

## **Bisphosphonates and their indication to prevent bone density loss in cancer therapy**

**Bisfosfonatos e suas indicações para prevenir a perda de densidade óssea na terapia contra o câncer**

**Bisfosfonatos y su indicación para prevenir la pérdida de densidad ósea en terapia contra el cáncer**

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### **Abstract**

**Aim:** To establish a protocol for patients medicated with bisphosphonates, through literature review, to avoid osteonecrosis and to provide professional guidance to accomplish the appropriate treatment. **Methodology:** On line searches were accomplished for the construction of this paper, which included as databases Web of Science, PUBMED Central, BVS/BIREME, Science Direct, The Cochrane Library and also PROSPERO. **Results:** The following characteristics were observed in the research of this protocol: Drugs with antireabsorption properties, RANK-L Inhibitor, Antiangiogenic agents, Clinical Manifestations, Drug-related risk factors, Local risk factors to be observed, Systemic and demographic risk factors, High risk factors considered. **Conclusions:** Bisphosphonates may be a helpful therapy for patients with organic consequences related to the therapy applied with them. Appropriate anamnesis and assessment of the systemic conditions for patients using them are mandatory requirements before their prescription.

**Keywords:** Osteoporotic fractures, Osteoporosis; Fractures, closed; Bone density conservation.

### **Resumo**

**Objetivo:** Estabelecer um protocolo para pacientes medicados com bisfosfonatos, por meio de revisão da literatura, para evitar a osteonecrose e fornecer orientação profissional para a realização do tratamento adequado.

**Metodologia:** Foram realizadas buscas on-line para a construção deste artigo, as quais incluíram como bases de dados Web of Science, PUBMED Central, BVS / BIREME, Science Direct, The Cochrane Library e também PROSPERO. **Resultados:** As seguintes características foram observadas na pesquisa deste protocolo: Medicamentos com propriedades antireabsorção, Inibidor de RANK-L, Agentes antiangiogênicos, Manifestações clínicas, Fatores de risco relacionados a medicamentos, Fatores de risco locais a serem observados, Fatores de risco sistêmicos e demográficos, Elevados fatores de risco considerados. **Conclusões:** Os bisfosfonatos podem ser uma terapia útil para pacientes com consequências orgânicas relacionadas à terapia aplicada com eles. Anamnese adequada e avaliação das condições sistêmicas dos pacientes que os utilizam são requisitos obrigatórios antes de sua prescrição.

**Palavras-chave:** Fraturas por osteoporose, Osteoporose; Fraturas fechadas, Bone density conservation agents.

### Resumen

**Objetivo:** Establecer un protocolo para pacientes medicados con bifosfonatos, a través de una revisión de la literatura, para evitar la osteonecrosis y brindar orientación profesional para la realización del tratamiento adecuado. **Metodología:** Se realizaron búsquedas en línea para la construcción de este artículo, que incluyeron Web of Science, PUBMED Central, BVS / BIREME, Science Direct, The Cochrane Library y también PROSPERO como bases de datos. **Resultados:** Se observaron las siguientes características en la búsqueda de este protocolo: Fármacos con propiedades antirresortivas, Inhibidor de RANK-L, Agentes antiangiogénicos, Manifestaciones clínicas, Factores de riesgo relacionados con el fármaco, Factores de riesgo locales a observar, Factores de riesgo sistémicos y demográficos, Factores de alto riesgo considerados. **Conclusiones:** Los bifosfonatos pueden ser una terapia útil para pacientes con consecuencias orgânicas relacionadas con la terapia aplicada con ellos. Una adecuada anamnesis y evaluación de las condiciones sistêmicas de los pacientes que los utilizan son requisitos obligatorios antes de su prescripción.

**Palabras clave:** Fracturas osteoporóticas; Osteoporosis; Fracturas cerradas; Conservadores de la densidad ósea.

## 1. Introduction

Bisphosphonates (BFs) can be defined as a class of drugs able to prevent bone density loss. They were denominated this way due to the word formation *di-* or *bis-*phosphonates [PO(OH)].

They have been described in the current literature as anti-absorbent drugs which specifically act on osteoclastic activities; indicated for many clinical situations, including prevention and treatment of primary and secondary osteoporosis (with the aim of inhibiting mineral density loss process in the bones), Paget's disease, hypercalcemia, multiple myeloma and osteolysis associated with bone metastases of malignant oncological tumors. There have been growing evidence of fracture risk reduction in post-menopausal women bearers of osteoporosis (Eriksen, 2014; Serrano, 2013; Gauthier, 2012; Watts, 2010).

One of their main serious adverse events is the occurrence of osteonecrosis in the maxillaries associated with the use of bisphosphonate compounds, being defined as bone exposure areas with necrotic tissues, unable to heal spontaneously in an estimated period of eight weeks, affecting both maxillaries in patients using bisphosphonates without history of maxillary radiotherapy (Abtahi, Agholme and Aspenberg, 2013).

Osteonecrosis is designated as bone destruction due to lack of blood supply needed in the affected area. Such event is based on the ischemic effect of bisphosphonates on the blood vessels, which inhibits the vascular endothelial growth factor, diminishing blood flow and therefore causing necrotic lesions in the bones. They are regarded as endogenous regulators of bone mineralization, with chemical structure similar to inorganic pyrophosphate molecules, differentiated mainly by to the presence of a phosphorus-carbon-phosphorus (PCP) bond, which makes them resistant to biological degradation and resistant to hydrolysis (Choudhary, 2003). It acts on the surface of the bone in resorptive process due to its affinity for calcium, reducing the clastic activity while inducing their apoptosis, resulting in increased mineral density. In addition to its proven action on the osteoclasts, several studies have demonstrated an indirect action on osteoblasts, preventing bone turnover or bone neoformation (Maruotti, 2012).

The lesion is characterized by the exposure of necrotic bone in the maxillary or mandibular region, usually caused after the performance of invasive dental treatment (Scully, 2013). Other patients with no apparent treatment, may develop mandibular osteonecrosis associated with the continuous use of bisphosphonates, for periods of 1.5 to 3 years. The main

location in such cases is the maxillo-mandibular sites. Therefore, extra care should be taken to reduce the risk of maxillo-mandibular osteonecrosis in patients treated with bisphosphonates (BF).

The present study aims to establish a protocol, through literature review, to avoid osteonecrosis caused by the use of bisphosphonates, and, in case it is already established, provide professional guidance to accomplish the appropriate treatment, according to the current literature, and offer information about its indications, mechanism of action, adverse effects on the oral region and guide therapeutic alternatives for medication replacement by other approaches that produce the expected effects on antiresorptive therapy.

## 2. Methodology

For the construction of this paper, on line searches were accomplished concerning bisphosphonates and their main effects and side-effects available in both on line and gray literature, in search of information concerning their characteristics, properties, clinical manifestations, risk factors to guide the readers as for what concerns the clinical procedures for patients medicated with them who need dental assistance. Therefore, the research included as databases the following platforms: Web of Science, PUBMED Central, BVS/BIREME, Science Direct, The Cochrane Library and also PROSPERO.

## 3. Literature Review

One of the main problems concerning the clinical treatment of patients whose pathologies implies in bone resorption is the fracture risk, and naturally as it seems, the consequences thereafter.

Bisphosphonates are drugs with a high affinity to bone tissue, and are usually administered in patients in need of bone resorption. They are generally well tolerated by the body and can be administered orally or intravenously, being the bioavailability of the latter much higher than former (Otto, 2015). Bisphosphonates administered intravenously (eg. zoledronate), are considered more potent, and are indicated for treatments that need rapid bone destruction since they are maintained in the body in a high bioavailability. When used orally (eg. alendronate), are usually indicated for continuous use in patients with osteoporosis, presenting low bioavailability (Gracis, 2013). However, the long-term effects of oral bisphosphonates is still a matter of substantial clinical concern, since Alendronate, with 17 million prescriptions, has been listed as the 19<sup>th</sup> most prescribed drug in 2003 (Hewitt, 2007).

More recently yet, it has been suggested that mandibular osteonecrosis does not appear as classic osteonecrosis, but from osteomyelitis, characterized by bone inflammation with cortical and spinal involvement, usually triggered by local bacterial invasion (Tardasta, 2015). Nevertheless, the oral mucosa has been suggested to play a pertinent role in mandibular osteonecrosis. One of the main possibilities is that bisphosphonates that accumulate in bone tissue may exert direct toxic effects on the oral epithelium, therefore inhibiting the normal healing process of the lesions, which are usually caused by dental intervention or some other associated trauma to an excessive suppression of the remodeling.

BFs, when chosen to be used intravenously, especially for cancer therapy, have been associated with osteonecrosis of the jaws, almost the double when compared to the maxilla. This fact has been observed after the prescription and usage of high-dose intravenous administration in patients under cancer therapy (Woo, 2006). In virtually 60% of the cases, there have been reports of dental surgical procedures, especially those involving bone. Therefore, it has been suggested that the treatment with BFs be postponed until after any dental procedures have been accomplished, in order to eliminate the potential sites and location of infections.

The etiopathogenesis of osteonecrosis is not well defined in the literature, but the main hypotheses for the occurrence of mandibular osteonecrosis associated with bisphosphonates include changes in bone turnover, including suppression of bone resorption, inhibition of angiogenesis, microtrauma, immunity suppression, vitamin D, soft tissue toxicity due to drug

accumulation, inflammation and infection (Salvatore, 2014). This may be due to the fact that mandibular bone metabolism becomes less active in patients with chronic use of bisphosphonates, which could allow bacterial contamination which would not be combated rapidly by the patient's immune response (Tardasta, 2015).

In cases of chronic use, several renal and hepatic complications, in addition to osteonecrosis, have been reported. Osteonecrosis, when installed, is difficult to treat and often persists for a long time. The currently the treatment is focused on progress control to limit the effects of secondary infection through prolonged antibiotic therapy, cleaning of the area with topical antiseptics (0.12% chlorhexidine), and small debridement interventions.

Pamidronate and Zoledronate are nitrogen bisphosphonates (aminobisphosphonates) widely used in cancer treatment, which are characterized by accumulation and permanence in the bone matrix for long periods, being this crucial fact for the development of osteonecrosis of the jaws (Carter, 2003). Aminobisphosphonates act in various ways against tumor metastases: by inducing tumor cell apoptosis (programmed cell death), by inhibiting tumor cell adhesion to the extracellular matrix and by inhibiting tumor invasion. In patients with multiple myeloma and bone metastatic lesions especially derived from adenocarcinomas of the breast, prostate, lung and kidney, these drugs have an important indication and their use has resulted in a drastic reduction of the skeletal complications associated with tumoral bone dissemination, such as bone pain, (Ruggiero, 2014). In the present study, the authors concluded that there was no significant difference in the quality of life of these patients.

The antireabsorptive properties of bisphosphonates increase approximately 10-fold between generations of the drug. The so-called endovenous ones are those used in cancer patients and oral ones for the treatment of other diseases that cause bone lysis, among them osteoporosis and, in rare cases, Paget's disease and imperfect osteogenesis in childhood (Martins, 2009).

These changes in molecular chemical structure present definite biological purposes, such as: increasing bone affinity, increasing potency, adapting to selectivity, and decreasing drug toxicity (Migliorati, 2005).

BFs are used in many clinical situations, including the prevention and treatment of primary and secondary osteoporosis, Paget's disease (osteitis deformans), hypercalcemia, multiple myeloma and osteolysis associated with bone metastases of malignant tumors (oncological diseases).

According to Khosla et al. (2010), the different stages and clinical manifestations of osteonecrosis associated with the use of bisphosphonates depend directly on the route and time of administration of the drug. The risk of developing osteonecrosis by oral medication gradually increases from 0.1% to 0.21% after four years of use of the drug, whereas in patients receiving intravenous treatment this risk is 0.5 to 0.6% in the first year, 0.9 and 1.1% in the second year and 1.1 and 1.3% in the third year of use of the drug.

Osteonecrosis associated with BF may be asymptomatic for several weeks, months, or years. Some signs and symptoms can be identified before the clinical development of osteonecrosis such as: pain, dental mobility, mucosal enlargement, erythema, ulceration, drainage of secretion in the mouth, bone exposure, osteomyelitis and pathological fracture. In most cases, the lesions are symptomatic when there is infection and local tissue inflammatory response.

The recent definition of the positioning paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) of 2014 included significant modifications compared to the position paper on the diagnosis of mandibular osteonecrosis. According to the definition of 2014, the following characteristics were defined: 1) current or previous treatment with antiresorptive agents (denosumab, cathepsin and bisphosphonates) or antiangiogenic therapies (sunitinib or bevacizumab); 2) exposed bone or bone that can be probed through an intraoral system or extra-oral fistula (e) in the maxillofacial region that has persisted for more than 8 weeks; 3) No history of radiation therapy for the jaws or evident metastatic disease of the jaws (Ruggiero, 2014).

Ruggiero (2009) proposed a clinical classification of osteonecrosis associated with the use of BF in some stages. This classification is didactical, and sometimes the stages may be intertwined.

Stage 0 - there is no clinical evidence of bone exposure, but patients have nonspecific signs and symptoms that can characterize osteonecrosis, such as orofacial pain, tooth mobility, suppuration and radiographic enlargement of the space corresponding to the periodontal ligament without apparent cause.

Stage 1 - is characterized by exposure and asymptomatic bone necrosis;

Stage 2 - by exposure and bone necrosis associated with pain and infection;

Stage 3 - showing necrotic and exposed bone tissue in patients with pain, infection, pathological fracture, extraoral fistula and extensive osteolysis.

## **Drugs with ant reabsorption properties**

### **Bisphosphonates (BFs)**

BFs are synthetic analogues of inorganic pyrophosphate, a naturally occurring compound in the body and a physiological regulator of calcification and inhibitor of bone resorption, which have been mentioned above.

### **RANK-L Inhibitor**

RANK-L is one of the osteoclasts activating proteins. The RANK-L inhibitor, in turn, is an antibody that prevents RANK-L binding to its nuclear receptor, thus not allowing osteoclastic activity. This inhibition of osteoclasts hinders bone regeneration, increases bone density, and reduces the risk of fracture. Drugs with this function, such as Denosumab, are used in the treatment of bone disorders, such as osteoporosis and bone metastasis of malignant tumors. However, these drugs also play an important role in the pathogenesis of ONJ maxillary osteonecrosis (Eid, 2014).

Osteonecrosis of the jaw-related drug-ONMRM occurs as a dose-dependent adverse effect of Denosumab as well as BF. However, the time of action of Denosumab is lower than that of BF, it makes feasible the treatment of patients in the occurrence of side effects such as ONM (Yoneda, 2017). Mechanisms of action between drugs are different, but their effects on bone tissue are similar and the specific characteristics of Denosumab in ONMRM are still not entirely clear.

### **Antiangiogenic agents**

The Vascular Endothelial Growth Factor (VEGF) cell receptor plays an important role in cancer progression; however, it can be controlled by antiangiogenic drugs (Sivolella, 2013). These drugs, such as Bevacizumab, have antiangiogenic properties that favor tumor reduction but, on the other hand, may compromise the integrity of microvessels, lead to lesions of bone tissue, and hinder the action of VEGF, which may have direct deleterious effects on the cellular differentiation and the bone function and, in this way, to cause a failure in the repair of a physiological trauma and to induce ONMRM (Yoneda, 2017).

Few cases of ONV related to Bevacizumab have been described in the literature; the early diagnosis of ONM has led to conservative treatment or surgery, it presents a relatively rapid therapeutic response but there is insufficient information to allow a comparison with ONF related to BFs (Santos-silva, 2013).

These drugs accumulate in the bone matrix and are slowly released over prolonged periods of time, with a half-life of approximately 10 years (Papapoulos, 2007). Therefore, they represent a risk for the development of dose-dependent NMSM. Even after discontinuation of the drug, the risk of developing ONMRM remains (Ruggiero et al., 2014).

### **Clinical Manifestations**

There is a characteristic triad that includes the presence of pain (ranging from acute and severe to mild discomfort in the affected area), fistulas associated with drainage of purulent exudate and areas of bone exposure. However, the three components are not always present and some patients may present only pain, without being associated with the area of bone exposure or fistula with paridia and drainage of exudate without associated pain, especially in the early stages of the osteonecrosis process (Mawardi, 2009).

This knowledge is fundamental, since the early diagnosis of osteonecrosis is essential for the establishment of the best therapy and so that patients can be offered more conservative management options, with a better prognosis.

### **Drug-related risk factors**

- Potency of bisphosphonates (Zoledronate> Pamidronate> Oral bisphosphonates). The higher the power, the greater the risk.
- Duration of therapy. The longer the therapy, the greater the risk (Ruggiero, 2009).

### **Local risk factors to be observed**

- Dentoalveolar surgery (dental extractions, dental implants, periapical surgery) increases the risk of maxillary osteonecrosis associated with the use of bisphosphonates (OMAB) 7 times.

- Local anatomy: lesions are more frequent in the mandible relative to the upper jaw (ratio 2/1) and in regions with less thick mucosa on bony prominences: lingual torus, mylohyoid crest, palatine torus.

Concomitant oral disease: Patients with concomitant dental inflammatory disease are 7 times more likely to develop OMAB (Ruggiero, 2009).

### **Systemic and demographic risk factors**

- Age: increased risk by 9% for each decade of life.
- Raça: greater risk in Caucasians.
- Type of malignant neoplasia: greater risk in patients with multiple myeloma followed by breast cancer.
- Osteopenia / osteoporosis diagnosed concomitantly with malignant neoplasm (Ruggiero, 2014).

### **High risk factors considered**

- Patients under use of corticosteroids, diabetes, tobacco consumption, alcohol consumption, deficient oral hygiene and chemotherapy (Ruggiero, 2009).

After the detection of these risk factors, the possible evidence found should be taken into account in the planning of new conduits with preventive measures to osteonecrosis associated with bisphosphonates, thus maximizing the predictability of dental treatment in patients with bisphosphonates.

The adequacy of the dental treatment plan is an important preventive factor. Thus, the American Academy of Oral Medicine (AAOM) has suggested the protocol of examination in patients presented, and this protocol is described below:

### **Recommendations for Preventive Treatment of Osteonecrosis**

- Intraoral, extraoral, and radiographic examination to aid in the diagnosis of caries, periodontal disease, third molar evolution, identification of cancerous metastases and other pathologies;

- Periodontal examination to diagnose some type of periodontal disease. It is important to eliminate any plaque retention factor, such as over restoration and calculation. If diagnosed, the disease should be treated properly;
- Dental extractions should be done as soon as possible;
- Defective restorations or cavities should be replaced / restored;
- Fixed crowns or bridges are not appropriate for this type of patient.
- Removable prostheses should be re-evaluated for shape, stability, and occlusion. If necessary, adjustments should be made;
- Good prophylaxis should be done along with oral hygiene instruction. The patient should also be informed about the risk of developing osteonecrosis and should be advised about the first signs and symptoms of osteonecrosis;
- At the end of treatment, the patient should be maintained on supportive therapy. (Migliorati, 2005).

For patients who use bisphosphonates and do not present osteonecrosis, the following precautions and treatment are adopted at the Instituto de Medicina Integral Professor Fernando Figueira (IMIP):

- Antibiotic prophylaxis - 2g (4 tablets) of oral amoxicillin one hour before the intraoral treatment or Clindamycin 600 mg orally if allergic to penicillin. Based on the action of antibiotics that they can kill (bactericidal) or prevent the growth of bacteria (bacteriostatic) in established infections, they can also do so in the blood or at specific sites preventing an infectious process from occurring.
- Prophylaxis with chlorhexidine at 0.12% (mouthwash). Chlorhexidine has a broad spectrum of action, acting on gram-positive, gram-negative, fungal, yeast and lipophilic viruses (Tortora, 2000).

For absolute isolation to be carried out with rubber dam, ligatures are used to avoid soft tissue trauma. In absolute isolation, the clamp is generally used to retain / hold the rubber dam on the tooth, and thus, the treatment has the complementary function of keeping the rubber dam close to the tooth's neck, but in such cases, it is adopted only the placement of the lattice, avoiding the use of the clamps so that there is no trauma to the tissues.

#### • **Caution during the endodontic procedure, in order to prevent overinstrumentation**

Overinstrumentation is a questionable resolution iatrogenic. Once it is observed, it is feasible to remove it, as the persistence of the gutta percha cone beyond the root apex may favor the formation of apical biofilm, which would interfere with the apical repair process (Nair, 2007). However, it is not always possible to remove the gutta percha cone, either immediately or in late periods at the endodontic filling. Although this material is biocompatible and relatively well tolerated by the periapical tissues (Key, 2006), when fragmented, mainly in the mechanical act of removal, it causes an intense and localized tissue response, characterized by the presence of macrophages and giant cells (Sjögren, 1995).

When overfeeding occurs, the case should be carefully analyzed, assessing the risks of attempted removal or the preference to keep it intact. Therefore, the less exposed the sealing cement line between the foraminal aperture and the extruded percha gut cone, the less microleakage of microorganisms and substance exchanges between the root canal and the periapical tissues. Thus, any attitude that favors a better apical sealing should be attempted.

#### • **Do not perform exodontia**

Patients who underwent dental extractions are more likely to develop osteonecrosis and, over time after extraction, further increases the risk of developing osteonecrosis associated with the use of Bisphosphonate, with more than 57% of patients with multiple myeloma developing osteonecrosis (Badros, 2006).

#### **Dental treatment for patients with osteonecrosis**

- Routine restorations should be done in the most atraumatic way possible;

- Scraping and prophylaxis should be made as atraumatic as possible, with care with soft tissues;
- Avoid extractions except on teeth with mobility grade III or higher. The patient's postoperative period should be monitored weekly in the first 4 weeks until the alveolus is fully healed;
- Teeth with extensive caries should be considered for endodontic therapy;
- The ONC area should be treated only for the purpose of eliminating bone spicules that can traumatize soft tissue. Debridement can be done, if necessary, to avoid trauma to adjacent tissues. If there is, in the area around the exposed bone, erythema and suppuration, antibiotic therapy and 0.12% Chlorhexidine Gluconate should be used until healing of the area;
- Prostheses with resilient material can help cover the necrotic bone by avoiding soft tissue trauma;
- Existing prostheses should be re-evaluated. If necessary, shape and contour fit should be performed, minimizing trauma and soft tissue pressure;
- Odontogenic infections should be treated with a systemic antibiotic. Penicillin is the antibiotic of first choice and may be associated, if necessary, with Clindamycin. (Migliorati, 2005).

#### **Patients with maxillary osteonecrosis associated with bisphosphonates (ONMAB) and their treatment, according to the stages presented**

Areas of necrotic bone tissue that provide a constant source of irritation to soft tissues should be removed without additional bone exposure. All bone abductions should be removed without exposure to healthy bone tissue; - Debridement may be effective in the eradication of necrotic bone;

- The extraction of symptomatic teeth in areas of exposed and necrotic bone should be considered;

It may be advantageous to use a removable shield at the sites of osteonecrosis;

- Treatment with hyperbaric oxygen has not yet been shown to be effective.

#### **Therapeutic approaches that may assist or replace treatment with bisphosphonates**

Bisphosphonates have been shown to be effective in reducing bone metastasis pain in breast cancer, the incidence of new metastases, pathological fractures, bone marrow compression, development and progression of bone pain, as well as the need for irradiation or bone surgery in women with advanced breast cancer and with clinical evidence of metastases.

The drug was also effective in the prevention and treatment of mineral bone loss of the lumbar spine induced by the chronic use of corticosteroids (Allen, 2004), as well as in the reduction of vertebral and non-vertebral fractures in women with osteoporosis after menopause (Cranney, 2004).

The incidence of osteonecrosis at any site is reported to be four times higher in cancer patients than in the general population (Tarassof, 2003). In view of this fact, the therapeutic approaches that will be described, mostly refer to cancer patients.

It is important to consider the substitution of the drug, but the general condition of the patient, his well-being and the risk-benefit relationship should be evaluated by a multidisciplinary team.

#### **Pentoxifylline and tocopherol in the treatment of patients with osteoradionecrosis**

Pentoxifylline is a derivative of methylxanthine that acts on inflammatory mediators, such as TNF- $\alpha$ . It causes vasodilation, inhibits inflammation, stimulates the proliferation of fibroblasts and the formation of extracellular matrix. It eliminates oxygen radicals in situations of oxidative stress and participates in the resolution of fibrosis. In this way the interest in its use in situations of ORN is verified, favoring the healing process. It inhibits tumor necrosis factor alpha (TNF $\alpha$ ), and

tocopherol is a special reactive oxygen scavenger which, in combination, has shown a synergistic effect, an effect on the progression of osteoradionecrosis.

Some authors suggest that prophylactic administration of 400 mg of pentoxifylline twice daily for eight weeks in association with 1000 IU of tocopherol should be administered one week before the procedure and the administration should be continued for 8 weeks (Iyer, 2012). These two drugs in combination have shown a positive synergy and effect on the progression of fibrosis and inflammation lesions arising from radiotherapy treatment, most notably in the study by Delanian et al. (2005), where the lesions in all 18 patients showed considerable improvement, and 16 completely resolved.

Another study has shown recovery in cases of refractory ORN with results close to 100% (Beech, 2014).

### **Plasma enriched with leukocyte fibrin in the treatment of mandibular osteonecrosis associated with the use of bisphosphonates**

Recently, advances in the areas of cell and molecular biology allowed us to present the functions of growth factors and their participation in the different phases of wound healing, and can be applied in cases of osteonecrosis of the jaw, specifically L-PRF, which results in an acceleration in the cure, reducing the risk of contamination, edema and postoperative pain, being a completely harmless method, since it is prepared from the patient's own blood, eliminating the possibility of transmission of parenteral diseases as well as allergies or immune reactions of rejection. This helps in homeostasis, prevents gingival dehiscence and promotes remodeling and healing of soft and hard tissues. In fact, the biological activity of the fibrin molecule is responsible for the cicatricial capacity promoted by L-PRF5.

However, the use of L-PRF is a treatment option for stage 2 mandibular osteonecrosis, since it stimulates and accelerates bone repair and soft tissue healing, being a conservative and low-complexity treatment.

## **4. Conclusion**

Bisphosphonates, when well indicated, may be an excellent therapy for patients with pathologies that show, as an organic consequence, bone resorption that may lead to fractures and destruction of noble tissues protected by hard mineralized bone structures. Osteonecrosis of the jaws can be decreased or prevented following the cares described in this paper. Anyhow, appropriate anamnesis and the knowledge of the systemic conditions of the patients are mandatory requirements for their prescription and final outcome of the treatments offered.

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