ISOTRETINOIN: POSSIBLE INTERFERENCE IN POSTEXTRACTION HEALING

ISOTRETINOINA: POSSÍVEL INTERFERÊNCIA NA CICATRIZAÇÃO PÓS-EXODONTIA

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Resumo

A farmacovigilância é definida como "a ciência e atividades relativas à identificação, avaliação, compreensão e prevenção de efeitos adversos ou quaisquer problemas relacionados ao uso de medicamentos". Todos os medicamentos têm tanto o potencial de causar danos quanto o de trazer benefícios. O ácido 13-cis-Retinoico ou isotretinoína é um retinoide antiacne de referência no tratamento de doenças dermatológicas não responsivas a terapias convencionais, como a acne cística severa. Os efeitos adversos descritos na bula do medicamento implicam alterações em vários sistemas do corpo humano. Aqueles relacionados ao tecido ósseo, como a calcificação dos ligamentos e tendões, a redução na densidade óssea, o fechamento epifisário e hipercalcemia, possuem maior relevância na odontologia, levantando a hipótese para possível interferência na cicatrização dos alvéolos, após exodontia. Este artigo teve por objetivo realizar uma revisão de literatura reunindo informações sobre a possibilidade de interferência da isotretinoína em cirurgias maxilofaciais. Apesar da escassez de dados científicos conclusivos sobre a interferência da isotretinoína na cicatrização alveolar em humanos, estudos recentes sobre as vias de sinalização dos retinoides abrem novas perspectivas de pesquisa na influência dos retinoides no tecido ósseo alveolar. Esta possibilidade reforça a importância de uma atualização sobre os efeitos adversos da isotretinoína, bem como da anamnese criteriosa em pacientes com histórico de acne severa a fim de evitar complicações.

Palavras-chave: Antiacne. Ácido 13-cis-Retinoico. Isotretinoína. Acne vulgar. Efeitos adversos. Cicatrização. Cirurgia maxilofacial.

Abstract

Pharmacovigilance is defined as "the science and activities related to identification, evaluation, understanding and prevention of adverse effects or problems related to the use of drugs". All drugs have both the potential to cause harm and benefit. 13-cis-Retinoic acid or isotretinoin is a reference anti-acne retinoid in the dermatological diseases treatment not responsive to conventional therapies, such as severe cystic acne. The drug-related side effects described in the medicine package insert imply changes in various human body systems. Those related to bone tissue, such as ligaments and tendons calcification, bone density reduction, epiphyseal closure and hypercalcemia, have great relevance for dentistry, raising the hypothesis of a possible interference in alveoli wound healing after extraction. This article aimed to conduct a literature review in gathering information about the possibility of isotretinoin interference in maxillofacial surgeries. In despite of the scarcity of conclusive scientific data about the influence of isotretinoin on human alveolar wound healing, recent studies on retinoid signaling pathways open new research perspectives for the isotretinoin interference on alveolar bone tissue. This possibility reinforces the importance of an isotretinoin drug-related side effects update, as well as a patients' careful anamnesis with historical severe acne, in order to avoid complications.

Keywords: *Anti-acne. 13-cis-Retinoic Acid. Isotretinoin. Acne vulgaris. Drug-related side effects. Wound Healing. Maxillofacial Surgery.*

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INTRODUCTION

Vitamin A (*all-trans* retinol) and its metabolic derivatives are important regulators of the cell cycle, influencing the proliferation, apoptosis and differentiation of several cell types, through the activation of nuclear receptors and subsequent action on the DNA molecule or pathway genomics (classical); as well as by the direct activation of cytoplasmic factors in a mechanism independent of gene activation (non-classical) (1-4). Molecular changes in retinol produced compounds with better safety margins. The first generation of retinoids preserves the β-ionone ring of vitamin A in its structure and includes isotretinoin (13-*cis*-*RetinoicAcid* [RA]), tretinoin (*all-trans*-RA) and alitretinoin (9-*cis*-RA). The second generation of retinoids, or aromatic retinoids, was synthesized by altering the terminal cyclic group and includes acitretin. The third generation of retinoids, or arotinoids, includes tazarotene and baxarotene (5,6).

Isotretinoin was registered in Brazil by Hoffman-La Roche in 1982 under the trade name Roacutan®(7). It is prescribed for the treatment of a variety of dermatological conditions, such as severe acne, abnormal skin scarring, keloid or hypertrophic scarring and in cases of acne resistant to systemic antibiotics and topical agents (8). This treatment is more common among adolescents and young adults, a period in which active bone mineralization reaches maximized lifetime reserves. Therefore, any change in bone mineral acquisition or storage at that time becomes permanent (9,10). Considering that during adolescence it is common to seek dental treatments that involve bone remodeling, such as orthodontics and extraction of premolars, third molars and orthognathics, the use of anti-acne medication could influence the execution of these procedures.

The literature points to relationships between the use of retinoids and the activation/inhibition of osteogenic cells. Studies have shown that the recommended daily dose of 7.5 mg/kg/day for the treatment of cystic acne in humans has accelerated the alveolar repair of *Wistar* rats after extraction, as well as the repair in rodent skullcaps (10, 11); however, its overdose is related to bone resorption (10).

The purpose of this study was to conduct a literature review on the mechanisms of action and adverse effects of isotretinoin in humans to point to a possible interference in alveolar bone healing after extraction.

LITERATURE REVIEW

A bibliographic search was performed in the Medline, Lilacs, SciELO and PubMed databases. Articles published between 1990 and 2019 in English and Portuguese that had an abstract available were selected. The keywords used were "Isotretinoína" and/or "ácido retinoico" and/or "reações adversas" and/or "Remodelação óssea" and/or "extração" and their English language equivalents "*Isotretinoin" and/or "retinoic acid" and/or* "RAM" *and/or "Bone remodeling" and/or "extration"*. The information contained in the package insert of the drug sold in Brazil was also used in this study.

The retinoids

Retinoids are natural and synthetic compounds with the functional properties of vitamin A (12) (Figure 1). Retinoic acid (*all-trans-4-hydroxy Retinoic Acid*) regulates the vitamin functions required for growth and development. Consequently, several cells respond to retinoic acid (RA), such as those involved in embryonic development and the cells of the skeletal and immune system. The multiplicity of responses to AR has a positive aspect from a therapeutic point of view, such as the therapeutic use of retinoids for the treatment of a variety of dermatological conditions, but they also have negative consequences for their use, such as "retinoic acid embryopathy", characterized by severe damage to the fetus (teratogenic action), which include: craniofacial anomalies; damage to the central nervous system; changes in the cardiovascular system; and liver and thymic lesions. As a craniofacial anomaly, the formation of cleft palate and defects of the ear that present as microtia and low implantation of the ear auricle are described. Damage to the central nervous system includes microcephaly, hydrocephalus, mental retardation, among others. Common damage to the cardiovascular system often includes the transposition of large vessels, tetralogy of Fallot, ventricular septal defects, and aortic arch defects. Mental retardation can appear even in the absence of other malformations (6,8).

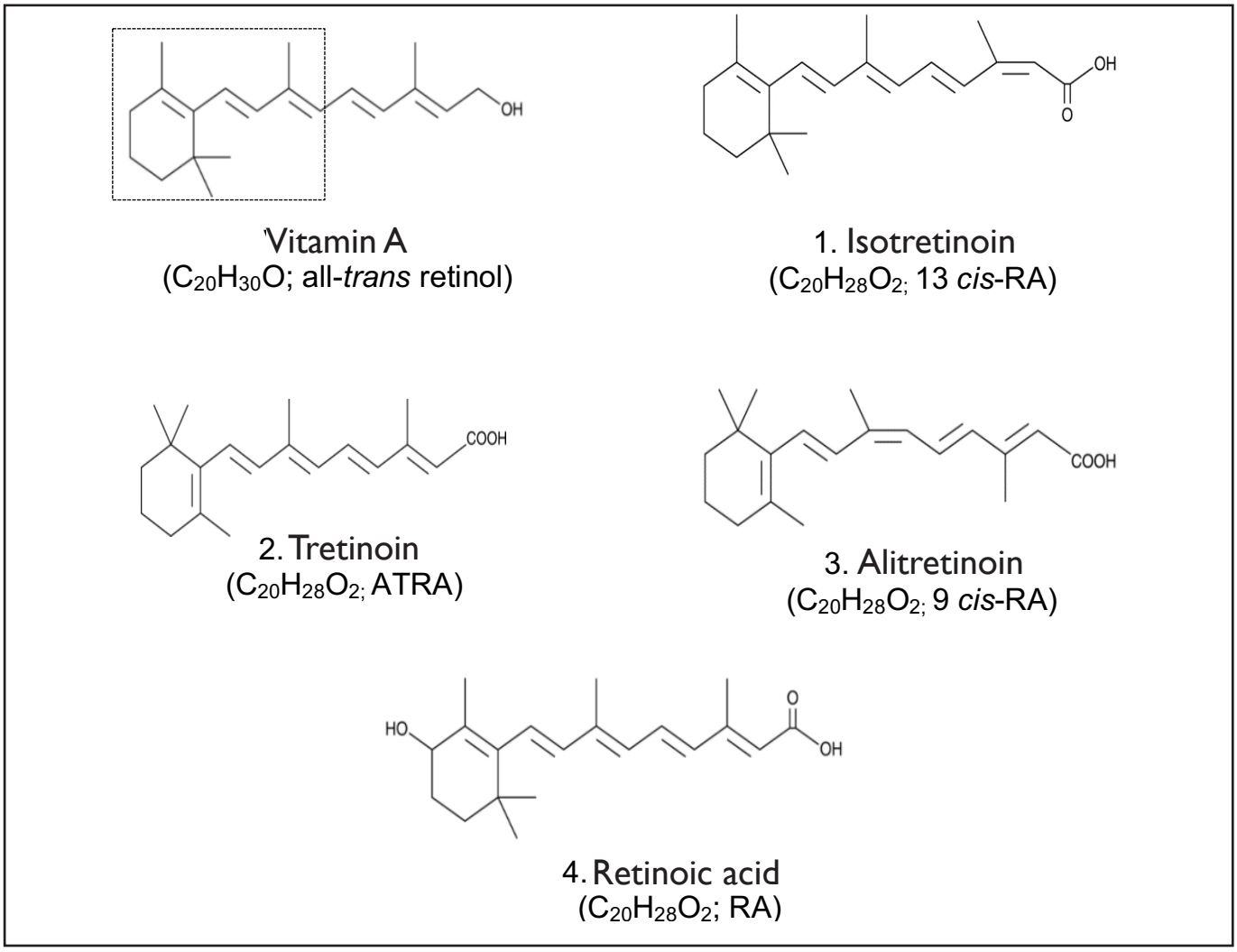

Figure 1 - **Structural formula of vitamin A and 1st generation retinoids.**
As highlighted above, the β-ionone ring of the structural formula of Vitamin A (*all-trans* retinol) is preserved in 1st generation retinoids. Abbreviations: ATRA (*all-trans*-retinoic acid), 13 *cis*-RA (13-*cis* -retinoic acid), 9 *cis*-RA (9-*cis*-retinoic acid), RA (*all-trans*-4-hydroxyretinoic acid) (12).

Mechanism of action of retinoids

The biological effects exerted by retinoids result from genomic action (classical) and by the activation of cytoplasmic proteins (non--classical).

Classic pathway

Two families of nuclear retinoid receptors stand out in the classical pathway and are formed by six well-defined regions, called A-F, and intermediate regions ("hinges"): RAR (*Retinoic Acid Receptors*) and RXR (*Retinoid X Receptors*). Both families of receptors consist of three Isotypes, α, β and γ, encoded by distinct genes and resulting from post-transcriptional processing (RNA *splicing*), therefore contributing to the diversification of responses in different cells (13).

RAR and RXR are transcription factors activated by ligands and, therefore, present in their structures: a) binding domain for lipophilic molecules or ligands (LBD: *Ligand-Binding Domain*); b) highly conserved regions of interaction with the DNA molecule (DBD; *DNA Binding Domain*) called "*zinc fingers*"; c) complex of protein factors regulating RNA polymerase activity, including cofactors (basal transcription factors) and other associated factors (general transcription factors). RXRs belong to the superfamily of steroid, thyroid, vitamin D and nuclear receptor hormones, including RAR, PPAR (*Peroxisome Proliferator-Activated*

Receptor), LXR (*Liver X Receptor*) for cholesterol metabolites, bile acid receptor (FXR: Farnesoid X Receptor) and the receptor directly related to the metabolism of xenobiotics and steroid hormones (PXR: *Pregnane X Receptor*) (13). RXRs are regulatory cofactors for RAR and, therefore, are necessary for the efficient interaction of the latter with responsive elements in the DNA molecule (RARE: *Retinoic Acid Response Elements*). Thus, the RXR-RAR heterodimer formed is translocated from the cytoplasm to the nucleus where it will bind in the promoter region of the DNA molecule, through the "zinc fingers" domains present in the receptors/transcription factors (1,6,13). The interaction of the ligand (L) at the retinoic receptor will induce a conformational change in the RAR (Helix12) allowing for the formation of the RAR•RXR heterodimer and the interaction with transcriptional proteins. In the absence of ligands, the RAR•RXR heterodimer binds to co-repressor proteins that result in chromatin condensation and inaccessibility to DNA. The interaction of retinoids leads to the dissociation of co-repressor proteins and subsequent binding of cofactors (6).

RXRs are regulatory cofactors necessary for the efficient binding of RAR to DNA sequences (RARE), located within the promoter region of DNA. RXR forms heterodimers with many other nuclear receptors (1,13). RARs have binding sites for two natural RA stereoisomers (Figure1), ATRA and 9-*cis* RA, while RXRs are activated exclusively by 9-*cis* RA (Figure 2) (14,15). Heyman et al. described that 9-*cis* RA is a product of ATRA metabolism, 40 times more potent than ATRA on RXRα (14). Regarding the ability to activate RARα, 9-*cis* RA is equipotent to ATRA (14). Regarding isotretinoin (13-*cis*-RA), the target of this study, it is known to have little to no affinity for RAR and RXR receptors. However, isotretinoin is converted inside the cells (prodrug) into five biologically active metabolites on RAR and RXR: 13-*cis*-4-*oxo*-retinoic acid (4-*oxo*-isotretinoin), ATRA, *all-trans*-4-oxo-acid retinoic (4-*oxo*-tretinoin), 9-*cis*-retinoic acid and 9-*cis*-4-*oxo*-retinoicacid (16).

Non-classical pathway

Retinoids are able to perform functions by other signaling pathways in addition to the formation of the RAR•RXR complex. For example, RA modulates PKC activity by a direct action on the enzyme's C2 domain (3). Hoyos et al. demonstrated that vitamin A and retinoids bind to the cysteine-rich region of the regulatory domain (C2 domain) of various PKC isoforms, including α, δ, ζ and μ, and the consequent PKC-dependent activation of the CREB transcription, which controls cell proliferation, survival and cell cycle in many cell types, including vascular smooth muscle cells (3).

An important biological activity attributed to all-trans retinoic acid (ATRA) is its ability to induce differentiation in cells of promyelocytic leukemia acute (LPA) (17). Lal et al. demonstrated rapid phosphorylation of the ribosomal protein S6 kinase beta-1 (p70S6 kinase) during treatment of the cell line NB4 (LPA), induced by ATRA. The authors demonstrated that ATRA induced the phosphorylation of ribosomal protein S6 in Ser235/236 and Ser240/244,

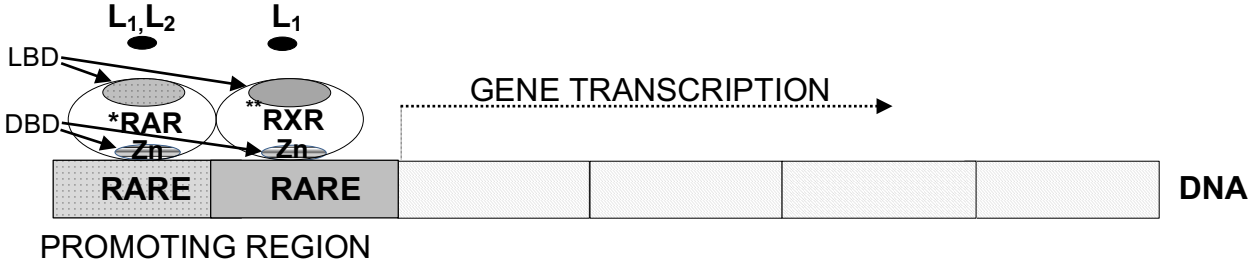

Figure 2 - **Illustrative model for genomic action of retinoids (Classical pathway).**
L: Ligands (L_1: ATRA; L_2: 9-*cis* RA). LBD: Binding domain for lipophilic ligands. DBD: Binding Domain of type "zinc fingers" for DNA. Zn: Binding region of the DNA molecule recognized as "zinc fingers". RARE: Elements responsive to retinoids in the DNA molecule. RAR and RXR represent the isotypes of nuclear retinoid receptors: (*) RARα, RARβ, RARγ; (**) RXRα, RXRβ, RXRγ. DNA: deoxyribonucleic acid.

suggesting that the activation of p70S6 kinase plays an important role in the generation of signals necessary for the translation of messenger RNA (17). Phosphorylation of p70S6k by the retinoid triggers protein synthesis. Other studies have demonstrated the action of retinoids on the AMPc-PKA signaling pathway. ATRA triggered a rapid increase in AMPc levels and PKA activity during ATRA-induced cell maturation of NB4 cells. These findings open the way for new therapies to fight cancer (18).

The action of retinoids on a family of cytoplasmic proteins brings to light effects resulting from the signaling pathway by tyrosine kinases because of its non-genomic pathway. Cellular retinoic acid binding proteins <(*CRABPs*) are proteins present in mammals with high affinity for binding to retinoids. This family of cytoplasmic proteins has two members, CRABP1 and CRABP2, both highly conserved during evolution (19). Although the function of CRABPs continues to be the subject of debate, binding to CRABP1 is believed to facilitate the metabolism of retinoids, thus modulating the concentration and type of metabolites produced in cells. In cells responsive to retinoids, such as those involved in embryonic development, CRABP1 could act in two ways: 1) by mediating the retinoid catabolism by the cytochrome P450 system (CYP450), thus reducing its toxicity on embryonic cells. Retinoic acid bound to CRABP1 is suggested to be a better substrate for CYP450 (Phase II metabolism) compared to the free form; 2) as a cytoplasmic protein for activating the ERK signaling pathway, which in turn would control p27, a protein that mediates the interruption of the cell cycle by blocking the transition from G1 to S (19).

Isotretinoin (*13-cis-RA*)

Since isotretinoin (13-*cis*-RA) was introduced in Brazil by Hoffmann–La Roche in 1982, it became a reference in the treatment of severe recalcitrant acne. The excessive production of *sebum* and pro-inflammatory mediators alters the composition of *sebum* (*acne sebum*) and constitutes the main components in the pathogenesis of acne. Of all the anti-acne drugs on the market, isotretinoin has a strong sebum suppressive effect, capable of leading to apoptosis of sebocytes, epithelial cells that form sebaceous glands (20,21). Nelson et al. demonstrated that TNF protein related to ligand-induced apoptosis (TRAIL) and lipocalin associated with neutrophilic gelatinase (NGAL) contribute to the pro-apoptotic effect of isotretinoin in human sebocytes (22). In 2016, Kelhälä et al. described the increased expression of TRAIL and NGAL proteins in the skin of patients with acne and treated with isotretinoin (23).

All drugs have the potential to cause damage and bring benefits. Regarding isotretinoin, teratogenic action is the most relevant risk, but there are reports of depression, suicide, intestinal inflammation, increased lipid and transaminase levels and influences on the skeletal system, such as thickening of the cortical bone, hyperostosis, premature bone fusion, osteoporosis and thinning of long bones (21,10). Therefore, isotretinoin is a medication whose prescription must be accompanied by: a "Special Control Prescription" for systemic retinoids; an "Informed Consent Form", emphasizing the need for contraception and pregnancy prevention; in addition to information on pregnancy prevention, transmitted to patients in oral and written form (7, 24).

INTERFERENCE OF RETINOIDS IN BONE HEALING

Post extraction healing

Post extraction healing follows tissue damage and is a physiologically important process for restoring tissue integrity after trauma (25). Healing comprises three stages: inflammatory, fibroblastic and remodeling. Skin wounds are classified into two types of healing: first intention and second intention. Healing by first intention translates into a wound with close opposite margins. Healing by second intention occurs when there is great loss of cells and tissues, leaving the margins separated. This repair process is more complicated, as the regeneration of parenchymal cells cannot fully restore the original architecture.

According to Hupp, alveolar healing usually occurs by second intention, with remodeling being established by tissue healing and bone repair (26). A tooth extraction triggers a

scar sequence in the mucosa (inflammation, epithelialization, fibroplasty and remodeling) and bone tissue. In the case of bone healing, osteoblasts and osteoclasts are recruited to repair the damaged tissue to remodel the bone.

When a tooth is removed, the alveolus fills with blood which, after coagulation, seals the alveolus (25,26). Inflammation starts right after extraction, when the leukocytes enter the alveolus, removing bacteria and other debris. The epithelium migrates into the alveolus through its wall until it finds the epithelium on the other side of the alveolus or the bed of granulation tissue (tissue filled with numerous immature capillaries and fibroblasts) under the blood clot. Degranulated platelets and inflammatory cells release prostaglandins and other cytokines, which activate osteoprogenitor cells in the periosteum, medullary cavity and surrounding soft tissue, stimulating the action of osteoblasts (27). Osteoclasts originate from mononucleated precursors stemming from the bone marrow (hematopoietic system) which, in contact with bone tissue, unite to form multinucleated osteoclasts. The activated osteoclasts measure the resorption of the bone crest and the necrotic bone. In the second week, there is a large amount of granulation tissue filling the socket. Osteoblasts then start the bone formation process by secreting osteoid (organic portion of non-mineralized matrix of bone tissue) and various proteins (26). These proteins include type I collagen and non-collagen proteins. Type I collagen forms the framework of the matrix, responsible for 90% of the organic component's weight. Osteoblasts deposit collagen both in a random wave, known as woven bone (immature, or *woven bone*), and in an ordered form of lamellar bone layers. These non-collagen proteins bind to the matrix and are grouped according to their function (adhesion proteins, calcium-binding proteins, mineralization proteins, cytokines and growth factors). Bone proliferation, maturation and cellular metabolism are regulated by cytokines and growth factors (27). When the osteoid becomes mineralized, it and the surrounding bone cells develop into new, more organized bone tissue; this process is completed in approximately 3-6 months (26). During the following four weeks, the socket is filled with granulation tissue as well as simultaneous deposition of the non-mineralized bone matrix. Only between the sixth and eighth weeks does bone formation become radiographically evident. About four to six months after extraction, the cortical bone that lines the alveolus is completely reabsorbed to be replaced by trabecular bone (26). The newly formed bone fills the socket until the epithelium is at the same level as the gingiva of the adjacent bone crest (25).

While the mucosa heals by repair, the bone is one of the few tissues that heals by regeneration and therefore heals without leaving marks (scar) and with properties similar to those before the injury. The process takes months until the bone scar can no longer be distinguished from the bone surrounding the wound (26). The preservation of alveolar bone volume after extraction facilitates the subsequent placement of dental implants, removable or fixed prostheses, leading to a better aesthetic and functional result (25).

Healing after extraction, therefore, is a dynamic process that involves many variables, such as age (the older the individual, the slower the repair process); nutritional status (malnourished individuals have difficulty forming a scar due to the absence of proteins, metals and vitamins important for collagen synthesis); immune status (impaired immunity prolongs the inflammatory phase and predisposes infections to occur); local oxygenation (in the event of anoxia, inflammatory cells have difficulty reaching the injured area, making fibroblast proliferation and collagen synthesis difficult); tension in the wound (vomiting, coughing and excessive physical activity produce tension and interfere with wound healing); hemorrhage (the accumulation of blood creates dead spaces that interfere with healing); and, mainly, the use of medications, especially steroids, which can delay healing (28,29).

There are no records yet that point to an action of retinoids on the cells responsible for post-tooth healing (BMU or BRC) in humans. Bergoli studied the effect of isotretinoin on alveolar repair after maxillary incisor extraction in Wistar rats (10). Daily doses of isotretinoin equivalent to that used to treat cystic acne in humans resulted in accelerated alveolar healing.

Retinoids for bone healing

Bone healing is a complex process in which bone tissue responds to its surroundings.The set of cells responsible for this process is collectively called Basic Multicellular Units (BMU) and comprises a group of cells of osteoclastic (pre-osteoclasts and osteoclasts) and osteoblastic lineage (pre-osteoblasts, osteoblasts, osteocytes and cells coating) (30). Hauge et al. were the pioneers in demonstrating that the BMU's constituent cells are not in direct contact with the connective tissue, but gathered in a closed space and separated from the outside by a set of cells that form in the dome (usually known as canopy) and that constitute the external limit of a specialized structure, named "Bone Remodeling Compartment" (BRC) (31).

Despite the fact that the nuclear retinoid receptors, RAR and RXR, are expressed as osteoclasts and osteoblasts, the actions exerted by retinol in bone mineralization are still conflicting, since in the few articles dealing with the theme, there was no standardization of the models used, the concentrations used and, much less, of the cell lines used (32).

DiGiovana et al. studied the effects of isotretinoin on bone mineral density in patients with severe, recalcitrant nodular acne. The authors reported cases of ossification similar to that seen in Diffuse Idiopathic Skeletal Hyperostosis, DISH), premature closure of epiphyses and periosteal thinning, hypercalcemia and osteoporosis as adverse reactions to the use of isotretinoin (33). Another group demonstrated the increased risk of fractures triggered by isotretinoin as a consequence of the increase in the formation of osteoclasts, responsible for bone resorption and, therefore, for the decrease in cortical bone mass (34).

Rohde et al. demonstrated that vitamin A antagonizes the action of vitamin D in rats (35). The authors suggest the possibility of a physiological antagonism at the molecular level, as both vitamins bind to the RXR receptor, but they do not rule out the interference of vitamin A on the absorption, transport and conversion of vitamin D into its active form or by stimulation of metabolic degradation high doses of vitamin A compromised the action of vitamin D, impairing the ability to maintain normal serum calcium levels, stimulating the formation of osteoclasts and suppressing osteoblastic action (35).

DISCUSSION

For many people who suffer from severe acne, over the counter drug treatments are not effective. Medicinal acne treatment follows a strict international standard to ensure that dermatologists and doctors are consistent in their treatment. Regarding isotretinoin, there are precautions and restrictions on use, especially with regard to pregnancy and lactation. All exposed fetuses can potentially be affected. ANVISA highlights the importance of transmitting information to patients and verifying the strict adherence to contraceptive measures during substance use (24). In addition to the teratogenic action, there are reports of depression, suicide, intestinal inflammation, increased lipid and transaminase levels and musculoskeletal disorders (7).

DiGiovana et al. described bone changes attributed to isotretinoin, such as early closure of epiphyses, hyperostosis, calcifications of tendons and ligaments that persist after continuing using of the drug. He adds that these occurrences manifested after several years of the administration of high doses, indicated for the treatment of keratinization disorders. The daily dose is cumulative and the duration of treatment for these patients generally exceeds that recommended for the treatment of acne (33). Recently, Miziołek et al. demonstrated a greater predisposition to bone loss in patients who used isotretinoin and who presented low bone mineral density values before starting treatment (34). In contrast, Oliveira demonstrated greater bone neoformation in *Wistar* rats (11). Despite using rodents, the author used doses of isotretinoin common for the dermatological treatment of cystic acne in humans in the rat experiments. Hypocalcemia has also been described, similarly to what occurs in hyperostosis.

The beneficial effects of drugs are assessed during the clinical and commercial phases. Pharmacovigilance basically consists of activities for reporting and recording adverse drug reactions (ADRs) verified during the clinical trials to which the drugs are subjected before their commercialization (36). ADR is defined as any unintended harmful or undesirable response to a

drug during the administration of typically used doses. ADR is characterized by the existence of a specific causal relationship between the drug and the occurrence; ADR is often cited as a synonym for adverse effect, which is a mistake. An adverse effect (AE) is defined as any harmful effect that occurs during or after the use of the medication, in which there is a reasonable possibility of a causal relationship between treatment and effect (37). Therefore, it is essential that during the anamnesis, the dental surgeon investigates the use of medication used momentarily by the patient, as well as those already used in the past.

During anamnesis, the dentist must identify patients who are treated with medications that may affect dental procedures. Take, for example, the bisphosphonates (BFs) indicated for the pharmacological treatment of osteoporosis in menopause. The use of BFs may be related to AE in women who completed their treatment 10 years ago, as "bisphosphonate-induced osteonecrosis" (BIO) is a complication in the maxillofacial complex. BIO occurs exclusively in the maxillary bones, with the mandible being the most affected (38,39). Considering the BIO seen in patients who completed treatment years ago; the warnings and precautions for the use of isotretinoin (7,24); and the influence of retinoids on bone tissue (6,8,9,20,21,33,34), this study raises the importance for the dentist to keep up to date on the adverse effects of isotretinoin. The importance of a careful anamnesis is also emphasized for the prevention of complications, especially in patients with a history of severe acne.

The absence of scientific articles on the interference of isotretinoin in alveolar healing, mainly in humans, was a limitation of this study. Despite the scarcity of conclusive scientific data, this article was a pioneer in associating the topic retinoids with post-extraction healing and to serve as an incentive to academic studies that can elucidate the mechanisms of action involved in the effects of retinoids on alveolar bone tissue.

CONCLUSION

During the post-extraction healing process, bone repair has as its protagonists osteoclasts, responsible for the resorption of necrotic bone and bone that needs to be remodeled, as well as osteoblasts, which deposit the matrix necessary for calcification. Some authors suggest an interference of isotretinoin in the mechanisms of bone remodeling after rodent extraction. Despite the lack of studies in humans, the results suggest a possible change in alveolar remodeling. Thus, it is imperative for the dental surgeon to know the risks of isotretinoin, not only in cases of dental extractions, but also in grafting, implants, fractures, orthognathic surgery, orthodontic movement and periodontal treatments. In addition, this paper evinces the importance of updating the topic addressed by the professional, as well as careful anamnesis in patients with a history of severe acne who use or have used isotretinoin, to prevent complications.

The authors declare no conflicts of interest

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