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### Subantimicrobial Dose Doxycycline in Treatment of Periodontitis

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#### Abstract

Host inflammatory response to periodontal pathogens is double edge sword. It aims at limiting disease progression, but maximum amount of destruction in periodontal disease is attributed to host response to periodontal pathogens. Host modulation therapy (HMT) has potential to modulate and reduce the amount of periodontal tissue destruction by ameliorating excessive or pathologically elevated inflammatory processes. Various drugs have been evaluated for modulating host response. However, subantimicrobial dose doxycycline (SDD) is only drug approved for use in periodontitis. In this review, use of SDD in treatment of periodontitis is discussed.

**Keywords:** Host modulation therapy, subantimicrobial dose doxycycline, periodontitis

#### Introduction

Although periodontal disease is initiated by subgingival microbiota, progression of disease is influenced by response of host to oral microbiota<sup>[1]</sup>. Traditional periodontal treatment includes scaling and root planing, surgical procedures and antimicrobial therapy to suppress bacterial loads in periodontal pocket. However, due to increased knowledge on pathogenesis of periodontal disease, host modulation therapy (HMT) is considered to be an important part of periodontal treatment. HMT means modifying or modulating destructive or damaging aspects of inflammatory host response that develops in periodontal disease as a result of chronic challenge presented by subgingival bacterial plaque.

Various drugs have been tried to modulate host response such as nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates and tetracycline family of compounds and their chemically modified analogues. However till today, subantimicrobial dose doxycycline (SDD) is only drug that has been approved for host modulation in periodontal therapy. SDD is approved by the US Food and Drug Administration, the UK Medicines and Healthcare Products Regulatory Agency, and by similar agencies in other countries throughout the world. It was introduced under the trade name Periostat (Colla Genex Pharmaceuticals Inc, Newtown, PA). It is a 20-mg dose of doxycycline hyclate that is taken twice daily for periods of 3-9 months as an adjunct to root surface instrumentation in the treatment of periodontitis.

#### Mechanism of action for SDD

Matrix metalloproteinases (MMPs) are family of zinc-dependent enzymes capable of degrading a variety of extracellular matrix molecules, including collagen. Excessive quantities of MMPs are secreted in inflamed periodontal tissues and balance between MMPs and their inhibitors is disrupted, resulting in breakdown of connective tissues. Doxycycline has ability to down-regulate MMPs through various mechanisms<sup>[2]</sup>. SDD directly inhibits active MMPs by cation chelation (dependent on Ca<sup>2+</sup> and Zn<sup>2+</sup> binding properties) and inhibits oxidative activation of latent MMPs. SDD down regulates expression of key inflammatory cytokines (interleukin-1, interleukin-6 and tumor necrosis factor  $\alpha$ ) and prostaglandin E<sub>2</sub>. SDD scavenges and inhibits production of reactive oxygen species produced by neutrophils. SDD inhibits MMPs and reactive oxygen species thereby protecting  $\alpha$ 1-proteinase inhibitor, and thus indirectly reducing tissue proteinase activity. SDD stimulates fibroblast collagen production and reduces osteoclast activity and bone resorption. SDD directly influences proliferation and differentiation of osteoprogenitor cells<sup>[3]</sup>. SDD does not alter oral microbiota<sup>[4]</sup> and does not lead to antibiotic resistance<sup>[5]</sup>.

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### Studies on SDD as an adjunct to periodontal therapy

In randomized controlled trial, adjunctive treatment of SDD with SRP in patients with moderate chronic periodontitis, resulted in better improvement of clinical attachment level and probing depth than patients treated with SRP alone [6]. Long term study found beneficial effects of adjunctive use of SDD in terms of improvement in clinical parameters and decrease of MMP 8 in GCF [7]. Difference revealed in periodontal microbiota due to adjunctive treatment with SDD is due to anti-inflammatory and anti-collagenolytic effect of SDD and is not attributed to anti-microbial action of doxycycline [8]. However, no difference in subgingival microbiota with use of SDD is reported in other study [9]. Along with improvement in clinical parameters, reduction in GCF laminin-5 gamma2 chain levels is also reported with adjunctive treatment of SDD [10]. Intact laminin-5 serves to anchor epithelial cells on basement membrane. On other hand, cleaved laminin induces inflammation and stimulates apical migration and proliferation of epithelial cells [11] resulting in periodontal pockets and is chemoattractant for leucocytes [11]. Reduction in cleaved laminin with SDD may be another mechanism responsible for clinical improvement in periodontitis. GCF extracellular matrix metalloproteinase inducer (EMMPRIN), a unique upregulator of MMP expression is significantly reduced with adjunctive treatment of SDD [12]. SDD reduces levels of tissue plasminogen activator in GCF [13]. Tissue plasminogen activator is responsible for initiation and progression of periodontal disease [14]. One study reported significant reduction in clinical parameters and MMP-8 in GCF without any difference in tissue inhibitors of MMPs, IL-6 and MMP-9 of GCF [15]. In coronary artery disease patients, SDD with SRP resulted in significant improvement in pocket depth, gingival index and serum levels of apoprotein A and high density lipoprotein [16]. SDD is also advantageous in geriatric patients with chronic periodontitis [17]. SDD is well tolerated with a low incidence of discontinuations due to adverse events [18]. After cessation of long term therapy with SDD, no rebound effect is noted in clinical and microbiological parameters depicting that stable results achieved with SDD are maintained after therapy [19]. SDD for periodontitis reduces HbA1c in patients with type 2 diabetes mellitus [20]. In post-menopausal women on supportive periodontal therapy, no benefit of SDD is reported [21]. In smokers, conflicting results with no effect [22] to additional benefits with SDD are reported [23].

### Conclusion

SDD is beneficial as an adjunct to SRP in treatment of periodontitis by modulating host response. To increase compliance for adjunctive therapy with SDD, patients should be explained rationale of HMT.

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