

THE IMPACT OF PURINE DERIVATIVES THERAPY FOR PATIENTS WITH MEDICATION-RELATED OSTEONECROSIS OF THE JAW: PRELIMINARY RESULTS FROM A PILOT STUDY

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ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) is a severe side effect of antiresorptive drugs - Bisphosphonates (BPs) and RANKL inhibitor (denosumab) - prescribed for treatment of bone malignancies and severe osteoporosis. Non-surgical treatment may be a valid option for MRONJ in patients ineligible for surgery. Published observational studies have demonstrated that a common purine derivative - pentoxifylline in combination with tocopherol are potentially useful in the nonsurgical management of MRONJ. The aim of this study was to assess the therapeutic impact and possible side effects of treatment with pentoxifylline in combination with tocopherol in patients with MRONJ. Patients were subdivided into two groups: the test group, comprising of 20 patients, underwent treatment with 800 mg pentoxifylline in combination with 1000 IU of tocopherol, whereas the other patients formed the control group. After the 6-month treatment course, the statistically significant results of our study show that treatment with pentoxifylline in association with tocopherol is efficacious for managing MRONJ nonsurgically. However, larger clinical studies are needed to optimize dose and duration. No serious adverse effects occurred.

Keywords: MRONJ, purine derivatives, Pentoxifylline, tocopherol,

INTRODUCTION

The therapeutic management of MRONJ remains controversial. Various therapeutic approaches have been implemented that include extensive surgical procedures or more conservative therapies as local antiseptics and broad-spectrum antibiotics (1). The use of complementary therapies such as hyperbaric oxygen, laser therapy, platelet-rich plasma, recombinant

human parathyroid hormone has also been proposed (2).

Recently, it has been proposed that the combination of pentoxifylline with tocopherol might have a good therapeutic effect on medication-related osteonecrosis of the jaw (MRONJ) (3). Pentoxifylline belongs to the class of purine derivatives agents that are used as peripheral vasodilators agents to manage chronic occlusive vascular disorders

(4). Tocopherol is a potent oxygen radical scavenger with antioxidant and anti-inflammatory properties (5).

The aim of this study was to assess the therapeutic impact and possible side effects of treatment with pentoxifylline in combination with tocopherol in patients with MRONJ.

MATERIAL AND METHODS

We retrospectively analyzed a cohort of MRONJ patients referred between July 2022 and July 2024 to the "Prof.dr.Dan Theodorescu" Clinical Hospital of Oral and Maxillofacial Surgery (OMFS), București, Romania. This study was approved by the Research Ethics Commission of the "Prof.dr.Dan Theodorescu" Clinical Hospital of OMFS (nr.6030/28.07.2022). This work was compliant with the principles set out in the Declaration of Helsinki on medical protocol and ethics. All participants signed informed patient consent form.

The clinical study included patients with MRONJ that were treated with pentoxifylline and tocopherol as treatment of the osteonecrosis lesions. Null hypothesis was that the application of the PENTO-E protocol had no effect on MRONJ.

Inclusion criteria were:

- MRONJ patient with Stage I, II or III according to the staging criteria of the AAOMS of 2022 (6)
- adult cancer patients with intake of one or more MRONJ-related drugs including intravenous BPs (zoledronate) or RANKL inhibitor (denosumab) for over a period of 6 month;

Exclusion criteria: MRONJ related to oral BPs.

The patients divided into two groups. In the test group (20 patients), each patient was subjected to pharmacological treatment with pentoxifylline (800 mg/day) and tocopherol (1000 I.U. 1/day), for six months.

The patients of the control group (157 patients) consisted in patients suffering from hypersensitivity to xanthine derivatives, acute myocardial infarction, coronary disease, risk of increased intracranial/retinal bleeding or metastases.

In both groups, the patients were monitored with regular checks at one month and at 6 months. During the follow-up, clinical and radiographic evaluation was performed, and bone healing was assessed; the assessment was defined by the area of exposed bone: partial healing (mucosal coverage of the exposed bone); no change and progression (increase in size of the exposed bone). Radiological follow-up was carried out with orthopantomography and/or Cone Beam-CT at the 6 months.

The comparisons of outcomes between the two groups were made using parametric tests (Student's *t*-test). Pearson's chi squared test was used for comparing the frequencies. The statistical analysis was performed using Stata 16 (StataCorp LLC, USA). A value of $p < 0.05$ will be considered an indicator of a significant difference.

RESULTS AND DISCUSSION

Overall, in the studied group, the symptomatology improved, compared to the control group (study group percentage 100%

vs control 5.73% $p < 0.001$, Fisher's exact test)
(Table 1).

Table 1. Distribution of patients according to evolution under conservative treatment

0, test; 1, control	0, worse; 1, stationary; 2, improve			
	0	1	2	Total
0	0	0	20	20
	0.00	0.00	100.00	100.00
1	5	143	9	157
	3.18	91.08	5.73	100.00
Total	5	143	29	177
	2.82	80.79	16.38	100.00

Pearson Chi2 = 115.07 Prob = 0.0000

First row has *frequencies* and second row has *row percentages*

No statistically significant difference was determined in the duration of antiresorptive treatment, localization of the lesions, diabetes diagnosis and treatment outcomes.

There is a lack of consensus in the current literature regarding how to best manage exposed bone associated with medication-related osteonecrosis of the jaw (MRONJ); treatments can be surgical and conservative, considering the stage of MRONJ (6).

Current literature suggest that the use of pentoxifylline and tocopherol (PENTO-E protocol) displays good therapeutic results of these agents against osteoradionecrosis, due to their antioxidant and antifibrotic properties, but limited data has been found regarding the efficacy of this protocol in

management of MRONJ (7). Pentoxifylline is a methylxanthine derivative which promotes blood circulation and is mainly used to treat peripheral vascular diseases (8). Pentoxifylline is a safe drug and is well tolerated; the side-effects are dose-related and the most common are those of the gastrointestinal tract (9). Tocopherol is an antioxidant, whose main role *in vivo* is to stabilize the active free radicals (10), involved in the pathogenesis of MRONJ.

Currently, pentoxifylline in combination with tocopherol are considered as having a synergistic therapeutic efficacy in treating osteoradionecrosis and MRONJ (11). Delanian et al. (12) reported a case series of patients diagnosed with refractory mandible osteoradionecrosis and showed results

referring to complete recovery in 100 % of the cases. Also, some recent clinical studies have studied the therapeutic value of the pentoxifylline and tocopherol therapy in the management of medication-related osteonecrosis of the jaw. Thus, Bohn et al. (13) claimed to have achieved 100% success in MRONJ treatment and Seo et al. (14) reported recovery in the majority of patients treated. However, the pentoxifylline and tocopherol association mechanism of action in MRONJ remains unclear (15).

Pentoxifylline and tocopherol used in association with broad-spectrum antibiotics seems to decrease areas of exposed bone (7). In our study there are no statistically significant difference between antimicrobial therapy at patients treated with tocopherol and pentoxifylline and treatment outcomes.

According to the results of our study, patients in the test group experienced no relapse and no complications during six months after initiation of therapy. Currently there is no validated protocol that establishes the ideal duration and the optimal dosing of

pentoxifylline and tocopherol therapy for MRONJ treatment. Most of the studies use a daily intake of 800mg of pentoxifylline with 800 UI of tocopherol, but it is not clear how long the patient should remain under treatment. It has been pointed out that treatment should be administered for at least 6 months or when lesion regression is observed (16), but it should be considered that severe cases responded to a maximal response after an average of two years (17). Additional clinical studies are needed to determine the ideal duration of PENTO therapy for MRONJ treatment.

CONCLUSIONS

This limited study, in addition to the other reviewed studies, estimates that the PENTO-E therapy

may have a positive benefit in MRONJ patients. This well-tolerated and cost-effective protocol should be instituted when healing of tissue lesions was not achieved by conventional conservative methods. We recommend large prospective studies to be carried out to further validate these findings.

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