THE EFFECTS OF THE ADJUNCTIVE THERAPY WITH SUBANTIMICROBIAL DOSES OF DOXYCYCLINE IN PATIENTS WITH OSTEOPOROSIS AND CHRONIC PERIODONTITIS

Irina-Georgeta Ursărescu*, Liliana Păsărin, Sorina-Mihaela Solomon, Daniel Cioloca, Cristala Diana Nitescu, Mădălin Boatcă, Silvia Mârțu

"Grigore T. Popa" University of Medicine and Pharmacy - Iași, Romania, Faculty of Dental Medicine, Department of Periodontology

*Corresponding author: Irina – Georgeta Ursarescu, DMD, PhD
"Grigore T. Popa" University of Medicine and Pharmacy - Iași, Romania;
e-mail: irina_ursarescu@yahoo.com

ABSTRACT

The **aim of the study** was to analyse the periodontal clinical changes generated by the adjunctive periodontal therapy with sub-antimicrobial doses of doxycycline in patients with chronic periodontitis and osteoporosis. **Materials and methods**: The study was conducted on 26 subjects with chronic periodontitis and osteoporosis, divided in study group (classical periodontal debridement and sub-antimicrobial doses of doxycycline for 3 months) and the control group (classical debridement only). We analysed the probing depth, clinical attachment level, the PBI and PI indices at baseline, in the last day of medication and at 3 months after the drug therapy. **Results and discussions**: The reduction of the moderate and profound pockets was higher for the study group when compared to the control group. In the control group, the sites with an initial depth of 0-3mm presented a slight attachment loss at 3 and 6 months, while the same depth sites in the study group presented 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, inflammatory response modulation, doxycycline

BACKGROUND

The periodontal treatment was mainly focused along the 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 proinflammatory mediators and the cytokines which are produced by the host cells, along with the proteolythical enzymes (like matriceal 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 with the main purpose of reducing the bacterial and inflammatory loading.

Up until 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 inhibit certain MMPs (like colagenase and gellatinase) [2], including those which mediate the bone resorption [3,4]. Various studies discovered that these drugs can stimulate the osteoblast activity, the production of collagen and bone neo-formation [5,6,7]. One of the maladies which could benefit of this type of therapy is osteoporosis [8]. Moreover, Williams et al. [9] demonstrated that minocycline could enhance the bone production and lower the resorption, with a higher bone mineral density in ovariectomized rats.

AIM OF THE STUDY

The present study aims to analyse the changes in clinical periodontal parameters which can be exerted by host response modulation therapy with sub-antimicrobial doses of doxycycline in patients with periodontal disease and osteoporosis.

MATERIAL AND METHODS

The study was conducted on 26 patients, with the age between 44 and 65 years old, during February 2012- November 2014, in the Periodontology Clinic of ”Grigore T. Popa” UMPh, Iași.

The methodology of the study respected the principles stated in the Declaration of Helsinki; every subject was informed regarding the methods and the 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 as pathological on 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 planning) 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 planning was conducted with Gracey curettes (Hu-Friedy).

Each patient was given oral hygiene indications, according to each particular case.

The following periodontal parameters were analysed: probing depth, clinical attachment level, PBI and PI indices at baseline, at the last day of drug therapy and at 3 months after the therapy cessation (at 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 (≥7mm).

The changes in probing depth and clinical attachment level were considered measures of efficiency. The obtained data were statistically analysed. The mean values of PBI, PI, probing depth (PD) and clinical attachment level (CAL) were calculated per

patient and on an 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 two main groups: study group (n=13) and control group (n=13). The demographic data are presented in Table 1.

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 (Table 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 1. Demographic data of the study groups

	Study group	Control group
Age (mean value± standard deviation)	54,23±6,65 yrs	55,41±5,78 yrs
Age interval	48-67 yrs	50-68 yrs
Male : Female	1:12	2:11
Urban : Rural	7:6	8:5

Table 2. Distribution of subgroups according to the probing depth at baseline

Probing depth	Study group	Control group	Total
0-3mm	638 (36,21%)	660 (39,76%)	1298
4-6mm	748 (42,45%)	686 (41,32%)	1434
≥7mm	376 (21,34%)	314 (18,92%)	690
Total	1762	1660	3422

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

	Study group			Control group		
	Initial	At 3 months	At 6 months	Initial	At 3 months	At 6 months
Probing depth 4-6mm	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 4-6mm	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 ≥7mm	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 ≥7mm	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)						

Even though the mean value of the reducing for moderate and profound sites was higher for the study group than for the control (moderate: 1.8mm and 1.46mm, respectively;

profound: 3.38mm and 2.57mm, respectively), the difference was not significant (p>0.05). The analysis at 3 months of the sites with an initial depth ≥7mm 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 ≥3mm was significantly higher (p=0.011) for the doxycyline group when compared to the control group (73.4% and 49.7%, respectively) (figure 1).

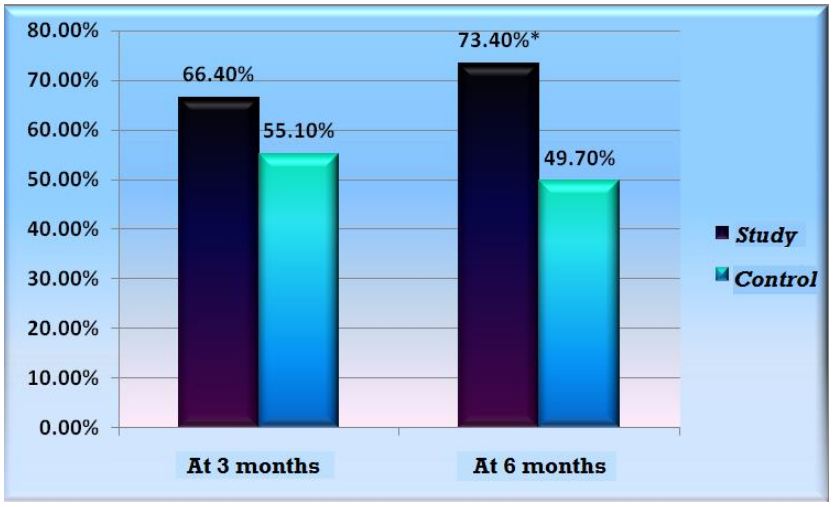

Figure 1. The percentage of profound pockets which presented probing depth decreases higher than 3mm from baseline; *significant difference from the control group (p<0.05)

The clinical attachment level at baseline did not present significant differences in the sites of the 3 subgroups (p>0.05) (Table 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 (-0.04mm at 3 months, -0.03mm 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 (1.12mm) when compared to the control group (0.78mm), there was not a significant difference (p>0.05) (Table 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.

DISCUSSIONS

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

Doxycyline can inhibate the activity of MMPs, a capacity which was confirmed in numerous studies. Minocycline, doycycline and tetracycline can inhibit the collagenase activity, while other antibiotics do not present an effect on collagenase [2]. Doxycyline 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 by 50% the collagenase level, when compared to other tetracyclines [10]. Moreover, doxycycline proved to be more efficient in blocking the activity of PMN colagenases (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 proinflammatory mediators (including IL-1 and TNFα) [13], and by an uprising collagen production, of the osteoblast formation and bone formation [2]; the latter aspect is of major importance particularly for the osteoporosis patient, on whom the bone mass is affected.

In our study the majority of patients were of female gender; 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 aspect are critical if we are talking also about an associated inflammatory disease such as periodontitis.

Caton et al. established that decreases of PD of at least 3mm are clinically relevant [15]. In our study, the percentage of profound sites with decreases of at least 3mm 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 surgical interventions and also the discomfort associated with these.

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 proinflammatory markers, and on systemic level, by correlations with the bone mineral density.

CONCLUSIONS

We demonstrated in our study that the adjunctive therapy with sub-antimicrobial doses of doxycycline (intake of 20mg 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 which could prevent the necessity of surgical interventions.

We also demonstrated that the relatively superficial sites (0-3mm) 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.

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.

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