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Sakshi Gaind
Senior Lecturer, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Manish Khatri
Professor and Head, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Mansi Bansal
Professor, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Komal Puri
Reader, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Mohd. Rehan
Reader, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Sourabh Mehrotra
Senior Lecturer, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Corresponding Author:
Sakshi Gaind
Senior Lecturer, Department of Periodontology, Institute of Dental Studies and Technologies, Modinagar, Ghaziabad, Uttar Pradesh, India

Host modulation as a therapeutic strategy

Sakshi Gaind, Manish Khatri, Mansi Bansal, Komal Puri, Mohd. Rehan and Sourabh Mehrotra

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Abstract
Periodontal diseases are bacterial-induced inflammatory disease characterized by a complex interplay between the pathogens and the host tissue. A disturbance in the equilibrium between bacteria and host, results in periodontal tissue destruction. As periodontal disease progresses, a series of events occur in bacterial plaque, gingival sulcus, junctional epithelium, connective tissue, and bone, due to alteration in tissue homeostasis. This increasing awareness and knowledge of the host microbial interaction in periodontal pathogenesis has presented the opportunity for exploring new therapeutic strategies for periodontitis by means of targeting host response via host modulating agents. This has lead to the emergence of the field of "Perioceutics" i.e. the use of pharmacotherapeutic agents including antimicrobial therapy as well as host modulatory therapy for the management of periodontitis. These host modulating agents used as an adjunct tip the balance between periodontal health and disease progression in the direction of a healing response.

Keywords: Host modulation, Nonsteroidal anti-inflammatory drugs, tetracycline, bisphosphonates

Introduction
Periodontitis is one of the most ubiquitous diseases. It is characterized by the destruction of connective tissue and dental bone support following an inflammatory host response secondary to infection by periodontal bacteria [1]. The first clinical manifestation of periodontal disease is of periodontal pockets, which offer a favorable niche for bacterial colonization. It can be diagnosed by clinical examination with the periodontal probe to determine pocket depths in combination with X-ray imaging, using microbiological techniques for a precise analysis of the infectious agents [2].

According to current concepts of the multifactorial etiology of periodontal disease, it is caused by the interaction among single or multiple microbial agents, a host with some degree of susceptibility, and environmental factors that influence on both. Although a single model of the etiopathogenic of periodontal disease has yet to be validated, it is broadly accepted that periodontal disease results from the action of the bacterial biofilm on the periodontium of the susceptible individual. Bacteria can survive and grow in the complex ecosystem of this biofilm because they produce of virulence factors. These factors also confer a greater resistance to host defense mechanisms, i.e., they increase the capacity of the bacteria to overcome the inflammatory reaction and immune response to antigen presentation [3].

According to a review by Offenbacher in 1996, the presence of bacteria in the periodontal pocket triggers a reaction that starts with the intervention of the neutrophil antibody-complement axis, stimulating different cell types [4].

Host modulatory therapy is a new treatment modality that has been incorporated into dental therapeutics. Still it has not been well implemented in the dental practice due to the easy unavailability of host modulatory agents in India. Host can be defined as "the organism from which a parasite obtains nourishment," or in the transplantation of tissue, "the individual who receives the graft". Modulation is defined as "the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment." The Host modulation with chemotherapeutic agents or drugs is a promising new adjunctive therapeutic opportunity for managing of periodontal diseases.

The concept of host modulatory therapy was first introduced to dentistry by Williams and Golub *et al.* and then expanded by many other researchers in the dental profession. Golub and colleagues discussed "host modulation with tetracyclines and their chemically modified analogs" [5].
Three potential approaches to host modulation have been considered: 1) inhibition of matrix metalloproteinases (MMPs) with antiproteinases, 2) blocking the production of proinflammatory cytokines and prostaglandins with anti-inflammatory drugs, and 3) inhibiting activation of osteoclasts with bone-sparing agents [6].

Host Response: Concepts of the etiology of periodontal disease have changed noticeably in the last four decades. In 1985 research began to focus on bacterial-host interactions. Several specific subgingival oral bacteria, including porphyromonus gingivalis, actinobacillus aggregatibater, prevotela intermedia, bacteroides forsythus and perhaps others such as campylobacter rectus, fusobacterium nucleatum, and spirochetes are associated with a severe type of periodontal diseases [7]. Protective aspects of the host response include recruitment of neutrophils, production of protective antibodies, and possibly the release of anti-inflammatory cytokines, including transforming growth factor (TGF-β), interleukin-4 (IL-4), IL-10, and IL-12. Persistent bacterial aggression disrupts homeostatic mechanisms and results in the release of proinflammatory cytokines (e.g., IL-1, IL-6, tumor necrosis factor- α (TNF-α), proteases (e.g., Matrix Metallo proteinase's), and prostanoids (e.g., prostaglandin E2 [PGE2]), which can endorse extracellular matrix destruction in the periodontium and stimulate bone resorption, tooth mobility, and tooth loss [8].

Host Modulation: 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. 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), are few host modulating agents that are being recommended. Systemic flurbiprofen and topical ketoprofen are NSAIDS that act by inhibiting PGE2. Bisphosphonates modulates the osteoclast function, and subantimicrobial dose doxycycline uses the anticollagenase properties of tetracycline (TC), which is lone permitted drug by FDA. Future prospect lies for chemically modified tetracycline (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 [9]. In addition, a number of local host modulatory agents have been investigated in clinical trials for their potential use as adjuncts to surgical procedures not only to improve upon wound healing but also to stimulate regeneration of lost bone, periodontal ligament, and cementum, restoring the complete periodontal attachment apparatus. These have included enamel matrix proteins (Emdogain), bone morphogenetic proteins (BMP-2 and BMP-7), growth factors (platelet-derived growth factor and insulin-like growth factor), and tetracyclines. The only host modulatory agent currently approved by the FDA for adjunctive use during surgery is Emdogain [10].

Classification of the various host modulation therapies
A. Kenneth S. Kornman, 1999 [11]
i. Host Modulation
1. Blocking Direct Effectors of Bone and Connective Tissue Destruction E.g. bisphosphonates, MMP inhibitors ii. Host Modulation
2. Blocking Host Mechanisms That Influence Clinical Outcomes E.g. NSAIDs, inhibitors of IL-1 and TNF iii. Host Modulation
3. Host Mechanisms That Influence Bacterial Control E.g. agents that reduce levels of PGE2, IL-1, TNF

B. Reddy MS, Geurs NC, Gunsolley JC, 2003 [12]
1. Anti-proteinases - E.g.: tetracyclines
2. Anti-inflammatory agents - E.g. NSAIDs
3. Bone sparing agents - E.g. Bisphosphonates

C. Anarthe RD, Mani DA, Marawar DPP, 2013 [13]
A. Inhibition of matrix metalloproteinase (MMPs): This is achieved by chemically modified tetracyclines (CMTs)

B. Inhibition of arachidonic acid metabolite: Through NSAIDs
a. COX-1 inhibitors: Indomethacin, Flurbiprofen, Naproxen.
b. COX-2 inhibitors: Rofecoxib.
c. COX and LOX inhibitors: Triclosan, Topical ketoprofen.
d. LOX inhibitors: Lipoxins.

C. Modulation of bone metabolism
a. Bisphosphonates
b. Hormone replacement therapy (HRT)
c. Calcium supplementation.

D. Regulation of immune and inflammatory response
a. Suppressing pro-inflammatory cytokines: IL1 and TNF-α receptor antaonist.
b. Nitric oxide inhibition.
c. Generation of protective antibodies through vaccination.
d. Infusion/ supplementary anti-inflammatory cytokines: IL-4 and IL-10.

D. Carranza, Newman, Takei, Klokkevold [14]
1. Systemically administered agents- NSAIDs, Bisphosphonates, Subantimicobial-dose doxycycline (SDD)
2. Locally administered agents; NSAIDs, Enamel matrix proteins (EMP), Growth factors, Bone morphogenetic proteins.

Chemically Modified Tetracyclines: Tetracyclines were first introduced in 1948 and were soon recognized as highly effective against Rickettsiae, several Gram-positive and Gram-negative bacteria, and other organisms. These nonantibiotic tetracyclines analogs are nothing but the tetracycline molecules which have been modified to eliminate the antimicrobial property, but retain the host modulatory, anticollagenolytic property. Furthermore, these drugs, known as broad spectrum antibiotics [15].
Chemically Modified Tetracyclines are used as Host Modulating agents in the management of periodontitis by inhibition of Matrix Metalloproteinases, inhibition of proinflammatory cytokines, inducible nitric oxide synthase

(iNOS) and inhibition of bone resorption, enhancement of the attachment of fibroblasts and connective tissues to the tooth surface.[16] The anti- Matrix Metalloproteinases actions of Chemically Modified Tetracyclines include direct inhibition of the active MMPs by the virtue of Ca2+ and Zn2+-binding sites, inhibition of reactive oxygen species-mediated activation of pro-MMPs, proteolysis of pro-MMPs into enzymatically inactive fragments, protection of α-1 proteinase inhibitor from MMPs, reduction in the activity of serine proteinases. Polymorphonuclear leucocytes (PMNs) provide the major source of collagenases that mediate the connective tissue breakdown during inflammatory periodontal disease, while the fibroblasts contribute the collagenase required for connective tissue remodeling in normal gingiva. The anti-collagenase activity of CMTs is specific against the collagenase produced from neutrophils but not the fibroblasts [16].

SDD-Sub Antimicrobial Dose of Doxycycline: SDD is the only systemic host response modulator specifically indicated as adjunctive treatment for periodontitis and it is approved by USFDA and UK medicines and health care products regulatory agency. It is marketed as periostat, 20mg dose of doxycycline hyclate BD for 3-9 months has the ability to down regulate MMPs [17].

Mechanism of Action [11].

1. In junctional epithelium inhibition of production of epithelial derived MMPs by inhibiting cellular expression and synthesis.
2. In connective tissue - Direct inhibition of active MMPs by cation chelation Inhibition of oxidative activation of latent MMPs, down regulates the expression of key inflammatory cytokines including interleukin IL1,IL6,and tumor necrosis factor (TNF)α,as well as prostaglandin E2 (PGE2)Scavenges and inhibits production of reactive oxygen species (ROS) produced by PMNs (e.g.HOCl, which activates latent MMPs),Inhibition of MMPs and ROS protects α1 proteinase inhibitor (α1PI) thereby indirectly reducing tissue proteinase activity, Stimulates fibroblast collagen production.
3. Alveolar bone- Reduces osteoclast activity and bone resorption, blocks osteoclast MMPs, Stimulates osteoblast activity and bone formation.

Crout *et al.* 1996 - In a study of 14 patients with chronic periodontitis, after removal of subgingival plaque and calculus, patients were randomised to receive either SDD for 2 months, then no drug for 2 months, then SDD for 2 months or placebo for 2 months, then no drug for 2 months, then placebo for 2 months SDD resulted in significantly improved probing depths and attachment levels compared with placebo, but did not affect plaque index or gingival inflammation [18].

Al-Shammari *et al.* 2001 - SDD was given to 12 patients with chronic periodontitis for 2 months following a course of subgingival instrumentation. Six patients were prescribed placebo. At baseline, months 1 and 2, GCF samples were collected and analysed for MMP-8, MMP-13 and ICTP (carboxyterminal peptide, a pyridinoline-containing fragment of type-1 collagen). The 2-month regime of SDD resulted in statistically significant reductions in GCF concentrations of ICTP, MMP-8 and MMP-13 compared with placebo. This was the first study that demonstrated in human subjects that SDD results in a simultaneous reduction of elevated MMP activity with a concomitant reduction in levels of collagen degradation fragments. SRP alone has no effect on GCF ICTP levels [18].

Bisphosphonates: The bisphosphonates are bone-seeking agents that inhibit bone resorption by disrupting osteoclast activity [11].

Mechanism of action

Bisphosphonates acts on osteoclast function at Tissue, Cellular and molecular levels

1. Tissue level: Decrease bone turnover due to decreased bone resorption, Decreased number of bone multicellular units, Net positive whole body bone balance
2. Cellular level: Decreased osteoclast recruitment, Increased osteoclast apoptosis, Decreased osteoclast adhesion, Increased osteoblast differentiation and number
3. Molecular level: Inhibit mevalonate pathway, Decreased post translational phenylation of GTP binding proteins [19].

Rocha *et al.* used oral route of alendronate as host modulating agent and found that there is decreased alveolar bone resorption, decreased tooth mobility and decreased clinical parameters [20].

Pradeep AR *et al.* used Alendronate as local drug delivery as 1% gel and found that there isincrease percentage of bone fill, decreased probing depth and clinical attachment level [21].

Other host modulatory agents

i. **Probiotics:** Probiotics have demonstrated significant potential as therapeutic options for a variety of disease as they have been known to modulate cytokine secretion profiles, influence TR09;lymphocyte populations, protect against physiologic stress, and enhance intestinal epithelial cell function and antibody secretion [22]. Teughels *et al.* explored the use of probiotics in influencing the periodontal microbiota and periodontal health and concluded that probiotics might offer opportunities to manipulate the oral microbiota, and periodontal health by either direct microbiological interactions or by immunomodulatory interactions [23].

ii. **Periodontal Vaccine:** George Hajishengallis reported that toll like receptors (TLRs) may offer novel targets for host R09; modulation therapy in periodontitis since manipulation of TLR signalling may contribute to control of infection or regulation of inflammation and, moreover, synthetic or natural TLR agonists could serve as novel periodontal vaccine adjuvants [24].

Summary and Conclusion: The improved understanding of the host bacterial interactions and the host immune inflammatory response leading to periodontal tissue destruction has led to the development of Host Modulation Therapy. Subantimicrobial dose doxycycline (SDD) is the only HMT currently approved and indicated as an adjunct to SRP for treating periodontitis. In the future a range of HMTs targeting different aspects of the destructive cascade of breakdown events in the periodontal tissues are likely to be developed as adjunctive treatments for periodontitis. The further development of these agents will permit dentists to treat specific aspects of the underlying biochemical basis for periodontal disease. The goal is to maximize the treatment response by reducing inflammation and inhibiting destructive processes in the tissues, which will result in enhanced periodontal stability after conventional periodontal treatments such as SRP.

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