

Host Modulatory Agents in Periodontics: A ReviewDr.Swetha Gadde^{1*}, Dr.Chakravarthy Mupalla²¹Senior Lecturer, Department of Periodontics& Implantology, Ragas Dental College, Chennai, India.²Senior Lecturer, Department of Periodontics& Implantology, Care Dental College, Guntur, India.**Corresponding Author:** Dr. Swetha Gadde, Senior Lecturer, Department of Periodontics& Implantology, Ragas Dental College, Chennai-600119, Tamilnadu**Type of Publication:** Review Paper**Conflicts of Interest:** Nil**Abstract**

Chronic periodontitis is a polymicrobial inflammatory disease of multifactorial origin. Microbial biofilm and associated host responses are involved in the pathogenesis of periodontitis. The host response is essentially protective by intent but paradoxically can also result in tissue damage. Host modulation therapy has emerged in recent years as a valid treatment concept for the management of periodontal disease and represents a significant step forward for the clinician as well as patients with periodontal disease. This review aims at focusing on various host modulatory agents that have been developed or proposed to modulate host responses for the treatment of periodontitis.

Keywords: Bisphosphonates, chronic periodontitis, host response, interleukins, matrix metalloproteinases.**Introduction**

Chronic periodontitis (CP) is a polymicrobial disease due to an imbalance in the host defence mechanism and virulence factors of pathogenic micro-organisms, resulting in an immune-inflammatory response that can result in harmful changes in the tooth supporting structures [1]. A small group of microaerophilic bacteria, gram-negative, or anaerobic bacteria in the biofilm are important for induction and advancement of periodontal destruction.

The microbial defence consists of virulence factors such as gingipains (GPs), and lipopolysaccharides [2]. Therefore for the management of periodontal disease, conventional approaches aim at reducing the bacterial load, either by mechanical procedures such as scaling and root planning (SRP) and surgery, or by the supportive use of antibiotics. In later years, other adjunctive approaches that aim to eradicate or drastically reduce the bacteria have included pharmacological measures, which require the use of systemic as well as topical antimicrobial medications. However, recent research into the pathogenesis of periodontal diseases has led to an important paradigm shift, in the way we view periodontal disease progression. The importance of the host inflammatory response in periodontal pathogenesis presents the opportunity for exploiting new treatment strategies for periodontitis. 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[3]. 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, allow for more predictable management of patients, and possibly even work as preventive agents against the development of periodontitis. With this understanding of the host response, various therapeutic modalities have been developed to modulate periodontal tissue destruction, which is known as host modulation therapy (HMT). This present review highlights various host modulation therapeutic agents and ongoing development of safe and effective pharmacotherapies that specially target host response mechanism.

Definition [4]

HMT is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or downregulating destructive aspects of the host response and upregulating protective or regenerative responses.

Rationale [5]

HMT do not switch off the normal defence 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 downregulating the destructive aspects or up regulating the protective aspects of the host response.

Host Modulating Agents Classification And Mechanism Of Action (Salvi And Lang, 2005[6])

1. Modulation of AA metabolites.

For example, nonsteroidal anti-inflammatory drugs (NSAIDs), triclosan.

2. Modulation of MMPs.

For example, tissue inhibitor metalloproteinases (TIMPs), tetracyclines.

3. Modulation of bone remodelling.

For example, bisphosphonates.

4. Modulation of host cell receptors

For example, blockade of receptors for IL-1, tumour 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:

NSAIDs

AA liberated from membrane phospholipids of cells after tissue damage or stimulus is metabolically transformed, via cyclooxygenase (COX) or lipoxygenase pathways, into compounds with potent biological activities[7]. Over decades, AA metabolites have been established as mediators of tissue destruction in various inflammatory diseases including rheumatoid arthritis and periodontal diseases. In periodontal diseases, level of PGE2 has been extensively increased in gingival tissues and in the gingival crevice fluid, which correlates with inflammation and bone resorption.

NSAIDs have been used to treat pain of acute or chronic inflammation. They are effective in inhibition of PG synthesis. They limit the progression of periodontitis through their ability to reduce inflammation and bone resorption[8]. Many authors have demonstrated the role of NSAIDs like flurbiprofen,[9] indomethacin,[10] and naproxen,[11] in inhibiting gingivitis and progression of periodontitis. However, adverse effects associated with prolonged systemic administration of nonselective NSAIDs that possess both (COX-1 and COX-2 inhibitory activity include gastrointestinal upset and haemorrhage, and renal and hepatic impairment. These adverse events associated with systemic use of NSAIDs have precluded their incorporation into treatment regimens.

Recently, selective NSAIDs called coxibs (COX-2 inhibitors, nimesulide) have been developed that causes

significantly fewer serious gastrointestinal adverse events.[16] To overcome these adverse effects, topical administration of NSAIDs has been studied. Lipophilic nature of these drugs facilitated their absorption into gingival tissues. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine rinse and S-ketoprofen dentifrice[12].

Triclosan

A non -ionic compound which has received interest as both an antibacterial and anti-inflammatory agent is triclosan. It inhibits COX and lipoxygenase, and thus may interfere with the production of AA metabolites[13]. Use of a dentifrice containing sodium fluoride (0.243%) and triclosan (0.3%) reduced the frequency of deep periodontal pockets and the number of sites exhibiting attachment and bone loss in patients deemed highly susceptible to periodontitis.

Modulation of MMPs

The MMPs are an important family of zinc- and calcium dependent endopeptidases secreted or released by a variety of host cells (fibroblasts, keratinocytes, neutrophils, macrophages, and endothelial cells) that function at neutral pH and utilize the various constituents of the extracellular matrix as their substrates[14]. These proteinases are involved in a number of physiological events such as embryonic development, tissue remodelling, and tooth eruption, in addition to various pathological processes such as periodontal disease, arthritis, cancer, diabetes, and osteoporosis[15]. Inflammatory mediators such as IL-1, TNF- α , and PGE2 have been shown to upregulate MMP production in several in vitro models. MMPs activation plays an important role in extracellular matrix and basement membrane degradation as well as in the modification of cytokine action and activation of osteoclasts during periodontal tissue destruction [16]. Inflammatory cells

such as neutrophils and macrophages apart from producing collagenase, produce MMPs which are effective at degrading proteoglycans and fibronectin; and thereby further increasing collagenase activity in periodontal disease.

Subantimicrobial dose doxycycline (SDD) remains, at present, the only systemic host response modulator specifically indicated as an adjunctive treatment for periodontitis. SDD is approved by the US Food and Drug Administration (FDA), the UK Medicines, and Healthcare Products Regulatory Agency, and by similar agencies in other countries throughout the world, and was introduced under the trade name Periostat (CollaGenex 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. Doxycycline, similarly to other members of the tetracycline family, has the ability to downregulate MMPs by a variety of synergistic mechanisms independent of any antibiotic properties[17].

Effect of SDD

- Direct inhibition of active MMPs by cation chelation (dependent on Ca²⁺ and Zn²⁺ binding properties)
- Inhibits oxidative activation of latent MMPs (independent of cation-binding properties).
- Downregulates expression of key inflammatory cytokines (IL-1, IL-6, and TNF- α) and PGE₂.
- Scavenges and inhibits production of reactive oxygen species produced by neutrophils.
- Stimulates fibroblast collagen production.
- Reduces osteoclast activity and bone resorption.

Modulation of bone remodeling

Bisphosphonates are widely utilized in the management of systemic metabolic bone disease due to their ability to inhibit bone resorption. Recently, new uses of this unique

class of pharmacological agents have been suggested. Given their known affinity to bone and their ability to increase osteoblastic differentiation and inhibit osteoclast recruitment and activity, there exists a possible use for bisphosphonates in the diagnosis and management of periodontal diseases. The effect of bisphosphonates on bone metabolism is mediated through the suppression of the interactions between the receptor activator of nuclear factor kappa B (RANK) and its ligand (RANKL) as well as osteoprotegerin. Given their affinity to bind to hydroxyapatite crystals and inhibition of the development of osteoclasts, induction of osteoclastic apoptosis, [18] reduction of activity, [19] and stimulation of production of an osteoclast inhibitory factor [20,21]. It has also been shown that the bisphosphonate alendronate caused a rise in intracellular calcium levels in an osteoclast-like cell line and downregulation of bone resorption. Non-nitrogen-containing bisphosphonates cause osteoclast apoptosis through activation of the caspase pathway [22]. Conversely, more potent nitrogen containing bisphosphonates are not metabolized and appear to affect protein prenylation and osteoclasts through inhibition of the mevalonate pathway [23]. Limitations of these drugs on prolonged use may lead to inhibition of bone mineralization and subsequent osteomalacia, change in white blood cell counts, and osteonecrosis of jaw (ONJ). However, newer generation of bisphosphonates appear to minimize this activity. Currently they are still under investigation and may be soon available for treatment of periodontitis [24].

Modulation of Cytokines and Their Receptors

Cytokines are regulatory proteins not only control the survival, growth, differentiation and functions of cells but also play a key role in all stages of immune response of periodontal disease. Cytokines function as a network, are produced by different cell types, and share overlapping

features. This phenomenon is called biological redundancy. Most of biological responses are mediated by several different cytokines. Thus, blocking one inflammatory mediator or cytokine will not assure that a receptor-mediated response will not be activated by alternate pathways. This would require the development of polypharmaceutical approaches controlling all pathways associated with inflammation and tissue destruction. Proinflammatory cytokines such as TNF- α and IL-1 β have a key role in the initiation, regulation, and perpetuation of innate responses of periodontal disease. It is established that both IL and TNF have a variety of biological activities that are known as the underpin tissue damage in chronic inflammation, like in periodontitis [25].

Modulation of nitric oxide synthase (NOS) activity

NO is a short-lived molecule implicated in a wide range of biological processes ranging from immune homeostasis to cancer. It is synthesized in vivo from the substrate L-arginine in response to inflammatory stimuli such as bacterial LPS via inducible forms of NOS (iNOS). NO is a highly reactive free radical reacting with metal and thiol residues leading to lipid peroxidation, protein, and deoxyribonucleic acid (DNA) damages and stimulation of cytokine release. An exaggerated production of NO has been implicated in the pathophysiology of several inflammatory processes such as arthritis, colitis, and ileitis.

Mercaptoalkylguanidines

Animal experiments have shown that pharmacological inhibition of iNOS with mercaptoalkylguanidines was associated with decreased inflammation, hemorrhagic shock, and arthritis scores [26]. This may be explained by the fact that this class of drugs (e.g., mercaptoethylguanidines (MEGs) are able to: 1. Inhibit COX 2. Scavenge peroxy nitrite (i.e., the product of NO and superoxide) 3. Block iNOS.

Since NO activity has not been detected in the gingival tissues of sterile animals, oral bacteria have been postulated to trigger iNOS upregulation in periodontal tissues.

Other Locally Administered Host Modulatory Agents

A number of local host modulatory agents like enamel matrix derivatives (EMDs), growth factors, and bone morphogenic proteins have been investigated for potential use as adjuncts to surgical therapy, not only to improve healing but also to stimulate regeneration of lost tissues, periodontal ligament, and cementum; and thus completely restoring complete periodontal attachment apparatus. The only local host modulatory agent approved by FDA for adjunctive use during surgery is Emdogain[27]. Other host inflammatory mediators being investigated for modulation include nuclear factor kappa B (NF- κ B) and endothelial cell adhesion molecules. However, the role of these inflammatory mediators in periodontitis needs to be evaluated[28].

Miscellaneous Host Modulating Agents

In addition to the above-discussed host modulating agents, there have been certain other agents which were thought to modulate the periodontal disease progression. These have been summarized below:

Hypochlorous acid (HOCl) and taurine-N-monochloramine (TauCl) the end-products of the neutrophilic polymorphonuclear leukocyte respiratory burst are HOCl and TauCl, play an important role in the periodontal inflammatory process. They act together to alter the inflammatory response by arresting the production of PGs, IL-6 and other proinflammatory substances [29].

Cimetidine Histamine (H₂) receptor antagonist cimetidine, blocks histamine's inhibitory effects on immune response, and thus acts as an immuno-inflammatory modulator by increasing cyclic adenosine monophosphate levels and

downregulating cytokines and arresting neutrophil chemotaxis and superoxide production. In a study conducted by Hasturk et al. prove that topically active cimetidine is a potent inhibitor of Porphyromonas gingivalis induced periodontal inflammation, can inhibit tissue destruction and influence the inflammatory cells [30].

Probiotics Oral administration of probiotics can benefit periodontitis patients. The periodontal pathogens could be targeted by means of antagonistic interactions, with the application of Lactobacillus reuteri, which have shown the reduction of gingival bleeding and inflammation. The number of periodontal pathogens such as Bacteroides, Actinomyces, Staphylococcus intermedius, and Candida albicans were lowered by probiotic strains included in periodontal dressings at an optimal concentration of 10⁸ CFU ml [31].

Aloevera (AV) AV is a herbal product with antioxidant, anti-inflammatory, antimicrobial, healing-promoting, and immune-boosting properties. In a study by Pradeep et al.,[32] AV gel used as an adjunct to SRP in the treatment of patients with Type 2 diabetes mellitus and CP, showed significantly greater improvement in clinical parameter compared to placebo group.

Future Prospects

Immunoglobulin Y (IgY), GP are recommended to be an effective immunotherapeutic agent in the treatment of periodontitis. Pre-treatment of GP with IgYGP was related with active inhibition of cell detachment, an antibody against GP activity in vitro [33].

Conclusion

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. Multicentre clinical trials are necessary to fully evaluate the benefits of these agents and to weigh their usefulness against the risks associated with their long-term administration. Furthermore, continuous research in this field would also enable fabrication of individualized treatment for periodontal disease targeting inflammatory host response.

References

1. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. *J Clin Periodontol* 2005;32 Suppl 6:108-29.
2. Oringer RJ; Research, Science, and Therapy Committee of the American Academy of Periodontology. Modulation of the host response in periodontal therapy. *J Periodontol* 2002;73:460-70.
3. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV. Novel host response therapeutic approaches to treat periodontal diseases. *Periodontol* 2000 2007;43:294-31
4. Reddy S, Prasad Mgs, Kaul S, Asutkar K, Bhowmik N, Amudha. Host modulation in periodontics. *E J Dent* 2011;1;51-62.
5. Bathla S. Host modulatory therapy. In: Bathla S, editor. *Periodontics Revisited*. 1st ed. JP Medical Pub; 2011. p. 292-5
6. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. *J Clin Periodontol* 2005;32 Suppl 6:108-29.
7. Offenbacher S, Heasman PA, Collins JG. Modulation of host PGE2 secretion as a determinant of periodontal disease expression. *J Periodontol* 1993;64:432-44.
8. Howell TH, Williams RC. Nonsteroidal antiinflammatory drugs as inhibitors of periodontal disease progression. *Crit Rev Oral Biol Med* 1993;4:177-96.
9. Heasman PA, Offenbacher S, Collins JG, Edwards G, Seymour RA. Flurbiprofen in the prevention and treatment of experimental gingivitis. *J Clin Periodontol* 1993;20:732-8.
10. Nyman S, Schroeder HE, Lindhe J. Suppression of inflammation and bone resorption by indomethacin during experimental periodontitis in dogs. *J Periodontol* 1979;50:450-61.
11. Howell TH, Jeffcoat MK, Goldhaber P, Reddy MS, Kaplan ML, Johnson HG, et al. Inhibition of alveolar bone loss in beagles with the NSAID naproxen. *J Periodontal Res* 1991;26:498-501.
12. Howell T, Fiorellini J, Weber HP, Williams RC. Effect of the NSAID piroxicam, topically administered, on the development of gingivitis in beagle dogs. *J Periodontal Res* 1991;26:180-3.
13. Oringer R. Research, Science, and Therapy Committee of the American Academy of Periodontology. Modulation of the host response in periodontal therapy. *J Periodontol* 2002;73:684
14. Tüter G, Kurtis B, Serdar M, Aykan T, Okyay K, Yu'cel A, et al. Effects of scaling and root planing and subantimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease. *J Clin Periodontol* 2007;34:673-81.
15. Overall C, McCulloch C, Sodek J. Identification of polymorphonuclear leukocyte collagenase and gelatinase activity in mouthrinse samples: correlations with periodontal disease activity in adult and juvenile periodontitis. *J Periodontal Res* 1990;25:257-67.

16. David. Paquette & ray c. Williams, Modulation of host inflammatory mediators as a treatment strategy for periodontal diseases, *Periodontology* 2000;24:239-52.
17. Ryan ME, Ramamurthy S, Golub LM. Matrix metalloproteinases and their inhibition in periodontal treatment. *Curr Opin Periodontol* 1996;3:85-96.
18. Hughes DE, Wright KR, Uy HL, Sasaki A, Yoneda T, Roodman GD, et al. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. *J Bone Miner Res* 1995;10:1478-87.
19. Sato M, Grasser W. Effects of bisphosphonate on isolated rat osteoclasts as examined by reflected light microscopy. *J Bone Miner Res* 1990;5:31-4
20. Hughes DE, MacDonald BR, Russell RG, Gowen M. Inhibition of osteoclast-like cell formation by bisphosphonates in long-term cultures of human bone marrow. *J Clin Invest* 1989;83:1930-5.21)
21. Vitte C, Fleisch H, Guenther HL. Bisphosphonates induce osteoblasts to secrete an inhibitor of osteoclast-mediated resorption. *Endocrinology* 1996;137:2324-33.
22. Benford HL, McGowan NW, Helfrich MH, Nuttall ME, Rogers MJ. Visualization of bisphosphonate-induced caspase-3 activity in apoptotic osteoclasts in vitro. *Bone* 2001;28:465-73
23. Luckman SP, Coxon FP, Ebetino FH, Russell RG, Rogers MJ. Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: Evidence from structure-activity relationships in J774 macrophages. *Miner Res* 1998;13:1668-78
24. Nakaya H, Osawa G, Iwasaki N, Cochran DL, Kamo K, Oates TW. Effects of bisphosphonate on matrix metalloproteinase enzymes in human periodontal ligament cells. *J Periodontol* 2000;71:1158-66.
25. Thomson RG. Modulating the host response as an adjunctive treatment for periodontitis. *Periodontol* 2001;22:26-34.
26. Zingarelli B, Southan GJ, Gilad E, O'Connor M, Salzman AL, Szabó C. The inhibitory effects of mercaptoalkylguanidines on cyclo-oxygenase activity. *Br J Pharmacol* 1997;120:357-66.
27. Brookes SJ, Robinson C, Kirkham J, Bonass WA. Biochemistry and molecular biology of amelogenin proteins of developing dental enamel. *Arch Oral Biol* 1995;40:1-14.
28. Brennan PA, Thomas GJ, Langdon JD. The role of nitric oxide in oral diseases. *Arch Oral Biol* 2003;48:93-100.
29. Mainnemare A, Mégarbane B, Soueidan A, Daniel A, Chapple IL. Hypochlorous acid and taurine-N-monochloramine in periodontal diseases. *J Dent Res* 2004;83:823-31.
30. Hasturk H, Kantarci A, Ebrahimi N, Andry C, Holick M, Jones VL, et al. Topical H₂ antagonist prevents periodontitis in a rabbit model. *Infect Immun* 2006;74:2402-14.
31. Meurman JH, Stamatova I. Probiotics: Contributions to oral health. *Oral Dis* 2007;13:443-51.
32. Pradeep AR, Garg V, Raju A, Singh P. Adjunctive local delivery of Aloe vera gel in patients with Type 2 diabetes and chronic periodontitis: A randomized, controlled clinical trial. *J Periodontol* 2016;87:268-74.
33. Yokoyama K, Sugano N, Rahman AK, Oshikawa M, Ito K. Activity of anti-*Porphyromonas gingivalis* egg yolk antibody against gingipains in vitro. *Oral Microbiol Immunol* 2007;22:352-5.