

REVIEW ARTICLE



Host modulation therapy: An updated review

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Keywords

Bisphosphonates, chronic periodontitis, host response, interleukins, matrix metalloproteinases, statins

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Received 12 March 2017;

Accepted 20 April 2017

doi: 10.15713/ins.jcri.157

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. With increasing awareness and understanding of host-microbial interaction in periodontal pathogenesis has led the use of pharmacotherapeutic agents including antimicrobial therapy as well as host modulatory therapy for the management of periodontitis. 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 therapies that have been developed or proposed to modulate host responses for the treatment of periodontitis.

Introduction

Chronic periodontitis (CP) is polymicrobial disease due to an imbalance in the host defense 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. Chronic bacterial exposure is sine qua non for gingival inflammation and destruction of tooth supporting structure.^[1]

A small group of mainly microaerophilic bacteria, Gram-negative, or anaerobic bacteria in the biofilm are important for induction and advancement of periodontal destruction. Pathogens actively involved as etiologic agents include *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Tannerella forsythia*. The microbial defense consists of virulence factors such as gingipains (GPs), and lipopolysaccharides.^[2] Hence, 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. The focus of research on host modulation has shifted recently from the old concept of targeting inhibition to newer concepts of usage of agonists to stimulate key points within the control of endogenous mechanisms for resolving inflammation.

The therapeutical agents or periocutics that are mainly used to control periodontitis is a rising branch in the treatment of periodontal diseases along with mechanical debridement.^[3] 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), subantimicrobial 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. BP modulates the osteoclast function, and subantimicrobial dose doxycycline (Periostat) uses the anticollagenase 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 equipment to conventional mechanical debridement, which could improve and make the clinical therapeutic outcome more predictable, in a susceptible host.^[4]

This review focuses on various host modulating agents and clinical applications of host modulatory therapeutic regimens as supportive to conventional periodontal treatment modalities.

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 downregulating the destructive aspects or up regulating the protective aspects of the host response.

Modulation of arachidonic acid (AA) metabolites

PGs were described first in 1939 by Von Euler as vasoactive fatty acids which are capable of lowering blood pressure in rabbits and is derived from human seminal vesicle fluid.^[1] PGs are metabolized through the cyclooxygenase (COX) pathway and leukotrienes through the lipoxygenase (LOX) pathway to produce free AA. Various studies have shown that an important mediator of bone loss in periodontitis is PGs.

COX isoenzymes (COX1 and 2) activity are blocked by NSAIDs drugs. Many studies authenticate the role of NSAIDs such as flurbiprofen,^[5] indomethacin,^[6] and naproxen,^[7] in arresting gingival inflammation and progression of periodontal destruction. Endogenously generated LXs *via* cell-cell signaling late in inflammation, when a second LOX (e.g., 5 LOX) interacts with a LOX product (e.g., hydroxyeicosatetraenoic acid) generated earlier from AA,^[8] also possess both anti-inflammatory and proresolving potential. LXs can be used as targets for HMT against periodontal diseases as it can reduce neutrophil recruitment and infiltration, reactive oxygen species generation and blocking cytokines, thus prevent bone loss and connective tissue.^[9]

Cytokine suppressing anti-inflammatory drugs are new class of drugs, that are being described as SKF 86002 prototypes. These drugs are efficient and selective inhibitors of one of the mitogen-activated protein kinase family termed alternately p38, RK or cytokine suppressing anti-inflammatory drugs binding protein.^[10]

Lipid-inflammatory mediators as targets for HMT

Resolvins, protections, and recently identified maresins are endogenous chemical mediators known to mediate a resolution of acute inflammation in extreme condition. Omega 3 polyunsaturated fatty acids, eicosapentaenoic acid, and docosahexaenoic acid are precursor of these mediators via sequential steps involving LOX, and COX.^[9,11,12] These endogenous chemical mediators act via suppression of neutrophil recruitment which is similar in action to that of LXs.^[11] Excessive acute inflammation is counter-regulated, molecular and cellular events that explain resolution is triggered by these mediators.^[13] Therefore, designing therapeutics agents for HMT from naturally occurring proresolving mediators offers exciting new targets for drug design.^[14]

Modulation of matrix metalloproteinases (MMP)

MMP, zinc and calcium-dependent endopeptidases secreted or liberated by a 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 $\alpha 2$ macroglobulin and tissue inhibitors of MMPs.^[15]

TCs in host modulation

TC is major antiproteinase used in periodontal therapy. Low dose capsules containing 20 mg of doxycycline is a recent approach to non-antibacterial periodontal treatment and is most potent collagenase inhibitor which is commercially available. The group of CMTs constitute of at least 10 analogs plus few special modified CMTs that vary in their MMP specificity and potency.^[16]

Modulating agents acting against cytokines

Proinflammatory (e.g., interleukin-1 α [IL1 α], IL1 β , IL6, tumor necrosis factor α [TNF α], 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.^[17]

These treatment modalities focus at antagonizing the proinflammatory cytokines via different mechanisms:

- a. Antagonist of cytokine receptor: Inhibit the cytokine from binding to the target cell. E.g., commercially available Kineret (Anakinra, Amgen), which is IL1 receptor antagonist (IL1ra).^[18,19]
- b. Anticytokine antibodies: Few anticytokine antibodies that are recently available are:
 1. TNF α receptor antagonist: Certolizumab pegol, adalimumab, golimumab, etc.
 2. IL6ra: Tocilizumab
 3. IL15ra: AMG714
 4. IL12 and IL23ra: Ustekinumab
 5. IL17ra: AIN457.^[18]
- c. Soluble cytokine receptors:

These receptors can be found in blood, and extracellular fluid and downregulation 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.^[19] Methylxanthine 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.^[20] 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 downregulation of toll-like receptor in diseased periodontal tissues.^[21]

Modulation of bone remodeling by

1. BPs:

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.^[22]

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.^[23]

2. Metformin (MF):

MF is the most common oral antihyperglycemic 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.^[24]

3. 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.

Different studies conducted by Pradeep *et al.* using statins such as 1.2% ATV gel, 1.2% simvastatin gel, and 1.2% rosuvastatin gel as LDD in adjunct to SRP showed greater improvement in clinical parameter than the placebo group.^[25]

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.^[26]

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.^[27]

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.^[28]

Aloe vera (AV)

AV is a herbal product with antioxidant, anti-inflammatory, antimicrobial, healing-promoting, and immune-boosting properties. In a study by Pradeep *et al.*,^[29] 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*.^[30]

Conclusion

Traditional periodontal therapy is the gold standard in the treatment of maximum cases of periodontal diseases. However, there are susceptible and high-risk groups where HMT may be utilized as an adjunctive treatment modality. In addition, more research is required to make treatment response more predictable and to enhance periodontal stability. The clinician can be benefited by both established treatment strategies and with new systemic and local drug treatment by host modulation in high-risk groups.

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How to cite this article: Ipshita S, Kurian IG, Dileep P, Guruprasad CN, Singh P, Pradeep AR. Host modulation therapy: An updated review. *J Adv Clin Res Insights* 2017;4:55-58.

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