

Purine Derivatives in the Management of Antiresorptive Drug-Related Osteonecrosis of the Jaw

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ABSTRACT: Purinic derivatives has recently attracted attention as a potential therapeutic agent, with preliminary evidence suggesting its utility in the management of osteonecrosis of the jaw. work aims at providing an update of the current literature, shedding light on the purinic derivatives treatment for patients who received intravenous antiresorptive drugs and developed osteonecrosis of the jaw. A retrospective study was conducted at the Oral and Maxillofacial Surgery Department of "Prof. Dr. Dan Theodorescu" Clinical Hospital in Bucharest, Romania, involving 160 consecutive patients diagnosed with refractory, established antiresorptive drug-related osteonecrosis of the jaw between 2022 and 2024. A study group of 23 consecutive patients was selected to receive adjunctive therapy with pentoxifylline (800 mg/day) and vitamin E (1000 IU/day) for six months, while the remaining 137 patients who were not eligible for pentoxifylline treatment formed the control group. Bone healing outcomes were assessed based on the extent of exposed necrotic bone. The study results indicate the fact that 100% of patients in the study group experienced symptomatic improvement, despite a higher prevalence of stage III medication-related osteonecrosis of the jaw, provides strong evidence supporting the therapeutic efficacy observed in this sample population. Post-hoc power analysis showed that the study was strongly powered to detect the observed differences, supporting the reliability of the results. Treatment with purine derivatives demonstrates significant therapeutic potential in the management of antiresorptive drug-related osteonecrosis of the jaw and should be considered as complementary to the standard therapy, particularly in advanced stages of the disease.

KEYWORDS: Antiresorptive drug-related osteonecrosis of the jaw, pentoxifylline, antioxidative agents.

Introduction

Antiresorptive drug-related osteonecrosis of the jaw is a severe, progressive condition characterized by the destruction of maxillary and mandibular bone following exposure to osteoclast inhibitors and antiangiogenic monoclonal antibodies such as denosumab [1,2].

Currently, there are no standardized or universally accepted guidelines for the management of antiresorptive drug-related osteonecrosis of the jaw [3,4].

Treatment strategies range from conservative approaches-such as systemic antibiotic therapy to surgical interventions, including sequestrectomy and resection of necrotic bone [5,6,7].

In addition, a variety of adjunctive therapies have been explored, such as low-level laser therapy, fluorescence-guided surgery and hyperbaric oxygen therapy, though evidence supporting these interventions remains limited [8,9,10].

One therapeutic regimen that has attracted increasing attention in recent years is the

combination of purine derivatives such as pentoxifylline and tocopherol [11,12].

This pharmacologic strategy has shown promise in the treatment of osteoradionecrosis, demonstrating improvements in symptomatology and tissue healing [13].

In light of the growing clinical interest and the theoretical benefits of this combination therapy, the present study aims to evaluate the efficacy of conservative management of antiresorptive drug-related osteonecrosis of the jaw using a pharmacological regimen consisting of purine derivatives and vitamin E.

Materials and Methods

The retrospective study included 160 consecutive presentations referred for refractory established antiresorptive drug-related osteonecrosis of the jaw between 2022 and 2024 in the Oral and Maxillofacial Department of "Prof. dr. Dan Theodorescu" Clinical Hospital, Bucharest, Romania.

All patients had been treated with intravenous antiresorptive agents for management of metastatic bone tumors/multiple myeloma.

Inclusion criteria consisted of a antiresorptive drug-related osteonecrosis of the jaw diagnosis according to the American Association of Oral and Maxillofacial Surgeons criteria.

Exclusion criteria were as follows: patients with a history of using oral antiresorptives; patients who have received pentoxifylline and/or vitamin E in the last 12 months; patients with systemic contraindications to the administration of pentoxifylline or vitamin E; concomitant medication that interferes with pentoxifylline or vitamin E.

The study group, consisting of 23 patients treated with pentoxifylline (800 mg/day) and vitamin E (1000 IU/day) for six months. The control group, consisting of the remaining 137 patients, included people who were not eligible for pentoxifylline therapy.

All patients, regardless of group, had surgical criteria and were monitored through regular evaluations at one month and six months; during the follow-up period, clinical and radiographic evaluations were performed, and bone healing was assessed according to the exposed bone surface.

All patients provided written informed consent permitting the use of their medical records for scientific research and data reporting.

Patient data were retrospectively extracted from medical records and included the following variables: age (years), location of osteonecrotic lesions (mandible/maxilla), stage of osteonecrosis (I-III), symptomatic progression (worsening, stable, improved) and use of

pentoxifylline combined with vitamin E (yes/no).

Statistical analyses were conducted using Stata 16 (StataCorp LLC, USA).

Age was the only continuous variable extracted from the medical records and included in the present analysis.

Prior to applying the independent samples Student's t-test, the distribution of age was assessed for normality using the Shapiro-Wilk test and Kolmogorov-Smirnov tests.

For categorical variables we used Pearson's chi-square test and Fisher's exact test (when expected cell counts were <5).

Statistical significance was defined as $p < 0.05$, with values between 0.05 and 0.10 considered marginally significant.

A post-hoc power analysis was conducted for the chi-square test of independence applied to the distribution of clinical evolution across groups.

Clinical evolution was categorized into three outcomes: aggravated, stationary, and improved. The test yielded a Pearson chi-square statistic of 107.45 with 2 degrees of freedom. The effect size was calculated as Cohen's w . The achieved power was estimated with the chi-square goodness-of-fit procedure implemented in `statsmodels.stats.power.GofChiSquarePower` (Python).

Results

Participants in the study group had a mean age of 60.7 years (SD=9.1), whereas those in the control group 1 were older on average, with a mean age of 67.3 years (SD=9.3) (Table 1).

Table 1. Distribution of cases according to age.

Group	N	Mean Age	Note
Study	23	60.739	-
Control	137	67.294	-

Variable	N1	N2	Mean1	Mean2	Difference	t value	p value
Age	23	137	60.739	67.294	-6.555	-3.15	0.002

An independent samples t-test confirmed that this difference was statistically significant ($p=0.002$).

For the study group, the Shapiro-Wilk test indicated no significant deviation from normality ($p=0.698$), and the Kolmogorov-Smirnov test yielded a consistent result ($p=0.975$).

For the control group, the Shapiro-Wilk ($p=0.925$) and Kolmogorov-Smirnov ($p=0.747$)

tests similarly supported the assumption of normality.

Among cases involving the mandible ($n=110$), 12.8% (14 cases) were assigned to the study group and 87.2% (96 cases) to the control group.

For cases involving the maxilla ($n=50$), 18.4% (9 cases) were in the study group and 81.6% (41 cases) in the control group.

A Pearson chi-square test indicated no statistically significant association between anatomical location and group allocation, $\chi^2(1)=0.41$, $p=.523$.

In the study group, most participants were classified as Stage III (65.2%), followed by

Stage II (30.4%), with only one case in Stage I (4.3%).

Overall, Stage II accounted for nearly half of all cases (48.8%), with Stage III representing 32.5% and Stage I 18.8% (Table 2).

Table 2. Distribution of clinical stage examined across the study and control groups.

Stage	Study (0)	Control (1)	Total
Stage I (0)	1	29	30
Stage II (1)	7	71	78
Stage III (2)	15	37	52
Total	23	137	160

Stage	Study (0) %	Control (1) %	Total %
Stage I (0)	4.35	21.17	18.75
Stage II (1)	30.43	51.82	48.75
Stage III (2)	65.22	27.01	32.50
Total	100.00	100.00	100.00

Pearson Chi2=13.67, $p=0.0011$

A Pearson chi-square test revealed a statistically significant association between disease stage and group allocation, $\chi^2(2)=13.67$, $p=.001$.

The evolution of patients according to the stage of osteonecrosis did not present statistically significant differences in the control group ($p=0.4498$), with most patients having a stationary evolution, regardless of stage, which suggests that the initial severity of the lesion did not significantly influence the direction of clinical evolution.

Table 3 provides an overview of the treatment outcomes. The analysis of

symptomatic progression revealed statistically significant differences between the two groups.

In the study group, 100% of patients experienced symptomatic improvement, whereas only 6.57% of patients in the control group reported such improvement.

These differences were supported by a highly significant chi-square test result ($p < 0.001$).

The post-hoc power analysis confirmed that, given the large effect size (Cohen's $w \approx 0.82$), the study had virtually complete power (≈ 1.00) to detect differences in clinical outcomes between groups.

Table 3. Distribution of patient responses across study groups

Evolution	Study (0)	Control (1)	Total
Aggravated (0)	0	5	5
Stationary (1)	0	123	123
Improved (2)	23	9	32
Total	23	137	160

Evolution	Study (0) %	Control (1) %	Total %
Aggravated (0)	0.00	3.65	3.12
Stationary (1)	0.00	89.78	76.88
Improved (2)	100.00	6.57	20.00
Total	100.00	100.00	100.00

Pearson Chi2=107.45, $p=0.0000$

Discussion

The precise pathophysiology of antiresorptive drug-related osteonecrosis of the jaw remains incompletely elucidated but is widely considered to be multifactorial.

Systemic comorbidities known to impair wound healing, notably diabetes mellitus, may further exacerbate susceptibility to antiresorptive drug-related osteonecrosis of the jaw [14].

Given the growing list of pharmacologic agents associated with antiresorptive drug-

related osteonecrosis of the jaw, several mechanistic hypotheses have been advanced, including alterations in bone remodeling, antiangiogenic effects leading to compromised vascular supply, and persistent inflammation or infection of hard and soft tissues [15,16,17].

Surgical debridement and removal of necrotic bone remain the primary interventions for advanced stages of antiresorptive drug-related osteonecrosis of the jaw.

However, standardized guidelines for medical or nonsurgical management are currently lacking. Several adjunctive and conservative strategies have been explored, each with variable degrees of success [18].

Pentoxifylline, a purine derivative traditionally used for peripheral vascular disorders, is thought to enhance microcirculatory perfusion by lowering blood viscosity, promoting fibrinolysis, and increasing erythrocyte flexibility.

Though its exact mechanism remains incompletely understood, pentoxifylline also exerts anti-inflammatory and antioxidant effects, partly through inhibition of neutrophil activation and reduction of circulating levels of tumor necrosis factor alpha (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6) [19,20].

Tocopherol (vitamin E), a potent lipid-soluble antioxidant, scavenges reactive oxygen species, thereby protecting cellular membranes, attenuating inflammatory processes, and suppressing procollagen gene expression.

The synergistic action of these agents is hypothesized to facilitate wound healing [21].

The combination of purine derivative and tocopherol has emerged as a promising and relatively inexpensive nonsurgical alternative, initially investigated for osteoradionecrosis of the jaw [22].

The pharmacological rationale rests on the synergistic effects of pentoxifylline—a purine derivative known to reduce blood viscosity, enhance microcirculation, and exert anti-inflammatory properties—and tocopherol, a potent antioxidant that protects cellular membranes and modulates fibrosis.

This review examined the evidence supporting the efficacy of this combination in Antiresorptive medication-related osteonecrosis of the jaw management.

Epstein et al. conducted the first case series exploring pentoxifylline and tocopherol for medication-related osteonecrosis of the jaw, involving six patients with stage III disease after prolonged osteoclast inhibitors therapy [23].

Patients received 400 mg pentoxifylline and tocopherol twice daily, along with chlorhexidine rinses, but no systemic antibiotics.

Over a mean follow-up of ten months, all patients exhibited significant clinical improvement, with reduction of the area of exposed bone, and complete resolution in one patient. Importantly, all patients were free of pain and signs of local infection at the end of follow-up, and no adverse events were observed.

A subsequent case report by Magremanne et al. described a patient with stage III medication-related osteonecrosis of the jaw complicated by persistent infection, pain, and paresthesia despite extensive prior antibiotic therapy [24].

Treatment with 400 mg pentoxifylline and 500mg tocopherol twice daily resulted in rapid symptomatic improvement.

After one year, the patient achieved resolution of pain and paresthesia, and imaging confirmed satisfactory bone healing without the need for surgical intervention. No recurrence or adverse effects were reported after discontinuation of therapy.

The largest series to date by Owosho et al. involved seven patients with varying medication-related osteonecrosis of the jaw stages who had received an average of nearly 42 bisphosphonate doses [25].

Patients were treated with pentoxifylline (400mg) and tocopherol (400 IU) twice daily, chlorhexidine rinses, and antibiotics as indicated.

While outcomes varied, two patients achieved complete resolution of exposed bone, two had partial resolution, and one showed no change.

Notably, all patients reported pain relief at the conclusion of therapy, and imaging revealed bony defect fill in those initially presenting with radiolucencies.

Our study results clearly suggest the significantly increased effectiveness of the combined treatment applied in the study group—purine derivatives in combination with vitamin E, even in more severe clinical conditions.

The fact that 100% of patients in the study group experienced symptomatic improvement, despite a higher prevalence of cases classified as stage III osteonecrosis of the jaws, represents solid evidence in support of the therapeutic efficacy observed in the subjects in the study sample.

The post-hoc power analysis indicated that the study had more than adequate power to

detect the observed group differences, supporting the robustness of the findings.

Nonetheless, as post-hoc calculations depend on the effect sizes observed, they should be interpreted cautiously and complemented by prospective power estimations in future research.

Collectively, the limited but encouraging evidence for pentoxifylline and tocopherol suggests this regimen may contribute to symptom control and bone healing in medication-related osteonecrosis of the jaw, complementing existing conservative and surgical approaches.

Future randomized clinical trials and larger cohort studies are necessary to validate these findings, establish standardized protocols, and better define the optimal role of purine derivatives and tocopherol within the broader management of medication-related osteonecrosis of the jaw.

Conclusions

Preliminary evidence indicates that this pharmacological regimen may promote comparable levels of hard and soft tissue healing while imposing relatively low risk, cost, and treatment burden compared with other nonsurgical modalities.

Nonetheless, further well-designed prospective studies are necessary to clarify the optimal dosage, duration of therapy, and long-term efficacy of pentoxifylline and tocopherol in the management of antiresorptive drug-related osteonecrosis of the jaw.

Author Contributions

Conceptualization: F.N. and D.O.M.; Methodology: V.G.C. and B.M.B.; Data collection and/or processing: F.N. and D.O.M.; Data analysis: V.G.C. and B.M.B.; Writing: F.N. and D.O.M.; Supervision: B.A. All authors read and approved the final manuscript. F.N. and D.O.M. had equal contributions to the article.

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilized therein were approved by the Institutional Review Board (Ethics Committee) of Prof.dr. Dan Theodorescu

Clinical Hospital (Decision No. 6030/28.07.2022).

Consent Statement

All human subjects involved in this study provided a written informed consent prior to participation, including the consent of publishing their anonymized data.

Data availability

All data presented in the manuscript are available from the authors upon request.

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