World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

Check for updates

Prevention and treatment of osteonecrosis of the jaws using Pentoxifylline and tocopherol: A case series of patients under antiresorptive or antiangiogenic agents inducing osteonecrosis of the jaws

Alfred SEBAN and Steven Perez *

Department of oral surgery, hospital foundation, Adolphe de Rothschild, Paris.

World Journal of Advanced Research and Reviews, 2023, 17(03), 927–936

Publication history: Received on 19 February 2023; revised on 27 March 2023; accepted on 30 March 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.17.3.0520

Abstract

Introduction: Medication-related osteonecrosis of a jaw can occur in patient taking antiresorptive medication mainly as Nitrogen-containing Bisphosphonates, longer and intravenous treatment by bisphosphonates and patient who received tyrosine kinase inhibitor. We report an evaluation of the association of Pentoxifylline-Tocopherol to reduce or to treat the side effects on jawbone of the antiresorptive medications.

Patients and methods: Six patients were selected two of them with intractable cases of MRONJ due to antiresorptive medication (Nitrogen-containing bisphosphonates and tyrosine kinase inhibitor) and four of them regarded as risky patients because taking Nitrogen-containing Bisphosphonates for at least two years and having to undergo jawbone surgery.

Results: following the prescription of pentoxifylline -tocopherol, to prevent the occurrence of an MRONJ or to protect the surgical procedure for surgical removal of necrotic exposed bone, at the last follow up no adverse effects were identified and clinical appreciation was confirmed by radiological examinations.

Conclusion: the association Pentoxifylline -Tocopherol has proven its efficacy in preventing or treating MRONJ bu. It was also critical to highlight the MRONJ risk in patients under monoclonal antibodies at the time of these molecules are rising, and to emphasize on the action of pentoxifylline-tocopherol in the management of the side effects of various monoclonal antibodies on the jaw bone

Keywords: Osteonecrosis; Antiresorptive; Necrotic; Bisphosphonates; Monoclonal antibodies; Pentoxifylline; Tocopherol

1. Introduction

Marx (1) described the first cases of osteonecrosis of the maxilla in 2003 linking this painful and debilitating clinical condition to an anti-resorptive therapy: bisphosphonates which are molecules indicated in the treatment of osteoporosis, Paget's bone disease and in some cases bone metastases or multiple myeloma. The frequent prescription of bisphosphonates, intravenous or oral forms in patients with metastasis cancer or severe osteoporotic patients with fracturing risk, has shown an increasing osteonecrosis case of the jaws. More recently other classes of agents, monoclonal antibodies, that have revolutionized the management of cancer or chronic inflammatory diseases are involved in osteonecrosis of the jaws (2;3). In addition, osteonecrosis of the jaw was observed in patients whose received tyrosine kinase inhibitor having anti-angiogenic activity; this adverse event is probably concomitant to the inhibition of the vascular endothelial growth factor (VEGF). This leads to an increase in the prevalence of osteonecrosis

* Corresponding author: Steven Perez

cases and the need to implement a treatment protocol to improve the living conditions of these patients. Osteonecrosis cases are no longer rare, and our only oral surgery department accepts one to two cases per month for risk evaluation and management of patients with medication -related osteonecrosis of the jaw (MRONJ).

Osteonecrosis of the jaw usually affects the mandible and more rarely the maxilla. This is clinically manifested by an exposure of a necrotic bone through the mucosa without natural healing during several weeks. As this bone disorder progresses Several clinical features and potential risk factors are associated as: Pain and oral swelling, tooth mobility, non-healing extraction socket, disease site infection (presence of enterococci, streptococci or assimilated bacteria and a low rate of actinomycosis) (4), oroantral fistula, encroachment on the mandibular canal associated with paresthesia or anesthesia, pathologic bone fracture. The Cone Beam Computer Tomography (CBCT) is the first line imaging for an early diagnosis of the disease and to evaluate the extent of the lesion (5): the periosteal reaction, sequestrum separation and the osteolytic radiolucency are fully detected as well as the necrotic bone surrounded by a resorptive circumference and cortical perforations. As a result of boundaries of conventional radiography such as being a two-dimensional modality and anatomical superimposition, the CBCT could be a good preliminary option along with clinical examination to avoid delay in accurate diagnosis and treatment planning as well as contributing to differential diagnostics with other pathological lesions (6,7). For some authors the enhance of the bone mineral density occurs commonly near necrotic lesions which justifies the use of CBCT to detect early osteonecrosis by tri dimensional analysis of the bone micro-architecture (8,9).

Despite the lack of studies evaluating the consequence of different molecular agents on the osteonecrosis of the jaw; it seems that the prevalence of MRONJ IS significantly higher with bisphosphonates.

Bisphosphonates are synthetic pyrophosphate, differentiating only by the presence of a central nonhydrolyzable carbon, part of molecules demonstrating their anti-resorptive effectiveness by inhibiting osteoclastic activity and are thus indicated in most bone pathologies which are generally characterized by an increase in bone resorption. First-generation bisphosphonates include etidronate, tiludronate, and clodronate; these lack a nitrogen side chain or hydroxyl group and do not have as strong bone specificity as the second-generation drugs (10,11).

The potency of bisphosphonate, for bone resorption inhibition leading to suppression of bone turnover, increases with the presence of an amine (amino bisphosphonates) radical found in the second and third generation of bisphosphonates such as: alendronate, pamidronate, ibandronate, risedronate, and zoledronate (12). Adverse side effects of bisphosphonates are associated with osteonecrosis of the jaw in patients with no history of radiation therapy in the cranio-facial area and bisphosphonate – related osteonecrosis of the jaw (BRONJ) defines in the literature this weakening condition of the jaws (13). Authors' estimates for potent bisphosphonates such as alendronate suggest a biological half-life of more than 10 years after a single intravenous dose (12, 14).

The current understanding of the mechanisms by which bisphosphonates exert their effects on osteoclasts is their interference with the internal enzymatic cell system of osteoclasts leading to cytoskeletal disruption with apoptosis of osteoclasts. Antiangiogenic effects of bisphosphonates have been documented by various groups that described a decrease in circulating levels of vascular endothelial growth factor (VEGF)Antiangiogenic (15) and Current knowledge shows that the progenitor cells of angiogenesis decrease the osteonecrosis risk of the maxilla (16) which shows a second side effect of bisphosphonates on neovascularization.

Emerging anti-resorptive and anti-angiogenic medications such as, Monoclonal antibodies, VEGF decoy receptors and tyrosine kinase inhibitors that block the VEGF receptors have a potential implication in the development of osteonecrosis of the jaw .

Currently interest grows in a Pento protocol to treat medication-related osteonecrosis of the jaw; it is a non-surgical treatment combining two molecules Pentoxifylline and tocopherol. Pentoxifylline primarily used to treat the symptoms of lower limb arteritis (disease of the leg arteries causing painful cramps in walking) and minor neurological disorders related to aging. This drug derived from Purine is used as an anti-tumor necrosis factor (TNF)-α effect, rising erythrocyte flexibility, vasodilates, preventing inflammatory reactions, avoiding human dermal fibroblast proliferation and extracellular matrix (ECM) production, and enhancing collagenase activity in vitro. Pentoxifylline and its metabolites improve blood flow by decreasing its viscosity (17). Tocopherol represents different components of Vitamin E, improves endothelial function by its potent scavenging action on free oxygen radicals which impact necrosis (18).

2. Case reports

Table 1 Patients with MRONJ treated by Pento

Case number	Sex	Age	Medical History	Treatment name and duration	Disease	Duration of PENTO protocol	Site	Type of surgery
1	F	56	OSTEOPOROSIS multiple history of fractures	Risedronate 3 years	APICAL CYST	4 MONTHS	MAXILLARY	EXTRACTION DEBRIDMENT
2	F	58	OSTEOPOROSIS Multiple history of fractures	Alendronate 2 years	Multiple Apical cyst	6 Months	Maxillary and mandibular	Extraction debridement implants
3	F	65	Osteoporosis and osteopenia	Risedronate 6 years	None	6 months	mandibular	Bone graft and implants
4	F	83	Osteoporosis Multiple history of fractures	Ibandronate Zolendronate Risedronate 4 years	Osteonecrosis of the jaw Bone sequestrums Open wound	6 months	mandibular	Bone sequestrum removal Sanitation Wound healing
5	F	78	Osteoporosis Multiple fractures history	Zoledronate 2 years	None	6 months	Maxillary and mandibular	Implant rehabilitation
6	F	68	Kidney cancer metastasis	Anti-angiogenesis tyrosine kinase (cabozantinib)	Osteonecrosis of the jaw and bone sequestrum	6 months	Mandibular	Bone sequestrum removal Sanitation Wound healing and bone regeneration

Prior to Pento processing: a patient (# 4) had a necrosis of the right posterior mandibular region with bone exposure close to a dental implant in place of the first bicuspid tooth which implant must be removed for rehabilitation of the right mandibular area. two patients (# 1 and # 2) have apical dental cysts and planned dental care are therefore at infectious risk with a risk of osteonecrosis related to taking Risedronate and Alendronate. two patients (# 3 and # 5) respectively on risedronate and zoledronate, for multiple history of fractures, wish an implant rehabilitation of edentulous areas. One patient (#6) presented a delayed post extraction healing with alveolar bone sequestration.

All bisphosphonates prescribed to the five patients have a nitrogen group and are called Nitrogen-containing bisphosphonates showing clinically an increased antiresorptive potency and affects binding to hydroxyapatite (20). The antiresorptive actions of each of the molecules is such that some of them have a completely reversible effect like alendronate and others a reversible minimal effect like pamidronate (21). Thus, complicating a dental implant rehabilitation decision that must be taken in a multidisciplinary way by assessing the risk of osteonecrosis of the jaw (ONJ) induced by each Nitrogen-containing bisphosphonate. Tyrosine kinase inhibitor (carbozantinib) prescribed to the sixth patient in this study reduces metastasis by targeting VEGF and is therefore able to disrupt bone remodeling after dental extraction leading as is the case exposed to osteonecrosis: unlike nitrogen-containing bisphosphonates all new emerging treatments such as monoclonal antibodies and anti VEGF ending the treatment removes the side effects.

3. Results

Summary of patients follow-up: they were six female patients ranged in age from 56 to 78 years. six female patients with an average age of 68 years. Five of them taking the most potent class of bisphosphonates (nitrogen-containing

bisphosphonates) and one of them taking a Tyrosine kinase inhibitor (carbozantinib) targeting VEGF and of which many adverse effects are reported especially on the upper and low jaw. Treatment duration of Pentoxifylline and tocopherol, to prevent or to treat side effects of MRONJ, ranged from 4 TO 6 months in beginning the treatment one month before any surgery. Two patients were classified as MRONJ and for patients were categorized at risk of MRONJ due to the time taken nitrogen-bisphosphonates. Sequestrum was removed in 2 patients (case 4 and 6) leaving a perfectly vascularized residual bone to appear after curettage and successful soft tissue closure of exposed bone was achieved; on CBCT assessment at six-months post-surgery there was evidence of new bone fill of radiolucent. In patient (case 4) a guided bone regeneration was realized allowing implant-supported fixed prostheses. The patient (case 6) did not wish, although it was possible, a dental implant therapy. In patient (case 1) Apicectomy was performed with a radiological image of bone healing at one year post surgery. In patient (case 2) extraction and cyst removed was done and complete vascularization of residual extraction socket was observed before a traditional suture of the wound edges; a successful dental implant therapy was accomplished after radiographic evaluation attesting no development of MRONJ.In patient (case 5 and 3) successively bone graft dental implant and dental implant for case 3 were made without any evidence of disruption of vascularization and without development of MRONJ in a long term follow-up. In all extraction socket a delayed healing was showed without any further consequences.

4. Discussion

Diagnosis of osteonecrosis of the jaw associated with bisphosphonate is often advanced when the bone is exposed most often after a dental extraction. Imaging can play a preventive role and, although there is no specific method related, imaging is fully involved in the early detection of bone lesions and their extent. Unlike panoramic radiography which gives inaccurate images, the CBCT provides, by its resolution, reconstruction software's and a low dosimetry accurate information of cortical and trabecular bone structures especially in the predilection zone of the posterior mandibular area where occurs most often osteonecrosis because the thickness of the cortical plate which is greater compared to other anatomical region of jaws. Mainly osteonecrosis appearing on CBCT imaging is characteristic of a densified bone with radiolucent edges testifying to bone sequestration (22). In severe cases CBCT imaging observation shows large lytic and sclerotic bone surfaces affecting basal bone, including sequestrum, cortical perforation, pathologic fractures. In addition, the CBCT revealed a major advantage over conventional radiological techniques in quantifying the boundary of necrosis (fig 1;fig 2).

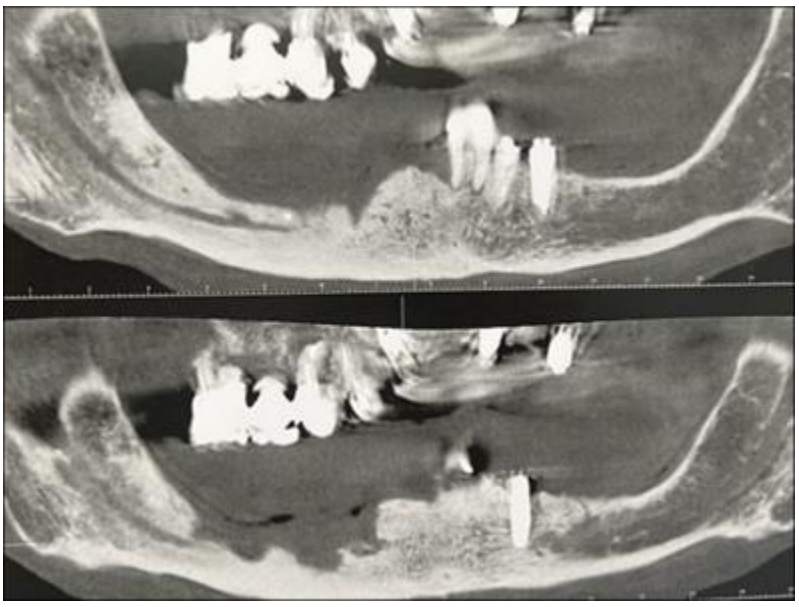

Figure 1 CBCT panoramic reconstruction showing the extensive bone necrosis of posterior and lateral right mandibular region with encroachment of the mandibular canal and perforation of the cortical bone plate

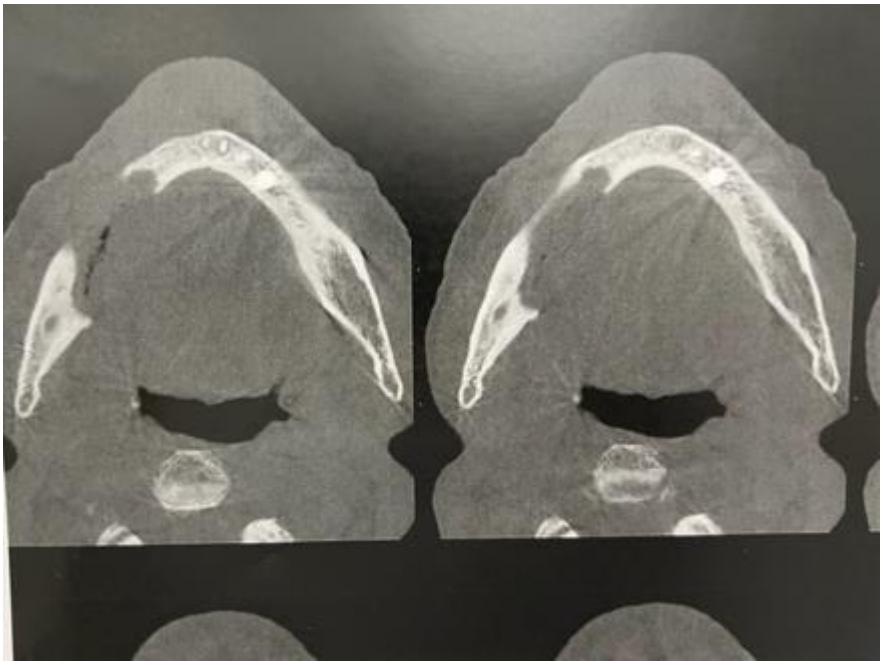

Figure 2 CBCT axial reconstruction showing the lytic bone destruction of lingual bone plate

One of the aims of this article is to solve the management of patients with medication related osteonecrosis of the jaw when a dento-alveolar surgery procedure is envisaged, and this management is currently Based on two facts:

- No standard treatment protocol is described
- Recommendation for minimally invasive treatment is preferred by all authors (24).

Hyperbaric treatment has been considered as an adjuvant therapy inducing stem cell mobilization, vasculogenic, mitochondrial biosynthesis (23); clinical results show that this complementary treatment is effective when bisphosphonates are discontinued (25).

The use of Platelet Rich in Plasma has been proposed either to prevent an undesirable event of MRONJ before dental extraction (26) or after debridement and curettage on a osteonecrosis site (27). Referring to the properties of the PRP (28) which is the product of platelet activation by centrifugation, and which releases various molecules including growth factors which activate cell differentiation and stimulate the healing process; the PRP will limit the recurrence of an MRONJ and will also function as an anti-inflammatory and antimicrobial agent (29).

Patients at risk of osteonecrosis of the jaw or with osteonecrosis has often treated by antibiotic prophylaxis or antibiotic therapy such as amoxycillin/ clavulanic acid 3g per day for 10 days or in case of allergy with clindamycin 600MG per day for 10 days (prescription in our department of oral surgery) and this to cover any surgical procedure. Synergetic effect OF sanitation combined with the supply of antibiotics reduces the variety of bacteria found in MRONJ bacterial but antibiotics could not modify the low bone turns over associated with MROJN (30) .

Pentoxifylline and Tocopherol (PENTO protocol), is currently growing for MRONJ management with varying success rates, no guidelines are established for the medical prescription of Pento protocol, only the confirmation of the efficacy of the treatment and the few adverse effects are related by various authors (31;32). the aim of the PENTO protocol is to counter-act the effect of Antiresorptive and antiangiogenic drugs that cause tissue hypoxia, hypocellularity, hypo vascularity that were previously shown as implied in the development of MRONJ. In favoring the microcirculation and reducing local inflammation Pento protocol allowed us, after disruption of bisphosphonates or new emerging therapies associated with ONJ, to resolve some challenge as the placement of dental implants and guided bone regeneration for example with the following clinical case:

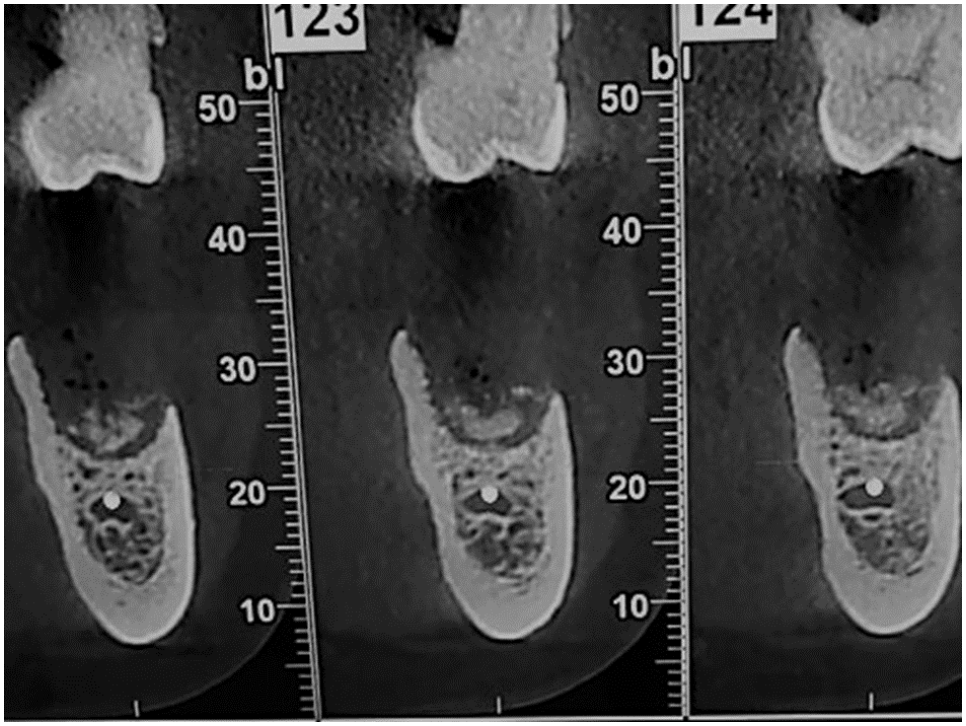

Figure 3 Patient on carbozantinib for 3 years: post-extractional alveolar ridge not healed at 4 months with sequestration of the alveolar bone

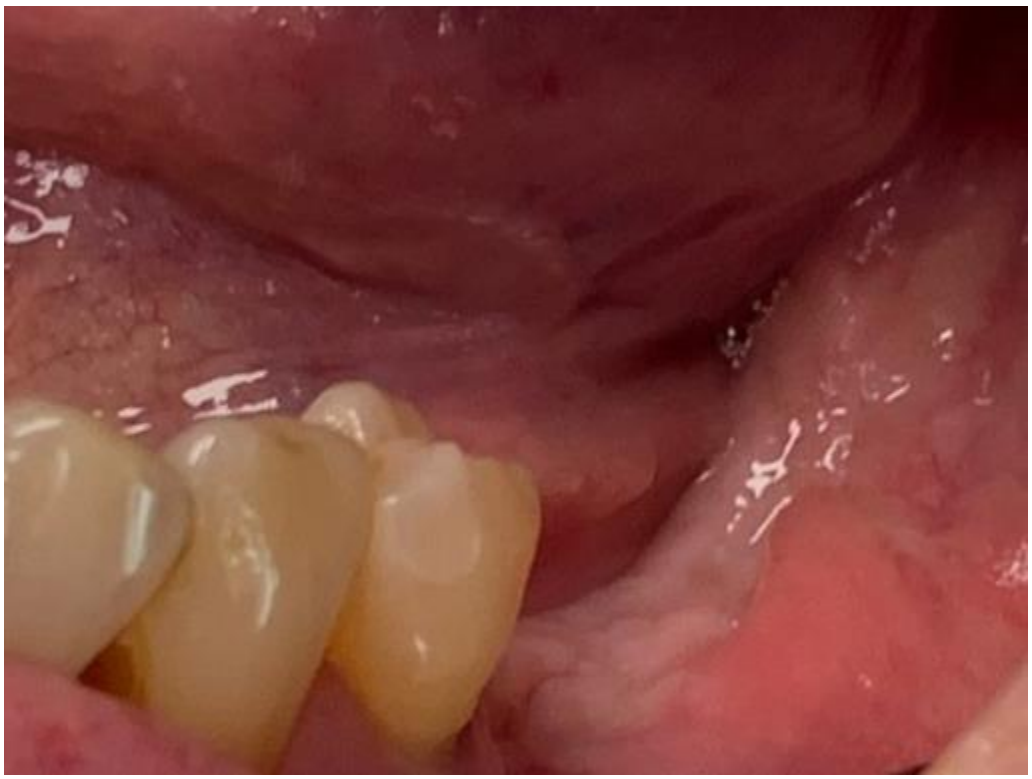

Figure 4 After one month of PENTO protocol and disruption of carbozantinib removal of the sequestrum, debridement and complete healing of the alveolar mucosa

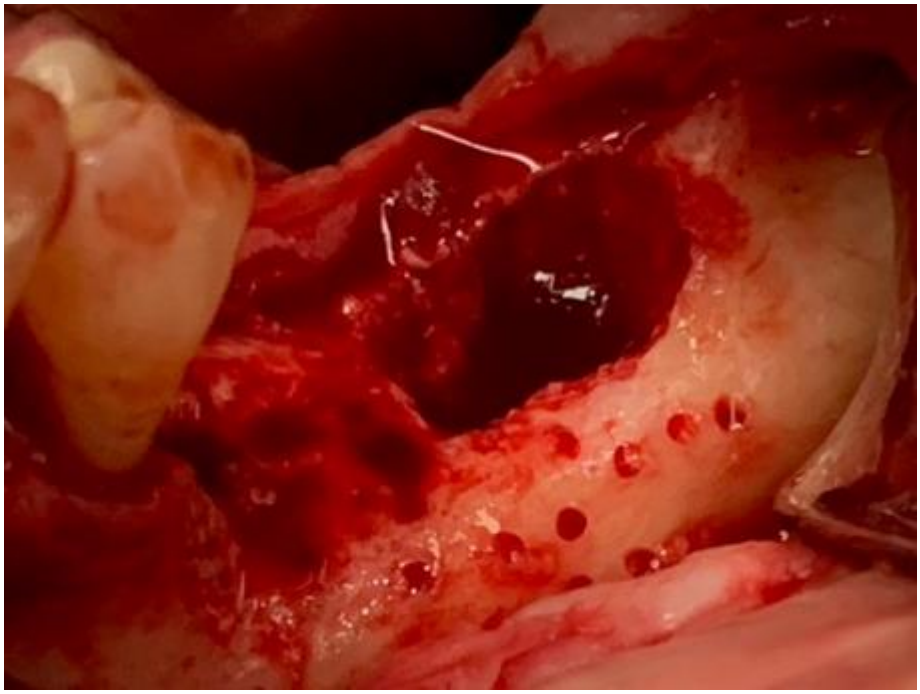

Figure 5 3 months after healing, bone decortication prior to guided bone regeneration under uninterrupted Pento protocol and disruption of carbozantinib

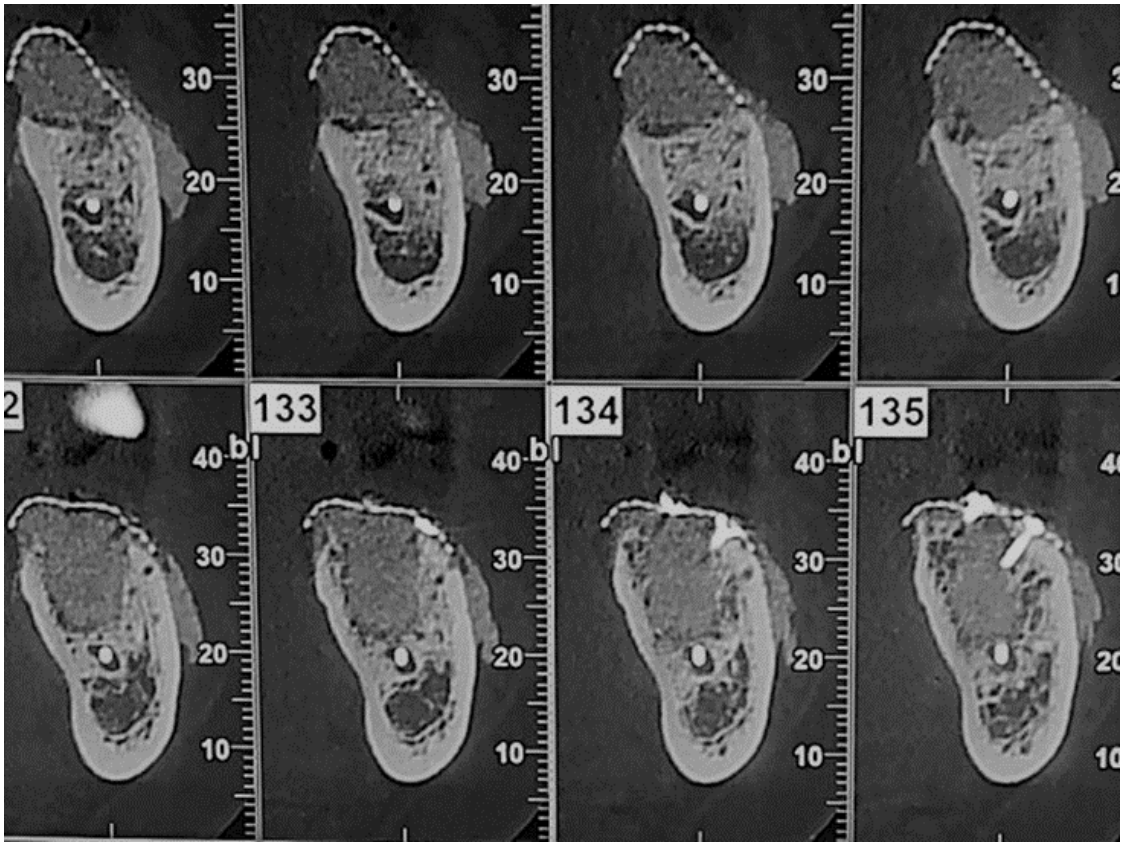

Figure 6 Guided bone regeneration with titanium mesh and allogenic bone particles

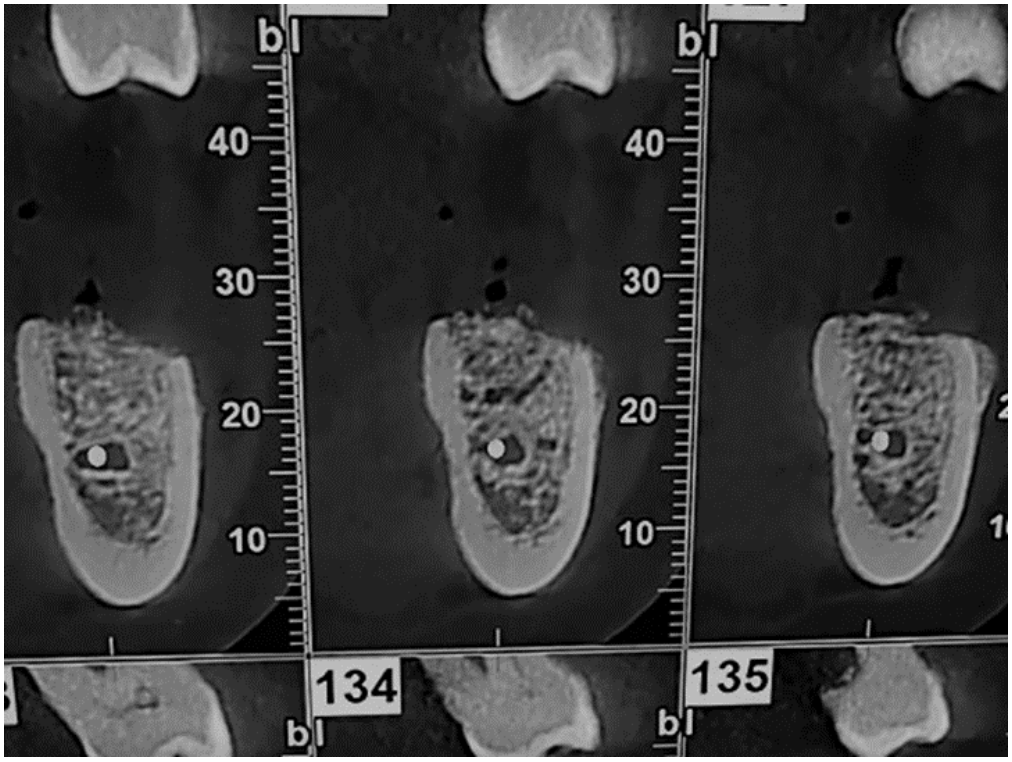

Figure 7 9 months after guided bone regeneration the formation of new bone appears to be similar in grafted and non-grafted site: the adjunctive Pento protocol allowing easier vascularization of the defect site

The above clinical case justifies the indication of Pento protocol as it is explained previously. Pento protocol has multiple actions (33) in, minimizing tissue damage, enhancing tissue survival, treating vasculo-occlusive disorders, contributing of healing of the oral-mucosa soft tissues (34) and in addition antioxidant and anti- inflammatory properties.

5. Conclusion

prevention and treatment of osteonecrosis of the maxilla have made a good forward in regard to the combined action of pentoxifylline and tocopherol However for safety issue, a broad spectrum knowledge of drugs is essential especially with patients taking bisphosphonate nitrogen who's pharmacokinetic is difficult to manage with Pento and a multidisciplinary opinion is necessary to minimize the risks.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Robert E Marx. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg.2003 Sep, 61(9):1115-7.

[2] Sivolella, S., Lumachi, F., Stellini, E., et al. Denosumab and Anti-Angiogenetic Drug Related Osteonecrosis of the Jaw: An Uncommon but Potentially Severe Disease. Anticancer Res 2013 May, 33(5):1793-7.

[3] Pakosch D, Papadimas D, Munding J, Kawa D, Kriwalsky MS. Osteonecrosis of the mandible due to anti-angiogenic agent, bevacizumab. Oral Maxillofac Surg 2013 Dec, 17(4):303-6

[4] Dissard A, P Dang N, Barthelemy I, Delbet C, Puechmaille M, Depeyre A, Pereira B, Martin F, Guillemin F, Biau J, Mirafzal S, Mom T, Gilain L, Saroul N . Efficacy of pentoxifylline-tocopherol-clodronate in mandibular osteoradionecrosis. Laryngoscope. 2020 Nov, 130(11):E559-E566.

[5] Walton K, Grogan TR, Eshaghzadeh E, Hadaya D, Elashoff DA, Aghaloo TL, Tetradis S Medication related osteonecrosis of the jaw in osteoporotic vs oncologic patients-quantifying radiographic appearance and relationship to clinical findings. Dentomaxillofac Radiol. 2019 Jan, 48(1):20180128.

[6] Kashtwari D, Ruprecht A, Katz J. Medication-related osteonecrosis of the jaw: Should cone-beam CT be considered as standard of care for diagnosis and treatment? J Oral Maxillofac Radiol 2020, 8:36-40

[7] Ogura I, Ono J, Okada Y. Use of cone-beam computed tomography for evaluation of surgical specimen of medication-related osteonecrosis of the jaw. J Oral Maxillofac Radiol 2018, 6:17-20

[8] Y. Takaishi, T. Ikeo, M. Nakajima, T. Miki, and T. Fujita, "A pilot case-control study on the alveolar bone density measurement in risk assessment for bisphosphonate-related osteonecrosis of the jaw," Osteoporosis International, vol. 21, no. 5, pp. 815–825, 2010

[9] André Ferreira Leite, Fernanda dos Santos Ogata, Nilce Santos de Melo, Paulo Tadeu de Souza Figueiredo, "Imaging Findings of Bisphosphonate-Related Osteonecrosis of the Jaws: A Critical Review of the Quantitative Studies", International Journal of Dentistry, vol. 2014, Article ID 784348, 11 pages, 2014.

[10] Kimmel DB. Mechanism of action, phatmacokineoc and pharmac:odynamic profile, and clinical applicanons of rutrogen-containing bisphosphonates.J Dent Res 2007, 86:1022-1033.

[11] Shannon J, Shannon J, Modelevsky S, Grippo AA. Bisphosphonates and osteonecrosis of the jaw. J Am Geriatr Soc. 2011 Dec, 59(12):2350-5

[12] Drake M, Clarke BL, Khosla S. Bisphosphonates: Mechanism of action and role in clinical practice. Mayo Clin Proc 2008, 83:1032-1045

[13] Cavalcante R C, Tomasetti G. Pentoxifylline and tocopherol protocol to treat medication-related osteonecrosis of the jaw: A systematic literature review. J Craniomaxillofac Surg. 2020 Nov, 48(11):1080-1086

[14] Khan SA, Kanis JA, Vasikaran S, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res. 1997, 12(10):1700–1707.

[15] Ruggiero, S. L. et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw–2014 update. J. Oral Maxillofac. Surg. Off. J. Am. Assoc. Oral Maxillofac. Surg. 72, 1938–1956 :2014

[16] Tamari, T., Elimelech, R., Cohen, G. et al. Endothelial Progenitor Cells inhibit jaw osteonecrosis in a rat model: A major adverse effect of bisphosphonate therapy. Sci Rep 9, 18896 (2019)

[17] Fan, H., Kim, S.M., Cho, Y.J. et al. New approach for the treatment of osteoradionecrosis with pentoxifylline and tocopherol. Biomater Res 18, 13 (2014). https://doi.org/10.1186/2055-7124-18-13

[18] On SW, Cho SW, Byun SH, Yang BE.Various Therapeutic Methods for the Treatment of Medication-Related Osteonecrosis of the Jaw (MRONJ) and Their Limitations: A Narrative Review on New Molecular and Cellular Therapeutic Approaches. Antioxidants (Basel). 2021 Apr 27, 10(5):680.

[19] Adepitan A Owosho , Cherry L Estilo , Joseph M Huryn , SaeHee K Yom. Pentoxifylline and tocopherol in the management of cancer patients with medication-related osteonecrosis of the jaw: an observational retrospective study of initial case series. Oral Surg Oral Med Oral Pathol Oral Radiol 2016 Oct, 122(4):455-9

[20] Twiss IM, van den Berk AH, de Kam ML, Bosch JJ, Cohen AF, Vermeij P, Burggraaf J. A comparison of the gastrointestinal effects of the nitrogen-containing bisphosphonates pamidronate, alendronate, and olpadronate in humans. J Clin Pharmacol. 2006 Apr, 46(4):483-7

[21] van Beek ER, Cohen LH, Leroy IM, Ebetino FH, Löwik CW, Papapoulos SE. Differentiating the mechanisms of antiresorptive action of nitrogen containing bisphosphonates. Bone. 2003 Nov, 33(5):805-11

[22] Olutayo J, Agbaje JO, Jacobs R, Verhaeghe V, Velde FV, Vinckier F. Bisphosphonate-Related Osteonecrosis of the Jaw Bone: Radiological Pattern and the Potential Role of CBCT in Early Diagnosis. J Oral Maxillofac Res 2010 Jul 1, 1(2)

[23] de Souza Tolentino E, de Castro TF, Michellon FC, Passoni ACC, Ortega LJA, Iwaki LCV, da Silva MC. Adjuvant therapies in the management of medication-related osteonecrosis of the jaws: Systematic review Head Neck 2019 Dec, 41(12):4209-4228.

[24] Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F, American Association of Oral and Maxillofacial Surgeons American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg. 2014 Oct, 72(10):1938-56.

[25] Freiberger JJ, Padilla-Burgos R, Chhoeu AH, Kraft KH, Boneta O, Moon RE, Piantadosi CA. Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. J Oral Maxillofac Surg 2007 Jul, 65(7):1321-7

[26] Toro LF, de Mello-Neto JM, Santos FFVD, Ferreira LC, Statkievicz C, Cintra LTÂ, Issa JPM, Dornelles RCM, de Almeida JM, Nagata MJH, Garcia VG, Theodoro LH, Casatti CA, Ervolino E. Application of Autologous Platelet-Rich Plasma on Tooth Extraction Site Prevents Occurence of Medication-Related Osteonecrosis of the Jaws in Rats. Sci Rep. 2019 Jan 10, 9(1):22

[27] C Sánchez-Gallego Albertos 1, J-L Del Castillo Pardo de Vera, A Viejo Llorente, J-L Cebrián Carretero. Medication related osteonecrosis of the jaws (MRONJ): Factors related to recurrence after treatment with surgery and platelet rich plasma (PRP) placement. Med Oral Patol Oral Cir Bucal 2021 Nov 1, 26(6):e684-690

[28] Voja Pavlovic 1, Milan Ciric 2, Vladimir Jovanovic 3, Predrag Stojanovic . Platelet Rich Plasma: a short overview of certain bioactive components. Open Med (Wars 2016 Aug 12, 11(1):242-247

[29] Fabbro M, D, Bortolin,M, Tachieri,S, Ceci,C, Weinstein,R,L. Antimicrobial properties of platelet-rich preparations. A systematic review of the current pre-clinical evidence. Platelets 2016 , 27(4):276-85.

[30] H Katsarelis , N P Shah , D K Dhariwal , M Pazianas. Infection and medication-related osteonecrosis of the jaw. J Dent Res 2015 Apr, 94(4):534-9

[31] Heifetz-Li JJ, et al. Systematic review of the use of pentoxifylline and tocopherol for the treatment of medication-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019

[32] N M H McLeod , C A Pratt, T K Mellor, P A Brennan. Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience. Br J Oral Maxillofac Surg 2012 Jan, 50(1):41-4

[33] Hayes DW Jr, Mandracchia VJ, Considine C, Webb GE. Pentoxifylline. Adjunctive therapy in the treatment of pedal frostbite. Clin Podiatr Med Surg. 2000 Oct, 17(4):715-22

[34] M W Dion , D H Hussey, J F Doornbos, A P Vigliotti, B C Wen, B Anderson. Preliminary results of a pilot study of pentoxifylline in the treatment of late radiation soft tissue necrosis. Int J Radiat Oncol Biol Phys 1990 Aug, 19(2):401-7.