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Clinical Assessment of Drug Adjunctive Therapy Effects in Association with Chronic Generalized Periodontitis and Osteoporotic Disease*

SUMMARY

***Aim**: The present study proposes an assessment of the clinical effects on periodontal level generated by the adjunctive periodontal therapy with sub-antimicrobial doses of doxycycline in patients with chronic periodontitis and osteoporosis. **Materials and Methods**: The study group comprised 26 patients with chronic periodontitis and osteoporosis, divided in the study group (classical periodontal debridement and sub-antimicrobial doses of doxycycline for 3 months) and the control group (classical debridement only). We analyzed the periodontal parameters (probing depth, clinical attachment level, PBI and PI indices) at baseline, in the last day of medication and at 3 months after the drug therapy. **Results and Discussion**: The reduction of the moderate and profound pockets was higher for the group with drug adjunctive therapy. The sites with an initial depth of 0-3mm in the study group presented also a slight attachment gain. **Conclusions**: The therapy with sub-antimicrobial doses of doxycycline generated significant clinical improvement in patients with chronic periodontitis and osteoporosis, an improvement which can reduce the necessity of surgical procedures.*

Keywords: Chronic Periodontitis; Osteoporosis; Drug Adjunctive Therapy

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Introduction

Periodontal treatment was mainly focused along time on reducing the bacterial loading and disorganizing the biofilm by mechanical methods. Still, recent research led to a shift in the concept of the evolution of periodontal disease. Therefore, today it is well known that the lesions of superficial and profound periodontal tissues are a result of the immune and inflammatory defence mechanisms of the host[1]. It is clear that the pro-inflammatory mediators and cytokines, which are produced by the host cells, along with the proteolytic enzymes (like matrix-metalloproteinases - MMPs), have a significant role in the onset and evolution of the periodontal disease. These effects, especially those exerted on bone tissue, a result of the activation of the RANK/RANKL axis, are even more profound in cases of systemic impairment (like osteoporosis).

The importance of the inflammatory response of the host in the periodontal disease allows the opportunity to explore new therapeutic strategies by means of host response modulation. The modulation therapy can be associated to classical therapy of periodontal disease, with the main purpose of reducing the bacterial and inflammatory loading. Up to now, the only approved systemic therapy of host response modulation in the periodontal disease is the therapy with sub-antimicrobial doses of doxycycline (Periostat®), which inhibit the MMP activity. The tetracyclines and their analogues can

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inhibit certain MMPs (like collagenase and gelatinase)[2], including those which mediate the bone resorption[3,4]. Various studies discovered that these drugs can stimulate the osteoblast activity, production of collagen and bone neo-formation[5-7]. One of the maladies which could benefit of this type of therapy is osteoporosis[8]. Moreover, Williams[9] demonstrated that minocycline could enhance bone production and lower the resorption, with a higher bone mineral density in ovariectomized rats.

The present study aims to analyze changes in clinical periodontal parameters that can be expressed as a consequence of host response modulation therapy with sub-antimicrobial doses of doxycycline in patients with periodontal disease and osteoporosis.

Materials and Method

The study comprised 26 patients, with the age between 44 an 65 years old, done between February 2012 and November 2014 at the Periodontology Clinic of "Gr.T.Popa" UMPh, Iasi. The study followed principles stated in the Declaration of Helsinki; every person was informed regarding methods and purpose of the present study, and a signed informed consent was obtained from every patient.

In order to avoid any risk of biased results, smokers, patients with systemic infectious/inflammatory diseases (except osteoporosis), allergic patients or patients under therapy with bisphosphonates, patients with periodontal or antibiotic therapy in the last 3 months were excluded from the study.

Each patient was submitted to a clinical examination, which included a rigorous periodontal assessment. We evaluated the attachment loss (probing depth) by periodontal probing; probing depths higher than 3mm were considered to be pathological for teeth without gingival recessions. In case of gingival recession, the total attachment loss comprised the dimension of the recession plus the probing depth.

The patients were randomly divided in two groups: study group (n=13), with classical debridement therapy (scaling and root planing) plus sub-antimicrobial doses of doxycycline (20mg twice a day), for 3 months and the control group (n=17), on which only classical debridement therapy was performed.

The scaling was performed manually (with scalers) (Hu-Friedy) and ultrasonic; the root planing was conducted with Gracey curettes (Hu-Friedy). Each patient was given oral hygiene indications, according to each particular case.

The following periodontal parameters were analyzed: probing depth, clinical attachment level, PBI and PI indices at baseline, at the last day of drug therapy (i.e. 3 months from baseline) and at 3 months after the therapy cessation (i.e. 6 months from baseline). The periodontal sites were grouped according to the probing depth in: group 1 - superficial (0-3mm), group 2 - moderate (4-6mm) and group 3 - profound (≥7 mm).

The changes in probing depth and clinical attachment level were considered as measures of efficiency. The obtained data were statistically analyzed. The mean values of PBI, PI, probing depth (PD) and clinical attachment level (CAL) were calculated per patient and on a group and sub-group level. Mann-Whitney test and Wilcoxon test were used to assess the changes in time. P-values <0.025 were considered as significant. Mann-Whitney test with $p<0.05$ was used to assess the differences between groups.

Results

In the present study 30 patients were initially enrolled but 4 of them could not finalize the doxycycline therapy. Thus, the study used 2 main groups: study group (n=13) and control group (n=13). The demographic data are presented in table 1.

Table 1 Demographic data of investigated patients

	Study group	Control group
Age (mean value ± SD)	54.23±6.65 years	55.41±5.78 years
Age interval	48-67 years	50-68 years
Male : Female	1:12	2:11
Urban : Rural	7:6	8:5

We assessed a total number of 3422 sites. The site distribution at baseline is presented in table 2. The distribution of superficial, moderate and profound sites was very similar between groups ($p>0.05$). There was not a significant difference between groups at baseline concerning the probing depth (Tab. 3). Significant differences for superficial sites could not be observed ($p>0.05$). Moderate and profound sites presented significant lowering of probing depth ($p<0.025$).

Table 2 Distribution of the probing depth results at baseline

Probing depth	Study group	Control group	Total
0-3 mm	638 (36.21%)	660 (39.76%)	1298
4-6 mm	748 (42.45%)	686 (41.32%)	1434
≥7 mm	376 (21.34%)	314 (18.92%)	690
Total	1762	1660	3422

Even though the mean value of the reducing for moderate and profound sites was higher for the study group than for the control (moderate: 1.8 mm and 1.46 mm, respectively; profound: 3.38 mm and 2.57 mm, respectively), the difference was not significant ($p>0.05$). The analysis at 3 months of the sites with an initial depth ≥7 mm demonstrated a higher percentage of reductions of at least 3mm following the doxycycline intake (66.4%), when compared to the control group sites (55.1%), without reaching a significant level ($p>0.05$). Still, at 6 months the percentage of sites with an improvement ≥3 mm was significantly higher ($p=0.011$) for the doxycycline group (Fig. 1) when compared to the control group (73.4% and 49.7%, respectively).

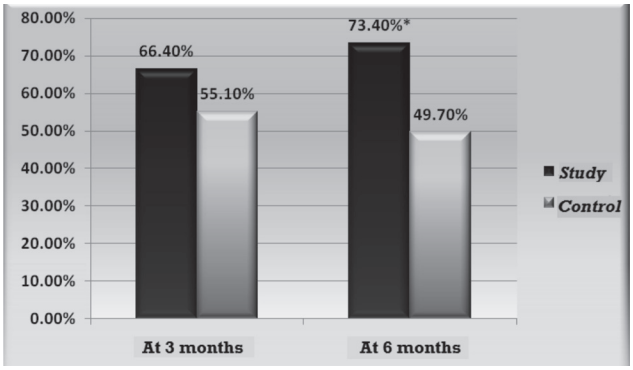

*Figure 1. The percentage of profound pockets which presented probing depth decreases higher than 3 mm from baseline; *Significant difference from the control group ($p<0.05$)*

Table 3 Probing depth and clinical attachment level at baseline, at 3 months and at 6 months

	Study group			Control group		
	Initial	After 3 months	After 6 months	Initial	After 3 months	After 6 months
Probing depth 4-6 mm	4.97±0.08	3.23±0.13*	3.17±0.13*	4.97±0.07	3.44±0.10*	3.51±0.15*
Attachment 4-6 mm	6.16±0.18	5.17±0.17*	5.04±0.17*	6.11±0.30	5.10±0.27*	5.33±0.32*
Probing depth ≥7 mm	7.67±0.10	4.45±0.30*	4.29±0.26*	7.43±0.08	4.65±0.15*	4.86±0.25*
Attachment ≥7 mm	8.63±0.29	6.79±0.30*	6.48±0.28*	8.12±0.21	6.38±0.39*	6.36±0.40*

*Signification level from baseline ($p<0.025$)

The clinical attachment level at baseline did not present significant differences in the sites of the 3 subgroups (Tab. 3). The moderate and profound sites demonstrated significant attachment improvements at 3 and 6 months, when compared to baseline ($p<0.025$). The superficial sites did not present significant changes throughout the study period ($p>0.05$).

The superficial sites in the control group presented a slight attachment loss (-0.04 mm at 3 months, -0.03 mm at 6 months). On the other hand, the superficial sites in the study group manifested a slight attachment gain, but without reaching a significant level between groups. Even though the attachment gain in moderate and profound sites was higher for the study group (1.12 mm) when compared to the control group (0.78 mm), there was not a significant difference (Tab. 3).

PBI and PI values presented significant improvements between baseline and the re-evaluations at 3 and 6 months ($p<0.025$), with no significant differences between groups.

Discussion

The present study proposed an evaluation of the efficiency of the classical periodontal therapy associated with sub-antimicrobial doses of doxycycline (20mg twice a day, for 3 months) *versus* classical therapy alone in patients with osteoporosis and periodontal disease.

Doxycycline can inhibit the activity of MMPs, a capacity which was confirmed in numerous studies. Minocycline, doxycycline and tetracycline can inhibit the collagenase activity, while other antibiotics do not present an effect on collagenase[2]. Doxycycline has a much lower inhibitory concentration (IC50515 mM) than minocycline (IC505190 mM) or tetracycline (IC505350 mM), thus indicating the fact that a much lower dose of doxycycline may be necessary to reduce the collagenase level by 50%, when compared to other tetracyclines[10]. Moreover, doxycycline proved to be more efficient in blocking the activity of PMN collagenases (MMP-8) than of the fibroblastic collagenases (MMP-1)[11,12], suggesting the fact that doxycycline could be a safe therapy measure

in reducing the collagenase levels without interfering with the normal turnover of the connective tissue.

Doxycycline contributes to lowering the connective destruction by inhibiting the pro-inflammatory mediators (including IL-1 and TNFα)[13], and by an uprising collagen production, osteoblast formation and bone formation[2]; the latter aspect is of major importance particularly for the osteoporosis patient, where bone mass is affected.

In our study the majority of patients were females; this fact supports the literature data, which present a higher frequency of osteoporosis in female patients than in male patients. The females present a total bone mass lower than the males and the maximal bone mineral density (BMD) is reached on lower age for females (around 25 years old, with 98% of total definition of skeletal mass up to 20 years old) than in males (around 30 years old). The females reach menopause at a mean age of 50-51 years old; the lower oestrogen level in peri-menopause period (3-5 years before menopause) and after menopause (1 year without menstrual cycle) determines an accelerated bone loss[14]. These aspects are also critical if we talk about an associated inflammatory disease such as periodontitis.

Caton et al[15] established that decreases of PD of at least 3 mm are clinically relevant. In our study, the percentage of profound sites with decreases of at least 3 mm was significantly higher at 6 month for the doxycycline group. This result has a special importance if we consider the fact that such profound sites are candidates for surgical procedures. Therefore, we can state the fact that the adjunctive doxycycline therapy can reduce the probability of need for surgery and discomfort associated with this. Further studies are necessary to assess the impact of such therapy in patients with periodontitis and osteoporosis also on molecular level (by gingival crevicular fluid examination), on the pro-inflammatory markers, and on systemic level, by correlations with the bone mineral density.

The 3 months intake therapy was well tolerated, without adverse effects (gastro-intestinal troubles etc.). This aspect might suggest that the modulation therapy with doxycycline could represent a safe approach in the long term treatment of the periodontal disease.

Conclusions

We demonstrated that the adjunctive therapy with sub-antimicrobial doses of doxycycline (intake of 20 mg twice a day, for 3 months), associated to the classical debridement therapy, generated significant clinical improvements in patients with periodontal disease and osteoporosis, improvements which persisted throughout the study period and that could prevent the necessity of surgical interventions.

We also demonstrated that the relatively superficial sites (0-3 mm) from the study group presented a slight attachment gain, while this subgroup of sites in the control group presented a slight attachment loss; this fact supports the efficiency of the therapy of the host response modulation with sub-antimicrobial doses of doxycycline.

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