REVIEW ARTICLE

Host Modulation Therapeutics in Periodontics: Role as an Adjunctive Periodontal Therapy

Muhammad Saad Shinwari[1], Farzeen Tanwir[2], Pakiza Raza Hyder[3] and Muhammad Humza Bin Saeed[4]

ABSTRACT

Host Modulation Therapy (HMT) is a treatment concept that reduces tissue destruction and stabilizes or even regenerates inflammatory tissue by modifying host response factors. It has been used for treating osteoporosis and arthritis for several decades. However, its use in dentistry has only been recently reported. The objective of this article is to present a review of the various literatures available on HMT and also its role as adjunct therapy in periodontics. For identifying studies for this review, a PUBMED search was carried out in 2013 for all articles published till December 2012. The search was restricted to English language publications only. Longitudinal prospective and retrospective studies were included in the search. The key words used were: Host Modulation Therapy; Sub antimicrobial dose doxycycline and Non-Surgical Periodontal Therapy. The main outcomes sought were host modulation therapeutics in periodontics. Exclusion criteria included cross sectional studies, short case series as well as studies with short follow-up periods. There is a paucity of literature on HMT in periodontics although the only drug approved by United States Food and Drug Administration (FDA) is a subantimicrobial dose of doxycycline (SDD) with highly predictable results as a host modulating agent in periodontal diseases and also an effective adjunctive therapy in various diseases of periodontium. However, more randomized controlled trials are needed to obtain clinical guidelines on the usage of other host modulating agents as adjunct as well as definite therapy for periodontal diseases. SDD is an effective adjunct therapy when used in dosage of 20mg twice daily for minimum 3 months duration in various periodontal diseases with predictable clinical outcomes. It is also recommended that future clinical research on anti cytokine drugs, chemically modified tetracycline and other HMT agents should be conducted so that new drugs are available with highly predictable results.

Key Words: *Host modulation therapy. Non-surgical periodontal therapy. Sub-antimicrobial dose of doxycycline (SDD). Periodontal disease.*

INTRODUCTION

Periodontal disease is a common chronic infectious disease of periodontium that has been attributed as one of the major causes of dentition loss.[1] Current data suggests that plaque biofilm and associated host response are mainly involved in the pathogenesis of periodontitis. Certain putative periodontal pathogens predominantly Gram-negative, anaerobic bacteria within biofilm are associated with periodontal disease initiation and progression.[2] The microbial challenge consisting of antigens, lipopolysaccharide and destruction is primarily by the host responses. The host responses are of mainly two types: anti-inflammatory or protective and proinflammatory or destructive.

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Figure 1: Flowchart of the literature search for host modulation therapy in periodontics.

[1] *Department of Periodontology, Pakistan Air Force Hospital, Islamabad.*
[2] *Department of Periodontology, Ziauddin University, Karachi.*
[3] *Department of Dentistry, Federal Government Polyclinic Postgraduate Medical Institute, Islamabad.*
[4] *Department of Community Dentistry, Islamic International Dental College, Islamabad.*

Correspondence: Dr. Muhammad Saad Shinwari, House No. 70/1-E, Opp. UBL Building, F-6/1, Nazim-ud-Din Road, Islamabad.
E-mail: msaadshinwari@gmail.com

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the first phase of the search, the titles of the articles were screened for appropriateness with the topic. Then full text articles for all relevant articles were obtained, each article was assessed independently. There were two reviewers involved in this search. The literature search has been illustrated in Figure 1.

Despite extensive basic and clinical research on pathogenesis of periodontal diseases over the years the contemporary treatment still focus on effective scaling and mechanical therapy on the root surface.[3] There has been a very little change in the treatment of periodontitis over the centuries; mechanical plaque biofilm disruption by the clinicians remains the mainstream of periodontal therapy.[4,5] A variety of other treatment modalities have been suggested for the treatment of periodontitis but only as adjunct to scaling and root planning such as systemic antibiotics, topical antimicrobials, laser therapy etc.[6,7]

The concept of host modulation has been universally implemented since last few decades by the physicians in treatment of chronic diseases such as rheumatoid arthritis and osteoporosis.[7] Although, Paul Goldhaber and Max Goodson began to implicate arachidonic acid metabolites as important inflammatory mediators of the bone loss in periodontitis in the 1970s but the concept of host modulation in dentistry was introduced by William and Golub in 1990. They concluded that "There are compelling data from animal and human trials indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be effective in slowing progression of periodontal disease".[8]

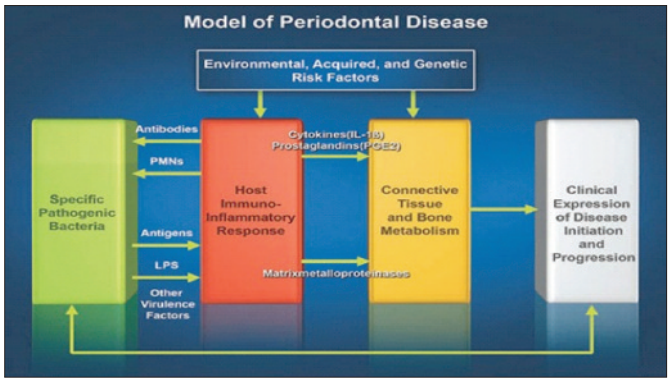

Figure 2: Mechanism of pathogenesis in periodontal disease.

Table I: Major proinflammatory and anti-inflammatory mediators*.

Proinflammatory mediators	Anti-inflammatory mediators
Interleukins(IL): IL-1α, IL-1β, IL-6, IL-8	Interleukins (IL): IL-4, IL-10, IL-11, IL-12
TNF-α	TNF-β
Prostaglandin E2, Thromboxane B2	Lipoxin A4, Lipoxin B4
Immunoglobulin (Ig): Ig E, Ig G	Immunoglobulin (Ig): Ig A, Ig G
Proteolytic Enzymes: MMPs, Dentilisin, PrtH, RgpA, RgpB etc.	
Lipopolysaccharide (LPS)	
Heat Shock Proteins (HSP) and its homologs e.g. GroEL, GroEs, DnaK, HtpG	
Toll like receptors	

**Adopted from references (2,10,13,14)*

In 1992, Golub and colleagues discussed host modulation with tetracyclines and their chemically modified analogues.[9] After introduction of this concept by William (1990), various host modulation agents have been developed and are currently being investigated, examples of these agents are NSAIDs, tetracyclines, chemically modified tetracycline, anticytokines agents (IL-1/TNF blockers), recombinant human IL-11, recombinant tissue inhibitor of matrix metalloproteinase, synthetic matrix metalloproteinase inhibitors and bisphosphonates.[3,10] All of these agents modulate specific component of disease pathogenesis which includes regulation of arachidonic acid metabolites, excessive production of matrix metalloproteinases (MMPs), immune and inflammatory responses and bone metabolism. However, currently only one systemically administered agent, subantimicrobial dosage doxycycline (SDD), has been approved by the United States Food and Drug Administration to be used for host modulation in periodontal disease.[1]

The aim of host modulation therapy (HMT) is to reduce the tissue damage and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of host response and up regulating protective or regenerative responses. The host immune and inflammatory response is primarily responsible for the periodontal tissue destruction. Various HMT developed block the specific pathways responsible for the destruction of periodontal tissue e.g. antiproteinases, anti-inflammatory etc.[11]

Pathogenesis of periodontal disease: Periodontal disease pathogenesis is associated with parasite-host interactions that are elicited predominantly by plaque biofilm endotoxins, lipopolysaccharide (LPS), a major component of the outer cell membrane of Gram negative bacteria, initiating a cascade of events (Figure 2).[12]

LPS and other virulence factors stimulate host immune and inflammatory responses which initially results in disease limited to gingiva or initiation of periodontal destruction due to persistent microbial challenge. Protective host response includes recruitment of neutrophils, production of protective antibodies and release of anti-inflammatory cytokines including transforming growth factor-β (TGF- β), interleukin (IL)-4, IL-10, IL-11 and IL-12. The destructive host response includes release of proinflammatory mediators; cytokines (e.g. IL-1, IL-6, Tumor Necrosis Factor-α [TNF-α]), proteases (e.g. matrix metalloproteinases) and prostanoids (e.g. prostaglandin E_2 [PGE_2]). Homeostasis is essential in between proinflammatory and anti-inflammatory mediators, disruption of which results in extra-cellular matrix destruction and bone resorption and

the resultant clinical manifestation as a periodontal disease (Table I).[13,14] Various environmental, acquired or genetic risk factors e.g. smoking, diabetes mellitus that cause excessive host response or hyper inflammation will lead to increased periodontal tissue damage.[2]

Matrix Metalloproteinases (MMPs) and its patho-physiological role: MMPs are a family of calcium- and zinc-dependent endopeptidases responsible for number of physiological events (e.g. hard and soft tissue remodeling, tooth eruption, wound healing and immunity, angiogenesis) and pathological destructive processes (e.g. tumour progression/metastasis, fibrosis, bone resorption etc). MMPs were initially described by Jerome Gross and Charles Lapiere in 1962 who observed its enzymatic activity i.e. collagen triple helix degradation.[15,16]

MMPs are the prime mediators involved in tissue destruction in various pathological conditions e.g. periodontitis. MMPs can be classified either on the basis of its substrate specificities and physical structure or its source of production.

On the basis of substrate specificities and physical structure MMPs are divided into the following subgroups:[16,17]

1. Collagenases
   a. Interstitial Collagenases 1 (MMP-1)
   b. Neutrophil Collagenases 2 (MMP-8)
   c. Collagenases 3 (MMP-13)
2. Gelatinases [MMP-2, MMP-9]
3. Metalloelastases [MMP-12]
4. Membrane-type MMPs [MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, MMP-25] and
5. Other MMPs
   a. Stromelysin (MMP-3, MMP-10, MMP-11)
   b. Matrilysin 1 and 2 (MMP-7 and MMP-26)
   c. MMP-18, MMP-19, MMP-21

MMPs can also be classified on the basis of their source of production;[18-20]

1. Host derived MMPs: These are produced by the number of infiltrating cells (e.g. neutrophils, macrophages etc) or resident cells (e.g. fibroblasts, epithelial cells, osteoblasts, osteoclasts and other messenchymal cells etc.).

2. Bacterial derived MMPs: These are produced by several periodontal pathogens e.g. Actinobacillus, Actinomycetemcomitans and Porphyromonas gingivalis.[21]

Endogenous MMPs are considered to be the major destructive enzymes responsible for tissue destruction and progression of disease. Increased quantities of MMPs are released in inflamed tissues and are present in high concentration in gingival crevicular fluid (GCF) and saliva resulting in degradation of extracellular matrix.[10] In periodontitis, the predominant MMPs are MMP-8 (collagenases-2), MMP-9 (gelatinases-B) and MMP-13 (collagenases; bone and cartilage destruction) whereas in healthy tissue normal collagen turnover is regulated predominantly by MMP-1 (fibroblast derived collagenases).[22] All these destructive enzymes are primarily secreted by neutrophils and responsible for degradation of type I collagen in periodontal tissue.[7]

Inhibition of MMP: It is well document that activated MMPs level and their endogenous inhibitors plays a pivotal role in determining tissue destruction. Contemporary periodontal modulation therapy aims at reduction of activated MMPs level and/or increasing the MMPs inhibitors either endogenous (host derived) or exogenous (synthetic) inhibitors. Inhibition of MMPs activity causes decrease in collagen destruction which ultimately leads to gain in clinical attachment levels and probing depth reduction.[10]

MMPs inhibitors can be classified as follows:[7,16,17]

1. Endogenous (natural) inhibitors: These MMPs inhibitors are natural or host derived produced and secreted by various body cells found in serum and saliva which includes:
   a. Tissue Inhibitors of Metalloproteinases (TIMPs): TIMPs binds irreversibly with activated MMPs forming non-covalent complexes e.g. TIMP-1, TIMP-2, TIMP-3 etc.
   b. μ^2-macroglobulin: It causes regulation of MMP in body fluids.
2. Exogenous (synthetic) inhibitors: These inhibitors are synthetically developed to cease the effect of MMPs by different pathways. Following are exogenous MMP inhibitors:
   a. Zinc- and Calcium-Chelating Agents: e.g. Ethylenediaminetetraacetic acid (EDTA).
   b. Phosphorus containing peptide.
   c. Sulphur based inhibitors e.g. Mercaptan derivatives.
   d. Peptidyl hydroxamine acid derivatives.

A number of synthetic inhibitors have been developed and studied for the treatment of various chronic pathologic conditions e.g. periodontitis, non-healing corneal ulcers, breast and ovarian carcinoma, malignancies of prostate and gastro-intestinal tract e.g. SDD (Subantimicrobial dosage doxycycline), Galardin, Batimastat, Marimastat etc.[16]

Biomarkers of periodontal disease: A biomarker is a substance that is measured objectively and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[23]

The ideal periodontal disease diagnostic tools and tests using biomarkers assessment is developed on principles

that can detect the presence of active disease, predict future disease progression and evaluate the response to the periodontal therapy thereby improving the management of periodontal disease. Along with these properties, diagnostic tools developed should be easy for usage, cost-effective and non-invasive as with the traditional diagnostic tools and tests e.g. radiographic and clinical methods to assess probing depths, bleeding on probing, clinical attachment level etc.[24] The diagnostic tools and tests for biomarker based periodontal disease diagnosis should be capable of identification of biomarker from easily accessible and small quantities of samples e.g. plaque biofilms, gingival crevicular fluid (GCF), saliva etc.

Periodontal disease biomarkers can be microbial factors (cultures or DNA probes of putative periodontal pathogens), host response and inflammatory mediators (e.g. cytokines, immunoglobulin, prostaglandins, collagenases etc), tissue specific biomarkers (e.g. collagen telopeptide fragments, osteocalcin, laminin etc.).[23,25] Among all of these several biomarkers studied following two have more relevant clinical implication in periodontal disease i.e. MMP-8 and collagen telopeptide fragments such as pyridinoline cross-linked carboxy-terminal telopeptide of type-I collagen (ICTP) in GCF. The use of hand held portable diagnostic device called Integrated Microfluidic Platform for Oral Diagnostics (IMPOD) allows for rapid, non-invasive chair-side detection of MMP-8 and other biomarkers concentration in saliva in 3 to 10 minutes duration.[26] MMP-8 level in saliva is a reliable indicator for predicting, diagnosing and assessing the progression of periodontal disease. Its level is clearly associated with progressive periodontitis as their concentration is ten times higher in pathological involved periodontal sites as compared to healthy sites.[1] ICTP and other pyridinoline cross-linked components are specific for bone degradation and have high serum concentration in several metabolic diseases including osteoporosis, rheumatoid arthritis, Paget's disease etc.[27] Due to its specificity for bone resorption, they are potentially valuable biomarker in periodontics to differentiate between reversible (gingivitis) and irreversible (periodontitis) periodontal disease. It may also aid in diagnosing active periodontal or peri-implant bone destruction and to assess the treatment outcome of periodontal therapies.[28]

Current diagnostic tools being developed focuses on measurement of periodontal diseases at molecular, cellular and tissue level with the help of polymerase chain reaction (PCR), DNA-DNA hybridization, laser capture microdissection, ELISA and histomorphometry.[23]

Host modulation therapeutics: Modulation is the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment.[29] In periodontics the concept of host modulation therapy is to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of host response and up regulating protective or regenerative responses. As discussed earlier in pathogenesis of periodontal disease the prime destructive agents are MMPs, cytokines, arachidonic acid metabolites which result in increased probing depths (PD), clinical attachment loss (CAL), bleeding on probing (BOP) and alteration in levels of bio-chemical markers such as MMPs, ICTP, laminin.[1,25] Therefore, the current host modulation therapies focus on reductions of these destructive enzymes by either systemic or local administration of host modulating agents.[1,10,11]

1. Tetracycline, synthetic tetracyclines and chemically modified tetracyclines (CMTs): Tetracycline is a broad spectrum antibiotic prescribed for many systemic and periodontal infections. Due to its high concentration and secretion in GCF they provide effective antimicrobial cover locally for periodontal pathogens on non-vascular wall of periodontal pocket. In addition to its anti-bacterial property, tetracyclines also possess anti-collagenases effect due to inhibition of MMPs activity.[16] MMPs are Zinc and Calcium dependant endopeptidases. Tetracycline causes chelation of these ions thereby directly inhibiting the tissue degradation by these enzymes. Also, tetracyclines scavenge and inhibit production of oxygen metabolites (e.g hypochlorous acid) by PMNs thereby decreasing host inflammatory responses and prevent destruction of endogenous MMPs inhibitors. Direct inhibition of MMPs and anti-inflammatory effect by blockade of hypochlorous acid, both these effects of tetracyclines also prevent the activation of latent pro-MMPs, therefore, further reducing the tissue destruction. Tetracyclines also inhibit osteoclast and osteoblast derived MMPs thus lead to reduction of alveolar bone resorption.[7,30]

Minocycline and doxycycline are synthetic tetracyclines, both these drugs have the characteristics to inhibit collagenase enzymes. But much focus and research attention have been gained by doxycycline as it posses most potent anti-collagenases properties at a much lower inhibitory concentration than minocycline and tetracycline.[22] Lower inhibitory concentration of drugs allows much lower dose of doxycycline to inhibit MMPs activity. Doxycycline is also more effective in blocking PMN type collagenases (MMP-8) than fibroblast type collagenases (MMP-1), thus it does not interfere with the normal tissue turnover.[7]

CMTs are developed by either addition or deletion of functional groups in the central structure of tetracyclines.[31] Currently, there are about ten CMTs developed and under clinical trials mainly; CMT-1 (4 dedimethyl-aminotetracycline), CMT -2 (tetracyclino-nitrile), CMT-3 (6-deoxy-6-demethyl-4-de-dimethylamino-tetracycline), CMT-4 (7-chloro-4-de-dimethylamino-tetracycline), CMT-5

(tetracycline pyrazole), CMT-6 (4-dedimethyl amino. 4-hydroxytetracycline), CMT-7 (12_-deoxy-4-dedimethyl amino-tetracycline) and CMT-8 (4-dedimethylamino-doxycycline). CMTs cause inhibition of MMPs activity, reduction of proinflammatory mediators, scavenge reactive oxygen species (ROS) and reactive nitrogen species.[30,31] CMTs in contrast to conventional tetracyclines do not cause gastrointestinal upsets and its therapeutic effects can be achieved with less frequent administration. CMTs offer promising therapeutic outcomes in experimental periodontitis models and other clinical conditions, therefore, they can be the key host modulating agents of the future.

Sub-antimicrobial dose doxycycline (SDD): It is well documented that tetracycline and its synthetic family members are effective in reducing collagenases enzymes. However, its prolonged usage has not been indicated due to its adverse reactions on the gastrointestinal tract, skin, renal and hepatic organs and also due to emergence of resistant strains. To overcome this sub antimicrobial dose doxycycline (SDD), was introduced in 1998 for host modulation therapy. Currently, this is the only available agent approved by United States Food and Drug Administration (FDA) for usage as host modulation agent in periodontics.[1] Many studies have been conducted to evaluate the role of SDD as an adjunct with mechanical and surgical periodontal therapy for the treatment of periodontitis. Results have shown more clinical improvements in PD, CAL, BOP and serum biomarkers optimal levels in patients who received adjunct SDD as compared to patients on placebo or who received scaling and root planning alone.[22,32,33] Caton *et al*., also demonstrated in their study that adjunctive SDD lead to resolution of more percentage of sites with moderate to severe pocketing as compared to placebo group, thereby predicting better treatment outcomes.[34]

SDD administration in dose of 20 mg twice a day as an adjunct for the treatment of chronic periodontitis both in short term duration of 1 - 3 months and longer duration of up to 9 months showed more improved and predicable treatment outcomes without the emergence of adverse effects of doxycycline and any alterations in subgingival microflora when administered in dosage of 50 - 100 mg/day for its antimicrobial effect.[35] Some authors have recommended minimum three months duration therapy for its prolonged therapeutic effects.[12] The serum concentration of doxycycline is much lower for SDD which is 0.7 - 0.8 μg/dL whereas its antimicrobial dose serum concentration is 3 - 4 μg/dL.[34,35]

Adjunctive SDD usage have also been studied in a sample of smokers' population and results suggest better treatment outcomes after SRP were achieved in smokers on adjunctive SDD therapy as compared to placebo group.[36,37] Caton *et al*.[34] and Preshaw *et al*.[22] performed larger clinical trials on treatment outcomes in chronic periodontitis by the adjunctive SDD usage and their results demonstrated significant greater mean probing depth reductions and attachment level gains as compared to SRP alone. These results were maintained even after 3 months of cessation of drug. In one study of 36 weeks duration, SDD was used as adjunct for treatment of chronic periodontitis in two cycles each of 12 weeks duration. SDD was used for initial 12 weeks along with SRP, separated by 12 weeks period of no drug and then again 12 weeks of SDD showed increased mean CAL gains and reductions in probing depth as compared to SRP alone.[38]

To assess treatment outcome in diabetic patients, many studies have shown clinically significant results with SRP and SDD therapy as compared to SRP alone. SDD therapy in diabetic patients have also shown reduction in long term glycemic control marker i.e. hemoglobin A1c levels. Also in women with osteoporosis, improvement in alveolar bone height and bone density have been reported along with clinical attachment gains and no attachment loss in a number of sites over prolong periods with SDD and SRP as compared to SRP alone.[6]

A larger clinical trial about the safety data of SDD for longer durations even up to 24 months demonstrates that it is well tolerated with very low incidence of adverse effects.[12,39] Common adverse effects associated with SDD are headache, dyspepsia, rash and diarrhea.[22,34]

2. Non-steroidal anti inflammatory drugs (NSAIDs): As discussed earlier, elevated PGE2 levels[40] and other amino acid (AA) metabolites have been reported in GCF and have been associated with destruction of periodontal tissue.[22] Therefore, AA metabolites reduction has been focused since decades to prevent the progression of periodontal disease. NSAIDs inhibit the enzyme cyclooxygenase (CO) and lipooxygenase (LO), thereby inhibit production of prostaglandins, prostacyclines, thromboxanes, leukotrienes and other hydroxyeicosatetraenoic acids by these pathways. Reduced synthesis of prostaglandin causes decrease in bone resorption in experimental models. Systemic NSAIDs e.g. indomethacin, naproxen, piroxicam, ibuprofen and flurbiprofen have been extensively studied for their role in inhibiting alveolar bone resorption and retarding the progression of periodontal disease.[41-46] However, on cessation of therapy, immediate recurrence of disease occurred thereby requiring its prolonged administration to sustain its therapeutic effects. Topical NSAIDs such as piroxicam,[44] ketoprofen,[47] flurbiprofen,[48] ibuprofen,[49] meclofenamic acid[49] administration in the form of cream, gel or dentifrice use have also been advocated due to its lipophilic nature and their quick absorption into periodontal tissue to cause its therapeutic effect with greater efficacy at lower doses and with fewer adverse effects.[50]

Prolonged administration of NSAIDs is cautioned due to its adverse effects including gastrointestinal upset, renal, hepatic and hemorrhage impairment due to non-selective inhibition of COX-1 and COX-2 enzymes.[51,52] Therefore current clinical trials focus on the use of selective NSAIDs (COX-2) inhibitors, as these are associated with similar clinical effects with fewer gastrointestinal adverse effects as compared to non-selective NSAIDs.[40,53,54] Currently, FDA has not approved any NSAID formulation for host modulation therapy in periodontics and future research is required to determine its suitability as a host modulating agent.

Triclosan (2,4,4-trichloro 2-hydroxydiphenyl ether) possesses non-ionic antimicrobial activity and anti-inflammatory property by inhibiting CO and LO pathways.[55] Due to this dual activity, triclosan provides an effective remedy to prevent attachment loss in periodontitis. Triclosan/copolymer dentifrices are available in market indicated for patients susceptible to periodontitis by reducing plaque and calculus deposits and resolving gingivitis.[56]

3. Bone sparing agents (Bisphosphonates): Bisphosphonates are analogs of pyrophosphate having high affinity for calcium phosphate in bone tissue.[57] Bisphosphonate (e.g. Alendronate) inhibit osteoclasts activity and posses property of inhibiting ions dependant enzyme activity (MMPs) through chelation of cations.[58,59] These agents inhibit the loss of bone density and prevent normal bone turnover.[11] At cellular level, they inhibit osteoclast recruitment and adhesion, increase osteoblast number by differentiation and decrease release of cytokines by macrophages/ neutrophils.[1]

Few clinical studies have been performed to determine bisphosphonate usage for treatment of periodontitis as an adjunct with SRP. These studies have shown significant[60] and modest[61,62] improvements in bone levels when evaluated by clinical and radiographic methods. One larger 12 months study on 70 subjects demonstrated modest clinical improvement but no improvements in radiographic bone mass after bisphosphonate usage.[63] Despite conflicting results in bone levels in various clinical studies, bisphosphonate therapy shows improvement in CAL, PD and BOP. Its prolonged usage in periodontics is cautioned due to its adverse effects such as osteonecrosis of the jaws (ONJ); however, the incidence of ONJ is much lesser with oral bisphosphonate therapy as compared to high dose intravenous bisphosphonate therapies. Currently, FDA has approved bisphosphonates for systemic bone loss only, therefore, more extensive clinical research is required for its indication as adjunct host modulating agent in periodontics.[64]

4. Cytokines (immune) modulation: As discussed previously in pathogenesis of periodontal disease host cell derived proinflammatory cytokines and anti-inflammatory cytokines production determines the extent of destruction of connective tissue and alveolar bone. Immune modulation therapy aims at reduction of proinflammatory cytokines and/or increasing anti-inflammatory cytokines level.

The use of cytokine receptor antagonist (IL-1/TNF blocker) have been investigated and showed reduction in periodontal disease progression in experimental models.[65,66] Anti-inflammatory cytokines (IL-4 and IL-10) inhibits the release of IL-1, TNF-α, nitrous oxide (NO) and other destructive molecules by the host cells. IL-4 is also responsible for increasing the number of IL-1 receptor antagonist thereby decreasing the tissue destruction.[67] The exogenous administrations of IL-4 and recombinant IL-11 in experimental models have been associated with reduction in disease progression e.g. in Arthritis, Periodontitis etc.[68,69]

However, the long term effects of immune modulation are not well understood at this time and further research is necessary to determine its systemic effects and its safety and efficacy.

CONCLUSION

Currently, with the improved understanding of etiology and pathogenesis of periodontal disease, new treatment modalities are being introduced for prevention of disease initiation and slowing disease progression. HMT is gaining interest among periodontists as an additional therapeutic option for treatment of periodontal diseases. The conventional treatment only focus on removal of plaque biofilm by mechanical therapy based on non-specific plaque hypothesis whereas modern treatment strategy depends on successful implementation of mechanical therapy, modification of risk factors and host modulation therapy.[7]

It is evident that mechanical therapy remains the primary focus for successful treatment whereas HMT is only recommended as an adjunct to conventional therapy for better clinical outcome. Also the modification of risk factors either modifiable (e.g. smoking, uncontrolled diabetes) or non-modifiable (e.g. genetics, gender etc) plays a pro-vital role in successful treatment. There are many clinical situations in which desired clinical results can not be achieved with mechanical therapy alone e.g. presence of risk factors, presence of systemic disease etc., therefore, adjunct use of HMT is indicated.[12]

Periodontitis has been associated with systemic effects on cardiovascular diseases (e.g. artherosclerosis, myocardial infarction, stroke etc.), respiratory pathosis, premature births and other adverse effects on pregnancy due to release of immune and inflammatory mediators in response to microbial virulence factors.[70] HMT plays an important role in down regulation of immune and inflammatory mediators mainly by inhibiting MMPs, decreasing arachidonic acid metabolites and regulating osteoclast activity.[11]

Some authors have suggested combine usage of HMT agents with topical antimicrobial therapy,[71] NSAIDs[72] along with periodontal flap and implant surgeries[11,73] for better treatment outcomes.[25]

Recommendations: With the current available research data, authors recommend that SDD is an effective adjunct therapy when used in dosage of 20 mg twice daily for minimum duration of 1 - 3 months in cases of moderate to severe chronic periodontitis. SDD adjunct usage may also have clinically significant outcomes (e.g. decrease in probing depths, increased in attachment levels, predictable surgical treatment outcomes, slowing down progression of periodontal disease etc.) when used in dosage of 20 mg twice daily for 3 - 9 months duration for the treatment of aggressive periodontitis, patient with increased risk factors, recurrent and refractory periodontitis cases etc. but it should be indicated only after exhaustion of all anti-biofilm measures.[74] FDA has only approved SDD to in dosage of 20 mg B.I.D as an adjunct SRP for the treatment of chronic periodontitis, however, more randomized clinical trials (RCTs) are required in future to assess the efficacy of anti cytokine drugs, chemically modified tetracycline and other HMT agents in treatment of different periodontal conditions so that new agents are available with clinically highly predictable results.

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