1), 36-39 (2017). Doi: https://doi.org/10.2500/ajra.2017.31.4395

62. P.J. Voss, P. Poxleitner, R. Schmelzeisen, A. Stricker, W. Semper-Hogg, Update MRONJ and perspectives of its treatment, *Journal of Stomatology, Oral and Maxillofacial Surgery*, **118**(4), 232-235 (2017). Doi: https://doi.org/10.1016/j.jormas.2017.06.012

63. G. Maluf, M. Correia de Pinho, S.R.d.B. da Cunha, P.S. da Silva-Santos, E. Rodrigues-Fregnani, Surgery combined with LPRF in denosumab osteonecrosis of the jaw: Case report, *Brazilian Dental Journal*, **27**(3), 353-358 (2016). Doi: https://doi.org/10.1590/0103-6440201600662

64. R. Schoenhof, A. Munz, A. Yuan, A. ElAyouti, H. Boesmueller, G. Blumenstock, S. Reinert, S. Hoefert, Microarchitecture of medication-related osteonecrosis of the jaw (MRONJ); a retrospective micro-CT and morphometric analysis, *Journal of Cranio-Maxillofacial Surgery*, **49**(6), 508-517 (2021). Doi: https://doi.org/10.1016/j.jcms.2021.02.018

65. S. Otto, C. Pautke, T.V. den Wyngaert, D. Niepel, M. Schiødt, Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases, *Cancer Treatment Reviews*, **69**, 177-187 (2018). Doi: https://doi.org/10.1016/j.ctrv.2018.06.007

66. G. Dupic, D. Collangettes, A.-F. Dillies, L. Calvet, O. Tournilhac, J.-O. Bay, H. Mahammedi, Ostéonécrose des maxillaires liée aux bisphosphonates et denosumab: épidémiologie, diagnostic et traitement, *Bulletin du Cancer*, **102**(12), 1010-1019 (2015). Doi: https://doi.org/10.1016/j.bulcan.2015.10.009

67. S. Otto, C. Pautke, T.V. den Wyngaert, D. Niepel, M. Schiødt, Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases, *Cancer Treatment Reviews*, **69**, 177-187 (2018). Doi: https://doi.org/10.1016/j.ctrv.2018.06.007

68. A.L. Soares, S. Simon, L.H. Gebrim, A.C.P. Nazário, M. Lazaretti-Castro, Prevalence and risk factors of medication-related osteonecrosis of the jaw in osteoporotic and breast cancer patients: a cross-sectional study, *Supportive Care in Cancer*, **28**(5), 2265-2271 (2020). Doi: https://doi.org/10.1007/s00520-019-05044-0

69. T. Dennis, M. Gahan, The prosthodontic management of medication-related osteonecrosis of the jaw: A case report, *British Dental Journal*, **230**(1), 23-26 (2021). Doi: https://doi.org/10.1038/s41415-020-2500-z

70. K. Okuyama, S. Hayashida, S. Rokutanda, A. Kawakita, S. Soutome, S. Sawada, S. Yanamoto, Y. Kojima, M. Umeda, Surgical strategy for medication-related osteonecrosis of the jaw (MRONJ) on maxilla: A multicenter retrospective study, *Journal of Dental Sciences*, **16**(3), 885-890 (2021). Doi: https://doi.org/10.1016/j.jds.2020.12.007

71. M.-H. Kang, D.-K. Lee, C.-W. Kim, I.-S. Song, S.-H. Jun, Clinical characteristics and recurrence-related factors of medication-related osteonecrosis of the jaw, *Journal of the Korean Association of Oral and Maxillofacial Surgeons*, **44**(5), 225-231 (2018). Doi: https://doi.org/10.5125/jkaoms.2018.44.5.225

72. H. Miyashita, K. Kameyama, M. Morita, T. Nakagawa, T. Nakahara, Three-dimensional radiologic–pathologic correlation of medication-related osteonecrosis of the jaw using 3D bone SPECT/CT imaging, *Dentomaxillofacial Radiology*, **48**(8), 20190208 (2019). Doi: https://doi.org/10.1259/dmfr.20190208

73. G.D.A. Ayala, V.J.E. Miranda, C.Y.J. Torres, C.A. Uribe, Actualización de medicamentos asociados a necrosis avascular de los maxilares. Perspectiva y revisión de literatura, *Revista ADM*, **77**(4), 197-202 (2020). Doi: https://doi.org/10.35366/95113

74. M.S. Puche, C.C. Astié, M. Fontana, E. Jorquera, G. Alonso, G. Caputo, F. Sansone, M. Porcel, C. Aguado, Agentes antirresortivos y antiangiogénicos y su relación con la osteonecrosis de los maxilares asociada a medicamentos. Revisión narrativa, *Revista de la Asociación Odontológica Argentina*, **107**, 72-78 (2019). URL: https://docs.bvsalud.org/biblioref/2019/09/1016110/puche-agentes-antirresortivos-y-antiangiogenicos-y-su-relacion.pdf

75. R. Mauceri, V. Panzarella, I. Morreale, G. Campisi. Medication-related osteonecrosis of the jaw in a cancer patient receiving lenvatinib, *International*

Journal of Oral & Maxillofacial Surgery, **48**(12), 1530-1532 (2019). Doi: https://doi.org/10.1016/j.ijom.2019.07.010

76. C.Y.S. Lee, J.B. Suzuki, Medication-related osteonecrosis of the jaws from once per year intravenous zoledronic acid (Reclast): Report of 4 Cases, *Implant Dentistry*, **24**(2), 227-231 (2015). URL: https://journals.lww.com/implantdent/Fulltext/2015/04000/Medication_Related_Osteonecrosis_of_the_Jaws_From.18.aspx

77. I. Ogura, Y. Sasaki, M. Sue, T. Oda, A. Kameta, K. Hayama, Tc-99m hydroxymethylene diphosphonate scintigraphy, computed tomography, and magnetic resonance imaging of osteonecrosis in the mandible: Osteoradionecrosis versus medication-related osteonecrosis of the jaw, *Imaging Science in Dentistry*, **49**(1), 53-58 (2019). Doi: https://doi.org/10.5624/isd.2019.49.1.53

78. O. Ristow, C. Gerngroß, M. Schwaiger, B. Hohlweg-Majert, M. Ristow, S. Koerdt, R. Schuster, S. Otto, C. Pautke, Does regular zoledronic acid change the bone turnover of the jaw in men with metastatic prostate cancer: A possible clue to the pathogenesis of bisphosphonate related osteonecrosis of the jaw? *Journal of Cancer Research and Clinical Oncology*, **140**, 487-493 (2014). Doi: https://doi.org/10.1007/s00432-014-1588-4

79. O. Nicolatou-Galitis, M. Schiødt, R.A. Mendes, C. Ripamonti, S. Hope, L. Drudge-Coates, D. Niepel, T.V. den Wyngaert, Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, **127**(2), 117-135 (2019). Doi: https://doi.org/10.1016/j.oooo.2018.09.008

80. A. Jose, A. Rawat, S.A. Nagori, S. Arya, D. Shukla, Outcomes of sequestrectomy and buccal fat pad reconstruction in the management of medication- related osteonecrosis of the jaws, *Oral and Maxillofacial Surgery*, **26**(1), 147-153 (2022). Doi: https://doi.org/10.1007/s10006-021-00973-9

81. S. Aljohani, R. Gaudin, J. Weiser, M. Tröltzsch, M. Ehrenfeld, G. Kaeppler, R. Smeets, S. Otto, Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series, *Journal of Cranio-Maxillofacial Surgery*, **46**(9), 1515-1525 (2018). Doi: https://doi.org/10.1016/j.jcms.2018.05.046

82. R.C. de Souza-Póvoa, D.A. Alves-Marlierè, H. Martins da Silveira, F. Ramoa-Pires, Denosumab-related osteonecrosis of the jaws: successful management with a conservative surgical approach, *Special Care in Dentistry*, **36**(4), 231-236 (2016). Doi: https://doi.org/10.1111/scd.12168

83. Y. Thiel, C. Ghayor, D. Lindhorst, H. Essig, F. Weber, M. Rücker, P. Schumann, Antimicrobial peptide gene expression in medication-related osteonecrosis of the jaw, *Pathology - Research and Practice*, **216**(12), 153245 (2020). Doi: https://doi.org/10.1016/j.prp.2020.153245

84. S. Kuroshima, M. Sasaki, H. Murata, T. Sawase, Medication-related osteonecrosis of the jaw-like lesions in rodents: A comprehensive systematic review and meta-analysis, *Gerodontology*, **36**(4), 313-324 (2019). Doi: https://doi.org/10.1111/ger.12416

85. G. Favia, A. Tempesta, L. Limongelli, A. Crincoli, E. Maiorano, Medication-related osteonecrosis of the jaw: Surgical or non-surgical treatment? *Oral Diseases*, **24**(1-2), 238-242 (2018). Doi: https://doi.org/10.1111/odi.12764

86. K. Kiho, S. Sumitomo, M. Tanaka, T. Hasegawa, C. Sakai, Y. Takitani, T. Yoshida, S. Kawano, Pulpal disease arising from medication-related osteonecrosis of the jaw: A case report, *Journal of Endodontics*, **46**(8), 1149-1154 (2020). doi: https://doi.org/10.1016/j.joen.2020.04.010

87. N. Ueda, K. Aoki, H. Shimotsuji, C. Nakashima, M. Kawakami, Y. Imai, T. Kirita, Oral risk factors associated with medication-related osteonecrosis of the jaw in patients with cancer, *Journal of Bone and Mineral Metabolism*, **39**(4), 623-630 (2021). Doi: https://doi.org/10.1007/s00774-020-01195-x

88. M. Kawahara, S. Kuroshima, T. Sawase, Clinical considerations for medication related osteonecrosis of the jaw: a comprehensive literature review, *International Journal of Implant Dentistry*, **7**(1), 47 (2021). Doi: https://doi.org/10.1186/s40729-021-00323-0

89. O. Ristow, C. Gerngroß, M. Schwaiger, B. Hohlweg-Majert, V. Kehl, H. Jansen, L. Hahnefeld, S. Otto, C. Pautke, Is bone turnover of jawbone and its possible over suppression by bisphosphonates of etiologic importance in pathogenesis of bisphosphonate-related osteonecrosis? *Journal of Oral Maxillofacial Surgery*, **72**(5), 903-910 (2014). Doi: https://doi.org/10.1016/j.joms.2013.11.005

90. T. Hasegawa, A. Kawakita, N. Ueda, R. Funahara, A. Tachibana, M. Kobayashi, E. Kondou, D. Takeda, Y. Kojima, S. Sato, *et al.*, A multicenter retrospective study of the risk factors associated with medication-related osteonecrosis of the jaw after tooth extraction in patients receiving oral bisphosphonate therapy: can primary wound closure and a drug holiday really prevent MRONJ? *Osteoporosis International*, **28**(8), 2465-2473 (2017). Doi: https://doi.org/10.1007/s00198-017-4063-7

91. H. Ikesue, M. Mouri, H. Tomita, M. Hirabatake, M. Ikemura, N. Muroi, S. Yamamoto, T. Takenobu, K. Tomii, M. Kawakita, *et al.*, Associated characteristics and treatment outcomes of medication-related osteonecrosis of the jaw in patients receiving denosumab or zoledronic acid for bone metastases, *Supportive Care in Cancer*, **29**, 4763-4772 (2021). Doi: https://doi.org/10.1007/s00520-021-06018-x

92. A. Wutzl, G. Eisenmenger, M. Hoffmann, C. Czerny, D. Moser, P. Pietschmann, R. Ewers, A. Baumann, Osteonecrosis of the jaws and bisphosphonate treatment in cancer patients, *Wiener Klinische Wochenschrift*, **118**(15-16), 473-478 (2016). Doi: https://doi.org/10.1007/s00508-006-0644-8

93. M. Kajizono, H. Sada, Y. Sugiura, Y. Soga, Y. Kitamura, J. Matsuoka, T. Sendo, Incidence and risk factors of osteonecrosis of the jaw in advanced cancer patients after treatment with zoledronic acid or denosumab: A retrospective cohort study, *Biological and Pharmaceutical Bulletin*, **38**(12), 1850-1855 (2015). Doi: https://doi.org/10.1248/bpb.b15-00385

94. S. Aljohani, R. Gaudin, J. Weiser, M. Tröltzsch, M. Ehrenfeld, G. Kaeppler, R. Smeets, S. Otto, Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series, *Journal of Cranio-Maxillofacial Surgery*, **46**(9), 1515-1525 (2018). Doi: https://doi.org/10.1016/j.jcms.2018.05.046

95. C.V. Lyttle, H. Paterson, Denosumab: A case of MRONJ with resolution, *British Dental Journal*, **220**, 623-625 (2016). Doi: https://doi.org/10.1038/sj.bdj.2016.443

96. N. Heim, W. Götz, F.-J. Kramer, A. Faron, Antiresorptive drug-related changes of the mandibular bone density in medication-related osteonecrosis of the jaw patients, *Dentomaxillofacial Radiology*, **48**(8), 20190132 (2019). Doi: https://doi.org/10.1259/dmfr.20190132

97. E.R. Carlson, J.D. Basile, The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws, *Journal of Oral and Maxillofacial Surgery*, **67**(5), 85-95 (2009). Doi: https://doi.org/10.1016/j.joms.2009.01.006

98. I. Ogura, Y. Sasaki, M. Sue, T. Oda, A. Kameta, K. Hayama, Tc-99m hydroxymethylene diphosphonate scintigraphy, computed tomography, and magnetic resonance imaging of osteonecrosis in the mandible: Osteoradionecrosis versus medication-related osteonecrosis of the jaw, *Imaging Science in Dentistry*, **49**(1), 53-58 (2019). Doi: https://doi.org/10.5624/isd.2019.49.1.53

99. C. Foncea, K. von Bischhoffshausen, C. Teuber, H. Ramírez, I. Goñi, C. Sánchez, I.N. Retamal, A. Vargas, Osteonecrosis de los maxilares asociada a medicamentos: revisión de la literatura y propuesta para la prevención y manejo, *Revista Médica de Chile*, **148**(7), 983-991 (2020). Doi: https://doi.org/10.4067/S0034-98872020000700983

100. K. Walton, T.R. Grogan, E. Eshaghzadeh, D. Hadaya, D.A. Elashoff, T.L. Aghaloo, S. Tetradis, Medication related osteonecrosis of the jaw in osteoporotic vs oncologic patients—quantifying radiographic appearance and relationship to clinical findings, *Dentomaxillofacial Radiology*, **48**(1), 20180128 (2019). Doi: https://doi.org/10.1259/dmfr.20180128

101. C. Klingelhöffer, F. Zeman, J. Meier, T.E. Reichert, T. Ettl, Evaluation of surgical outcome and influencing risk factors in patients with medication-related osteonecrosis of the jaws, *Journal of Cranio-Maxillofacial Surgery*, **44**(10), 1694-1699 (2016). Doi: https://doi.org/10.1016/j.jcms.2016.08.001

102. S. Matsuda, H. Yoshida, M. Shimada, H. Yoshimura, Spontaneous regeneration of the mandible following hemimandibulectomy for medication-related osteonecrosis of the jaw, *Medicine* (Baltimore), **99**(33), e21756 (2020). Doi: https://doi.org/10.1097/MD.0000000000021756

103. R. Ogawa, Y. Minami, J. Ono, Y. Kanri, E. Kobayashi, A. Tanaka, Y. Okada, I. Ogura, Medication-related osteonecrosis of the jaw in a patient with multiple myeloma: an unusual case with tumor in the surgical specimen, *Oral Radiology*, **38**(2), 288-291 (2022). Doi: https://doi.org/10.1007/s11282-021-00560-4

104. C. Blus, G. Giannelli, S. Szmukler-Moncler, G. Orru, Treatment of medication-related osteonecrosis of the jaws (MRONJ) with ultrasonic piezoelectric bone surgery. A case series of 20 treated sites, *Oral and Maxillofacial Surgery*, **21**(1), 41-48 (2017). Doi: https://doi.org/10.1007/s10006-016-0597-7

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