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ADVANTAGES OF USING PURINE DERIVATIVES IN LIMITING OSTEONECROSIS OF THE JAWS POST-ADMINISTRATION OF ANTIRESORPTIVE

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CONTENTS

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1. Farajollah N, Dincă OM, Vlădan GC, Niță T, Pădurariu LC, Bucur A. The impact of purine derivatives therapy for patients with medication-related osteonecrosis of the jaw: preliminary results from a pilot study. Romanian Journal of Oral Rehabilitation, 2024, 16(3):85-89
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https://rjor.ro/the-impact-of-purine-derivatives-therapy-for-patients-with-medication-related-osteonecrosis-of-the-jaw-preliminary-results-from-a-pilot-study/
2. Farajollah N, Dincă OM, Vlădan GC, Niță T, Pădurariu LC, Bucur A. The impact of purine derivatives therapy for patients with medication-related osteonecrosis of the jaw: preliminary results from a pilot study - the sequel. Romanian Journal of Oral Rehabilitation, 2024, 16(3):477-481
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https://rjor.ro/the-impact-of-purine-derivatives-therapy-for-patients-with-medication-related-osteonecrosis-of-the-jaw-preliminary-results-from-a-pilot-study-the-sequel/

PHD THESIS ABSTRACT

Introduction

Despite extensive research, the etiopathogenesis of osteonecrosis of the jaws after antiresorptive drug administration remains incompletely understood, involving a complex interplay between systemic, local and pharmacologic factors. In this context, one of the key pathophysiologic elements that has attracted the attention of the scientific community in the last decade is the involvement of oxidative stress in the pathogenesis of post antiresorptive drug-induced osteonecrosis of the jaws.

In case of osteonecrosis of the jaws after administration of antiresorptive drugs, the accumulation of reactive oxygen species may contribute to impaired bone microcirculation, inhibition of angiogenesis, decreased osteoblast activity and induction of osteocyte apoptosis, all leading to bone necrosis.

For this reason, I considered it opportune to study antioxidant medication of the purine derivative category as a potential adjuvant therapeutic strategy in osteonecrosis of the jaws after antiresorptive administration, able to reduce the negative effects of oxidative stress and favor bone tissue regeneration.

Starting from the hypothesis that therapy with purine derivatives and vitamin E could represent not only a method to combat oxidative damage, but also an active component of tissue regeneration and bone homeostasis, I have tried through the present research to establish the value of using purine derivatives in limiting the evolution of osteonecrosis of the jaws post-administration of antiresorptive drugs, considering that this therapeutic line could be integrated in a complex therapeutic plan, which could lead to the improvement of patients' quality of life and the prevention of severe complications associated with this reducible disease.

In conclusion, taking into account the impact of oxidative stress on bone homeostasis and on local inflammatory and regenerative processes, I consider as justified the rigorous investigation of the efficacy and safety of purine derivatives in patients with osteonecrosis of the jaws post-administration of antiresorptive drugs, as a prerequisite for the further

development of therapeutic protocols supported by solid scientific evidence, which could open new therapeutic perspectives in a pathology where current options are limited and often ineffective.

In the **general part of** the thesis the most recent data from the literature have been presented, regarding both the current therapeutic principles in the approach of osteonecrosis of the jaws post-administration of antiresorptive drugs and the use of antoxidizing pharmacologic agents. The objective of this part of the thesis is to understand the research topic and to integrate the results of the original study which has been detailed in the special part of the paper.

Chapter 1 presents the therapeutic methods applied to patients diagnosed with osteonecrosis of the jaws after administration of antiresorptive drugs, according to the practice guidelines developed by the Oro-Maxillo-Facial Surgery Clinic of the "Carol Davila" University of Medicine and Pharmacy and the American Association of Oro-Maxillo-Facial Surgeons (AAOMS), respectively.

Chapter 2 discusses the role of oxidative stress and reactive oxygen species in the onset and progression of osteonecrosis of the jaws after antiresorptive administration, documenting the preclinical evidence supporting the use of purine antioxidants in osteonecrosis and highlighting the need for their application in the clinical setting to be scientifically investigated.

The special (original) **part of** the PhD thesis presents the results of the evaluation to analyze the statistically significant differences between a group of patients undergoing conventional therapy recommended by the practice guideline "*Therapeutic algorithm in patients undergoing antiresorptive/antiangiogenic therapy*" [1] associated with the administration of a pharmacological combination of purine derivatives and vitamin E, respectively a control group, in order to identify the possible clinical benefits of the use of antioxidant medication.

Chapter 3: Working hypothesis and general objectives

In today's context, where surgical and drug treatments are constantly adapting to the individual patient's needs, my research aims to provide relevant data to support evidence-based therapeutic decision-making.

Also, the study aims to identify prognostic factors and possible correlations between disease stage, comorbidities and symptomatic course of osteonecrosis in a real clinical setting with practical relevance for therapeutic management.

***Main objectives of doctoral research**:*

1. Comparison of epidemiologic data (age, sex, background) between the two groups of patients diagnosed with osteonecrosis of the jaws after antiresorptive administration;
2. To investigate differences in the improvement in clinical symptomatology and initial stage of osteonecrosis of the jaws after antiresorptive administration;
3. To identify possible associations between osteonecrosis stage and therapeutic response, depending on the treatment applied;
4. Analysis of possible correlations between the most common systemic comorbidities (diabetes, hypertension - hypertension - hypertension) and the efficacy of treatment of osteonecrosis of the jaws after antiresorptive drugs;
5. Evaluation of the influence of associated pharamcologic therapies (antibiotics, corticosteroids) on the efficacy of treatment of osteonecrosis of the jaws after antiresorptive administration;
6. Formulation of recommendations for an effective therapeutic algorithm in osteonecrosis of the jaws post-administration of antiresorptive drugs.

Chapter 4: General research methodology

The study is retrospective, analytic and comparative, performed on a group of consecutive patients diagnosed with osteonecrosis of the jaws post-administration of antiresorbtiev, who presented between July 2022 and July 2024 at the Clinical Hospital of Oro-Maxillo-Facial Surgery "*Prof. Dr. Dan Theodorescu*" in Bucharest, Romania.

The research protocol was approved by the Ethics Commission of the Clinical Hospital of Oro-Maxillo-Facial Surgery "*Prof. Dr. Dan Theodorescu*" (no. 6030/28.07.2022) and complied with the principles of the Declaration of Helsinki on Ethics in Medical Research.

The study group of 20 patients included people treated with pentoxifylline (800 mg/day) and vitamin E (1000 IU/day) for six months.

The control group of 157 patients included people who were not eligible for pentoxifylline and vitamin E therapy.

All patients, irrespective of group, were followed up with regular assessments at one and six months; clinical and radiographic assessments were performed during the follow-up period, and bone healing was assessed in terms of the area of exposed bone.

Chapter 5: Results [2,3]

Results on the clinical effect of treatment for the two groups of patients with osteonecrosis of the jaws post-administration of antiresorptives

There were significant differences between the two groups. In the study group, 100% of the patients experienced symptomatic improvement, whereas in the control group, only 6.57% reported symptomatic improvement.

The differences are supported by a chi-square test with a highly statistically significant value ($p < 0.001$).

The proportional distribution of the therapeutic response between the two groups is evident, with a clear difference in the therapeutic responses observed for subjects in the two samples.

Results on the clinical effect of treatment for the two groups of patients with osteonecrosis of the jaws post-administration of antiresorptives according to the stage of the disease

In the study group, 65.22% of patients were in stage III (the most severe) compared to only 27.01% in the control group. This is essential to emphasize that despite a higher severity of osteonecrosis in the study group, the clinical outcomes were markedly superior.

The fact that 100% of the patients in the study group experienced symptomatic improvement, despite a higher prevalence of stage III osteonecrosis of the jaws after antiresorptive therapy, is strong evidence in support of the therapeutic efficacy observed in the study sample.

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

Results on the clinical effect of treatment for the two groups of patients with osteonecrosis of the jaws post-administration of antiresorptives in correlation with epidemiologic parameters

A moderate positive correlation, statistically significant in the study group, between therapeutic efficacy and age of the subjects, compared to the control group, was observed.

The mean age of the patients was significantly lower in the study group (60.74 years) compared to the control group (67.29 years), the difference being confirmed by Student's t-test ($p = 0.002$).

Results on the clinical effect of treatment for the two groups of patients with osteonecrosis of the jaws post-administration of antiresorptives
in relation to diabetes mellitus

Using Pearson correlation coefficients to analyze the relationship between diabetes mellitus and the type of therapy received by subjects in the two study groups, a marginally statistically significant difference was observed between the two groups ($p = 0.0728$).

The distribution of clinical course according to the presence of diabetes did not differ significantly in the control group ($p = 0.1178$).

Although diabetic patients had a slightly higher percentage of worsening (20%) compared to non-diabetics (3.4%), the small size of the diabetic subgroup in the control group (n=10) limits the validity of the observations.

Results on the clinical effect of treatment for the two groups of patients with osteonecrosis of the jaws post-administration of antiresorptives
in correlation with hypertension

In hypertensive patients, statistically significant correlations ($p = 0.0110$) were observed with the efficacy of treatment of osteonecrosis of the jaws after antiresorptive drugs administration, with differences being present in 54.74% of the control group and only in 26.09% of the study group.

Results on the clinical effect of treatment for the two groups of patients with osteonecrosis of the jaws post-administration of antiresorptives
in correlation with antibiotic therapy

In patients who received empiric antibiotic therapy simultaneously, there was a marginally significant difference ($p = 0.0721$) between the two groups investigated.
In the control group, no significant differences were identified between patients who did or did not receive antibiotic therapy ($p = 0.6760$).

Chapter 6: Discussion

The medical rationale that guided me to investigate the effect of purine derivatives in the treatment of patients diagnosed with osteonecrosis of the jaws post-administration of antiresorptive drugs was based on the following considerations:

- Osteonecrosis usually has a chronic course, with periods of stationary lesions;
- Early practice of invasive surgery creates conditions for expanding the area of necrosis;
- Surgical risk can be significant in elderly patients with multiple comorbidities.

Ristow [4] 45 considers that conservative treatment of osteonecrosis of the jaws after antiresorptive drugs is a therapeutic option especially in the early stages of the disease (stages 0 and I), as well as in patients with contraindications to major surgery.

The concept of conservative treatment, according to *Albanese* [5], is based on the premise that osteonecrosis of the jaws after antiresorptive therapy is a slow-onset condition and minimally invasive intervention may be sufficient to limit the extent of necrosis and reduce associated complications.

Cavalcante et al. [6] suggest on the basis of an extensive systematic literature review that treatment with pentoxifylline-type purine derivatives and vitamin E could be of significant benefit in the management of osteonecrosis of the jaws after antiresorptive drug administration, especially in the early stages of this severely progressive condition.

I believe that an essential element in the rationale for the administration of the drug combination of purine derivatives and vitamiana E is the timing of the introduction of the drug during the course of the course of osteonecrosis of the jaws post-administration of antiresorptive drugs, as argued by *Owosho et al.* [7].

Dissard et al. [8] regarding the individualized therapeutic algorithm according to the stage of osteonecrosis of the jaws after antiresorptive drug administration, the efficacy of purine derivative therapy appears to be substantially higher in cases where it is instituted early.

These data are concordant with the results I obtained during my doctoral research, so that a greater improvement under drug treatment with purine derivatives can be expected in cases of osteonecrosis of the jaws post-administration of antiresorptive drugs, before the onset of major complications.

With regard to the duration of treatment with purine derivatives in the treatment of osteonecrosis of the jaws after the administration of antiresorptive drugs, based on the results obtained from my research, I believe that this factor may have a definite influence on the course of the disease, consistently observing a clear trend towards healing of lesions after the administration of purine derivatives for an average period similar to that reported by other researchers (4-6 months), including *Fan et al*. [9] or *On* et *al.* [10].

The intimate substrate of this beneficial effect of the administration of purine derivatives in the care of patients diagnosed with osteonecrosis of the jaws after antiresorptive drugs could be the vasodilator and hemoreologic pharmacologic effect of pentoxifylline (which also exerts a moderate anti-inflammatory action), superimposed on the potent antioxidant impact of vitamin E, as noted by *McLeod et al.* [11].

Although the results of my research show that patients with osteonecrosis of the jaws after parenteral antiresorptive drugs, regardless of the stage of the disease, the information available in the literature shows that in advanced cases of disease progression the results are less predictable and surgery remains inevitable in most cases, as shown by *Favia* [12].

In these circumstances, it is questionable to consider this line of therapy as an option of first choice or only as an alternative in situations where surgical treatment cannot be performed due to contraindications.

The interpretation of the results obtained through personal research and the studies that I have consulted from the literature available at the time of writing this doctoral thesis is burdened by major methodological discrepancies from one study to another - mainly represented by the small number of subjects included in the study samples, the lack of randomization and the heterogeneity of the protocol of administration of purine derivatives - as commented by *Colapinto* [13].

In this regard, I believe that multicenter, rigorously designed trials are needed, taking into account clear patient selection criteria, as well as standardized assessment of clinical, imaging and molecular response.

At the same time, it is imperative to establish objective indicators of response - clinical scores, biomarkers of systemic inflammation and functional imaging methods.

Among the major impact effects of ageing - as noted by *Burkhardt, Frisch* and *Bartl* [14]) - are a reduction in bone capillary density and local blood flow. On the other hand, *Seeman* [15] argues that purine derivatives induce reduction of osteoblast activity and slowing of bone remodeling processes. At the same time, *Donato* [16] observes increased vascular stiffness and altered endothelial function, which may reduce the vasodilator benefits of purine derivatives such as pentoxifylline.

Data from the literature suggest that elderly individuals may benefit from treatment with purine derivatives, provided that the therapeutic response is slower and longer periods of administration are required. *Mozzati* [17] observes in elderly patients with osteonecrosis of the jaws post-administration of antiresorptive drugs an increased efficacy of treatment with purine derivatives in combination with vitamin E.

Conversely, in young people, purine derivatives might be useful in early forms of osteonecrosis of the jaws post-administration of antiresorptive drugs, reducing the risk of progression to pathologic bone fractures, as stated by *Nishii et al* [18].

It is possible that the tolerance to purine derivatives may be influenced by the age of the patient, with treatment usually being well tolerated, with minimal risk of side effects, in young adults.

The results of my study confirm that the age factor statistically significantly influences the response to treatment with purine derivatives, which explains the faster and more intense therapeutic response observed in younger patients compared to older patients - who may require a longer duration of treatment and close clinical supervision.

Tailoring purine derivative therapy in the treatment of post antiresorptive jaw osteonecrosis osteonecrosis according to age and comorbidities is essential to maximize efficacy and reduce risks.

The presented data show that age significantly influences both systemic availability and clinical response to purine derivatives used in the therapy of osteonecrosis of the jaws; I consider it essential to assess liver function and renal function before initiating treatment in elderly patients diagnosed with post-antiresorptive osteonecrosis of the jaws, and it may be necessary to adjust therapeutic doses or modify the regimen to avoid accumulation of metabolites and the development of adverse reactions.

In the study we conducted, we did not identify statistically significant differences between patients' biological sex and the efficacy of therapy in post-antiresorptive osteonecrosis of amxillary postresorptive osteonecrosis.

However, the results should be analyzed with caution, since it is possible that in reality the therapeutic efficacy of purine derivatives is not homogeneous in the two categories of patients; I believe that individualization of pentoxifylline treatment according to sex is justified; and monitoring of side effects should be done separately by sex.

Ionescu et al. [19] show that rural patients are more likely to abandon long-term treatments, either due to lack of medical education or financial constraints.

However, in the study sample that we investigated, clinical outcomes are only marginally significantly superior in favor of urban patients, which may be explained by higher compliance and possibly because the treatment is well monitored.

With regard to possible differences in therapeutic efficacy, I recall the study by *Popescu et al.* [20], who claim that patients treated with pentoxifylline in urban areas have an overall rate of partial remission twice as high as in rural areas.

On the basis of these data, I assess that urban-rural disparities are not essential influences on the outcomes of purine derivative treatment in the approach to post-antiresorptive osteonecrosis of the jaws.

Bearing in mind the limitations of the present study, mainly related to sampling, I emphasize that there is the possibility of a cleavage between the two population groups, justified by lower accessibility to specialized medical services, low availability of medication and low level of health education - in the case of rural patients.

Regarding the efficacy of combined treatment with pentoxifylline and vitamin E in reducing the symptomatology and extent of osteonecrotic lesions, *Delanian et al*. [21] showed that this treatment resulted in partial or complete clinical remission in more than 70% of cases of osteoradionecrosis, and the mechanism of action is also extrapolable to post-antiresorptive osteonecrosis of the jaws [22].

Another retrospective study by *Patel et al* [23] showed a reduction in lesion size and a significant improvement in pain symptoms in patients treated with pentoxifylline purine derivatives, especially in severe mandibular lesions.

It may be considered that given the differences in vascularization and bone metabolism, the mandible appears to benefit more significantly from treatments that improve microcirculation.

In cases of localized osteonecrosis of the jaw, pentoxifylline may help to create a tissue environment more conducive to bone regeneration and healing.

At the same time, for osteonecrosis localization to the maxilla, where tissue perfusion is relatively better, the impact of pentoxifylline therapy may be less, but remains justified in refractory cases or with extensive necrotic lesions.

Pritchett [24] states that treatment with purine derivatives may represent a valuable adjuvant therapeutic option in the management of osteonecrosis in patients diagnosed with diabetes mellitus, due to its favorable effects on microcirculation and inflammation.

As shown by *Ward and Clissold*, cited by *Innoue* [25], pentoxifylline-type purine derivatives act mainly by increasing erythrocyte flexibility, reducing plasma viscosity and inhibiting platelet aggregation, thus favoring microvascular perfusion, including bone tissue.

The anti-inflammatory effect is supported by the reduction in the synthesis of proinflammatory cytokines, such as TNF-α and IL-1β, involved in the pathogenesis of chronic inflammation in diabetic patients, as stated by *Skopinski et al.* [26].

In my study I did not find statistically significant differences between the diabetic patients included in the study group and the control group. In conclusion, the use of prurin derivatives needs to be individually tailored to patients with diabetes mellitus, and their long-term efficacy in the therapy of post-antiresorptive osteonecrosis of the jaws needs validation by controlled clinical trials.

In conditions where bone microvascularization is impaired, osteonecrotic lesions evolve, as a consequence of local ischemia, a phenomenon that can be counteracted by the administration of purine derivatives, which promote bone repair processes, as *Kyrgidis* [27] and Kerachian [28].

In my study I identified a statistically significant difference between hypertensive patients who responded positively to lead derivative therapy compared to those who did not receive this type of drug regimen.

Subject to the fact that I did not consider usual antihypertensive medication in my study (due to lack of information on possible interactions with purine derivatives), the data obtained demonstrate the efficacy of the pentoxifylline-vitamin E combined regimen in patients with advanced stages of osteonecrosis of the jaws, most likely by improving bone perfusion and reducing inflammation.

Although the results of my study, consistent with observations in the recent literature, demonstrate the potential beneficial effect of purine derivatives in the treatment of post-antiresorptive osteonecrosis of the jaws by improving tissue perfusion and reducing local inflammation, their efficacy may be influenced by the duration of treatment with antiresorptive agents - an aspect insufficiently explored by the studies available to date.

Research has reported that the efficacy of pentoxifylline is more pronounced in the early stages of osteonecrosis, when vascular integrity is still partially preserved, as *McLeod and Brennan* [29].

In my study we did not establish statistically significant differences between the two groups in relation to the duration of parenteral osteoclast inhibitor treatment.

Marx, Cillo, and Ulloa [30] demonstrated that turnover markers play an important role in monitoring bone resorption processes and are frequently used in assessing the risk of complications in patients with post-antiresorptive osteonecrosis of the jaws; among these markers, C-terminal telopeptide (CTX), which reflects the level of degradation of type I collagen, is considered a marker of bone resorption - low values may suggest excessive suppression of bone turnover, while high values may indicate intense osteoclastic activity.

Although no statistically significant differences were identified in my study group, I believe that CTX monitoring 6-12 weeks after the initiation of treatment may provide useful clues regarding the progression of osteonecrosis and response to purine derivative therapy, may guide therapeutic decisions and allow for the personalization of treatment of patients with osteonecrosis.

Further research is needed to define a standardized protocol to monitor these markers in the context of purine derivative therapy.

Chapter 7: Conclusions and personal contributions

1. Osteonecrosis of the jaws post-administration of antiresorptive drugs is the result of a profound imbalance in bone homeostasis, with direct involvement of oxidative stress as a central pathogenetic factor; reactive oxygen species contribute significantly to bone and vascular cell dysfunction, facilitating the onset of necrosis.
2. Understanding these mechanisms opens new directions for the prevention and management of osteonecrosis of the jaws post-administration of antiresorptive drugs, through approaches aimed at controlling oxidative stress. In this context, the use of antioxidants of the purine derivative class in combination with vitamin E may be considered to favor bone regeneration and reduce the extent of necrosis.
3. Our research on the use of antioxidant therapy with purine derivatives in chronic forms of osteonecrosis of the jaws refractory to conventional treatment indicates a favorable trend in terms of reduction of painful symptoms and stabilization of necrotic lesions.

Although these results are promising, in the absence of a standardized protocol of administration and objective indicators to assess therapeutic response, validation of the efficacy of purine derivative therapy requires large randomized clinical trials.

4. The study we conducted showed that purine derivative therapy in osteonecrosis of the jaws after antiresorptive administration shows variable efficacy depending on the biological age of the patient, but further research is needed to assess the impact of age on therapeutic response and to allow customization of treatment according to the patient's biological profile.
5. According to the data documented during the PhD, the clinical efficacy of purine derivative therapy in osteonecrosis of the jaws after antiresorptive administration has been shown to be affected by the patient's background, which may in turn be influenced by the accessibility of treatment, monitoring of clinical course and interaction with other elements of the therapeutic

regimen.

6. Purine derivative therapy may represent a therapeutic alternative in the treatment of osteonecrosis of the jaws after antiresorptive drugs in patients with diabetes mellitus, due to their potential to reduce oxidative stress and inflammatory response, as well as to favor tissue regeneration; the implementation of purine derivative therapy in diabetic patients should be integrated in a multidisciplinary approach, taking into account the need to ensure a rigorous glycemic control and the complexity of associated comorbidities.

7. The efficacy of purine derivative therapy in patients with osteonecrosis of the jaws post antiresorptive therapy diagnosed with hypertension, although a biologically based clinical hypothesis, was insufficiently validated in my study, and further studies based on systematic exploration of the interaction between antihypertensive therapy, blood pressure control and response to pentoxifylline therapy are needed.

8. The efficacy of antibiotic therapy in osteonecrosis of the jaws post-administration of antiresorptive drugs is often limited, especially in advanced stages, where microbial colonization is favored by the presence of necrotic bone, which is difficult for antibiotics to penetrate. The results of the present research outline the idea of multimodal therapy, in which the synergistic use of antibiotics and purine-derivative antioxidants may provide superior results compared to antibiotic monotherapy, but large controlled clinical trials are needed to establish the real efficacy, optimal doses and timing of antioxidant treatment in this context.

9. Treatment with purine derivatives (in combination with vitamin E) offers a significant therapeutic potential in osteonecrosis of the jaws after antiresorptive drugs should be considered as an adjuvant option, used in addition to the standard treatment recommended by AAOMS for the management of advanced stages of the disease, especially in cases where surgery is not feasible or has general contraindications.

10. Although the evidence from the present research does not allow firm recommendations to be made, the results of the scientific investigation suggest that this approach could make an essential contribution to improving the prognosis of osteonecrosis of the jaws after antiresorptive drug administration, justifying further research in this area.

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