ISSN: 2574-1241
DOI: 10.26717/BJSTR.2018.07.001513
Muna S Elburki. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

Mini Review Open Access

Systemic Host Modulation Therapy in the Treatment of Periodontal Disease

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Received: June 06, 2018; **Published:** August 01, 2018

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Abbreviations: SBU: Stony Brook University; HSDM: Harvard School of Dental Medicine; MMPs: Matrix Metalloproteinases; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; SDD: Sub-Antimicrobial-Doses of Doxycycline; CMTs: Chemically Modified Tetracyclines; ARDS: Acute Respiratory Distress Syndrome; CMC: Chemically Modified Curcumin; NOS: Nitric Oxide synth**ase**

Mini Review

In the mid1980s, Williams and his colleagues at the Harvard School of Dental Medicine (HSDM), and Golub and his group at Stony Brook University (SBU), addressed the importance of the Host Modulation Therapy (HMT) in periodontal disease by demonstrating

a) that non-steroidal anti-inflammatory drugs or NSAIDs such as flurbiprofen can inhibit alveolar bone loss in animal studies and in human clinical trials [1-4] and

b) that Tetracyclines, by NON-antibacterial mechanisms can inhibit host-derived Matrix metalloproteinases (MMPs) and osteoclast activity to suppress collagenase and bone resorption, processes essential for periodontal and other (e.g., Rheumatoid arthritis) diseases [5-7].

This paradigm shift at that time, with a focus on the host response, led to the search for novel therapies for periodontitis. These host-modulating therapies included:

The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

These are commonly used to treat pain and inflammation and include the inhibitors of the prostaglandins and other arachidonic acid metabolites which are associated with the pathogenesis of periodontitis [3,8,9]. Therefore, it was logical to use inhibitors of arachidonic acid metabolites, such as the NSAIDs, in treatment of periodontitis [1-4]. However, NSAIDs are frequently associated with gastrointestinal side effects, such as bleeding or perforation of gastroduodenal ulcers [10] and increased risk of CVD [11] and cannot be recommended for long-term use as a host modulating therapy [12]. Also, flurbiprofen, systemically administered did produce a "rebound" effect i.e., after stopping NSAID treatment, the disease severity rebounded and become even worse than that before this treatment was initiated [13].

The Tetracyclines

These are broad-spectrum antibiotics that unexpectedly were found to inhibit host-derived MMPs [14-16]. This property was first identified by Golub et al. [5-7] who demonstrated that a semi-synthetic tetracycline, minocycline had the ability to reduce pathologically-excessive collagenase activity even in a germ-free diabetic rat model. This was a seminal discovery for two reasons:

a) Because it identified for the first time that tetracyclines can inhibit mammalian (host-derived) collagenases and other MMPs

b) By mechanisms that were unrelated to their well-known antimicrobial activity [7].

Additional studies soon verified and expanded the use of tetracyclines as a potential treatment for periodontal disease because of these newly-recognized characteristics and their ability to inhibit pathologically-elevated collagenase activity [14,15,17,18]. The success of the tetracyclines was propelled into mass-market application when several novel formulations of TCs were developed including:

a) NON or sub-antimicrobial-doses of doxycycline (SDD), which were ultimately FDA approved for the treatment of periodontal disease (Periostat ®) [14,15,19-21] and later a NOVEL sustained-release formulation of SDD which was approved for treating the chronic inflammatory skin condition, rosacea (Oracea ®).

Although a number of researchers have tried to develop MMP-inhibitors (MMP-Is) to inhibit connective tissue degradation associated with inflammatory and other diseases, their efforts were not successful [22-24] for review); the only US-FDA approved systemically administered drug as MMP-Is are those based on TCs.

Doxycycline, when administered as a regular dose tetracycline, like most, if not all antibiotics, produces complications such as gastrointestinal disturbance, increased photosensitivity, and the emergence of antibiotic-resistant microorganisms [20,21]. They found, however, that lowering the dose of doxycycline to produce peak (C max) blood levels, <1μ g/mL, could eliminate these complications while providing essentially the same MMP inhibitory properties see [14,15,17] Other benefits to SDD include its low IC50 value and its proven safety in clinical trials on patients with both dental and medical conditions [16,25].

These data appear to be consistent with an earlier study by Lee et al. [5,7,10] in which humans requiring extensive periodontal surgery, allowing analysis of the excised gingival tissues, demonstrated that a combination of a low dose NSAID (which by itself was ineffective) combined with SDD synergistically reduced MMPs (collagenase, gelatinase and even PMNL elastase) in the excised gingival tissues. With SDD as an effective treatment for periodontal disease Golub et al. [5,6,7] then synthesized non-antibacterial analogs of tetracyclines and the first of these chemically-modified tetracyclines (4-dedimethylamino tetracycline; CMT-1) was generated by his team in 1987 [26] by the removal of the dimethyl amino group from carbon-4 of the TC molecule which is responsible for the antibiotic activity of this class of compounds. This chemical modification did not impair the MMP-I activity and some of these CMTs (such as CMT-3; 6-demethyl 6 deoxy 4-dedimethyl amino tetracycline) were in fact more potent MMP-Is than the antibiotic TCs [26]. A discussion of these follows.

Tetracycline Derived MMP-Is

Tetracycline analogs have been developed, i.e.., the chemically-modified tetracyclines (CMTs), which have lost their antibiotic activity, but which retained their calcium and zinc binding sites at carbon-11 and carbon-12 (a β-diketone moiety) and their proteinases-inhibitory properties. These have shown efficacy in experimental periodontitis and other diseases in animal studies [27,28] and in human clinical trials (see below). CMTs became an attractive option because, in theory, they would be able to reduce these pathologically elevated collagenase levels at higher doses than sub-antimicrobial-dose doxycycline without creating drug-resistant bacteria. A series of CMTs were synthesized and were tested for their potency as inhibitors of MMP activity [14]. Several CMTs such as CMT-1, CMT-2, CMT-3, and CMT-6 showed potential for the reduction of collagenase activity in various diseases. The lead compound, CMT-3, has shown efficacy in a pig-model of acute respiratory distress syndrome (ARDS), diabetes, arthritis and cancer [15,16,25-29] and in phase II clinical trials in humans with Kaposi's sarcoma, as an anti-angiogenesis drug. However, this compound did result in adverse events, specifically increased photosensitivity in these subjects [30-35] and to date, has not been developed further. However, a pilot study by Ryan et al. [16] using a much lower oral/systemic dose of CMT-3 (i.e., 10mg/day), rather than the 50-150mg/day in the phase I and II studies on cancer patients [33-35] did appear to reduce IL-1β and MMP-8 in human periodontal pockets [36].

Bisphosphonates

Are widely used in the treatment of systemic metabolic bone diseases as a result of their ability to inhibit osteoclast-mediated bone resorption. Because of their ability to increase the differentiation of fibroblast into osteoblast and to inhibit the activity of osteoclasts, it was tested in clinical trials in subjects with periodontitis [37,38]. However, within the last few years, the literature has indicated that bisphosphonate use, particularly intravenous preparations, may be linked to osteonecrosis of the jaws, and that their efficacy in periodontitis has not been consistent [39, 40].

Lipid Derived Mediators

Recently, new families of lipid-derived mediators, such as lipoxins, protectins, and resolvins, were found to possess potent anti-inflammatory/proresolving activity in vivo, specifically their ability to resolve acute inflammation [41]. More recently Naqvi et al. (2014) demonstrated that docosahexaenoic supplementation (an omega-6 fatty acid) combined with low dose aspirin significantly reduced periodontitis and gingival inflammation in humans in a double-blind placebo-controlled trial of 3 months duration [39].

Chemically Modified Curcumins (CMCs)

Numerous investigators have described various pharmacologic strategies to modulate the host response during periodontal disease, however only a non-antimicrobial tetracycline formulation is FDA approved for these patients. However, a significant drawback of the approved SDD is that this novel low-dose formulation cannot be increased in order to prevent the emergence of antibiotic-resistant bacteria. Evidence for the role of MMPs, cytokines, and other mediators in the pathogenesis of periodontal disease differentiates them as possible targets for a host modulation therapies. The properties of TCs and CMTs as inhibitors of MMPs is associated, at least in part, with zinc-binding by the compounds, in the catalytic domain of these proteinases [42]. Curcumin, which also has this enolic beta-diketone moiety was chosen as the next generation compound for MMP inhibition. However, due to curcumin's low absorption into the body and high rate of metabolism [43] it was modified in an attempt to increase its bioavailability and efficacy [42]. In order to increase the solubility and zinc-binding of curcumin, a series of curcumin analogs were synthesized with a carbonyl substituent at the C-4 position. Golub and his group recently designed new MMP-inhibitor compounds containing the same zinc-binding site as the tetracyclines, but which are bi-cyclic phenolic compounds rather than teracycles.

Golub and his group demonstrate that systemic administration of a newly developed chemically modified curcumin (CMC2.24) in locally and systemically-induced model of experimental periodontitis significantly inhibited alveolar bone loss and attenuated the severity of local and systemic inflammation [44-46]. Moreover, this novel chemically-modified-curcumin (CMC2.24) appears to reduce the pathologically-excessive levels of inducible MMPs to near normal levels but appears to have no significant effect on the constitutive MMPs required for physiologic connective tissue turnover. Additionally, a study performed on human monocytes

stimulated with endotoxin illustrated that CMC 2.24 was capable of reducing excessive levels of inflammatory mediators such as IL-1β, TNF-α, PGE2, and MCP-1 [42]. The same monocyte study also indicated that CMC 2.24 reduced the elevated levels of MMP-2, -9, -8, and -13 down to normal levels with potential host-modulation action [42]. There are additional novel host response therapeutic approaches (i.e. Nitric Oxide synthase (NOS) inhibitors, p38 MAPK inhibitors, NF-κB family inhibitors and TNF antagonists) to treat periodontal diseases currently in preclinical studies in various animal models with potential host-modulation action [47].

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2018.07.001513

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