REVIEW ARTICLE

The adjunctive use of locally delivered tetracyclines in periodontal therapy: A narrative review of the recent literature

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Abstract

Antibiotics belonging to the category of tetracyclines have been widely used in periodontal therapy due to their specific characteristics that makes them effective both against the microorganisms responsible of the periodontal disease and against the enzymatic products responsible of the periodontal breakdown. A search of the recent literature (January 2009-December 2014) was conducted in order to make a review of the use of tetracyclines for local use in periodontal therapy. From this review we can infer that the use of local tetracyclines brings significant advantages in periodontal therapy. However, to date, it is not possible to establish guidelines on the use of these agents given the heterogeneity in the protocols used in the various studies and the lack of a consensus accepted by the scientific community. The local locally delivered tetracyclines is effective in the treatment of periodontal disease when used in addition to the mechanical therapy and is particularly effective in cases of localized acute lesions or individual sites unresponsive to the causal therapy.

Introduction

Periodontitis is a multifactorial inflammatory disease with a bacterial etiology, characterized by loss of periodontal attachment and bone destruction and is associated with several risk factors.[1,2] Despite more than 700 bacterial species have been identified in the oral microbiota, only a small group of 10-15 species are significantly involved in the beginning and progression of periodontal diseases, among which *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythensis*, and *Treponema denticola* are the most common.[3]

Among the tissue destruction mechanisms implicated in the pathogenesis of periodontal disease, of particular importance is the action of proteolytic enzymes (released by periodontopathogens and from host defenses) such as matrix metalloproteases (MMPs), which have as main target of their destructive activity the collagene.[4]

The objective of the initial periodontal treatment is the re-establishment of the biological compatibility of the root surfaces affected by periodontal disease, in order to stop the progression of the disease. The non-surgical therapy seeks to remove from the tooth surface and the adjacent soft tissues both the living bacteria hosted in the biofilm and the microbial organisms in the calcified biofilm. The non-surgical therapy, while showing significant long-term success in periodontal treatment of most of the patients, presents some limitations as the difficulty to reach deep sites, winding pockets or furcation involvements, and the inability to remove bacteria from the dentinal tubules, lacunae, root hollows, and soft tissues. Antibiotic therapy may therefore be of considerable aid when used in addition to the mechanical therapy.

The systemic antibiotic therapy, mainly indicated in aggressive generalized conditions, has limitations and drawbacks such as the low concentration in the gingival crevicular fluid (GCF) and in the periodontal tissues, the induction of bacterial resistance, the possible systemic toxicity.[5]

Given the disadvantages of systemic therapy and the specific indication in aggressive conditions, while not being an alternative to scaling and root planing (SRP), there are localized forms of periodontitis wherein topical antibiotic delivery can be used in addition to SRP. Although there are no detailed guidelines, the main indications are represented by

deep active sites and sites with recurrent probing depth (PD) greater than or equal to 5 mm. In these situations, the overall effect of the application of the subgingival antimicrobials is statistically significant greater, in terms of PD and clinical attachment level (CAL) compared to the SRP alone. The benefit in the reduction of PD is most evident with the use the antibiotics of the tetracycline class.[6]

Tetracyclines

Tetracyclines are bacteriostatic antibiotics with broad spectrum, therefore effective both on Gram-negative and on Gram-positive, aerobic and anaerobic bacteria. They include tetracycline, minocycline, and doxycycline.

Most of the subgingival microorganisms are susceptible to tetracycline at a concentration of less than 1-2 μg/mL. The minimum inhibitory concentration required to inhibit the growth of 90% of the strains is less than 6 μg/mL.[7]

Unlike other antimicrobial agents, as amply demonstrated by clinical studies and in animals, tetracyclines are able to directly inhibit MMPs, and collagenases expressed by immune cells of the host and by microorganisms.[8,9]

Finally, doxycycline in particular has shown positive effects by stimulating the maturation and differentiation of osteoblast cell, increasing the activity of alkaline phosphatase, thus expounding an important effect on the periodontal regeneration.

Tetracycline

Normally, the topical administration of tetracycline in the pharmaceutical formulation in fibers. The application of subgingival fibers of tetracycline has showed relatively high concentrations of antibiotic in the GCF for 10 days.[11]

Patients who receive this type of adjunctive therapies with SRP can benefit from the application of topical tetracycline especially in the maintenance phase to 12 months of treatment, generally showing a modest gain in clinical attachment (CAL gain) and/or reduction of PD, when compared to SRP alone.[12]

Sachdeva and Agarwal, however, revealed that the use of combination therapy is actually more effective than SRP alone in improving the clinical parameters of plaque index (PI), gingival index (GI), PD, and CAL, anyway they only reported results at 3 months follow-up.[13]

An alternative to the use of the fibers of tetracycline is the application of a solution of tetracycline via microbrush, especially in sites where it is not recommended a vigorous mechanical therapy during maintenance programs, with a more favorable cost/benefit ratio for the patient.[14]

Minocycline

The release of subgingival minocycline has been studied in different forms. Applying a gel of minocycline in addition to SRP was effective in reducing the PD in sites with moderate to severe periodontal disease, although a recent study showed a statistically significant difference compared to the control represented by SRP alone.[15,16]

Currently, the topical formulation which is more used is a product with physical properties of a powder and consists of resorbable microspheres of minocycline. The effectiveness of the use of resorbable microspheres of minocycline (Arestin; OraPharma, Horsham, PA, USA) was evaluated in a split mouth randomized clinical trial on 60 sites in 15 patients with chronic periodontitis.[17] In each patient, two sites were treated with only the SRP and two sites were treated with the microspheres of minocycline in addition to the SRP. A significant reduction in all parameters considered (PI, GI, gingival bleeding index; PD) was observed in the test group after 6 months of follow-up. These results were confirmed in a recent study by Bland *et al.*[18] in which, at 30 days from the baseline, the use of minocycline microspheres in addition to the SRP has determined a statistically significant improvement in all the clinical parameters considered (PD, Bleeding on Probing [BoP] CAL) and all the microbiological endpoints defined as reduction in the proportions and in the number of bacteria of the red complex (*Tannerella forsythensis*, *Porphyromonas gingivalis*, *Treponema denticola*). The reduction of these bacterial species is significantly related to a reduction of PD, especially as regards *T. forsythensis*.

In another study, it was demonstrated the superiority of topical therapy with minocycline microspheres in addition to SRP in significantly improving the CAL when compared to treatment with metronidazole gel 25% + SRP, or simple SRP after 3 months of follow-up.[19]

Doxycycline

Numerous clinical studies have demonstrated the efficacy of controlled-release systems containing doxycycline when used in addition to SRP.[20,21]

The local delivery device used most often is the topical formulations of doxycycline gel, usually 10% (Atridox; Block Drug, Jersey City, NJ, US) or 14% (Ligosan Slow Release®; Heraeus Kulzer GmbH, Germany).

The clinical efficacy of both doxycycline gels, evaluated in terms of gain in clinical attachment in periodontal pockets, as well as their pharmacokinetics in GCF and saliva, has been investigated in several studies.[22,23]

The effectiveness of 10% topical doxycycline has been recently assessed in a clinical study on 60 sites (with PD between 5 and 7 mm) in 60 patients with chronic periodontitis.[24] Thirty patients were treated with 10% topical doxycycline + SRP while the remaining 30 with SRP + placebo containing glycerin. At 6 months from treatment, in deep pockets (>5 mm), statistically significant differences were observed between the two groups in favor of the test group as regards the average reduction of PD as well as regards the value of CAL-gain. For 5 mm pockets, there were no significant differences between the test group and the control.

Similarly, another recent study has shown that there are significant differences between the combination therapy and the SRP alone in the treatment of PD with pockets between 5 and 7 mm. The authors also claim that the application of topical

doxycycline 10% alone is equally effective to SRP alone in reducing the clinical signs of periodontitis from baseline to 3 months; however, the study presents a limited number of patients.[25]

The effects of a single topical application of 14% doxycycline in addition to the SRP, in patients with persistent/recurrent periodontitis, were analyzed in a randomized multicenter clinical trial, comparing them with the simple mechanical therapy.[26] A significant effect in the reduction of PD at 3 months was observed only for pockets with initial depth greater than or equal to 5 mm; a beneficial effect was observed at 6 months for 6 mm pockets; no benefit was observed at 12 months.

Two different studies have also evaluated the use of these two formulations containing doxycycline at different concentrations, as an adjunct to SRP in the treatment of multi-rooted elements with furcation involvements.[27,28] One of these two studies showed that, despite the local antibiotic therapy in addition to SRP can make a modest benefit in the short term (3 months) in helping to slow the progression of furcation involved, and sometimes significantly reduce the horizontal loss of attachment compared to the SRP alone, there are no statistically significant differences at 6 and 12 months between the two therapies.[27] The second study has clearly demonstrated that combination therapy does not bring significant benefits in reducing the degree of involvement of furcations than the simple non-surgical debridement.[28]

Two other studies have investigated further controlled release systems of doxicycline.[29,30] One study compared doxicycline "biodegradable implants" (polymer films based on poly-epsilon-caprolactone dissolved in dichloromethane and carbopol containing 60 mg of doxycycline hyclate) with a gel containing 25 mg of doxycycline which in contact with the GCF, allows a controlled release of the drug.[29] Thirty patients with chronic periodontitis with residual pockets greater than or equal to 5 mm were divided into three groups 2 weeks after causal therapy: The first group received the application of doxycycline gel, the second the biodegradable implants, and the third only SRP. Both groups of patients who received the drug treatment showed reductions of local PI, GI, PD, and CAL gain 90 days after initiation of therapy compared to the control group. Another study, however, has first tested *in vitro,* and then *in vivo*, the efficacy of the microspheres of doxycycline in patients with chronic periodontitis.[30] Fourteen patients were randomly assigned to two groups of 7 patients each. All patients received one session of SRP in full mouth; the control group received the application of microspheres doxycycline only at baseline, while the group tests at baseline, at 1 month and 3 months. At 6 months from baseline, the test group showed a statistically significant reduction of PD compared to the control group; other outcomes considered in the following study, relative attachment level, BOP and PI, showed no significant differences between the two groups.

Conclusions

The analysis of the current evidence shows heterogeneous results, in part due to the different protocols used in the studies, with clear differences in target populations, methods of study design and duration. The lack of uniformity in the use of protocols adopted in studies on these devices could challenge their real validity, although there are studies in which the benefit is clearly demonstrated.

In conclusion, many studies in the literature report encouraging results about the use of locally delivered tetracyclines, there aren't, however, sufficient evidence to support well-defined protocols or dosages to apply in certain clinical conditions. It is therefore necessary to define a consensus concerning the establishment of shared guidelines that can guide the clinician in selecting and using the different products available on the market today.

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