

Implants in Patients Under Denosumab Prescription: Protocol for Dentists

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Abstract

Introduction: Denosumab is a human monoclonal antibody. The goal of the drug is to stop bone loss. Before a dental surgery, it is important to know the benefit-risk ratio of the anti-resorptive drugs. When it comes to implant treatment, Denosumab has side effects, such as osteonecrosis of the jaws.

Objectives: Protocol for the dentist before, during and after the placement of implants and oral surgery. In patients medicated with. Epidemiology of ONJ. As a final objective, the treatment of implants was compared in patients treated with two similar drugs: Bisphosphonates and Denosumab.

Materials and Methods: The search was carried out through: Medline, Google academic, Cochrane, Scielo and Pubmed.

Results and Discussion: In this section the proposed objectives have been developed. It is essential to have a careful clinical history, in addition to a cooperation with the patient's specialist doctors, before the surgical treatment of implants. The professional must establish an early diagnosis of ONJ, with a correct treatment plan. Radiographic follow-up in oral surgery is crucial to be able to review the signs of osseointegration of the implants and the possible signs of osteonecrosis of the bone. The most common cases of osteonecrosis are given by oral surgery with several comorbidities that participate in the process of bone deterioration. The main advantage of Denosumab is its reversible effect: it does not persist for long periods of time in the bone.

Conclusion: Many studies concluded that the diagnosis of osteonecrosis can be given after intake of drugs such as Denosumab or bisphosphonates. Osteonecrosis is a complication of multifactorial origin and it is necessary to know both the pathology and the clinical protocols of action to perform the best possible a dental implant treatment.

Keywords: Denosumab; Osteonecrosis; Protocols and Odontology; Dental Implants and Oral Surgery

Abbreviations

ARONJ: Osteonecrosis of the Mandible Related to Anti-Resorptive Agents; MRONJ: Medication-related Osteonecrosis of the Jaw; ONJ: Osteonecrosis of the Jaw; AAOMS: The American Association of Oral and Maxillofacial Surgeons; BRONJ: Osteonecrosis of the Mandible Related to Bisphosphonates; DROJ: Osteonecrosis of the Jaw Related to Denosumab; RANKL: Receptor-activator of Nuclear Factor-Kappa Ligand; RANK: Receptor-activator of Nuclear Factor Kappa; LPRF: Fibrin Rich in Leukocytes and Platelets; PRP: Plasma Rich in Platelets; PRGF: Plasma Rich in Growth Factors;

ZA: Zoledronic Acid; MRO: Bone Replacement or Bone Remodeling Markers; ALP: Total Alkaline Phosphatase; BAP: Bone Alkaline Phosphatase; SO: Osteocalcin; P1CP: Propeptide C-terminal of Procollagen Type 1; P1NP: Propeptide N-terminal of Procollagen Type 1; TRAP: Tartrate-Resistant Acid Phosphatase; NTXT: Collagen Type 1 N-terminal telopeptide; PYD: Free pyridinoline; DPDi: Free Deoxypyridinoline; IOF: International Osteoporosis Foundation; β -CTX: Beta Cross-Laps or CTX Octapeptide; MKI: Multikinases Inhibitors; OM: Osteonecrosis of the Jaws; AR: Anti-resorptives; AA: Anti-angiogenics

Introduction

What is denosumab and the MRONJ?

Denosumab is a human monoclonal antibody, used to treat osteoporosis and for bone metastases; it acts by inhibiting the activity of osteoclasts, reducing bone resorption and increasing bone density [1].

In the document published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014, osteonecrosis related to medications (MRONJ) was defined. Within this classification are patients under current or previous treatment with Bisphosphonates or Denosumab or antiangiogenic drugs [13,17]. According to the AAOMS, MRONJ can be considered in patients who meet all of the following characteristics: Bone exposed through an intra-oral/extraoral fistula, in the maxillofacial region without healing, for more than 8 weeks. These patients must have a history of anti-resortive or antiangiogenic therapy, have not received irradiation therapy to the mandible, and have not had bone metastases in this area [13].

In 2010 the use and prescription of Denosumab was approved in the United States and from this antibody two drugs were developed: Prolia to treat postmenopausal osteoporosis and Xgeva for the prevention of bone metastases [4].

In the same year, cases of osteonecrosis associated with Denosumab began to occur. Although many people still confuse it with a bisphosphonate, Denosumab is actually a monoclonal antibody that inhibits RANKL [4].

In the paper by Camila-Carvalho de Oliveira, *et al.* Denosumab is defined as a monoclonal IgG2 antibody with high affinity and specificity for RANKL (Receptor activator of nuclear factor-kappa B ligand). It acts as an anti-resortive agent, inhibiting osteolysis and blocking the interaction between RANKL and RANK (Receptor Activator of Nuclear Factor κ B) preventing the differentiation and activation of osteoclasts. This drug has a different mechanism of action than bisphosphonates, as it acts on the precursors of osteoclasts, preventing their formation, differentiation and function through the inhibition of the action of RANKL [20].

RANKL is a cytokine found in multiple cells, including osteoblasts. It has a fundamental role in the function, activation and differentiation of osteoclasts and recent studies have shown that RANKL is an important factor for bone remodeling [1]. Thanks to

this research, we can conclude that Denosumab is an etiological factor of osteonecrosis of the jaws due to its excessive suppression of bone remodeling [4].

Treatment with Denosumab has a number of adverse effects including mainly Osteonecrosis of the jaw (ONJ). Although there is a low incidence of ONJ due to the use of Denosumab, when it occurs, it leads to serious functional and masticatory disorders, with negative consequences on the patient's quality of life [1]. Osteonecrosis of the jaws is a complication that sometimes occurs after treatment with anti-resortive drugs, as in the case of Denosumab; these anti-resortive agents increase bone strength and mineral density in order to reduce the risk of bone fractures [3].

What are the risk factors for MRONJ? How to act against MRONJ?

Osteonecrosis of the jaw related to medication (MRONJ) is primarily an adverse side effect of Denosumab or Bisphosphonates. It is important to know that preventive measures in recent years have reduced the risk of MRONJ in patients with bone metastases, but making decisions in dental patients who are going to undergo some surgical treatment, it is always necessary to balance two facts: the risk of osteonecrosis against the beneficial effects of treatment with Denosumab or Bisphosphonates on the skeletal health of patients [17].

In these types of patients, it is crucial to minimize the risk of developing osteonecrosis of the jaws; therefore, it is better to avoid trauma to the bone and the oral cavity in general, as well as to prevent and treat dental infections before and during treatment with Denosumab or Bisphosphonates.

If osteonecrosis of the jaws develops, surgery is ruled out as the first step. Therefore, the first step will be a conservative treatment, for example long-term antibiotic drugs or local disinfectant rinses in order to provide relief of symptoms. A surgical approach may be beneficial for symptom management and mucosal healing in the event of failure of the conservative attempt [17].

In general, a multidisciplinary approach and very close cooperation between doctors, oncologists and dentists must be adopted to resolve cases of osteonecrosis by medication; what is always prioritized is the patient's health and the management of his or her malignant skeletal disease, which may be osteoporosis or bone metastases.

Apart from the improvement in bone quality provided by these drugs, the main mechanism of action of Denosumab must be remembered: to inhibit the function of osteoclasts and increase apoptosis through different mechanisms, and this leads to altered bone remodeling, which is the main hypothesis of bone deterioration and the evolution of osteonecrosis of the jaw [3].

Another theory of the etiopathogenesis of ONJ in anti-resorptive treatments refers to periodontal, osseous or fibromucosal tissues that may have an infection or trauma; as in the case of adult teeth, which are often extracted because they have a large periapical or periodontal infectious focus; in this case it is known that extraction, such as the placement of implants, are high risk factors for the development of ONJ [3].

Are there other drugs similar to denosumab? Do they have the same side effects?

Osteonecrosis of the Jaw has been described, not only as a consequence of treatment with anti-resorptive drug, but also by anti-angiogenic medication. Patients medicated with one or both of these drugs at the same time, if they have the risk that the bone has been traumatized or injured, may remain exposed in the oral cavity for at least eight weeks without healing [3].

The inhibition of angiogenesis is another hypothesis that explains the appearance of ONJ. Anti-angiogenic agents prevent the development of new blood vessels and lead to the cessation of angiogenesis, which is a factor that promotes metastasis. In the paper by Toshiyuki Yoneda, *et al.* it has been shown that anti-angiogenic agents and tyrosine kinase inhibitors, which are essentially administered as adjuvants in the treatment of cancer patients, can cause ONJ or increase the incidence of ONJ when used concomitantly with bisphosphonates or Denosumab [2]. Also, in the paper of Sven Otto, *et al.* it is analyzed that there are clinical cases where it is possible that patients receiving anti-angiogenic drugs and tyrosine kinase inhibitors may promote osteonecrosis of the jaws, but there is data lack of solid evidence [17].

Objectives of the Study

1. To evaluate patients under treatment with Denosumab who are going to undergo Implant Surgery: Protocol for the dentist before, during and after the placement of implants and oral surgery.
2. To review the epidemiology of cases of ONJ by Denosumab in implants and oral surgery.

3. To compare in patients with implants or patients with future implant treatment, the effects of two similar drugs: Bisphosphonates and Denosumab.

Materials and Methods

The bibliographic search has been carried out in different databases; these are: Medline, with access through the library of the European University of Madrid with the aim of finding papers of high quality and impact factor. In addition to this source, we looked into Google academic, Cochrane, Scielo and Pubmed.

The initial search gave as results 40 articles, of which 32 were selected, due to the greater specificity in the subject matter.

To organize my search and filter the different articles extracted, I have followed some criteria of inclusion and exclusion; they are the following ones.

Inclusion criteria

- Articles that study in their content the drug Denosumab in relation to Osteointegrated implants and oral surgery.
- Articles on Denosumab published after 2009.
- Articles comparing Bisphosphonates with Denosumab.
- Articles about bisphosphonates and osteoporosis.
- Articles on the Osteonecrosis of the jaws.
- Preference of articles with impact factor.
- Preference of articles with greater scientific evidence: Meta-analysis, systematic reviews and clinical trials.

Exclusion criteria

- Articles with a language other than Spanish, English and Italian.
- Articles on Denosumab that have been published before 2009.
- Animal studies or "*In vitro*".

Keywords

To do this bibliographic research I have used keywords such as: Denosumab, Osteonecrosis, protocols and dentistry, dental implants and oral surgery.

The search words in English have been: osteonecrosis protocols, dentistry, dental implants and oral surgery.

Results and Discussion

To evaluate patients under treatment with denosumab and those who are going to undergo Implant Surgery: Protocol for the dentist before, during and after the placement of implants and oral surgery

Protocol for the dentist before implant placement and oral surgery

Before the placement of the implants it is necessary to know that the Denosumab, combined with risk factors, which are all those that involve "traumatizing" the oral environment such as implants, dental extraction, poor oral hygiene, the use of removable appliances, chemotherapy (including long-term corticosteroids) and radiotherapy, can promote the development of ONJ.

It is essential to identify patients with risk factors and to establish preventive measures prior to implant placement so that the onset of ONJ can be limited.

A careful clinical control twice a year together with intraoral x-rays, orthopantomography and CT scan, are the ideal diagnostic measures in prevention for patients suffering from osteoporosis and malignant metastasis; this is a way to identify the harmful effects of the medications they take and at the same time detect osteonecrosis in incipient stages in case of oral surgery [1]. The dentist must first of all know that: taking Denosumab or Bisphosphonates together with a dental extraction, poor dental hygiene and a removable prosthesis can favor osteonecrosis of the jaw.

According to Natalie H Beth-Tasdogan., *et al.* it is better to act preventively to avoid MRONJ; dental prophylaxis, caries control and conservative restorative dentistry are expected to minimize the number of bacteria and eliminate the entry of microorganisms, which reduces the risk of infection. Periodic dental evaluations during anti-resorptive or anti-angiogenic therapy may help to recognize the risks of significant osteonecrosis at an early stage and allow rapid action to be taken to counteract them [11].

According to Iván Herrera Ustariz., *et al.* the appearance of maxillary osteonecrosis by drugs other than bisphosphonates has been attributed to agents such as mononuclear antibodies Denosumab, Bevacizumab and anti-neoplastic inhibitors of multikinase, Sunitinib, Sorafenib and Doxorubicin, which is an antibiotic. Multikinase inhibitors (MKI) are a type of therapy aimed at inhibiting the chemical messenger kinases in tumor cells. By blocking these messengers, the cells stop growing and dividing. They are used in the

treatment of advanced thyroid cancer and in other types of cancer, such as liver or kidney cancer. MKI drugs do not cure cancer, but they can stop its progression for months, even years [31]. The oral health of patients who are going to be treated or are already being treated with these anti-angiogenic drugs should be monitored periodically because of the risk of developing MRONJ.

According to Claire Egloff-Juras., *et al.* the management of osteonecrosis by Denosumab is mainly preventive, so it is important to have a dental consultation before prescribing the anti-resorptive drug. During this consultation, it is necessary to emphasize to the patient the risk of necrosis and also to advise him on dental hygiene. It is also important to have regular dental follow-up: It is necessary to have revisions at least 4 times a year, so that the dentist can evaluate the state of oral health and whether it is necessary to place implants [25]. This is agreed by the authors Toshiyuki Yoneda., *et al.* therefore, adequate prevention before starting treatment with Denosumab, reduces the incidence of osteonecrosis of the jaws in patients treated with this drug, this attitude must be maintained especially before placing implants [2].

According to the article by Toshiyuki Yoneda., *et al.* ideally, all dental treatments should be completed 2 weeks before starting anti-resorptive treatment. However, in the event that anti-resorptive treatment cannot be delayed due to the progression of bone metastases or with a high risk of fracture, the administration of anti-resorptive agents in parallel with conservative dental treatments may be acceptable; this is a crucial point that must be assessed with the specialist physician before placement of the implants, which in this case would be contraindicated [2]. Apart from the pharmacological treatment with Denosumab, the dentist has to deal with cases of infection after oral surgery, and it is clear that according to Ana Boquete-Castro., *et al.* the only means of fighting against this, is antibiotic treatment and in more serious cases, such as osteonecrosis of the jaw to antibiotherapy, debridement and bone resection can be combined [1].

Regarding the classification of factors or events that may be harmful to the patient before and during a dental consultation, we compared the articles of Boquete-Castro., *et al.* and Toshiyuki Yoneda., *et al.* the latter coincides with the former in the fact that there must be concomitant risk factors associated with osteonecrosis of the mandible by anti-resorptive drugs; Furthermore, the authors Toshiyuki Yoneda., *et al.* consider that apart from dental extractions, invasive dental treatments such as dental implants and apical/periodontal surgery are definite local risk factors for JRONJ [2].

As proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS), the desirability of taking anti-resorptive drug breaks before, during, and after invasive dental treatments is widely discussed. In case of ONJ by anti-resorptives and in case of necessity to make a successful treatment of this complication, it is very important the interactive communication and the cooperation between doctors, dentists and oral surgeons [2]. About the therapeutic holidays in the anti-resorptive treatments, Claire Egl-off-Juras., *et al.* think that in case of the osteonecrosis of the jaws by Denosumab this confirmed, the medication will be suspended in agreement with the prescribing doctor. In spite of all this, the cure of osteonecrosis is long and it is possible to obtain a complete cure or not [25]. Once the oral cavity has been cleaned and all the time necessary for the healing of the tissues has been waited for, we will be able to consider the placement of implants; always under the advice of oncology specialists and maxillofacial surgeons. In this case According to Natalie H Beth-Tasdogan., *et al.* stopping anti-resorptive drugs before an invasive dental procedure (drug holidays) could be useful for the prevention of MRONJ. Due to pharmacokinetics, the anti-resorptive effect of Bisphosphonates is maintained for several weeks or months; therefore, cessation of anti-resorptive therapy for at least two months is required to significantly reduce the risk of MRONJ during invasive dental procedures [11].

According to Olga Di Fede., *et al.* therapeutic holidays before surgical dental treatment are important, especially the suspension of anti-resorptive drugs for cancer patients; the dentist must agree with the oncologist, according to table 1 reported below [32].

Drug Holiday in Cancer Patients		
Active pharmaceutical ingredient	Last administration	Resume Treatment
Biphosphonate (AR)	At least one week before	4 - 6 week after
Denosumab (AR)	At least one week before	4 - 6 week after
Bevacizumab (AA)	At least 6-7 weeks before	4 - 6 week after
Sunitinib (AA)	At least 1 week Before	4 - 6 week after
Everolimus (AA)	At least 1 week Before	4 - 6 week after

Table 1: From Di Fede O, Panzarella V, Mauceri R, Fusco V, Bedogni A, Lo Muzio L., *et al.* The Dental Management of Patients at Risk of Medication- Related Osteonecrosis of the Jaw: New Paradigm of Primary Prevention. Hindawi BioMed Research International. 2018 (Article ID 2684924):10 pages.

The last administration of the drug should be at least 1 week before the surgical procedure and then the anti-resorptive therapy should be resumed 4 - 6 weeks after the dental treatment [32].

In this case, according to Olga Di Fede., *et al.* if the patient does not have metastasis or cancer, the treatment with Denosumab is not maintained, while the bisphosphonates are removed one week before the surgical intervention and are resumed 4 - 6 weeks later [32].

There are some authors who show in their research, through tables, that bisphosphonates and Denosumab, apart from strengthening bone cells and delaying and reducing bone remodeling, improve the osseointegration of implants [9]. This is a controversy, about the benefits of anti-resorptive drugs during the placement of implants, therefore each case must be evaluated according to the reports of doctors specialized in oncology.

In the article by Toshiyuki Yoneda., *et al.* implants are not recommended in cancer patients receiving anti-resorptive treatment and alternative dental measures are recommended. On the other hand, in patients with osteoporosis, implant treatment can be performed in cases where doctors and dentists agree that dental implants are essential to improve the systemic and oral health of patients [2]. Before the placement of the implants, it is necessary to pay attention, as always, to the patient's clinical records, especially if he or she is under anti-resorptives; these medications alert us to the risk factors of ONJ, which in this case may be: dentoalveolar surgery or complex extractions, a scarce or absence of oral hygiene, prolonged taking of corticoids and finally, both fixed and removable prostheses [2].

Prior to oral surgery, X-ray and clinical diagnosis of bone disease is very important. In the bibliographic search, diagnostic possibilities have also been found, through osseous markers of resorption and bone formation in serum; before an oral surgery it is essential to make a proper diagnosis of the condition that the patient has or may have. As we see in the article by Toshiyuki Yoneda., *et al.* you can use the serum containing biochemical markers of bone replacement and ARONJ (of osteonecrosis by anti-resorptive agents) [2,18].

According to Martinez Garcia, to assess bone turnover, a number of substances can be studied in blood or urine whose concentration or activity reflects bone formation or resorption [18]. These agents are called "bone turnover or remodeling markers" (MROs) and can be used to diagnose ONJ, because they provide the level of bone mass [18].

According to scheme 1 and 2 that will follow we will see the most important formation and resorption markers.

M. Bone Formation	Tissue Origin	Sample
Total Alkaline Phosphatase (ALP)	Bone, Liver, Kidney, Placenta	Serum
Bone-Specific Alkaline Phosphatase (BAP)	Bone	Serum
Osteocalcin (SO)	Bone, Dentine	Serum
Procollagen type 1 C-terminal propeptide (P1CP) Procollagen type 1 N-terminal propeptide (P1NP)	Bone, skin, soft tissues	Serum

Table 2: Principal bone-formation biomarkers.

Source: From Martínez García M, Gómez Font R, Bascones Martínez A. *Evaluación de comportamiento de implantes osteointegrados en mujeres con osteoporosis en tratamiento con bisfosfonatos orales. Variabilidad en el tiempo y relación pronóstica del telopeptidocarboxiterminal CTX Crosslaps [Tesis Doctoral]. Universidad complutense de madrid facultad de odontología Departamento de Estomatología III (Medicina y Cirugía Bucofacial); 2012.*

Total alkaline and bony phosphatases are enzymes involved in bone formation and osteoid mineralization. Their determination is simple, it is done through self-analysers, although it presents the disadvantage of their non-specificity. Then there is Osteocalcin, which is the most abundant non-collagenic protein in the bone matrix; it is synthesized exclusively by osteoblasts and odontoblasts and intervenes in the regulation of bone mineralization. When formed, it passes directly into the blood, where its determination provides an index of osteoblastic activity. P1CP and P1NP: both peptides pass into the blood, where they can be measured by various methods, such as radio-immunoassay or enzyme immunoassay. P1NP is a sensitive and quite specific marker and can currently be considered the most suitable for assessing and monitoring the evolution of osteoporotic patients [18].

Tartar-resistant acid phosphatase is a lysosomal enzyme present in bone and other tissues such as prostate, spleen, erythrocytes, platelets; there are at least 6 isoenzymes. The isoenzyme 5 is produced by the osteoclasts and is released during the resorption phase and is therefore considered a marker of osteoclastic activity. Pyridinoline is especially abundant in type I collagen of bone and type II collagen of cartilage, while deoxypyridinoline is found

only in type I collagen of bone and dentin. Pyridinium bridges are formed when collagen molecules have been released into the extracellular environment, thus representing degradation products of mature collagen. β -CTX can be determined in both blood and urine, being the most sensitive and specific resorption marker currently available [18] (See chart 2).

Resorption biomarkers	Tissue Origin	Sample
Tartrate acid resistant Phosphatase (TRAP)	Bone, blood	Serum
N-terminal Telopeptide collagen type 1 (NTX) Octapeptide CTX or Beta CrossLaps (β -CTX)	Bone, skin	Urine, Serum
Free Piridinoline (PYD)	Bone, tendons, blood vessels, cartilage	Urine
Free Deoxypyridinoline (DPDi)	Bone, dentine	Urine

Table 3: Bone-resorption Biomarkers.

Source: From Martínez García M, Gómez Font R, Bascones Martínez A. *Evaluación de comportamiento de implantes osteointegrados en mujeres con osteoporosis en tratamiento con bisfosfonatos orales. Variabilidad en el tiempo y relación pronóstica del telopeptidocarboxiterminal CTX Crosslaps [Tesis Doctoral]. Universidad complutense de madrid facultad de odontología Departamento de Estomatología III (Medicina y Cirugía Bucofacial); 2012.*

The IOF (International Osteoporosis Foundation) has recently recommended the use of serum markers in the follow-up of patients with osteoporosis; specifically, P1NP must be revised as a formation marker and β -CTX as a resorption marker. On the other hand, both markers could also be useful to predict the risk of fracture and osteonecrosis [18].

The values of the serum biochemical markers of bone turnover are reduced by treatment with bisphosphonates and Denosumab. Therefore, these markers may be useful for the diagnosis, monitoring and evaluation of therapeutic effects in patients with ARONJ. At the same time the authors of the article believe that most clinical studies have not found a significant correlation between changes in serum markers of bone turnover and the emergence and progression or cure of ARONJ. Therefore, according to Toshiyuki Yoneda, *et al.* it is unlikely that the bone replacement markers currently in use, have prognostic value for ARONJ [2].

In the same article by Toshiyuki Yoneda, *et al.* the diagnosis of osteonecrosis in patients is differentiated according to the doses of medication; it is essential in the protocol for the dentist to take measures and request different complementary tests to resolve each type of clinical case [2].

For patients treated with low doses of anti-resorptive agents, and who do not have evident clinical manifestations of osteonecrosis of the mandible given by these drugs, intra-oral and panoramic radiographs together with an exhaustive clinical examination are sufficient for diagnosis. Intraoral X-rays, which have a high resolution, can reveal the site of infection in detail [2].

For cancer patients treated with high doses of anti-resorptive agents, intraoral x-rays of all existing teeth and panoramic x-rays are recommended to identify possible sites of infection, even if there are no signs of ONJ, as in these patients the risk of developing ONJ is potentially increasing [2].

According to Toshiyuki Yoneda, *et al.* it is important to underline the authors' idea about implants: placement is not recommended for cancer patients receiving anti-resorptive treatment and alternative dental measures are recommended.

For patients with clinical suspicion of ONJ, computerized axial tomography (CT) and CBCT are useful for detecting early changes in the trabecular and cortical bones of the mandible and for evaluating sequestration, fistula formation, periosteal responses and affected teeth. In the latter case, it is important that the CT can be combined with intraoral and panoramic radiographs [2].

Finally, for cases where a differential diagnosis between ONJ and malignant tumors is required, the use of CT and MRI is recommended instead of cone-beam CT [2].

On the subject of therapeutic holidays of anti-resorptive treatments or to continue with these, Toshiyuki Yoneda, *et al.* in their paper considered explain to us that there is a survey made and analyzed by the Osteoporosis Society of Japan among dentists and maxillofacial surgeons; In that survey there was no change in the incidence of ONJ in osteoporotic patients, even when bisphosphonates or Denosumab were suspended before dental treatment; so we can conclude that the benefits of anti-resorptive agents outweigh the harmful effects, for these professionals [2].

Before the surgical action, there are authors who emphasize the fact that patients who need anti-resorptive therapies do not have delays in the beginning of these; therefore it is essential that pa-

tients are treated surgically and reviewed by the dentist before the start of therapy with Denosumab.

Prior to the administration of Denosumab, physicians should instruct patients to attend routine dental appointments, for oral examination, and for surgical or conservative treatments. Dentists should immediately inform physicians of the results of oral examinations and dental treatments; once the oral cavity has been treated, anti-resorptive therapies can be started [2]. This point is also developed in the article by Ioana-Aurița Albu-Stan, *et al.* i.e. all patients should be evaluated by a dentist before starting anti-resorptive therapy; they should receive dental treatment for any pathology in the oral area, the state of oral hygiene, caries, active periodontitis and the need for surgical interventions should be evaluated [3].

Toshiyuki Yoneda, *et al.* propose to give relevant importance to the cooperation between doctors and dentists before and after the start of dental treatment, so a detailed clinical record is very useful for doctors. In the same article we see that in patients with osteoporosis, implant treatment is feasible. Therefore, it can be performed as long as the primary care physician and dentist agree that dental implants are essential to improve the systemic condition and quality of life of patients [2].

According to Toshiyuki Yoneda, *et al.* ideally all dental treatments should be completed 2 weeks before starting anti-resorptive treatment. However, in the event that anti-resorptive treatment cannot be delayed due to progression of bone metastases or high risk of fracture, administration of anti-resorptive agents in parallel with dental treatments may be acceptable [2].

According to Olga Di Fede, *et al.* in patients who are waiting to begin anti-resorptive treatments and who have cancer, dentoalveolar surgeries are considered indicated invasive dental procedures, i.e. they can be done; it would be advisable to minimize any bone manipulation and promote healing by primary intention.

Other invasive procedures (e.g. implant surgery, pre-implant bone surgery, and mucogingival surgery) are contraindicated, as they are not aimed at eliminating infection and often have an aesthetic or rehabilitative goal; in addition, these procedures will have an indefinite long-term risk of developing MRONJ after administration of ONJ-related drugs [32]. Dental treatments in cancer patients awaiting treatment with anti-resorptive or anti-angiogenics are described in table 4 below. Dental treatments, in patients without cancer, in the phase prior to treatment with AR we can classify them in the following table number 4. In general similarly, in this

group of patients, the main objective is to maintain and/or restore as soon as possible an acceptable level of oral health, possibly before the administration of AR drugs or within the first six months of the start of therapy [32].

Dental procedures on patients in the pre-treatment phase	Cancer patients	Non-cancer patients
Non surgical procedures		
Restorative dentistry	Indicated	Indicated
Endodontic treatment	Indicated	Indicated
Orthodontic treatment	Possible	Possible
Periodontal treatments: Oral Hygiene and non-surgical treatments	Indicated	Indicated
Prosthesis	Possible	Possible
Surgical Procedures		
Dentoalveolar surgery	Indicated	Indicated
Preimplant bone surgery	Contraindicated	Possible
Dental implant surgery	Contraindicated	Possible
Periodontal/Endodontic surgery	Indicated	Indicated

Table 4: Dental treatments in patients under Bone-modifiers (Pre-treatment).

Source 4: From Di Fede O, Panzarella V, Mauceri R, Fusco V, Bedogni A, Lo Muzio L., et al. *The Dental Management of Patients at Risk of Medication-Related Osteonecrosis of the Jaw: New Paradigm of Primary Prevention*. Hindawi BioMed Research International. 2018;(Article ID 2684924):10 pages.

From the first dose of ONJ-related drugs, the cancer patient is considered to be at high risk of developing MRONJ. Surgical procedures necessary to eliminate MRONJ outbreaks are defined as indicated for cancer patients and are being treated with AA or AR.

In table 5 we can see the comparison between cancer and non-cancer patients and we can classify the dental procedures that can or cannot be done, in other words, indicated and contraindicated [32].

Patients who do not have cancer are divided into two categories with respect to the risk of developing MRONJ: Category A, is one in which, patients who from 6 months to 3 years after the start of treatment, inform us that they have not had any risk factor (systemic and/or local), in this category there are also patients not yet treated with drugs related to ONJ.

Category B includes patients without cancer who have been on treatment for a period of time longer than 3 years or less than 3 years and at the same time affected by systemic or local risk factors; these patients will have an incremental and indefinable risk of developing MRONJ (See table 4 and 5) [32].

Olga Di Fede., et al. in their article, highlight the risk factors for osteonecrosis of the jaws related to anti-resorptive drugs and report them in schematic form (See table 5).

Dental procedures on patients in-treatment phase	Cancer Patients	Non cancer patients Category A	Non cancer patients Category B
Non surgical procedures			
Restorative dentistry	Indicated	Indicated	Indicated
Endodontic treatment	Indicated	Indicated	Indicated
Orthodontic treatment	Possible	Possible	Possible
Periodontal treatments: Oral Hygiene and non-surgical treatments	Indicated (every 4 months)	Indicated	Indicated
Prosthesis	Possible	Possible	Possible
Surgical Procedures			
Dentoalveolar surgery	Indicated	Indicated	Indicated
Preimplant bone surgery	Contraindicated	Possible	Possible
Dental implant surgery	Contraindicated	Possible	Possible
Periodontal/Endodontic surgery	Indicated	Indicated	Indicated

Table 5: Dental treatments in patients under Bone-modifier (In-treatment).

Source: From Di Fede O, Panzarella V, Mauceri R, Fusco V, Bedogni A, Lo Muzio L., et al. *The Dental Management of Patients at Risk of Medication-Related Osteonecrosis of the Jaw: New Paradigm of Primary Prevention*. Hindawi BioMed Research International. 2018;(Article ID 2684924):10 pages.

Protocol for the dentist AFTER implant placement and oral surgery

During osseointegration and in later phases of loading in patients taking Denosumab we can check in the radiological images that the implant is osseointegrating correctly or that it is suffering periimplantitis; it can happen that in a CT scan hypodense images are observed around the implant, coinciding with areas of osteonecrosis.

If we are dealing with a case of osteonecrosis of the jaw related to Denosumab, a treatment with a combined approach using the application of preventive measures with the aim of eliminating or reducing potential risk factors seems to be beneficial [1].

The preventive measures are based on an exhaustive control of oral hygiene, the control of caries in neighboring teeth to the implants, control of periodontal and peri-implant disease in a conservative way.

According to Blas Garcia Garcia, *et al.* osteonecrosis is usually associated with a severe infection, therefore antibiotics are administered (amoxicillin and clavulanic acid orally 875/125 mg, 3 times/day for 15 days associated with chlorhexidine rinses at 0.12%, 2 - 3 times/day) and a period of therapeutic holidays is established for treatment with Denosumab. This means that the next injection is not administered. In this case, if within two weeks of starting treatment there is an improvement in pain and periimplantitis, with disappearance of the suppuration, the patient can then be treated with subcutaneous Teriparatide 20g at low doses, through a daily injection for 6 months [5]. Regarding this type of antibacterial action, Claire Egloff-Juras, *et al.* also agree; according to the previous authors, in case of infection of the necrotic area, the use of antibiotics is necessary and regular monitoring will be established [25].

Protocol for the dentist AFTER implant placement and oral surgery

After placement of the implants in patients under treatment with Denosumab, it is important that the dentist knows the treatment alternatives for osteoporosis. Alternative drugs to Denosumab, such as Teriparatide, can be used to treat osteoporosis. 8 months after treatment with Teriparatide, if the patient is asymptomatic, and with a CT control we see a recovery of osteolytic bone lesions, the dentist may consider finishing the prosthetic rehabilitation on implants. If the osteolytic image and the infection have not recovered, we can act in a more aggressive way for the patient,

for example with an antibiotic treatment for infections combined with debridement and bone resection [1]. About the surgical action in case of osteonecrosis of the jaws, the authors Claire Egloff-Juras, *et al.* they do agree; according to the previous authors surgery is sometimes necessary to obtain the removal of the entire area of the necrotic bone and/or to eliminate a bone sequestration. Some more severe forms require the use of more invasive surgeries, such as mandibulectomy [25].

Anti-resorptive agents may interfere with the healing of surgical wounds after implant treatment, especially in the process of epithelialization; according to Toshiyuki Yoneda, *et al.* in this case, it may be necessary to temporarily interrupt AR treatment or switch to alternative therapeutic drugs, which are not associated with ONJ, until the surgical wounds have healed completely [2].

Authors like A Khan, *et al.* agree that if the risk of bone fracture due to fragility is low or moderate, discontinuation of therapy with bisphosphonates or Denosumab may be appropriate, until the surgical wound is closed, and finally resume anti-resorptive treatment [7].

If the risk of fracture or bone metastasis is well controlled, it is recommended that AR treatment be resumed approximately 2 months after the invasive dental procedure so that damaged alveolar bones have healed. The dentist should immediately inform the doctors about the healing of surgical wounds so that the administration of anti-resorptives can be resumed without delay, especially if the risk of fracture is high or if the bone metastasis progresses rapidly.

In the comparison of the first article by Boquete-Castro, *et al.* and the second by Toshiyuki Yoneda, *et al.* we can conclude that both agree on the importance of careful clinical and radiographic control before, during and after implant placement [1,2].

Boquete-Castro, *et al.* tell us that a good clinical examination should be done twice a year along with intraoral x-rays, orthopantomography and CT, because they are the ideal preventive measures for patients suffering from osteoporosis and malignant metastasis; this is a way to prevent the harmful effects of the drugs they take and at the same time detect osteonecrosis in case of oral surgery [1].

It should also be taken into account that if the patient presents osteonecrosis of the jaw after surgery, as a substitute therapy for Denosumab we can switch to the administration of Teriparatide;

among the problems of this drug is that it is contraindicated in patients with metastatic bone tumors, and that its total dose and period of administration are also restricted. Therefore, the advantages and benefits of teriparatide for ARONJ treatment have yet to be validated [2,11].

In the same article, the authors warn us that systemic administration at low doses of this parathyroid hormone (Teriparatide) resolves the symptoms of osteonecrosis of the jaw and promotes its cure. Studies in Japan have shown an improvement in bone regeneration and healing of ONJ lesions [2,11].

In the article by A Khan., *et al.* the authors agree that if the occurrence of bone fractures due to fragility is very probable and the risk of ONJ is also significant, it can be considered to change the therapy with Denosumab to Teriparatide in the absence of contraindications. Teriparatide has been associated with improved bone healing, as this means that it can be prescribed before oral surgery, preventively, or later, if we see signs and symptoms of osteonecrosis [7,11]. Natalie H Beth-Tasdogan., *et al.* agree on the use of Teriparatide as a non-surgical treatment, it is a recombinant form of parathyroid hormone that stimulates osteoblasts to increase bone density, when used intermittently [11].

Another alternative and non-surgical therapy is the use of Ozone, this has antimicrobial and wound healing properties, induces tissue repair by cleansing osteonecrotic lesions, leading to healing of mucosa and bone [11]. As surgical treatments in advanced stages of mandibular osteonecrosis, they may include a more conservative approach, sequestrectomy; or a more aggressive approach with surgical debridement, resections of an affected bone with reconstruction, or a mandibulectomy [11].

About the treatment of ONJ with Ozone and other alternative therapies, also agrees Iván Herrera Ustariz who in his article informs us that: Hyperbaric oxygen and Ozone can stimulate cell proliferation, soft tissue healing and pain reduction; currently there are several reports that indicate that the application of low intensity laser has a biostimulant effect on the repair process of the mucosa and bone, increasing the bony inorganic matrix and mitotic activity of osteoblasts [31].

Once the osteonecrosis of the jaws has been diagnosed by the Denosumab together with the associated surgical risk factors, such as dental extractions and implant placements, we have to think about the treatment plan for ONJ and the follow-up period of the patient with the appropriate measures.

In the case of Diz., *et al.* of 2012, osteonecrosis is referred to after dental extraction; osteonecrosis is combated with systemic and local antibiotic therapy: amoxicillin, with or without clavulanic acid associated with mouthwashes with 0.12% chlorhexidine solution. An alternative to this therapy is the administration of clindamycin or penicillin intravenously, especially in patients with trismus associated with metronidazole.

In more severe processes, antibiotic therapy can be combined with surgical debridement of exposed necrotic bone. In the post-treatment period of osteonecrosis, after 12 months, the patient had the need for long-term antibiotic therapy and curettage of bone sequestration [20].

Regarding antibiotic therapy, Iván Herrera Ustariz also agrees: "The treatment of maxillary osteonecrosis associated with Denosumab or other drugs lies in the use of chlorhexidine, in association with oral therapy with amoxicillin plus metronidazole, up to 14 days. There are studies that report that the use of Pentoxifylline and Tocopherol added to antimicrobial therapy, decreases the symptoms of osteonecrosis of the jaws, with consequent scarring in the area of exposed necrotic bone [31].

In the article by Camila-Carvalho de Oliveira., *et al.* reported a case of Otto., *et al.* of 2013, in this case is exposed, a patient with osteonecrosis who has come to the dentist for a dental extraction and implant placement. The antibiotic treatment for osteonecrosis was as follows: 100 mg of doxycycline twice a day before the operation for 10 days. While the surgical treatment was: removal of the necrotic bone by fluorescence-guided bone resection.

The patient had a good postoperative, the wound showed complete healing of the mucosa at 6 weeks after surgery and the patient was asymptomatic. There were radiological signs of bone remodeling in the panoramic radiograph taken 1 year after surgery [20].

These two cases are reported in table 6 below, where we can review Diz., *et al.* 2012 and Otto., *et al.* 2013 treatment plans [20].

In the paper by Gustavo Maluf., *et al.* several cases of patients who underwent implant treatment and developed osteonecrosis of the jaws are exposed, in this case the authors have several protocols of post-implantation. The first case deals with a 69-year-old male in treatment for lung cancer, with metastasis in the bone and liver; the patient received Denosumab continuously for the last 8 months in addition to chemotherapy treatment. The patient arrives at the dental office due to severe pain that began 4 months ago, right in

the area of the first molar and second lower left premolar, where an implant surgery had been performed. In the clinical examination, an area of bone exposure was observed around the implant of the first lower left molar with pain-associated purulent drainage. The clinical and CT diagnosis informs us that this is MRONJ. Antibiotic therapy with amoxicillin and clavulanic acid was initiated,

and the use of Denosumab was suspended for 4 months before the proposed surgical procedure: surgical resection and osteotomy of the affected area. Clinical follow-up of 4 months showed that the patient was asymptomatic with stabilization of disease progression, however, there was partial coverage of the wound in the mucosa [14].

Study	ONJ treatment	Follow up
Taylor, Middlefell, Mizen, 2010 [25]	Systemic and local antibiotic therapy Amoxicillin 500 mg orally (3 times/day for 7 days) Chlorhexidine gluconate (0.12%) for mouthwash.	The mucosa healed and the patient had no symptoms after 15 months
Aghaloo, Felsenfeld, Tetradis, 2010 [16]	Systemic and local antibiotic therapy Clindamycin 300 mg orally (4 times/day) Chlorhexidine 0.12% for mouthwash Propoxyphene, 100 mg for 4 to 6 h.	After 8 weeks, the patient presented for follow-up with minimal change in the area of exposed bone but with slightly more erythematous gingival tissue surrounding the bony exposure. Two weeks later, the patient returned presenting moderate, erythematous, tender submental swelling causing her difficulty swallowing, without dental or other source of infection. It was realized intravenous antibiotics and incision and drainage. While the patient was in surgery, a thorough oral examination revealed no direct etiology for the submental infection and no connection to the ONJ area. After the surgery, the infection subsided and the patient was discharged.
Diz <i>et al.</i> 2012 [17]	Systemic and local antibiotic therapy Amoxicillin Chlorhexidine Surgical debridement	After 12 months, there was need for long-term antibiotic therapy and bone sequestration curettage. An submental abscess, requiring extra-oral drainage, and increased osteolytic area adjacent to the 1st right lower molar, requiring surgical intervention for removal of the tooth and bone debridement. Until the last follow-up visit (June/2012), there was no evidence of recurrence.
Malan <i>et al.</i> 2012 [15]	Systemic and local antibiotic therapy Amoxicillin/Clavulanate 875 mg/125 mg, v.o., (2 times/day for 14 days) Chlorhexidine Gluconate 0.12% to mouthwash Surgical debridement Hydrocodone/acetaminophen 5 mg/500 mg orally (every 6 hours as needed for pain).	Over the next several months, the patient was maintained on daily chlorhexidine mouth rinses. A panoramic radiograph obtained 5 months after cessation of denosumab and 3 months after the initial debridement showed enhanced demarcation of a bony sequestrum in the right mandible and decreased height of alveolar bone at the right mandible. At 22 months after the extractions and 18 months after cessation of denosumab, the patient presented with a bone sequestrum that had spontaneously exfoliated.
Rachner <i>et al.</i> 2013 [12]	Antibiotic therapy Surgical Debridement	Not reported

Pichardo <i>et al.</i> 2013 [18]	Systemic antibiotic therapy Penicillin and metronidazole intravenously for 5 days followed by an 8-week oral regimen Surgical debridement	Three weeks after surgery there were again two small areas of exposed bone in the 35 and 44 region, with a discharging extra-oral fistula. Sixteen weeks after the first surgery the extra-oral fistula had not disappeared and bone could be probed through it with new abscess formation a second surgery was performed. During exploration from area 36 to 46 a significant amount of subperiosteal bone formation was seen on both buccal and lingual surfaces. The affected bone was removed.
Aghaloo <i>et al.</i> 2013 [14]	Suspension of Denosumab for 2 months Systemic and local antibiotic therapy Amoxicillin 500 mg orally (three times/day) Chlorhexidine 0.12% for Mouthwash (2 times/day) Surgical debridement with extraction of premolar and molar	Not reported
Otto <i>et al.</i> 2013 [8]	100 mg of doxycycline 2x/day preoperatively for 10 days. Removal of necrotic bone through bone resection guided by fluorescence.	The wound showed complete mucosal healing 6 weeks after surgery and the patient was asymptomatic. There were radiological signs of bone remodeling in the panoramic radiograph taken 1 year after surgery.
Neuprez <i>et al.</i> 2014 [13]	Surgical Debridement Treatment with bone anabolic agent (teriparatide 20 g/day, subcutaneous) Daily calcium supplement and vitamin D.	Not reported

Table 6: Treatments and follow-up of ONJ induced by denosumab cases.

Source: Carvalho de Oliveira C, Cavalcante Brizeno L, Bitu de Sousa F, Lima Mota M, Negreiros-Nunes Alves A. Osteonecrosis of the jaw induced by receptor activator of nuclear factor-kappa B ligand (Denosumab) - Review. *Oral Medicine and Pathology*. 2016;21 (4):431-9.

The use of LPRF should be considered as a treatment option in patients with ARONJ, especially if combined with bone resection of the affected area. Although this paper did not result in a complete tissue response in the treatment of osteonecrosis of the mandible related to anti-resorptive drugs, LPRF is still used because it aids in the process of tissue regeneration, especially in areas where the bone and mucosa are highly compromised [14].

Natalie H Beth-Tasdogan., *et al.* in their paper talk about platelet-derived growth factor preparations, such as PRP and PRGF, applied at the surgical site can accelerate wound healing, thus reducing the risk of infection. PRP and PRGF correspond to the denominations Plasma Rich in Platelets and Plasma Rich in Growth Factors [11].

Review the epidemiology of ONJ cases by denosumab in implants and oral surgery

According to the study of Boquete Castro, in a total of 8963 patients, with a variety of solid tumors, reported in seven randomized controlled trials and included in the systematic analysis the overall incidence of osteonecrosis of the jaws, in patients suffering from cancer and receiving Denosumab was 1.7% [1].

Factors associated with the onset of ONJ in patients receiving Denosumab without dose specification were associated with the following percentages [1].

As we see in table 7 among the risk factors, what is most associated with osteonecrosis of the jaw in patients under treatment with Denosumab is the surgical act as for example in this case dental extraction [1]. Unlike what is reported in the table, according to the study of Noam Yarom., *et al.* osteonecrosis of the jaws can also be spontaneous, i.e. not always need events or risk factors to occur [26].

Associated Risk factors to ONJ	Denosumab
Dental extraction	From 66% and 77% ONJ
Chemoterapy	From 64% and 75% ONJ
Poor oral higyene	From 55% and 77% ONJ
Dental appliances	From 48% and 77% ONJ
Anti-angiogenic therapy	20% ONJ

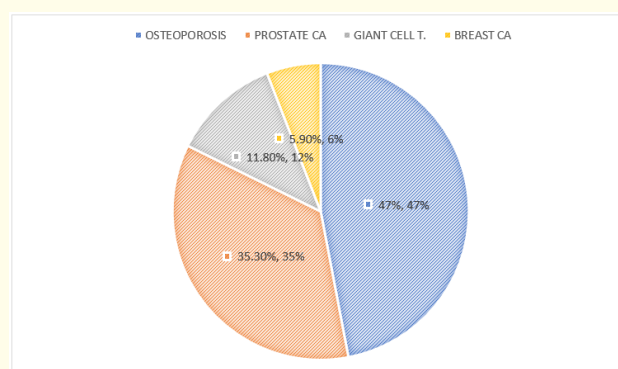
Table 7: Source: From Boquete-Castro A, Gómez-Moreno G, Calvo-Guirado JL, Aguilar-Salvatierra A, Delgado-Ruiz RA. Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. *Clinical Oral Implants Research* [Internet]. 2016 Mar [cited 2019 Feb 24];27(3):367–75. Available from: <https://search-ebscohost-com.ezproxy.universidadeuropea.es/login.aspx?direct=true&db=mdc&AN=25639776&lang=es&site=ehost-live&scope=site>.

An interesting study was conducted by Chawla., *et al.* (2013): they analyzed the typology, frequency and severity of side effects in patients treated with subcutaneous injections of 120 mg of Denosumab every 4 weeks. The authors studied a total of 282 patients, three of them with developing ONJ after treatment with denosumab for 13 to 20 months [1].

In the paper by Camila-Carvalho de Oliveira., *et al.* the authors report several studies of osteonecrosis of the jaw; Most cases of ONJ were reported in patients who received Denosumab for treatment of osteoporosis or osteopenia (47.0%), followed by therapy for prostate cancer (35.3%), giant cell tumor (11.8%) and breast carcinoma (5.9%). In graphic A below, we see the percentages of appearance of osteonecrosis, which are the results of the association between Denosumab and the pathology to be treated [20].

After a careful bibliographic review of the epidemiology of osteonecrosis of the mandible associated with Denosumab, it can be concluded that this is a multifactorial disease, the appearance of

which is predisposed by some local factors such as tooth extraction, implant placement, dental alveolar surgery, periodontal disease and trauma of poorly adjusted prostheses. Apart from the combination "Denosumab and surgery or trauma to the oral cavity", it is important to remember that osteonecrosis of the jaws by Denosumab is also due to associated systemic factors, such as malignant diseases such as breast, lung and prostate cancer, multiple myeloma, chemotherapy, chronic steroid therapy, smoking, diabetes and anemia [20].



Graph 1: ONJ in patients under denosumab treatment.

Source: From Carvalho de Oliveira C, Cavalcante Brizeno L, Bitu de Sousa F, Lima Mota M, Negreiros-Nunes Alves A. Osteonecrosis of the jaw induced by receptor activator of nuclear factor-kappa B ligand (Denosumab) - Review. *Oral Medicine and Pathology*. 2016;21 (4):431-9.

In the article by Toshiyuki Yoneda., *et al.* the incidence of Denosumab-RONJ in cancer patients is less than 2% and equivalent to that of BRONJ. The authors do not know the incidence of Denosumab-RONJ in patients with osteoporosis [2].

A study by a pharmaceutical company (Daiichi Sankyo) after the release of denosumab reported that 120 cancer patients treated with denosumab from April 17, 2012 to July 31, 2015, developed DRONJ and 58 of these patients had been treated with bisphosphonates before Denosumab [2].

The same study indicates that 20 osteoporosis patients treated with Denosumab from June 11, 2013 to December 31, 2015 developed DRONJ (osteonecrosis of the mandible associated with Denosumab) and 15 of these patients had received bisphosphonates prior to Denosumab [2].

Study	Disease type	Therapeutic regimen of Denosumab	Age	Sex	ONJ site	Risk factors associated with ONJ
Taylor, Middlefell, Mizen, 2010 [25]	Metastatic prostatic adenocarcinoma	120 mg, subcutaneous, every 4 weeks	60 years old	Male	Posterior mandible	Corticosteroid therapy
Aghaloo, Felsenfeld, Tetradis, 2010 [16]	Sacral giant cell tumor	120 mg, subcutaneous, once a week for 3 consecutive weeks. After a gap of 2 weeks, Patient received a single dose of 120 mg every 4 weeks.	65 years old	Female	Posterior mandible	Diabetes mellitus Morbid obesity Previous treatment with alendronate (4 months)
Diz <i>et al.</i> , 2012 [17]	Prostatic adenocarcinoma	120 mg, subcutaneous, every 4 weeks.	73 years old	Male	Posterior mandible	Dental extraction
Malan <i>et al.</i> , 2012 [15]	Prostatic adenocarcinoma	120 mg, subcutaneous, every 4 weeks for 22 months (total of 26 injections).	73 years old	Male	Posterior mandible maxilla	Dental extraction Obesity A smoker for 40 years
Rachner <i>et al.</i> , 2013 [12]	Osteoporosis	60 mg, subcutaneous. *The patient received only a single dose of Denosumab	75 years old	Female	Posterior mandible	Previous treatment with alendronate (3 anos) Corticosteroid therapy Inflammatory bowel disease Anaemia
Pichardo <i>et al.</i> , 2013 [18]	Prostate carcinoma	60 mg, subcutaneous, once a 6 months	74 years old	Male	Posterior mandible	Diabetes mellitus
Aghaloo <i>et al.</i> , 2013 [14]	Giant cell tumor	120 mg, subcutaneous, once a 3 months for 2 years. Therapy interrupted for about 1 year and then returned to 120 mg, subcutaneous, once a 1 or 2 months.	26 years old	Male	Posterior mandible	Not reported
Otto <i>et al.</i> , 2013 [8]	1. Osteoporosis	60 mg, subcutaneous.	58 years old	Female	Posterior mandible	Previous treatment with alendronate.
	2. Osteoporosis	60mg, subcutaneous, Once a 6 months.	68 years old	Female	Posterior mandible	Dental extraction Implant Placement
Neuprez <i>et al.</i> , 2014 [13]	Osteoporosis	60 mg, subcutaneous, once a 6 months. *The patient received only a single dose of Denosumab	58 years old	Male	Posterior mandible	Dental extraction
Sabater <i>et al.</i> , 2014 [20]	Osteopenia	60 mg, subcutaneous, once a 6 months.	78 years old	Female	Posterior mandible	Dental extraction Previous treatment with risedronate.
Olate <i>et al.</i> , 2014 [11]	Ductal carcinoma in breast.	60 mg, subcutaneous. *The patient received only a single dose of Denosumab	55 years old	Female	Posterior mandible	Dental extraction

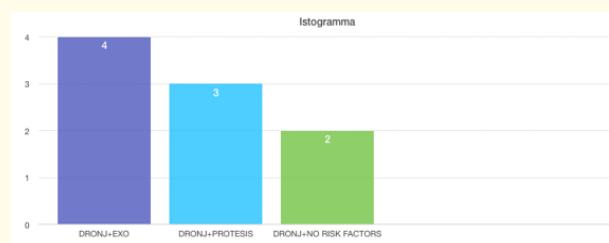
O'Halloran., <i>et al.</i> , 2014 [9]	1. Metastatic Prostatic carcinoma	120 mg, subcutaneous, monthly	60 years old	Male	Posterior mandible	Not reported
	2. Prostate carcinoma	120 mg subcutaneous, monthly	72 years old	Male	Posterior maxilla	Not reported
Tortajada, Gómez, Lozano, 2014 [10]	1. Osteoporosis and Rheumatoid Arthritis	60 mg subcutaneously, every 6 months	65 years old	Female	Mandible and maxilla	Previous treatment with Alendronate (5 years)
	2. Osteoporosis	Not reported	69 years old	Female	Posterior mandible	Previous treatment with Alendronate (10 years)
	3. Osteoporosis	Not reported	71 years old	Female	Posterior maxilla	Pretreatment with Alendronate and Risedronate (6 years) Previous treatment with Zoledronic Acid (1 year) Dental extraction

Table 8: Profile of patients affected by ONJ induced by denosumab.

Source: From Carvalho de Oliveira C, Cavalcante Brizeno L, Bitu de Sousa F, Lima Mota M, Negreiros-Nunes Alves A. Osteonecrosis of the jaw induced by receptor activator of nuclear factor-kappa B ligand (Denosumab) - Review. *Oral Medicine and Pathology*. 2016;21 (4):431-9.

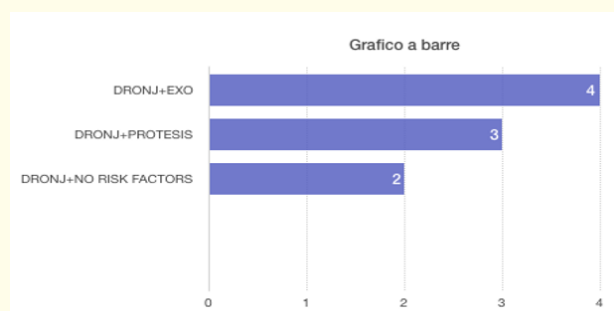
In the article by Martínez Ferrero., *et al.* in 2010 the authors point out that there are two types of Denosumab, one for the treatment of postmenopausal osteoporosis (Prolia®) and one for the prevention of bone metastases (Xgeva®) [4]. At the epidemiological level in the same article we see that the incidence of osteonecrosis of the jaws in patients treated with Denosumab varies from 0.9 to 5%. It is reported that patients medicated with Prolia® have an incidence between 0.7 - 1.9%, while the incidence when medicated with Xgeva® increases being comparable to that of Zoledronate, which is a bisphosphonate. Finally, the fact that the incidence increase proportionally with the longer duration of the treatment is underlined [4].

According to the article by Claire Egloff-Juras., *et al.* in a total of 141 patients treated with Denosumab (Xgeva) between January 2010 and December 2015. One hundred and thirty-eight Were treated with Denosumab after the occurrence of bone metastases and three for primary bone tumors. Of the 141 patients included in the study, 9 developed osteonecrosis of the jaw related to Denosumab [25].



Graph 2: Risk factors of DRONJ.

Source: From Egloff-Juras C, Gallois A, Salleron J, Massard V, Dolivet G, Guillet J., *et al.* Denosumab-related osteonecrosis of the jaw: A retrospective study. *Journal Of Oral Pathology & Medicine: Official Publication Of The International Association Of Oral Pathologists And The American Academy Of Oral Pathology [Internet]*. 2018 Jan [cited 2019 Feb 25];47(1):66–70. Available from: <https://search.ebscohost.com.ezproxy.universidadeuropea.es/login.aspx?direct=true&db=mdc&AN=28977694&lang=es&site=ehost-live&scope=site>.



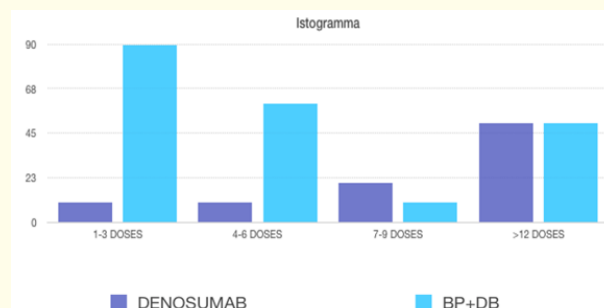
Graph 3: Risk factors of DRONJ.

Source: From Egloff-Juras C, Gallois A, Salleron J, Massard V, Dolivet G, Guillet J, et al. Denosumab-related osteonecrosis of the jaw: A retrospective study. *Journal Of Oral Pathology & Medicine: Official Publication Of The International Association Of Oral Pathologists And The American Academy Of Oral Pathology [Internet]*. 2018 Jan [cited 2019 Feb 25];47(1):66–70. Available from: <https://search-ebscohost-com.ezproxy.universidadeuropea.es/login.aspx?direct=true&db=mdc&AN=28977694&lang=es&site=ehost-live&scope=site>.

In graphs 2 and 3 we observe that in the study by Claire Egloff-Juras, et al. where the most obvious risk factor is confirmed once again that it is the surgical act, then the removable prosthesis is shown that "traumatizes the fibromucosa and the bone". The authors of this paper pay attention to the fact that osteonecrosis, in few cases, can occur without any potential risk factor [25].

In the epidemiological study of the ONJ it is interesting to report data from the article of Noam Yarom, et al. that talks about, osteonecrosis of the jaws that can appear spontaneously without any event or known triggering factor; for this reason two groups are analyzed that have respectively two different ONJ results: 72.7% of spontaneous osteonecrosis in patients in the group of bisphosphonates plus Denosumab and 77.8% of patients in the group of only Denosumab. In the study of the development of osteonecrosis independently of risk factors, the outcome is that there are more cases of the group that has taken only Denosumab. It is clear that ONJ induced by Denosumab could develop more rapidly in patients previously treated with bisphosphonates [26]. Here we have graph 3 that shows how osteonecrosis of the jaw evolves rapidly in patients who change from bisphosphonates to Denosumab, in those medicated with few doses, compared with those who carry more doses. That is to say that 1 - 3 doses or 4 - 6 doses of Denosumab with previous administration of Bisphosphonates give symptoms of osteonecrosis much faster than patients who have been medicated only with Denosumab [26].

It is clear that ONJ induced by Denosumab could develop more rapidly in patients previously treated with bisphosphonates [26]. Here we have graph 4 that shows how osteonecrosis of the jaw evolves rapidly in patients who change from bisphosphonates to Denosumab, in those medicated with few doses, compared with those who carry more doses. That is to say that 1 - 3 doses or 4 - 6 doses of Denosumab with previous administration of Bisphosphonates give symptoms of osteonecrosis much faster than patients who have been medicated with only Denosumab [26].



Graph 4: Number of denosumab doses before the onset of symptoms of osteonecrosis of the jaw.

Source: From Yarom N, Lazarovici TS, Whitefield S, Weissman T, Wasserzug O, Yahalom R. Rapid onset of osteonecrosis of the jaw in patients switching from bisphosphonates to denosumab. *Oral Surgery, Oral Medicine, Oral Pathology And Oral Radiology [Internet]*. 2018 Jan [cited 2019 Feb 25];125(1):27–30. Available from: <https://search-ebscohost-com.ezproxy.universidadeuropea.es/login.aspx?direct=true&db=mdc&AN=29102242&lang=es&site=ehost-live&scope=site>.

This graph shows the result of a study with two groups: the first has twenty-two patients, who have been medicated with bisphosphonates and subsequently with Denosumab. The second group, 9 patients who received only Denosumab. Both groups were similar for the known risk factors for ONJ, i.e. age, diabetes mellitus, and smoking. In the article the authors highlight the group of people who had been prescribed bisphosphonates previously to Denosumab, the symptoms of ONJ developed in 9 patients (41%), after administration of ≤ 3 doses of Denosumab, compared with the development of ONJ in only 1 patient (11%) who had no previous experience with bisphosphonates. This means that during the onset of treatment the symptoms of osteonecrosis are on the rise, and as time passes and the number of doses increases the symptoms decrease.

About drugs with antiangiogenic function with similar effect to Denosumab, we know Bevacizumab and Sunitinib. The British and French drug regulatory agencies reported 55 cases of

osteonecrosis of the jaws associated with the use of Bevacizumab in approximately 800,000 patients who have been treated with this drug. Twenty-seven cases of Sunitinib have been reported in approximately 100,000 patients. In the cases studied in Iván Herrera Ustariz's paper, bacterial colonization of *Actinomyces* is found, which could be an etiological factor in the development of ONJ. Another drug of which there are reports of OM is Doxorubicin, which as we have said before is an anthracycline antibiotic that exerts its effects on cancer cells by blocking the synthesis of DNA. Between October 2012 and January 2004, 179 people who took this drug presented this complication [31].

To compare in patients with implants or patients with future implant treatment, the effects of two similar drugs: Bisphosphonates and denosumab

Denosumab is a new therapeutic agent for osteoporosis and bone metastasis, with a half-life of approximately one month.

Unlike Bisphosphonates, which promote apoptosis in osteoclasts, Denosumab inhibits osteoclastic bone resorption without causing apoptosis, therefore we can say that it is a reversible action drug [2].

Bisphosphonates act most of the time irreversibly, especially if administered intravenously, because osteoclastic inhibition is complete, producing apoptosis [27].

Apart from the reversibility property of Denosumab which is therefore beneficial for the organism with respect to bisphosphonates, according to the article by Camila-Carvalho de Oliveira, *et al.* randomized studies have shown that Denosumab has many benefits over bisphosphonates, because it provides greater effectiveness and fewer acute adverse reactions such as pyrexia, arthralgia and renal toxicity [20].

According to Claire Egloff-Juras, *et al.* Denosumab and Bisphosphonates have common side effects that are hypocalcemia, hypersensitivity to products (such as allergic skin reactions, hypotension, dyspnea and angioedema); these drugs can also lead to atypical fractures of the femur and osteonecrosis of the jaw [25].

The difference between these drugs is at the site of action: While bisphosphonates act on mature active osteoclasts, denosumab acts on osteoclast precursors by inhibiting RANKL, preventing their formation, differentiation and function, as well as associated bone resorption [14].

Due to the foregoing, we deduce that the Denosumab has a more effective action.

Another advantage of Denosumab is that it is not deposited in the bone and therefore does not persist for long periods of time, as is the case with bisphosphonates, so the effects of denosumab are reversible.

The study by Claire Egloff-Juras informs us about the typical diagnosis of medication-related osteonecrosis of the mandible (MRONJ): a mucosal lesion of the maxillofacial region with necrotic bone exposure.

The American Association of Oral and Maxillofacial Surgeons (AAOMS) after many meetings has concluded that the diagnosis of osteonecrosis given by Denosumab or Bisphosphonates was common to both drugs, for this reason we speak of ARONJ: Osteonecrosis of the jaw related to anti-resorptive agents. In order to obtain the definitive diagnosis, the following three conditions are sought:

1. Patients must have a history of treatment with bisphosphonates or Denosumab.
2. Patients do not have to have a history of radiation therapy to the jaw. ARONJ bone lesions should be differentiated from the metastasis of jaw cancer by histological examination.
3. Exposure of the alveolar bone in the oral cavity, jaw and/or face is observed continuously for more than 8 weeks after first detection by a physician or dental specialist. Another measure of osteonecrosis detection is that the bone is palpable in the intraoral or extraoral fistula for more than 8 weeks [2].

The management of ONJ by bisphosphonates by dentists and oral surgeons has improved significantly. In contrast, there is still relatively little information on the management of ONJ by Denosumab. Since the inhibitory effects of denosumab are transient and reversible, the prognosis for Denosumab ONJ appears to be less serious than that for bisphosphonates ONJ. However, because the differences in pathophysiological characteristics between DRONJ and BRONJ are currently unclear, it is recommended that they be treated essentially the same way [2].

Finally, we can conclude as several authors tell us: Mandibular osteonecrosis by anti-resorptives is a rare and difficult complication to treat in patients with bone metastases and in patients with osteoporosis. It is very important to say that the data and studies on ARONJ supported by evidence-based medicine are still scarce [2]. However, on osteonecrosis of the mandible related to anti-resorptive drugs it must be emphasized, that clinical and radiological diagnosis, the evolutionary stages of infection, the classification of

risk factors and preventive and therapeutic approaches have advanced significantly in the last decade.

These pharmacological properties of Denosumab initially, after its market launch, led us to assume that ONJ is unlikely to occur from treatment with Denosumab. However, patients treated with Denosumab also developed ONJ, which was clinically indistinguishable from bisphosphonate osteonecrosis [2].

Denosumab has been shown to have an equal or greater ability to suppress bone turnover compared to bisphosphonates [1]. The use of Denosumab was associated with a significantly higher risk of ONJ compared to bisphosphonates [1].

In the study by Fizazi, *et al.* (2011), a higher percentage of ONJ cases was observed among patients treated with Denosumab compared to zoledronic acid (ZA), although the differences were not statistically significant [1]. At the same time but according to the paper by Blas Garcia Garcia, *et al.* unlike bisphosphonates, Denosumab is not incorporated into the bone matrix; this is why in the case of osteonecrosis of the jaws by Denosumab lesions could be cured with the possibility of greater success [5].

It is important to note that of 22 ONJ cases found in the Boquete-Castro, *et al.* study, in patients under treatment with Denosumab, only four were resolved completely, while with ZA, only one of twelve diagnosed cases could be resolved completely [1].

Regarding bisphosphonates, it is particularly remarkable that recent clinical studies have shown that the emergence of ONJ is significantly reduced by blocking oral infection through intensive oral health control, suggesting that infection is a key step in the development of this complication [2].

Several stages have been classically described to classify the symptoms of osteonecrosis of the mandible, which are also common to bisphosphonates and Denosumab:

- **Stage 0:** At this stage clinical symptoms are absence of exposure or bone necrosis, deep periodontal pocket, tooth mobility, oral mucosal ulcer, swelling, abscess formation, trismus, hyposthesia or numbness of the lower lip (Vincent's symptom), non-odontogenic pain. While the findings in the image are: sclerotic alveolar bone, thickening and sclerosis of the lamina dura, hollow alveolus after tooth extraction.
- **Stage 1:** The clinical symptoms in this case are asymptomatic bone exposure, necrosis with no sign of infection, or fistula in which the bone is palpable with a probe. The findings in the image are sclerotic alveolar bone, thickening and sclerosis of the hard lamina, non healed alveolus after tooth extraction.

- **Stage 2:** The symptoms associated with this stage are bone exposure and necrosis associated with pain, infection, fistula in which the bone is palpable with a probe, pathological fracture, extraoral fistula, formation of sinus or maxillary fistula.
- **Stage 3:** Clinical symptoms present are bone exposure and necrosis associated with pain, infection, fistula in which the bone is palpable with a probe. Exposure and bone necrosis over the alveolar bone. There is also pathological fracture or extraoral fistula, formation of fistula of the nasal fossa or maxillary sinus or advanced osteolysis that may run along the lower jaw border and the sinus of the upper jaw.

As a diagnostic imaging result: osteosclerosis/osteolysis of the surrounding bone (cheek, palatal bone), pathological mandibular fracture and osteolysis extending to the floor of the maxillary sinus [2,3,11,18,28].

About the clinical stages of osteonecrosis related to anti-resorptives, the data are reported in table 9 below [18].

Stage	Description
At Risk	There is no exposed or necrotic bone in asymptomatic patients treated with Bisphosphonates or Denosumab
Stage 0	There is no clinical evidence of exposed/necrotic bone, but with non-specific clinical and radiological symptoms of ONJ.
Stage 1	Asymptomatic necrotic exposed bone with no evidence of inflammation or infection
Stage 2	Exposed bone, necrotic with pain, erythema, infection with or without purulent drainage.
Stage 3	Exposed bone, necrotic with pain, inflammation or infection and one or more of the following characteristics: Extension outside the alveolar bone, pathological fracture, extraoral fistula, oroantral communication, nasal and osteolysis to the lower ridge of the mandible or to the sinus floor.

Table 9: Source: From Martínez García M, Gómez Font R, Bascones Martínez A. Evaluación de comportamiento de implantes osteointegrados en mujeres con osteoporosis en tratamiento con bisfosfonatos orales. Variabilidad en el tiempo y relación pronóstica del telopeptidocarboxiterminal CTX Crosslaps [Tesis Doctoral]. Universidad complutense de madrid facultad de odontología Departamento de Estomatología III (Medicina y Cirugía Bucofacial); 2012.

This table shows the description of the "at risk" phase, i.e. we have to inform the patient that, if he or she is being treated with anti-resorptives, there will always be the possibility of developing osteonecrosis, with or without associated risk factors [18].

With regard to the stages of osteonecrosis of the jaw, there are different types of treatment:

- **For stage 0-1:** Use of antimicrobial mouthwash, rinsing, fistula and periodontal pocket cleaning, topical application or injection of local antimicrobial agents.
- **For stage 2:** Use a combination of antimicrobial mouthwash; as pharmacological treatment multiple antimicrobial agents will be administered intravenously in the long term, as surgical treatment removal of the sequestration, necrotic bone curettage and osteotomy.
- **For Stage 3:** Elimination of sequestration, curettage of necrotic bone, osteotomy, extraction of teeth in exposed bone and necrotic bone, marginal or segmental resection of necrotic bone [2,28].

According to recent reports, it is suggested that implant procedures performed on patients with cancer or osteoporosis prior to treatment with bisphosphonates are probably not associated with the subsequent development of osteonecrosis of the jaw, if oral health is properly managed. However, the surgical act of implants performed during or after treatment with bisphosphonates is a potential risk factor for BRONJ. In the same paper it is unknown whether implants and oral surgery are a risk factor in patients receiving Denosumab [2].

According to the study by Martínez Ferrero., *et al.* he points out that it is still controversial when the Denosumab is removed before an oral extraction or any surgical treatment [4].

Since Denosumab is administered to osteoporotic patients once every 6 months, and the half-life of denosumab is approximately 1 month, there is a wide margin of time within the interval of 6 months to plan dental treatments [2]. In this interval of time with good cooperation of the doctor and dentist it can be assessed whether it is feasible to perform oral surgery on the patient treated with Denosumab, avoiding the secondary risks that may arise.

About the administration and dose of Denosumab as described in the article by Martínez Ferrero., *et al.* we must differentiate the drug in two actions: one serves to treat postmenopausal osteoporosis, the Prolia and another for the prevention of bone metastases,

the Xgeva [4]. Andreas Stavropoulos., *et al.* considers that the Prolia must be administered to patients every six months, subcutaneously with a dose of 60 mg. While Xgeva is administered subcutaneously, every 4 weeks with a dose of 120 mg; the latter being a specific drug for cancer, it should be administered with higher doses and more frequently [10].

The delay in healing given by Denosumab is controversial by many authors, such as J Goldhahn., *et al.* who in their analyses found that the use of Denosumab was not associated with late healing or any complications after fracture or surgical management [9].

The most evident side effects are observed in the two medications (Bisphosphonates and Denosumab) taken one after the other; Noam Yarom., *et al.* report data on the development of osteonecrosis of the mandible in patients taking both medications consecutively. In this study the clinical impression is that ONJ may develop more rapidly in patients who are prescribed bisphosphonates and then switch to Denosumab; this harmful effect is due to one of the properties of bisphosphonates, i.e. after years of interruption of treatment, traces of bisphosphonates may appear in the bone [26].

According to the study of Noam Yarom., *et al.* in patients with multiple myeloma and in patients with bone metastases from solid tumors (breast and prostate) has verified an incidence of ONJ in 1.8% of patients treated with Denosumab compared with 1.3% of patients treated with zoledronic acid (bisphosphonate). The incidence of ONJ in osteoporosis patients treated with Denosumab is much lower [26].

With regard to the route of administration of anti-resorptive drugs, it seems that there is an important difference between bisphosphonates and Denosumab; this difference is observed in the table reported in the article by Andreas Stavropoulos., *et al.* (table 3): all bisphosphonates are administered orally according to the case, while Denosumab is only administered subcutaneously [10].

Conclusion

To evaluate patients under treatment with Denosumab and who are going to undergo Implant Surgery: Protocol for the dentist BEFORE, DURING AND AFTER the placement of implants and oral surgery

- It is fundamental before the surgical act to carry out an attentive clinical history of the patient, to know if he has harmful habits or takes anti-resorptive medications that can be potential risk factors of osteonecrosis of the jaws.

Trade name	Generic name	Diagnosis	Administration route	Dosing interval	Dose
Fosamax	Alendronate	Osteoporosis	Oral	Weekly	70 mg
Alendronate	Alendronate	Osteoporosis	Oral	Weekly	70 mg
Fosavance	Alendronate + cholecalciferol (vitamin D3)	Osteoporosis	Oral	Weekly	70 mg+70 µg
Aclasta	Zoledronate	Osteoporosis	iv	Yearly	5 mg
Pamidronate sodium	Pamidronate	Osteoporosis	iv	Yearly	5 mg
Bonviva	Ibandronate	Osteoporosis	iv	Monthly	1 mg/ml
Bonviva	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Ibamyl	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Ibandronate "Stada"	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Ibandronic acid "medical valley"	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Optinate Septimum	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Risedronate sodium	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Riseostad	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Primadronat	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Prolia	Denosumab	Osteoporosis	sc	6 months	60 mg
Zometa: Zoledronate "Actavis" Zoledronate "SUN" Zoledronate "Hospira"	Zoledronate	Cancer	iv	3 - 4 weeks	4 mg
Pamifos Pamidronate sodium "Hospira"	Pamidronate	Cancer	iv	3 - 4 weeks	90 mg
Bonefos	Clodronate	Cancer	Oral	Daily	1,600 mg
Bondronate	Ibandronate	Cancer	iv	3 - 4 weeks	6 mg
Bondronate	Ibandronate	Cancer	Oral	Daily	50 mg
Xgeva	Denosumab	Cancer	sc	4 weeks	120 mg

Table 10: List of ARDs currently used for osteoporosis and cancer treatment. Updated February 2018.

Source: From Stavropoulos A, Bertl K, Pietschmann P, Pandis N, Schiødt M, Klinge B. The effect of antiresorptive drugs on implant therapy: Systematic review and meta-analysis. *Clinical Oral Implants Research* [Internet]. 2018 Oct [cited 2019 Feb 24];29 Suppl 18:54–92. Available from: <https://search.ebscohost-com.ezproxy.universidadeuropea.es/login.aspx?direct=true&db=mdc&AN=30306695&lang=es&site=ehost-live&scope=site>.

- In the case of the placement of implants, in patients under treatment with anti-resorptives, it is accepted to place them when they get osteoporosis and take Denosumab. Never place implants in patients who receive Denosumab at high doses.
- It may be acceptable cases of patients who need surgical dental treatments in parallel with the taking of anti-resorptives, are patients in which the progression of bone metastases is very fast or have a high risk of fracture, so it is not possible to state therapeutic holidays, suppressing the taking of Denosumab or Bisphosphonates.

Review the epidemiology of cases of ONJ by denosumab in implants and oral surgery

- The harmful effect of anti-resorptive drugs such as bisphosphonates and Denosumab is more serious if they are taken one after the other, i.e. the progression of osteonecrosis of the jaws is much faster if the patient takes bisphosphonates and is then replaced by Denosumab.
- Osteonecrosis of the jaws by Denosumab is a disease of multifactorial origin; there are not only local risk factors such as oral surgery that traumatizes and deteriorates the bone,

there are also co-morbidities that participate in the process of osteonecrosis, such as breast and prostate cancer, chemotherapy, corticosteroids and diabetes.

- The incidence of MRONJ has been maintained and increased over the years thanks to the release of new anti-resorptive drugs and/or anti-angiogenic, specifically Denosumab, Bevacizumab, Sunitinib, Sorafenib and Doxorubicin.
- An advantage of the drug Denosumab is its reversible effect: it is not deposited in the bone and therefore does not persist for long periods of time, as with bisphosphonates.
- After numerous studies it has been concluded that the diagnosis of osteonecrosis by Denosumab or Bisphosphonates was common to both drugs, so the American Association of Oral and Maxillofacial Surgeons speaks of ARONJ: Osteonecrosis of the jaw related to anti-resorptive agents.

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