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Review Article

Host Modulation Therapy- An Adjunctive Treatment Modality

Vaidehi N Patil[1]*, Suyog Dharmadhikari[2], Devanand Shetty[3], Arvind Shetty[4], Snehal Amberkar[2] and Apoorva Mhatre[1]

[1]Post Graduate Student, Department of Periodontics and Oral Implantology, D Y Patil School of Dentistry, Navi Mumbai, India

[2]Associate Professor, Department of Periodontics and Oral Implantology, D Y Patil School of Dentistry, Navi Mumbai, India

[3]Professor and Head of Department, Department of Periodontics and Oral Implantology, D Y Patil School of Dentistry, Navi Mumbai, India

[4]Professor, Department of Periodontics and Oral Implantology, D Y Patil School of Dentistry, Navi Mumbai, India

***Corresponding Author:** Vaidehi N Patil, Post Graduate Student, Department of Periodontics and Oral Implantology, D Y Patil School of Dentistry, Navi Mumbai, India.

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Abstract

Periodontitis is a polymicrobial infectious disease of multifactorial origin. Plaque biofilm and associated host responses are involved in the pathogenesis of periodontitis. Organisms strongly implicated as etiologic agents include Gram negative, anaerobic or microaerophilic bacteria within the biofilm. The microbial challenge consisting of antigens, lipopolysaccharide (LPS), and other virulence factors stimulates host responses which result in disease limited to the gingiva (i.e. gingivitis) or initiation of periodontitis. Until the 1970s, treatment strategies for periodontal diseases were primarily based on the understanding that plaque bacteria and their products mediated the tissue destruction in periodontal patients. 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 host immune-inflammatory response against bacterial plaque can thus be viewed as a "dual-edged sword," i.e. the response is protective by intent, yet in susceptible patients who exhibit an exaggerated inflammatory response to plaque, it ultimately is responsible for perpetuating the destruction of the periodontium. This shift in paradigms, with emphasis on host response, has led to the development of host modulatory therapies (HMTs) which can improve therapeutic outcomes, slow the progression of a disease, predictable management of patients, and as preventive agents against the development of periodontitis.

Keywords: *Lipopolysaccharide (LPS); Host Modulation Therapy (HMT)*

Introduction

The therapeutical agents or perioceutics that are mainly used to control periodontitis is a rising branch in the treatment of periodontal diseases along with mechanical debridement [1-5]. To lower excessive levels of enzymes, cytokines, prostanoids (prostaglandin E2 [PGE2]), as well to modulate osteoclast functions, host modulation therapy (HMT) are being used, but it should not reduce below constitutive levels. Nonsteroidal anti-inflammatory drugs (NSAIDS), sub antimicrobial dose doxycycline (Periostat), systemic bisphosphonates (BP), etc. are few host modulating agents that are being recommended. Systemic flurbiprofen and topical ketoprofen are NSAIDS that act by inhibiting PGE2. Bisphosphonate modulates the osteoclast function, and sub antimicrobial dose doxycycline (Periostat) uses the anti-collagenase properties of tetracycline (TC), which is lone permitted drug by FDA. Future prospect lies for chemically modified TC (CMT's), bone resorption uncouplers, anti-cytokine drugs, antimetabolites, and lipoxins (LXs). This provides clinician with supplementary equip-

ment to conventional mechanical debridement, which could improve and make the clinical therapeutic outcome more predictable, in a susceptible host [6].

Rationale of HMT

HMT do not switch off the normal defense mechanism or inflammation, instead, they ameliorate excessive or pathologically increased inflammatory processes to amplify the opportunities for wound healing and periodontal stability. Hence, basically it helps in modulating host responses by down regulating the destructive aspects or up regulating the protective aspects of the host response [6].

Classification and mechanism of action [7]

1. Modulation of arachidonic acid (AA) metabolites. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), triclosan.
2. Modulation of matrix metallo-proteinases (MMP). For example, tissue inhibitor metalloproteinases (TIMPs), tetracyclines.
3. Modulation of bone remodeling. For example, bisphosphonates.
4. Modulation of host cell receptors: For example, blockade of receptors for IL-1, tumor necrosis factor (TNF), and advanced glycation end products (AGEs).
5. Modulation of nitric oxide synthase (NOS) activity; For example, mercaptoethylguanide.

Modulation of arachidonic acid (AA) metabolites

Prostaglandins were described first in 1939 by Von Euler as vasoactive fatty acids which are capable of lowering blood pressure in rabbits and are derived from human seminal vesicle fluid [8]. Prostaglandins are metabolized through the cyclooxygenase (COX) pathway and leukotrienes through the lipoxygenase (LOX) pathway to produce free Arachidonic acid. Various studies have shown that an important mediator of bone loss in periodontitis is prostaglandins.

In the early 1970s, Paul Goldhaber and Max Goodson began to implicate arachidonic acid metabolites as important inflammatory mediators of the bone loss of periodontitis [9]. The arachidonic acid metabolites include a variety of fatty acid-derived compounds that are enzymatically produced and released in response to local tissue injury. These metabolites, such as prostaglandins, were implicated as major mediators of tissue loss in periodontal diseases because they are potent stimulators of bone resorption, are present in gingival tissues, and are elevated in diseased individuals.

Free arachidonic acid (AA) is produced in the hosts when phospholipase A2 acts on the phospholipids present in plasma membranes of the cells which can then be metabolized to produce prostaglandins *via* the cyclooxygenase (COX) pathway as well as leukotrienes *via* the lipoxygenase (LOX) pathway [10].

Non-steroidal anti-inflammatory (NSAIDs) drugs block the activity of both cyclooxygenase isozymes (COX-1 and -2) and many authors have demonstrated the role of NSAIDs like flurbiprofen [11], indomethacin [12] and naproxen [13] in inhibiting gingivitis and progression of periodontitis. Lipoxins (LX) which are generated endogenously late in inflammation *via* cell-cell interaction when a second lipoxygenase (e.g. 5-LOX) interacts with a lipoxygenase product (e.g. hydroxyeicosatetraenoic acid) generated earlier from arachidonic acid [14] also possess both anti-inflammatory and pro-resolving potential which have been summarized by Serhan., *et al*. as reduction of neutrophil infiltration and recruitment, blocking cytokines and reactive oxygen species generation, thereby preventing connective tissue and bone loss [15].

Lipid - inflammatory mediators as targets for HMT

Among the other endogenous chemical mediators resolvins, protectins, and newly identified maresins have shown to mediate resolution and counter-regulate excessive acute inflammation [16]. These are biosynthesized from precursors like omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) *via* sequential steps involving lipoxygenases (LOX), and cyclooxygenases (COX) [15,17,18]. The role of these endogenous chemical mediators is similar to that of lipoxins, i.e. inhibition of neutrophil recruitment *etc* [16,17]. These stereoselective players counter-regulate excessive acute inflammation and stimulate molecular and cellular events that define resolution [19]. Thus designing pharmacological mimetics of naturally occurring pro-resolving mediators offers exciting new targets for drug design [20], especially for host modulation therapy.

Modulation of matrix metallo-proteinases (MMP)

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 [21,22]. MMPs are the prime mediators involved in tissue destruction in periodontitis.

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. 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) [23]. All these destructive enzymes are primarily secreted by neutrophils and responsible for degradation of type I collagen in periodontal tissue.

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 [24].

There are various type of host cells that function at neutral pH and mediate the degradation of extracellular matrix macromolecules, along with interstitial and basement membrane collagens, proteoglycan core protein, laminin and fibronectin. Proteolytic inactivation of MMPs is self-regulated, and its action is also arrested by endogenous inhibitors like α2 macroglobulin and tissue inhibitors of MMPs. MMPs endopeptidases which are secreted by a variety of host cells, play key roles in the degradation of the extracellular matrix, basement membrane and modify the action of cytokines as well as activation of osteoclasts [25]. During active periodontal diseases, microbial attack leads to excessive production as well as activity of these MMPs which, if not adequately controlled by the endogenous metalloproteinases inhibitors, results in enormous tissue destruction. To impede this destruction of host tissues synthetic inhibitors of MMP as host modulating agents have been developed which generally contain a chelating group, inhibiting MMPs by binding to the catalytic zinc atom at its active site. Though numerous MMP inhibitors have been investigated, only tetracycline based host modulating agent, i.e. SDD - sub-antimicrobial dose of doxycycline (Doxycycline hyclate 20 mg; Periostat, CollaGenex, Pharmaceuticals Newton PA) has been approved by Food and drug administration (FDA) to be used as an adjunct to periodontal treatment [26]. A typical prescription for Periostat (20 mg doxycycline tablets) is for atleast 3 months (180 tablets, 1 tablet twice a day until complete) and refills may be provided for longer courses of therapy [27].

Effect of SDD

1. Direct inhibition of active MMPs by cation chelation (dependent on Ca^{2+} and Zn^{2+} binding properties).
2. Inhibits oxidative activation of latent MMPs (independent of cation-binding properties).
3. Down regulates expression of key inflammatory cytokines (IL-1, IL-6, and TNF-a) and PGE2.
4. Scavenges and inhibits production of reactive oxygen species produced by neutrophils.
5. Stimulates fibroblast collagen production.
6. Reduces osteoclast activity and bone resorption.

Modulating agents acting against cytokines

Proinflammatory (e.g. interleukin-1α [IL1α], IL1β, IL6, tumor necrosis factor α [TNFα], interferon γ, etc.) and anti-inflammatory cytokines (IL4, IL10, etc.) has immense potential for limiting the adverse effect of the host immune response, hence use of HMT against cytokines may be advocated as an effective line of treatment for periodontal diseases [28]. These receptors can be found in blood, and extracellular fluid and down regulation of cytokine is done by binding of the soluble receptor to cytokine and thus prevent signaling. Among all these soluble cytokine receptors only soluble IL-6R is an agonist in function rest all are antagonist [29]. Methyl xanthine derivative pentoxifylline, inhibit the synthesis of TNF-α and thus decrease the accumulation of TNF-α. It can stimulate anti-inflammatory cytokine production and can arrest the generation of inflammatory cytokines capacity [30]. Periodontal destruction is stimulated by inflammatory cytokines and is being regulated by anti-inflammatory mediators, their action is under the control of inhibition of cytokine signaling,

which decreases the signal as part of an inhibitory feedback loop. The amplified expression of cytokine signaling is known to be involved in the down regulation of toll-like receptor in diseased periodontal tissues [31].

Modulation of bone remodeling by:

Bisphonates

Factors that regulate osteoblast and osteoclast activity are important targets for designing pharmacological agents. The interaction between receptor activator of nuclear factor kappa B ligand and osteoprotegerin has recently received attention in periodontal research. Bone sparing agents BPs are used in the treatment of various bone-related diseases associated with bone resorption. These compounds represent a class of chemical structures related to pyrophosphate, and its osteoclastic activity is by blocking the acidification by local release [32]. Bisphonates are analogs of pyrophosphate having high affinity for calcium phosphate in bone tissue [33]. Bisphosphonate (e.g. Alendronate) inhibit osteoclasts activity and poses property of inhibiting ions dependant enzyme activity (MMPs) through chelation of cations [34,35]. These agents inhibit the loss of bone density and prevent normal bone turnover [36]. At cellular level, they inhibit osteoclast recruitment and adhesion, increase osteoblast number by differentiation and decrease release of cytokines by macrophages/neutrophils [37]. Few clinical studies have been performed to determine bisphosphonate usage for treatment of periodontitis as an adjunct with SRP. Various studies conducted by Pradeep., *et al.* using 1% alendronate gel, comparing with 1.2% atorvastatin (ATV) gel as an adjunct to nonsurgical periodontal therapy for the treatment of patients with CP and aggressive periodontitis, showed significant improvement in clinical parameter and improved bone fill compared to placebo gel [37].

Metformin (MF)

MF is the most common oral anti hyperglycemic agents used in the treatment regime of Type 2 diabetes mellitus. Bone-sparing properties of MF have recently provided a new vision in the field of periodontal research. Many studies conducted by Pradeep., *et al*. using MF gel at varying concentration 0.5%, 1%, and 1.5% MF gel as local drug delivery (LDD) in adjunct to SRP for the treatment of intrabony defects in patients with CP, showed significant improvement in clinical outcome [38,39].

Statins

Statins are a group of lipid-lowering drugs that are commonly used to treat hyperlipidemia and prevent cardiovascular morbidity. These drugs have pleiotropic effects such as vasodilative, antithrombotic, antioxidant, antiproliferative, and anti-inflammatory. They also inhibit the release of proinflammatory mediators, specifically cytokines and MMPs. Keeping in view these pleiotropic effects, statins have been studied to have effects on periodontium.

Modulation of nitric oxide synthase

Nitric oxide is a free radical with important physiological functions of maintaining homeostasis. While homeostasis requires low nitric oxide tissue levels, pro-inflammatory stimuli such as endotoxins leads to increased expression of the inducible nitric oxide synthase enzyme (iNOS) that produces a large amount of nitric oxide (NO) and peroxynitrite, which acts beneficially for the host as a cytotoxic molecule against the invading microorganism, yet, it may also cause deleterious effects to host such as DNA damage, lipid peroxidation, protein damage, and stimulation of inflammatory cytokine release [40-42]. Lohinai., *et al*. (1998) demonstrated the protective effects of mercaptoethylguanidine (MEG), which is a selective inhibitor of iNOS, against bone destruction in ligature-induced periodontitis in the rat [43].

Conclusion

The recognized importance of the host inflammatory response in the pathogenesis of periodontal diseases presents the opportunity to explore new treatment strategies. A variety of treatment strategies has been developed to target the host response to periodontal infection. This review has sought to provide mechanistic overviews and clinical applications on the use of host modulatory therapeutic regimens for periodontal disease management. The improved understanding of the host-bacterial interactions and host immune-inflammatory response leading to periodontal tissue destruction has led to the development of HMT. Although the efficacy and usefulness of

host-modulating agents have been demonstrated by many clinical trials and have been approved by FDA for the management of periodontitis, the risk/benefit ratio relating to the use of these drugs has yet to be established.

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