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Impact of Antiresorptive Agents on Maxillary Bones: a Narrative Literature Review

Impacto dos Agentes Antirreabsortivos nos Ossos Maxilares: uma Revisão de Literatura narrativa

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Abstract

Antiresorptive drugs operate in the bone metabolism modulation and are widely used in the treatment of bone metastases and bone losses related to hormonal deficiency. Although this therapy shows satisfactory results, there are adverse effects associated with its use, such as osteonecrosis of the jaws. Medication-related osteonecrosis of the jaws (MRONJ) is, therefore, a serious and challenging condition with important implications in dentistry. The aim was to conduct a narrative literature review on anti-resorptive drugs and their latest repercussions on the maxillary bones. The review was carried out through a bibliographic search using Decs/Mesh descriptors of interest, in Portuguese and English, in the PubMed, Virtual Health Library (VHL) and Scielo databases. After applying the inclusion and exclusion criteria, a total of 33 studies were selected for analysis. It can be noticed that therapy with anti-resorptive agents is complex, especially in dental practice, since MRONJ is a complication that is difficult to manage. Regarding the therapeutic options, these are divided into conservative, surgical or adjuvant therapy, however, there are no protocols in the literature, and there is no consistency regarding the indication of the suspension of the drug administration - "Drug Holiday". Thus, it is important that the multidisciplinary team seeks strategies that minimize complications and promote control over the use of these drugs. In addition, there is a need for investigations that contribute with guidelines for the management and control of adverse effects resulting from therapy with antiresorptive drugs.

Keywords: Bone Density Conservation Agents. Diphosphonates. Denosumab. Bisphosphonate-Associated Osteonecrosis of the Jaw.

Resumo

As drogas antirreabsortivas atuam na modulação do metabolismo ósseo e são indicadas para o tratamento de metástases ósseas e perdas ósseas relacionadas à deficiência hormonal. Ainda que esta terapia apresente resultados satisfatórios, observam-se efeitos adversos associados ao seu uso, como a osteonecrose dos maxilares. A osteonecrose dos maxilares associada ao uso de medicamentos (OMAM) é, portanto, uma condição séria e desafiadora com implicações importantes na Odontologia. O objetivo foi realizar uma revisão narrativa de literatura sobre as drogas antirreabsortivas e suas respectivas repercussões nos ossos maxilares. A revisão foi realizada através de busca bibliográfica utilizando descritores Decs/Mesh de interesse, em português e inglês, nas bases de dados PubMed, Biblioteca Virtual de Saúde (BVS) e Scielo. Após aplicação dos critérios de inclusão e exclusão, um total de 33 trabalhos foram selecionados para análise. Pode-se constatar que a terapia com agentes antirreabsortivos é complexa, sobretudo na prática odontológica, visto que a OMAM é uma complicação de difícil manejo. Em relação às condutas terapêuticas para esta condição, divide-se em terapia conservadora, cirúrgica ou adjuvante, todavia, não existem protocolos validados na literatura, bem como não há consistência quanto à indicação do intervalo de suspensão da administração da droga - "Drug Holiday". Desse modo, é importante que a equipe multidisciplinar busque estratégias que minimizem as complicações e promovam o controle no uso dessas drogas. Além disso, nota-se a necessidade de realizar investigações que contribuam com diretrizes para o manejo e controle dos efeitos adversos decorrentes da terapia com medicamentos antirreabsortivos.

Palavras-chave: *Conservadores da Densidade Óssea. Bisfosfonatos. Denosumabe. Osteonecrose Associada a Bisfosfonatos.*

1 Introduction

Antiresorptive drugs (ARD) are bone metabolism modulators widely used in patients with some physiological or pathological dysfunction of the skeletal system, which include different classes of drugs, such as bisphosphonates and monoclonal antibodies[1]. These drugs operate blocking bone resorption by inhibiting osteoclasts activity, which favors improvement in the clinical signs of many diseases[2].

There are several indications for these drugs, such as the treatment of metastases associated with cancer, especially of lung, breast, prostate and multiple myeloma[3], as well as bone loss related to hormonal deficiency, such as in osteoporotic patients, resulting in increased bone density, reduced risk of fractures and improved quality of life of individuals[4,5]. However, some adverse effects are associated with the use of ARD, such as myalgia, flue-like symptoms, atypical fractures and osteonecrosis. This last condition deserves to be highlighted, since it is a complication of extreme severity, mutilating and debilitating, with important implications in dental practice[3,6,7].

Osteonecrosis induced by bisphosphonates was first described in 2003, in a series of cases in which patients

presented necrotic bone exposed in the maxillary region, with painful symptoms associated with lesions and did not respond to medical and surgical interventions. All cases presented in common the treatment with the bisphosphonates pamidronate (Aredia®) or zoledronate (Zometa®) - antiresorptive class drugs[3,8].

Since then, the scientific literature has striven to understand and elucidate the mechanisms related to the adverse reactions of this group of drugs, especially severe bone necrosis[1,3]. Studies point out that the casuistic involved in the paradoxical effect of this group of drugs is associated with the inhibition of osteoclastic activity, which implies the suppression of bone renewal, induction to apoptosis and local antiangiogenic effect, which can trigger a cascade of cellular signaling, resulting in osteonecrosis[1,5].

The pathophysiology and etiology of this complication are not fully understood yet. However, it is known that the risk of developing osteonecrosis is different according to the type of medication used, dose, route of administration and association with local risk factors, such as trauma and microtrauma, in addition to systemic factors, such as alcohol and/or tobacco abuse, anemia and diabetes mellitus[1,9].

The role of bisphosphonates has been the target of increasing interest of the scientific community, however, the evidence on the other classes of anti-resorptive drugs and their repercussions on maxillary bones has still been little explored. The aim was to conduct a narrative literature review on anti-resorptive drugs and their latest repercussions on the maxillary bones.

2 Development

2.1 Methodology

This is a narrative literature review about ARD and its repercussions on maxillary bones, performed through the use of *PubMed,*Virtual Health Library (VHL) and *SciELO* databases. The descriptors DeCS/Mesh in Portuguese and English "Drogas antirreabsortivas/Antiresorptive Drugs", "Bisfosfonatos/Biphosphonates","Denosumabe/Denosumab","Complicações/Complications", "Osteonecrose Associada a Bisfosfonatos/Bisphosphonate-Associated Osteonecrosis of the Jaw" were used, associating the Boolean operators "AND" and "OR."

The inclusion criteria for the articles selection were publications that were in accordance with the proposed theme, with data related to anti-reactive drugs, mechanism of action, therapy and management of patients with complications under drug use; relevant publications over the past 08 years in Portuguese and English; clinical case reports, randomized clinical trials, quantitative and qualitative studies. Publications outside the proposed scope, articles duplicated or that did not present a summary on the search platforms were excluded from the research.

Initially, 431 articles were selected in the referenced databases. After deleting duplicates and reading abstracts, the studies were classified as selectable (n=36) and non-selectable (n=398), following the methodological evaluation criteria already described. After applying the inclusion and exclusion criteria, a total of 36 studies were selected for the study herein. The information contained in the selected journals was organized in tables and stored in a personal database for later comparative analysis.

2.2 Bisphosphonates

Bisphosphonates (BFs) are complex drugs that have as target enzymes involved in cellular bone metabolism. Their chemical structure involves alternating connections between carbon and phosphonates (P-C-P), resulting in a synthetic molecular analogue of pyrophosphate. Pyrophosphate (P-O-P) - a natural inhibitor of bone resorption, is not stable before hydrolytic challenges and therefore cannot be used as a therapeutic agent[1,10-12].

Thus, the replacement of the central oxygen molecule by carbon guarantees this group of drugs stability, making them non-hydrolysable. This mechanism increases the half-life of the drug, which allows a wide action in the cellular microenvironment. In addition, the addition of carbon admits the addition of branches, elements that define the activity and potency of BFs, which can be distributed in two classes according to the variation in the molecular structure of their lateral chains: simple bisphosphonates (S-BPs) and nitrogen containing bisphosphonates (N-BPs)[3,10,11].

The differences shown by BPs groups also distinguish in their cell action mechanism. S-BPs undergo metabolization for non-hydrolysable cytotoxic analogue compounds of adenosine triphosphate (ATP), which accumulate in the osteoclast and trigger its apoptosis[10]. N-BPs, however, are responsible for acting as potent inhibitors of the farnesyl diphosphate synthase (FPPS) enzyme which, in a complex cell signaling chain, impact on the cytoskeleton and vesicular traffic in the cytoplasm, triggering the apoptosis of osteoclasts[10-12].

The way in which BP accumulates in bone tissue is also influenced by molecular differences. It is known that nitrogenous drugs bind more strongly to the hydroxyapatite crystals of the bone matrix compared to non-nitrogenous drugs. The accumulation in the matrix intensifies and prolongs the effects, since the half-life of these drugs may exceed 10 years. Furthermore, osteoclasts, which operate on bone removal, now concentrate the drug inside, leading to the deactivation of these cells and reduction of bone remodeling process[10,11,13]. Thus , the release of the drug from the matrix is dependent on tissue renewal and, thus, BPs may remain in the bones for years[11,14].

Historically, BPs can be divided into three generations that have evolved in order to increasingly guarantee potency and assertiveness against diseases and lower toxicity to patients[15]. Advances in their chemical characteristics have built the basis

for studies of their pharmacodynamics and pharmacokinetics over the past five decades, in addition to several clinical studies, promoting their use in several diseases successfully[12,15].

The first generation of this class of drugs occurred in 977, with the Etidronate regulations. The first use of this drug was performed to control progressive ossifying fibro dysplasia and later, indicated for osteoporosis[12]. The second generation, represented by drugs that already allowed the addition of nitrogenous components in their lateral chains, appears in the drug scenario in 1991, with the creation of alendronate. Only in 2001, the third generation of BPs are characterized, from the creation of Zoledronates, with a significant increase in potency and half-life time[12,15].

The zoledronic acid binds more strongly to the bone matrix than the alendronate, and this in turn, more than the risedronate. This fact may affect the drug depuration, action in the organism, as well as the potency, dosage necessary and reversibility of its effects[14]. In this sense, the action of zoledronic acid and alendronate tends to be greater than that of risedronate. When potency is compared between drug classes, N-BPs can be between 100 and 10,000 times more potent than S-BPs[10].

This class of drugs is indicated for several bone diseases, ranging from the treatment of Paget's disease to multiple myeloma, hypercalcemia, osteoporosis and bone metastases. BPs have oral or intravenous administration, with specific indications according to the clinical signs presented by the patient. Although the use of BPs has positively influenced the control of several bone diseases, its use should be carefully evaluated, with multidisciplinary follow-up and adoption of preventive measures, since the association with adverse effects on maxillary bones has been widely evidenced in the literature[1,16,17].

Anti-resorptive drugs therapy is capable of inhibiting osteoclast genesis throughout the skeletal system, but osteonecrosis associated with the use of BPs occurs exclusively in maxillary bones[4]. In this sense, there is a broad discussion about the mechanisms that trigger the necrotic process. The reduction of bone renewal combined with the local antiangiogenic effect by the interleukins suppression , such as those related to T-gamma delta T γδ lymphocytes (IL-17A)[18], as well as the direct effect on local keratinocytes and fibroblasts, with reduction of the potential for the mucosa reepithelization , are phenomena pointed out as possible triggers of this condition. Added to this are hypotheses related to local inflammation and infection, trauma and microtrauma resulting from mechanical demand of the stomatognathic system or associated with dental interventions, accumulation of biofilm, immunosuppression and vitamin D deficiency[1-4].

In addition, a reduction in the expression of important factors regulated by T γδ cells was observed in patients with nitrogenous BFs-related osteonecrosis, such as RANK, RANK-L, Tumor Necrosis Factor -Alpha (TNF-α), Fibroblast Growth Factor-9 (FGF-9), as well as Connective Tissue Growth Factor (CTGF), Metalloproteinase-7 (MMP7) and Aryl Hydrocarbon Receptor (AHR). These factors play an important role in immunity, wound healing and barrier function, which reinforces the theory that the immune system and its regulation are directly related to bone metabolism, and therefore have an association with MRONJ pathophysiology[18].

2.3 Denosumab

Denosumab (DMB) is a monoclonal antibody (mAbs) that has been successfully used in antiresorptive drugs therapy. It is a drug that binds with great affinity and specificity to the circulating RANK-L and work on the axis of the Receptor activator of nuclear factor kappa ß/ligand (RANKL) and Osteoprotegerin (RANK/RANK-L/OPG), acting on bone metabolism[1,19].

RANK-L protein, expressed on the surface of precursor cells or mature osteoclasts, interacts with RANK produced by osteoblasts or mesenchymal cells. This phenomenon promotes the triggering of enzymatic activities and the release of chemical mediators that result in the multinucleation of pre-osteoclasts or activation of stagnant cells, starting the remodeling process. In order to maintain this physiological structure in balance, the OPGs work in RANK-L capitation, avoiding a decompress and excessive bone mass loss[1,4,10,12].

Different from BPs, DMB does not bind to bone tissue, but it plays its role in the extracellular medium of osteoclasts and their precursors expressing the RANK protein in a reversible way. DMB therefore works by mimicking OPG – an endogenous molecule – by binding to RANK-L and inhibiting its interaction with RANK. Thus, the drug is capable of influencing the formation, function and survival of bone cells[4,10].

Historical data demonstrate that synthesized mAbs have a greater capacity to preserve healthy cells when compared to standard cytotoxic therapies, characterizing them as a source of interest in the fight of bone neoplasms. Although the first studies to evaluate cancer therapy have not been successful, since 1975, with the first description of the mAbs, research has advanced significantly. Nowadays, the use of this biological tool as a signaling molecule, diagnosis and potent therapeutic agent is known and respected[1,20].

mAbs can be synthesized from different forms and assume improvements in their production methods to present greater similarities with human antibodies and to avoid hypersensitivity reactions[4,20]. The best known and used against cancer is DMB[20], which has a reversible effect and is excreted by the reticuloendothelial system, with a half-life of approximately 26 days. In addition, the effects of these drugs on bone remodeling reduce 6 months after their administration, one of the main pharmacodynamic differences in relation to BPs[1,3,14].

DMBs have demonstrated superior results compared to BPs when the bone density and fracture incidence criteria were evaluated. Since the presence of RANK-L is increased

in some diseases (Paget's disease, bone metastases and osteoporosis due to the release of cytokines and growth factors) and bone resorption is mediated by osteoclasts, it is easy to understand how DMB blocks the differentiation and function of these cells, being consolidated as an effective therapeutic option[1,3,4,10].

In contrast to BPs, there is no evidence that DMBs have an influence on angiogenesis or cause toxicities to soft tissues[3]. However, some publications relate the use of this drug to osteomyelitis or maxillary necrosis, besides hypocalcemia, skin hypersensitivity, hypotension, dyspnea and angiodema[1,4,10,19].

In a retrospective study with 141 patients in a Unit of High Complexity in Oncology in France, it was possible to directly relate the occurrence of osteonecrosis with the duration of the treatment. The values found were 3% in 1 year, 7% in 2 years and 8% from 30 months of treatment, showing dose-dependent potency to develop severe bone necrosis[19]. It is important to emphasize that the great majority of studies point to dental extraction as the main risk factor associated with osteonecrosis development[4,12,19]. Thus, there is a consensus approach to stimulate practices of continuous oral health education and to establish a clear dialog with the patient regarding the possible complications of this therapy[1,19,21].

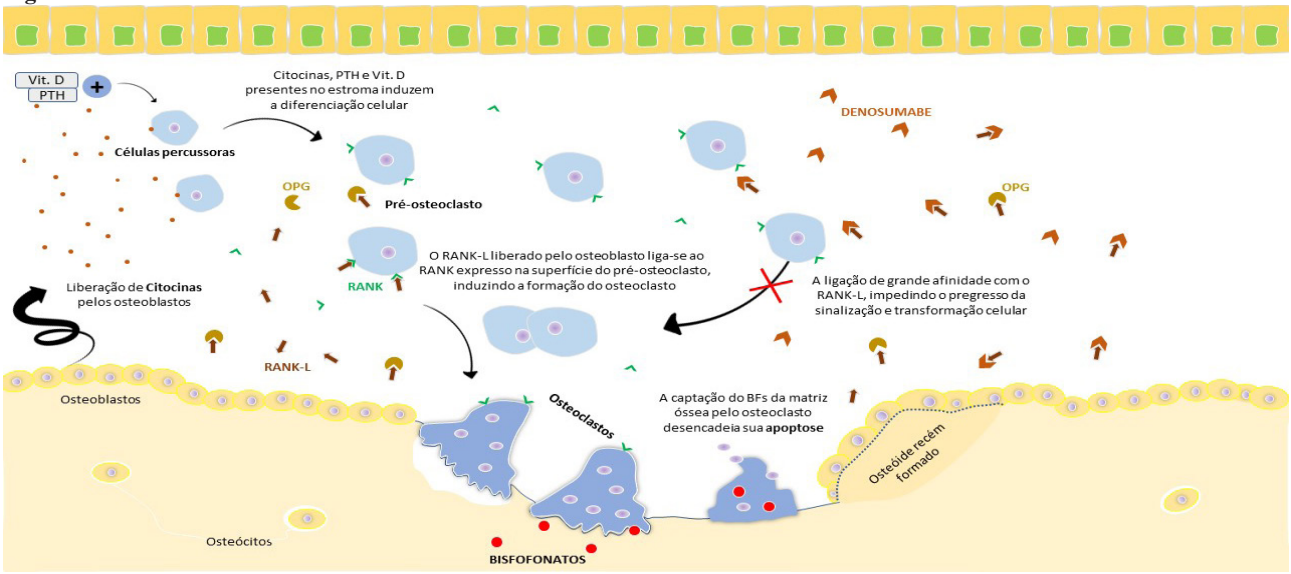
Table 1 shows the main types of drugs used in anti-resorptive therapy, their trade names, subtypes, indications, routes of administration and cellular action mechanism . Figure 1 shows didactically the mechanism of action of these drugs in relation to bone metabolism.

Table 1 - Main drugs involved in anti-resorptive therapy

Anti-resorptive agent and trade name		Subtype / Generation	Indication	Rout of Administration	Cellular action mechanism
Bisphosphonates					
Etidronate	Didrone®	Simple 1st Generation	Bone diseases treatment, such as Paget's disease	Oral or intravenous	Formation of non-hydrolysable cytotoxic analogues of ATP
Clodronate	Bonefos®	Simple 2nd Generation			
Pamidronate	Aredia®	Nitrogenous 2nd Generation	Malignant hypercalcemia, multiple myeloma and bone metastases	Intravenous	N-BPs Inhibition of Farnesyl diphosphate synthase (FPPS)
Alendronate	Fosamax®	Nitrogenous 3rd Generation	Osteoporosis	Oral	
Ibandronate	Bonviva®	Nitrogenous 3rd Generation	Osteoporosis	Oral	
Zoledronate	Zometa®	Nitrogenous 3rd Generation	Malignant hypercalcemia, multiple myeloma and bone metastases	Intravenous	
Risendronate	Actonel®	Nitrogenous 3rd Generation	Osteoporosis	Oral	
Denosumab					
Prolia®		Single	Osteoporosis, malignant hypercalcemia, multiple myeloma and bone metastases	Intravenous	Monoclonal antibody that inactivates RANKL
Xgeva®				Intravenous	

Source: Adapted from Kanwar et al.[1], Ruggiero et al.[3] and Chaves et al.[11].

Figure 1 - Action mechanism of BPs and DMB on bone metabolism



Source: The authors.

Figure 1 illustrates the action mechanism of BPs and DMB on bone metabolism, according to the sequence: 1. Mesenchymal precursor cells are stimulated by the release of growth factors by osteoblasts, presence of vitamin D and parathormone. 2. Undifferentiated cells become pre-osteoclasts, expressing on their surface the RANK-L binding protein 3A. RANK/RANK-L ligand triggers the pre-osteoclasts multinucleation. 4. As a result of the transformation, pre-osteoclasts become mature and metabolically active osteoclasts, initiating a natural bone reabsorption process. So that there is no imbalance in the bone remodeling process (absorption and deposition), the osteoprotegerine molecules (OPG) prevent the pre-osteoclasts maturation. 5. The mature osteoclast bonds to the BPs connected to the bone matrix and triggers its apoptosis 3B. Denosumab mimicks OPG, preventing the binding of key proteins (RANK-L/RANK), making bone reabsorption progression impossible by blocking cellular modifications.

2.4 Influence of anti-resorptive drugs on bone tissue and osteonecrosis of maxillary muscles associated with the use of medications - MRONJ

Bone resorption and deposition of skeletal system minerals are interlinked and interdependent processes. These mechanisms are performed by the main bone matrix cell set: osteoblasts, osteoclasts and osteocytes. Osteoblasts are the cells responsible for bone deposition, while osteoclasts act on reabsorption. Osteocytes, in turn, are cells derived from osteoblasts when confined to the newly formed and mineralized bone tissue. This set of cells, therefore, guide bone remodeling in response to mechanical stimuli and efforts[22].

Remodeling begins when osteocytes and osteoblasts release the RANK-L, which binds to RANK in osteoclasts and their precursors, leading to activation of these cells. Ionic changes in the osteoblast cytoplasm create an acid environment in the region in contact with the bone matrix that, associated with lysosomal enzymes, degrade the inorganic and organic components of the matrix[10]. In addition to inducing the osteogenic processes, osteoblasts can also suppress bone renewal by releasing OPG, which binds to RANK-L and prevents its binding to RANK[12]. This mechanism is important for homeostasis, and there are disorders in diseases that modify this molecular pattern, such as in cancerous metastases and Paget's disease[1,10,19].

Both BPs and DMB act in the osteoclasts inhibition and their activity, which convert to the bone renewal suppression. Thus, there may be indirect effects of these drugs based on the association with osteoblasts and other cells of the environment[6]. This is reflected in the clinical presentation, signs and symptoms presented by patients who develop severe bone necrosis, since the indirect synergistic effects of the drug have been pointed out as unfavorable to reepithelization and inductors of antiangiogenic effect[1,4,10,19,23].

In addition, cells and bone marrow have specific differences in their composition and may play distinct roles in each skeletal system region[6]. This fact seeks to explain why osteonecrosis occurs exclusively in the maxillary bones and is corroborated by Chang et al.[4], in a study that aimed to demonstrate the pathophysiological osteonecrosis mechanisms. Allied to this, the healing of the maxillary muscles seems to occur differently from other bones of the skeleton. It is also worth remembering that the alveolar bone *turnover* can be up to 10 times as high as the long bones, which influences the incorporation of more BPs or DMB in the jaws [22].

Osteonecrosis of the jaws induced/associated with (MRONJ) drugs is a severe and difficult to manage condition that has been associated with the use of antiresorptive and antiangiogenic drugs – with a great impact on the patients' quality of life. It is characterized by the progressive degradation of bone tissue, being more common in the jaw than in the maxilla, however, with the capacity to affect both[3,22,24].

It is characterized by a debilitating and painful condition, with a higher incidence in oncologic patients, who receive the drug at higher doses and intravenously, compared to osteoporotic, which mostly use oral BPs[3,24,25]. According to the American Association of Oral and Maxillo-Facial Surgery (AACOM), in its report conducted in 2009 and updated in 2014, MRONJ can be identified in patients who are or have been treated with anti-resorptive drugs, associated or not with antiangiogenic agents, who present bone exposure with the possibility of being probed by intraoral or extraoral fistula in the maxillo-facial region and which does not heal for a minimum period of8 weeks, without history of radiotherapy or metastatic disease in the region.

Its physiopathology has not yet been fully elucidated and the studies concentrate its analyzes on the following assumptions: excessive bone remodeling inhibition, infections and inflammation in the region of gnathic bones favoring trauma, soft tissue toxicity, immunity dysfunction, vitamin D deficiency and oral biofilm. Despite the inaccurate understanding of the form in which it occurs, the synergy between the drug that acts in the bone renewal reduction, the proximity of a naturally septic environment and the mechanical stress of chewing several times a day can be factors for the MRONJ development10[22,24].

BPs and DMBs act on distinct cellular components, but have in common the bone renewal suppression. Therefore, it is not inconsistent to associate MRONJ with this mechanism of excessive suppression and to correlate it with the other assumptions previously mentioned[22].

The MRONJ clinical manifestations vary and patients may present pain, inflammation, infectious conditions, as well as suppuration and intraoral fistula. With worsening of the signs, exposure of necrotic bone associated with extraoral fistulae, antral or nasal communication may be observed, and even greater risk of occurrence of pathological fractures[25-27].

Therefore, MRONJ can be classified in stages according to

the clinical manifestations presented. Thus, MRONJ staging system classifies the disease evolution from grade 0 to grade 3, which facilitates the adoption of disease care strategies (Table 2)[3].

Table 2 - Drug-induced Osteonecrosis staging

Stage	Clinical Manifestations
Stage 0:	No clinical evidence of necrotic bone; asymptomatic patient; clinical findings and nonspecific radiographic changes.
Stage 1:	Necrotic bone exposure or presentation of intraoral fistulae; asymptomatic patients (no pain) and no evidence of infection.
Stage 2:	Necrotic bone exposure or intraoral fistulae associated with infection; symptomatic patient (pain) and erythema in the exposed bone region, with or without purulent drainage.
Stage 3:	Necrotic bone exposure or intraoral/extraoral fistulae associated with infection; symptomatic patient (pain) and presenting at least one of the following signs: (a) exposed and necrotic bone that extends beyond the alveolar bone region and may trigger pathological fracture; (b) extraoral fistula; (c) antral or nasal oral communication or osteolysis of large proportions.

Source: adapted from Ruggiero et al.[3].

The risk for the MRONJ development depends on the type of drug used, the dose and the route of administration, in addition to the duration of the treatment. Among osteoporotic patients, the risk is about 100 times as low as among oncologic patients[3]. This is due to the fact that doses received for osteoporosis treatment are lower than oncologic therapy[24].

The study by Limnoes et al.[23], aimed to compare the development potential of osteonecrosis in patients under treatment with zoledronic acid (BF) or DMB at intervals of 12, 24 and 36 months. According to the analysis performed by the authors, it was possible to conclude that the use of DMB is associated with a significantly higher risk of developing osteonecrosis in comparison with BP, in all the periods evaluated. However, no significant statistical difference was found regarding the prognosis.

A systematic review aimed to identify populations at risk and determine which medical and dental comorbidities are more predisposing factors for the MRONJ development. In their findings, it was found out that dental extractions, followed by periodontal diseases and implant installation, were the most associated dental procedures with bone necrosis. When the systemic conditions were evaluated, the concomitant treatment of BP or DMB with chemotherapy was the most cited item, followed by the use of corticosteroids, smoking and diabetes mellitus[9].

In the attempt for a better understanding of the phenomena associated with the MRONJ and anti-resorptive therapy, studies have focused on the comparison between the therapy performed with BP and DMB. In one of these studies, it was observed that DMB presents a slight tendency toward the resolution of the MRONJ cases, in comparison with BPs. This may be related to the reversibility mechanism present in the DMBs group[23].

2.5 Therapeutic management of MRONJ

Patients who will undergo treatment with ARD should be advised about the risk of developing MRONJ[3]. These patients need to be monitored periodically by the dental surgeon and should be motivated to maintain satisfactory oral hygiene and abandon habits that constitute risk factors, such as smoking, alcoholism and other drug use. Furthermore, it is essential that all the invasive dental procedures be performed prior to the initiation of therapy, especially when the treatment is intravenous and with high doses[1,25].

Although there is no ideal protocol for the management of this condition, there are therapeutic strategies that aim to control pain, infection and lesion advancement in order to favor tissue healing. The treatment is based on the type of drug involved, the individual comorbidities and the MRONJ staging. According to AACOM, the approaches can be divided into 3 categories: conservative, surgical (minimally invasive or invasive) and adjuvant therapies[25].

The conservative treatment consists of the control of infectious foci by means of efficient oral hygiene associated with the use of oral antiseptics and antibiotics, according to the patient's need. Surgical treatment includes sequestrectomy, debridement and resection. The technique used depends on the extent and severity of the lesion[3,24,25].

Adjuvant therapies such as hyperbaric oxygen, ozone therapy, pentoxifylline and α-Tocopherol (vitamin E), in addition to low-power laser, have shown satisfactory results. In addition to these, it has been suggested the use of autologous platelet (AP) and plasma rich in growth factors (PRGF), with the aim of accelerating the healing of post-surgical wounds and reducing the risk of infections[3,24-26].

Another strategy, although controversial, is the temporary interruption of the administration of anti-resorptive drugs (*drug holiday*) in invasive procedures. This conduct should take into account the time of effect of each drug on tissues and should be discussed between the dental surgeon and the doctor responsible to consider the risk-benefit for each patient and their general health[25].

2.6 Drug administration suspension interval – *"Drug Holiday"*

The risk of developing MRONJ may be influenced by the time and frequency of the use of antiresorptive drugs associated with risk factors. Discussions about the suspension of the administration of these drugs in patients requiring dental intervention have generated a great debate about *the "Drug holiday"* – an expression of the English language that designates the drug suspension interval[26,27].

Although it is a much debated topic in the scientific environment, many dentists do not know the term related to the conduct and the data presented in the literature are still controversial and inconclusive as to the conduct to be adopted.

However, they all warn of the importance of multidisciplinary follow-up and effective communication between the medical and dental team in decision-making[8,29].

In a multicenter study conducted in 06 Dentistry schools, which aimed to assess the level of knowledge about MRONJ, it was identified that most participants knew the indication of anti-resorptive drugs and their action mechanisms, however, 68.4% of the 234 participants did not know the term "*Drug Holiday*". This finding emphasizes the need for awareness of the dental community in order to contribute to osteonecrosis prevention [30].

The interruption approach would aim to prevent MRONJ in patients who require more invasive dental procedures. However, it seems inconsistent, based on the physicochemical properties of BPs – which are deposited in the bone tissue and remain for a long period, that the interval in the administration of this drug would have a positive influence for MRONJ. Differently, the interruption of DMS, which have longer and shorter half-life administration intervals, acting on extracellular mechanisms, could result in a lower chance of developing this condition[3,28-31].

AACOM, in its 2014 report, suggests that the team should consider a 2-month interval without oral BPs for those patients who need to perform invasive dental procedures[3]. In addition, the International Osteonecrosis Task Force recommends "*Drug Holiday"* in cases of patients with higher risk. Therefore, patients who have been using BPs for more than 4 years and who have comorbidities that set up risk factors, such as diabetes and rheumatoid arthritis, as well as exposure to corticosteroids and who have a smoking habit, there should be a suspension of the use of medicines until the site is healed[28].

Suspension of antiresorptive therapy is recommended two months before invasive dental treatment because of the possibility of this medicine interfering in surgical wound healing, especially in tissue reepithelization. This decision should be made on the basis of the clinical picture presented by the patient and continuing education measures should be established in the case[3,28].

Similarly, Di Fede et al.[32], recommend the interval of administration in at least seven days before the dental intervention for BPs and DMS. The authors assumed that the reduction in drug management would promote a reduction in the antiangiogenic effect on the periosteum and soft tissue, which could contribute to the improvement of vascularization and a more accelerated healing process.

Several authors suggest that the moment of resumption of antiresorptive therapy after a "*Drug Holiday"* is dependent on the balance between healing of surgical trauma and primary control of the disease. Therefore, if the risk of bone fracture or metastasis is well controlled, the return to drug administration is recommended after the total wound closure and healing in the oral cavity, in a period that can range from 30 to 60 days[3,28].

Regarding DMB, there are hypotheses that state that patients can respond better to drug suspension than those who received zoledronic acid, for example, due to pharmacokinetic properties belonging to these drugs[33]. Thus, invasive procedures, when unavoidable, can be performed with 07 days of interruption of DMB use or even without interruption, provided that appropriate infection control is performed[28,32].

Despite this scope of information, all strategies addressed by the authors described above are based on the specialists opinion, associated with cellular evidence and the drug pharmacokinetics. All these recommendations still need robust and controlled studies, which support the recommendations. It is worth pointing out that the patient should always be informed about the conduct idealized by health professionals, highlighting the possible effects and risks of each practice[3,4,28,29,31,32].

In the study carried out by Shudo et al.[35], the authors observed that among the patients who underwent continuous oral BPs therapy and who underwent dental exodontics, those who presented higher cumulative BPs due to the time of drug administration were those who had the longest healing. In this study, the patients were not submitted to the "D*rug Holiday",* however, they performed a specific protocol for the extractions and had a positive result, without the MRONJ development.

Whereas in a retrospective study that aimed to evaluate risk factors and the momentary interruption of antiresorptive therapy in patients who used oral BPs, it was evidenced that the roots burial and dental extractions are the most associated procedures with MRONJ development. In addition, the proposed " *Drug Holiday*" has proved not to be effective for the osteonecrosis control , and there is no proof of its efficacy[34].

In addition to strategies to avoid the osteonecrosis development, a multicenter retrospective study with 427 patients, proposed by Hayashida et al.[29], tried to evaluate the efficacy of the types of MRONJ treatment (surgical and non-surgical) associated with drug suspension ("*Drug Holiday*"). The authors identified that the suspension of antiresorptive agent significantly increased the healing rate in patients with osteoporosis submitted to non-surgical treatment. However, in patients with malignant tumors submitted to the same therapy, the drug suspension was only associated with a better result of the treatment, without statistical significance. It is worth pointing out that, when surgical therapy is the method of choice of treatment, "*Drug Holiday"* showed no positive effect on results in patients with osteoporosis or malignant tumors.

In a systematic review that aimed to determine the efficacy of the high doses suspension to reduce the risk of developing MRONJ in cancer patients submitted to dental extractions, the authors identified divergences regarding the indication of "*Drug Holiday"*: While the mechanism was considered no effective for DMB in all the studies included, for BPs, there were no indications in two studies; three studies recommended and, in seven studies, the authors indicated the need for individual evaluation. They also pointed out that, due to the limited number of studies and patients included in the

investigations, it is still difficult to obtain high-level evidence and do not recommend the interruption of anti-resorptive therapy[36].

Thus, while the ideal mechanism of "*Drug Holiday"* is not established, it is duly recommended that dentists be inserted into a multidisciplinary care team so that, together, they act in the previous care, during and after the therapy with antiresorptive drugs. New clinical studies and robust randomized trials should be carried out in order to maximize knowledge and support the ideal moment, effectiveness and safety of the approach, increasingly minimizing the intercurrences of the use of these drugs.

3 Conclusion

Therapy with ARD is a complex phenomenon that requires individualization of drug protocols, since it can trigger osteonecrosis – a severe adverse condition and difficult to manage. Its indication entails a multidisciplinary approach with maximum attention to the assisted patients, aiming to find a balance between drug toxicity and efficacy.

Lack of more robust clinical investigations, the insufficient number of patients and the heterogeneity of scientific productions make it difficult to implement guidelines supported in high evidence for the management and control of complications resulting from this therapy. However, it is worth stating that the adoption of dental care strategies prior to treatment, as well as the follow-up of the individual during therapy are fundamental approaches to minimizing any complications of maxillary bones.

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