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Pentoxifylline, Tocopherol and Clodronate Combination for the Treatment of Osteoradionecrosis of the Jaws: A Systematic Review

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Abstract

Purpose of the Study: The purpose of this systematic review was to evaluate the efficacy and the tolerance of the pentoxifylline-tocopherol and clodronate combination (Pentoclo) as a new medical treatment for osteoradionecrosis of the jaws.

Materials and Methods: The bibliographic research was carried out on the databases Medline Via pubmed, google scholar and Cochrane library interface by using the key words; osteoradionecrosis, pentoxifylline, tocopherol, clodronate, jaws, mandible.

Results: After filtering articles based on inclusion and exclusion criteria and removing duplicates, 13 articles were retained in our study: 2 systematic reviews, 3 non randomised uncontrolled clinical trials and 6 descriptive studies. The Pentoclo combination seems to be effective and safe for the management of osteoradionecrosis of the jaws.

Conclusion: This protocol is well tolerated and could be promising for the treatment of osteoradionecrosis of the jaws. The greatest rates of healing and clinical improvement were seen in mild and moderate stages of ORN. Nevertheless, randomised, controlled clinical trials are needed to substantiate and confirm these data.

Keywords: *Pentoxifylline; Tocopherol; Clodronate; Osteoradinecrosis*

Introduction

ORN of the jaws is a severe and complex complications of radiotherapy for head and neck cancers [1] it is defined as a field of exposed bone in an irradiated area that failed to heal within a period of 3 months, with no evidence of malignancies (recurrence, metastasis) [2].

The prevalence of ORN varies widely in the literature and ranges from 0.4% to 56% of patients treated with radiotherapy for head and neck cancers with a reported mean age of onset of 55 years old [3].

Ewing was the first to use the term 'radiation osteitis' to describe changes that occur in the bone after radiotherapy. Later, many terms were proposed to name these changes in the irradiated bone, such as radiation osteitis, ORN and avascular bone necrosis [3].

In 1983, Marx defined ORN as 'an area larger than 1 cm of exposed bone in a field of irradiation that failed to show any evidence of healing for at least 6 months' [4].

In 1987, Marx and Johnson suggested the definition of ORN as: 'The exposure of non-viable bone which fails to heal without intervention'. Epstein., *et al*. defined ORN as 'an ulceration or necrosis of the mucous membrane, with exposure of necrotic bone for more than 3 months' [5]. Later, in 1997, Wong., *et al*. defined ORN as: 'a slow-healing radiation-induced ischemic necrosis of variable extent occurring in the absence of local primary tumor necrosis, recurrence or metastatic disease' [6]. ORN is more frequent in the mandible than in the maxilla because of its relatively poor blood supply, which is exclusively provided by the inferior alveolar artery.

This complication is mainly caused by dental trauma such as tooth extraction, oral surgery, dentures, and local infection however, in some cases, the condition can be spontaneous [3,6]. The patient is considered at a risk of developing this condition many years after the completion of radiotherapy; however a peak between 6 months and 2 years was reported [2].

Many risk factors can be incriminated in the onset of ORN. Treatment dependent risk factors include the modalities of the radiotherapy, the delivered dose and volume as well as its fractionation. Other risk factors to be mentioned are, the surgical treatment including the number of the interventions and finally the concomitant chemotherapy. The most incriminated patient dependent risk factor reported in the literature are, age and co morbidities including diabetes and collagen vascular disease as well as poor oral hygiene and alcohol and tobacco consumption [6].

Tumor dependent risks include the size of the tumor and its proximity to bone [6]. Clinical symptoms of ORN include ulceration of the mucosa with exposure of necrotic bone and pain. In severe cases trismus and suppuration may be present and heavily impact on the patient's quality of life [7].

This condition occurs often after a tooth extraction, with a delayed cicatrisation of the socket [3]. Biopsy is mandatory for final diagnosis in order to exclude metastasis or recurrence [1].

Different staging and scoring systems of ORN have been proposed.

These systems are based either on the response to hyperbaric oxygen (HBO) therapy [4] or to the degree of bone damage, clinical-radiological findings, duration of bone exposure and the treatment required [8,9].

Marx proposed a three-stage system for ORN based on bone exposure and its response to HBO therapy (Table 1) [4] while Notani proposed a staging system based on the extent of ORN (Table 2) [8] and Epstein proposed a staging system based on clinical findings (Table 3) [9].

The exact pathogenesis of the ORN remains unknown. Marx was the first to introduce the 3H theory: Hypoxia, Hypovascularity and Hypocellularity of the irradiated bone leading to a chronic non-healing wound [4].

This theory was criticized and not fully supported by the results of many scientific researches [10]. Others theories immerged but none of them were fully sufficient to explain the onset of the ORN [11].

Stage	Description
Stage I	Exposed bone in a field of radiation that has failed to heal for at least 6 months and do not have a pathological fracture, cutaneous fistula or osteolysis to the inferior border. • All patients receive 30 sessions of HBO at 2.4 atmospheres absolute for 90 minutes at depth. • Patients who respond to HBO alone (Stage I responder) demonstrate a softening of the radiated tissues and spontaneous sequestration of exposed bone with formation of granulation tissue.
Stage II	Patients who do not respond to the 30 sessions of HBO. • This group is characterised by a large amount of non- viable bone • Consequently, careful surgical debridement is required in addition to transoral resection with limited soft-tissue reflection. 10 postsurgical sessions of HBO
Stage III	Patients having a large quantity of non-viable bone and/or soft tissue. • In addition to 30 presurgical HBO treatments, each Stage III patient requires a continuity resection, stabilisation and 10 postsurgical sessions of HBO, and are scheduled for later reconstruction. Stage III patients are therefore those who fail to respond to Stage I and Stage II treatment and those who initially present with a pathological fracture, cutaneous fistula or osteolysis to the inferior border

Table 1: *Marx staging of ORN [4].*

Grade	Description
Grade I	ORN confined to the alveolar bone.
Grade II	ORN limited to the alveolar bone and/or the mandible above the level of the mandibular alveolar canal.
Grade III	Extends to the mandible under the level of the mandibular alveolar canal and a skin fistula and/ or a pathological fracture is present.

Table 2: *NOTANI staging system of ORN [7].*

Stage	Description	Symptoms
I	Resolved healed	None
Ia	No pathologic fracture	None or controlled
Ib	Pathologic fracture	
II	Chronic persistent non progressive	
IIa	No pathologic fracture	
IIb	pathologic fracture	Jaw dysfunction
III	Active progressive	Progressive
IIIa	No pathologic fracture	
IIIb	Pathologic fracture	Jaw dysfunction

Table 3: *Epstein classification of ORN of the mandible [8].*

Recently, Delanian introduced the theory of the radiation induced fibro-atrophic process (RIF) [12]. Based on this Theory, the author concluded on a phase II trial, that this condition (ORN) regressed with a combination of an antioxidant treatment combining pentoxifylline and tocopherol (PENTO) with or without the adjunction of Clodronate (PENTOCLO) [13,14].

However, the reported results remained controversial. In some cases, there were good results with a healing rate that reached 100% [14] but in other reports, there was only little improvement [15]. In the other hand, this protocol seemed to be safe and well tolerated while some authors reported severe intolerance and side effects especially to pentoxifylline [17].

Purpose of the Study

The purpose of this systematic review was to evaluate the efficacy and the tolerance of the pentoxifylline-tocopherol combination with or without Clodronate (Pentoclo/Pento) as a new medical protocol for osteoradionecrosis of the jaws.

Materials and Methods

To address this research purpose, a systematic review was designed and implemented in adherence to Preferred reporting items for systematic reviews and Meta-analysis Protocols (PRISMA-P) 2015 Statement [17]. The study sample was composed of all articles on the use of pentoxifylline and tocopherol with or without clodronate for the management of ORN of the jaws, every stage combined, and that are published on and before October 2019.

Therefore, a computerized database search was performed using the Pubmed, the Cochrane library and the google scholar databases. Specific ascertainment criteria were applied for the inclusion and exclusion of the eligible studies. We included in this study; Randomised controlled trials, The meta-analysis, the systematic reviews, The cohorts, the case-control studies and the Cross sectional studies.

Abstracts, review articles, editorials, comments and guidelines were excluded. Language was restricted to English and French.

All reviewers independently assessed the data to determine the eligibility of the articles.

Results

The article selection process is summarized in figure 1.

The initial PubMed search identified 19 articles, the number of the records identified through google scholar were 308 and no records were found in the Cochrane library. After duplicate removal, 215 articles were screened based on their titles and abstracts. Only 13 articles met the inclusion criteria. These articles were: 2 systematic reviews, 8 cross sectional studies, and 3 prospective trials (Table 4).

None of the studies was blinded, randomized, or controlled. We checked the methodologic quality of all of the papers selected for inclusion in this systematic review through a quality criteria checklist. Data extracted from the included articles are represented in table 5.

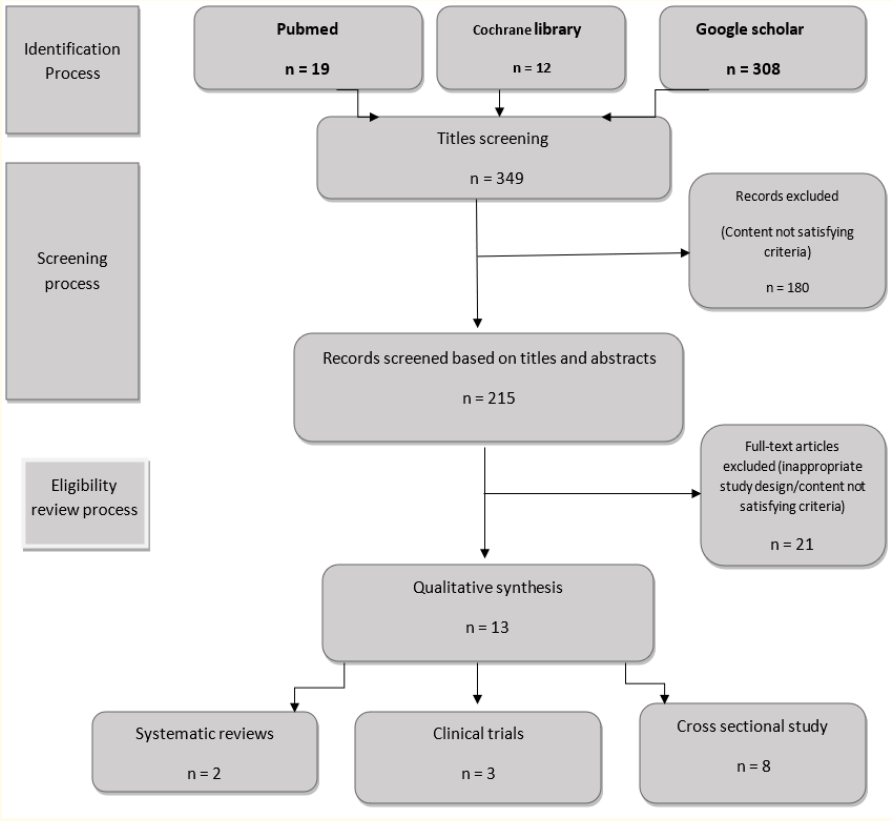

Figure 1: *Prisma flow diagram showing the process of the review.*

Study	Study design	Methodologic quality
Delanian S 2005 [13]	Phase II Clinical trials	Moderate
Delanian S., *et al*. 2011 [14]	Phase II clinical trials	Moderate
MC Leod., *et al*. 2012 [15]	Clinical review	Moderate
Choussy O., *et al*. 2013 [18]	Cross sectional study	Moderate
Delanian., *et al*. 2014 [19]	Prospective study	Moderate
Robard., *et al*. 2014 [20]	Retrospective study	Low
D'souza., *et al*. 2014 [21]	Prospective comparative study	Moderate
Lyons., *et al*. 2014 [22]	Prospective study	Moderate
Hayashi M., *et al*. 2015 [23]	Prospective study	Moderate
Kulkarni R., *et al*. 2015 [24]	Prospective study	Moderate
Patel v., *et al*. 2016 [25]	Retrospective study	Low
Martos-Fernandez M [26]	Systematic review	High
Kolokythas A., *et al*. 2018 [27]	Systematic review and meta-analysis	High

Table 4*: Study design and methodologic quality of the reviewed articles.*

Reference	Number of patients included	Stage of ORN	Proposed protocol	Results	Tolerance
Delanian S 2005	18	6p: Stg IIA 1p: Stg IIB 6p: Stg IIIA 6 P: Stg IIIB Epstein classification	4 weeks before Amoxclav: 2 g/d Fluconazole: 50 mg/j Methylprednisolone 16 mg/j 2 to 4 weeks before the protocol Protocol: Group 1 (10p) Ptx: 800 mg/d T: 1000 UI/D Group 2: (8 patients) Ptx+T+C: 1600 mg/d	• 89% recovery • 2/16 patients: improvement • 9 patients needed sequestrectomy	Excellent
Delanian S 2011	54	18p:II 36p: III Epstein classification	4 weeks before Amoxclav: 2 g/d Pd: 20 mg/d Cp: 1 g/d F: 50 mg/d Protocol: Ptx: 800 mg/d T:1000 UI/d C: 1600 mg/d	• Recovery rate 100% • 36 patients needed sequestrectomy	• Nausea • Vertigo • Insomnia • Headache
Mc leod 2012	12	6p: IIa 4p: IIIa 2p: IIIb	Ptx: 800mg/d T:1000UI/d	• 5 patients recovery • 5 patients stable • 2 aggravation • 3 patients needed resection +reconstruction	Severe intolerance in 1 patient
Choussy., *et al*.	22	NP	Antibiotherapy + protocol: Ptx+T+C	81% healing	100% tolerance
Delanian S 2014	29	Pathological fracture in all patient	Clindamycine + Ptx: 800 mg/d T: 1000 UI/d C: 1600 mg/d	• 100% recovery • 10 patients needed sequestrectomy	Well tolerated

Robard L., *et al*.	25	Own classification: 6p: Stage 1 14p: Stage 2 5p: Stage 3	Amoxclav: 2 g/d+Cp: 1 g/d F: 50 mg/d Pd: 20 mg/d O: 20 mg/d Protocol: P: 800 mg/d T: 1000 UI/d C: 1600 mg/d	• 64% recovery • 12 patients needed sequestrectomy	• Well tolerated • nausea
D'souza., *et al*.	25	Notani classification 12p: Grade I 3p: Gr II 10p: Gr III	Ptx: 800 mg/d T: 1000 UI/d Doxicycline:1 00 mg/d	5p: recovery 12p: stable 7p: aggravation • 5 patients needed resection+ surgical reconstruction	Well tolerated
Lyons., *et al*.	85	Own classification 28p: Stage 1 7p: Stage 2 12 p: Stage 3 38p: Stage 4	Ptx: 800 mg/d T: 1000 UI/d C for only 4 patients	• 49% recovery rate in stage1 patients • 25% recovery rate in stage2 • 25% recovery in stage3 • No healing in stage 4	NP
Hayashi., *et al*.	13	NP	Ptx: 800 mg/d T: 1000 UI/d	86 % recovery rate	Well tolerated
Kulkarni R., *et al*.	31	Notani classifiction	Ptx +T in 7 patients Ptx +T+C in 24 patients	42% recovery with Ptx+T 53% recovery with Ptx+T+C	Intolerance in 3 patients: nausea and headache
Kolokythas A., *et al*. 2018	211	Differents stages	Ptx+t+c/ P+T	126p fully recovered 60p remained the same 15p worsen	NP

Table 5: *Summary of the studies reviewed.*

Ptx: Pentoxifylline; T: Tocopherol; C: Clodronate; A: Amoxicillin-Clavulanate; F: Fluconazole; M: Methylprednisolone; Ptx: Pentoxifylline; T: Tocopherol; C: Clodronate; Cp: Ciprofloxacin; Pd: Prednisone; NP: Not Precised.

Discussion

The pathophysiology of ORN has evolved through the time. Reguade in 1922 was the first to describe it which came across many controversies [2]. First, microorganisms were considered to play an important role in the occurrence of osteoradionecrosis in irradiated bone [1].

Meyer concluded to his theory of a classic triad of radiation, trauma, and infection. According to Meyer, trauma to the irradiated bone creates path for the entry of microorganisms in the underlying bone which then creates a local infection due to lack of resistance offered by the irradiated bone [1].

Marx proposed the 3 H theory of hypoxia, hypocellularity, and hypovascularity. The author showed histologic findings of fibrosis of the mucosa, skin, and marrow spaces, hyalinization and thrombosis of vessels with loss of osteocytes and osteoblasts, and reduced vascularity of connective tissue. This condition leads to the appearance of a chronic non-healing wound. This wound can be considered as the first stage of the development of ORN [4].

Recently, a new theory has been proposed by Delanian; "the radiation induced fibroatrophic theory". This theory proposed that the progression of ORN is due to the activation and deregulation of fibroelastic activity that leads to atrophic tissues in the irradiated region. The radiation-induced fibroatrophic (RIF) process constitutes a late, local, irreversible and unavoidable sequela to high-dose radiotherapy [12].

For the management of the RIF, the author recommended firstly, the restriction of all aggravating factors, as well as co-morbidity related factors that have been proved to be helpful in controlling local RIF progression. Therefore, any local trauma such as surgery or biopsy should be avoided, and local infections treated with antibiotics and antiseptic agents [12].

Based on this theory, Delanian proposed a medical protocol combining, first, Pentoxifylline and Tocopherols (PENTO) to patients with severe ORN of the mandible, and then by the adjunction of clodronate (PENTOCLO) to patients who did not respond to the first protocol [13].

PTX is a methylxanthine derivative used to treat vascular diseases such as intermittent claudication. *In vivo*, it has been reported to have an anti-TNFa effect, increase erythrocyte flexibility, vasodilate, and inhibit inflammatory reactions. Many *in vitro* studies have indicated that PTX has antioxidant properties; inhibits human dermal fibroblast proliferation and extracellular matrix production and increases collagenase activity, While Vitamin E has anti-oxidant proprieties and can reduce free radical induced chromosomal damages [12].

Clodronate is a first-generation, non-nitrogenous oral bisphosphonate that can reduce osteoclast activity while it decreases the fibroblast and macrophage proliferation. This drug was proven to promote bone formation by osteoblasts and was not reported to be associated with the drug-induced osteonecrosis [13].

Studies have shown that combining pentoxifylline with tocopherol (PVe) and clodronate (PENTOCLO) enhances its antifibrotic effect, making it more effective than placebo or any of these agents alone [12].

The recommended doses used by the authors were: Pentoxifylline: 800 mg /day, Tocopherol; 1000 UI/day and Clodronate: 1600 mg/day [13-16,20,22] with a treatment duration that varied from 3 to 24 months [14,16]. There is actually no consensus on the optimal therapeutic doses of these drugs or the shortest treatment span [27].

Mc Leod., *et al*. [15], Patel., *et al*. [25], Hayashi., *et al*. [23] and D'Souza., *et al*. [21] did not include Clodronate in their treatment regimen and only prescribed Ptx and Tocopherol to all the patient, all stages of ORN included.

Mcleod., *et al*. [15] considered that their results were poorer that those of Delanian., *et al*. [13] and attributed that to the fact that their patients did not receive Clodronate. The authors reported that they avoided Clodronate because they did not want to make the addition of a drug that can induce osteonecrosis for patients who already have the condition. It's worth mentioning that there is little evidence for the development of bisphosphonate-associated osteonecrosis with clodronate. Moreover, this drug has been used as a substitute bisphosphonate in patients with bisphosphonate-associated osteonecrosis when they were unable to stop their bisphosphonate treatment [13].

For the same reasons, D'Souza., *et al*. proposed a modified protocol by substituting Clodronate with doxicycline. But the authors did not justify their choice of doxycycline [15].

These protocols (PENTO/PENTOCLO) were often associated to other drugs prescriptions that were started few weeks before the protocol for either their antibacterial or their anti-inflammatory proprieties [13,14,16,18,20].

The main combined prescribed drugs were, amoxicillin-clavulanic acid [13,14,18], methylprednisone [13,16,18] as well as ciprofloxacin [18].

The recovery rates varied in the reported studies. In the first study published in 2005, Delanian., *et al*. [13] reported a recovery rate of 89% without differences between the first (PENTO group) and the second group (pentoclo group). these results were confirmed in the second study published in 2011 with a success rate of 100% in a group of 54 patients with stage II and stage III ORN of the mandible treated with PENTOCLO seven days a week combined to Prednisolone and Ciprofloxacin only 2 days a week, for a mean treatment period of 9 months [16].

D'Souza., *et al*. [21] reported a healing rate of 20% (5 patients), while 12 patients remained stable and the condition worsen in 7 patients. These results were attributed to the non use of Clodronate for the reasons cited above and not to the stage of the complication. Patel., *et al*. [25] also used the PENTO protocol avoiding the prescription of Clodronate and reported a recovery rate of 56 % in the first group of patients who only received Pento protocol, 27% in the second group of patients who also received Antibiotics, 6% in the third group who had surgical debridement and 66% in the 4th group. The best results were found in the 4th group of patients, all of them had a stage III ORN of the jaws according to Notani Classification (Table 2) and have had surgical resection.

In fact, the surgical adjuvant treatments were necessary in the severe or refractory cases. The conservative sequestrectomy was indicated in 36 out of the 54 patients in the series of Delanain [16] and in 15 patients in the study of Lyons [22] who reported a healing rate of 25% in both stage 2 and stage 3 patients.

In all the studies, the best healing and clinical improvement rates associated with either PENTO or PENTOCLO treatment were obtained in mild and moderate ORN [26,27] however, in the advanced stages or in cases of refractory to conservative management, the surgical treatment (mandibular resection with reconstruction) remained the only therapeutic option available [15,21,22,26].

This drug therapy has shown ease of administration, safety profile and low cost [26,27]. Only few cases of intolerance or toxicity were reported. The main side effects were attributed to Ptx and were nausea, vertigo and headache [16,20,24]. No side effects to Clodronate were reported.

Conclusion

The strength of the current study comes from the application of a structured approach to literature search and quality assessment of the selected studies. However, till the date no randomized control trials were performed and further large, prospective, randomized, controlled trials are needed to substantiate these findings and to determine the optimal doses for the drugs given the long treatment periods required and their possible side effects.

This protocol is relatively new but seems well tolerated and could be promising for the treatment of the osteoradionecrosis of the jaws especially that no consensus with regards to the best management of this severe condition is available yet.

Bibliography

1. Ribeiro GH., *et al.* "Osteonecrosis of the jaws: a review and update in etiology and treatment". *Brazilian Journal of Otorhinolaryngology* 84.1 (2018): 102-108.

2. Thorn JJ and Hansen HS. "Osteoradionerosis of the jaws: clinical characteristics and relation to the field of irradiation". *Journal of Oral and Maxillofacial Surgery* 58 (2000): 1088-1093.

3. Syed N and Samman N. "Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patiens: a systematic review". *International Journal of Oral and Maxillofacial Surgery* 40.3 (2011):229-243.

4. Marx RE. "Osteoradionecrosis a new concept of its pathophysiology". *Journal of Oral and Maxillofacial Surgery* 41 (1983): 283-288.

5. Marx RE and Johnson RP. "Studies in the radiobiology of osteoradionecrosis and their clinical significance". *Oral Surgery, Oral Medicine, Oral Pathology* 64 (1987): 379-390.

6. Syed N and Samman N. "Risk factors for osteoradionecrosis after head and Neck radiation: a systematic review". *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 1 (2012): 54-69.

7. Reuther T., *et al.* "Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review". *International Journal of Oral and Maxillofacial Surgery* 32.3 (2003): 289-289.

8. Notani K., *et al.* "Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy". *Head Neck* 25.3 (2003):181-186.

9. Epstein J Wong F and Stevenson-Moore P. "Osteoradionecrosis: clinical experience and a proposal for classification". *Biomater RES* 18 (2014): 13-22.

10. Koteswara Rao Nadella and Rama Mohan Kodali. "Osteoradionecrosis of the Jaws: Clinico-Therapeutic Management: A Literature Review and Update". *Radiotherapy and Oncology* 73.2 (2004): 119.

11. Chronopoulos A., *et al.* "Osteoradionecrosis of the mandible: A ten year single-center retrospective study". *The Journal of Cranio-Maxillofacial Surgery* 43 (2015): 837-846.

12. Delanian S and Lefaix JL. "The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway". *Radiotherapy and Oncology* 73.2 (2004): 119-131.

13. Delanian S and Lefaix JL. "Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial". *Head Neck* 27 (2005): 114-123.

14. Delanian S and Lefaix JL. "Complete healing of severe osteoradionecrosis with treatment combining pentoxifylline, tocopherol and clodronate". *The British Journal of Radiology* 75 (2002): 467-469.

15. Mc Leod NM., *et al.* "Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience". *British Journal of Oral and Maxillofacial Surgery* 50.1 (2012): 41-44.

16. Delanian S., *et al.* "Complete restoration of refractory osteoradionecrosis by prolonged treatement with pentoxifylline-tocopherol-clodronate combination (Pentoclo): a phase II trial". *International Journal of Radiation Oncology Biology Physics* 80 (2011): 832-839.

17. Moher D., *et al.* "Preferred Reporting Items for Systematic Review and Meta- Analysis Protocols (PRISMA-P) 2015 statement". *Systematic Reviews* 4.1 (2015): 1.

18. Choussy O., *et al.* "Efficacité du protocol Pentoclo dans la prise en charge des osteoradionécrose". *European Annals of Oto-rhino-laryngology, Head and Neck Diseases* 130 (2013): A5.

19. Delanian S. "Fracture mandibulaire sur ostéoradionécrose: option conservatrice médicale "pentoclo". *Journal Can Radio* 18 (2014): 626.

20. Robard L., *et al.* "Medical Treatment of osteoradionecrosis of the mandible by Pentoclo: preliminary results". *European Annals of Oto-rhino-laryngology, Head and Neck Diseases* 131.6 (2014).

21. D'Souza J., *et al.* "Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible; experience from regional head and neck unit". *British Journal of Oral and Maxillofacial Surgery* 52.4 (2014): 356-362.

22. Lyons A., *et al.* "Osteoradionecrosis –a review of current concepts in defining the extent of the disease and a new classification proposal". *British Journal of Oral and Maxillofacial Surgery* 52.5 (2014): 392-395.

23. Hayashi M., *et al.* "The efficacy of pentoxifylline – tocopherol combination in the treatment of osteoradionecrosis". *Special Care in Dentistry* 35.6 (2015): 286-271.

24. Kulkarni R and Gymermen J. "The role of pentoxifylline-tocopherol-clodronate (PENTOCLO) in osteoradionecrosis of the mandible". *British Journal of Oral and Maxillofacial Surgery* 53.10 (2015): 62-63.

25. Patel V., *et al.* "Prophylactic use of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of the head and Neck". *British Journal of Oral and Maxillofacial Surgery* 54.5 (2016): 547-550.

26. Kolokythas A., *et al.* "Management of osteoradionecrosis of the jaws with pentoxifylline –tocopherol; a systematic review of the literature and meta-analysis". *Journal of Oral and Maxillofacial Surgery* (2018).

27. Martos Fernanadez M and Saez Barba M. "Pentoxifylline, Tocopherol and clodronate for the treatment of mandibular osteoradionecrosis: A systematic review". *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 125.5 (2018): 431-444.

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