

# Host Modulation Therapy: A Mini Review

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## Abstract:

Periodontal diseases are responsible for tissue destruction which acts as a supporter for dentition. These diseases are initiated by gram negative bacteria which forms biofilm and elicits host inflammatory responses. Mechanical debridement along with various pharmacology agents such as Nonsteroidal anti-inflammatory drugs, Doxycycline, aids in managing periodontitis. Host Modulatory Therapy is a treatment concept that focuses on the reduction of tissue destruction and stabilizing or regenerating the periodontium by modifying or decreasing the regulating destructive aspects of the host response and upregulating protective or regenerated responses. This manuscript reviews the Host Modulatory Therapy that acts as an effective tool adjunct to mechanical therapy in treating periodontal diseases.

**Keywords:** Biofilms, Nonsteroidal anti-inflammatory drugs, Doxycycline, Host Modulatory Therapy, Regenerated responses.

## Introduction

Dental Plaque is capable of causing direct damage to the periodontal tissue. It releases hydrogen sulfide, butyric acid, enzymes and mediators which causes inflammatory changes in the tissue that initiates destructive processes and hence, affecting the dentition in oral cavity<sup>1</sup>. The host response is essentially protective by intention but can contradictorily result in tissue damage that includes the breakdown of connective tissue fibers in the periodontal ligament and resorption of the alveolar bone. Host modulatory therapy does not shut off the normal defense mechanism of inflammation instead, they ameliorate excessive or pathologically elevated inflammatory process to enhance the opportunities for wound healing and periodontal stability. Pharmacological agents are used to stop the progression of periodontitis by intervention of the pathogenic mechanism. It is used as an adjunct with conventional periodontal disease treatment. It offers the opportunity for modulating or reducing destruction by treating chronic inflammatory response. The concept was introduced by William and Golub in 1990<sup>2</sup>. Initially adjunctive therapies were solely anti-microbial such as use of antibiotics and antiseptics. New approaches include modulation of host response.

## Classification

### 1. Systemically administrated agents:

1. NSAIDS ( Non steroidal anti-inflammatory drugs)
2. SDD ( Subantimicrobial dose of doxycycline)
3. Bisphosphonates
4. Modulation of NO (Nitrous oxide) activity

### 2. Locally administrated agents:

1. NSAIDS
2. Enamel Matrix Protein
3. Growth Factors

## Host Modulatory Agents

Various host modulatory therapy agents have been developed to prevent and management for the periodontal problems<sup>3</sup>. The most common mechanisms by which these acts are the following:

### 1. Inhibition of Matrix metalloproteinases (MMPs) -Through chemically Modified Tetracyclines (CMTs)

### 2. Inhibition of Arachidonic Acid metabolites-through NASIDs

- 1.COX-1 inhibitors: Indomethacin's, Flurbiprofen
- 2.COX-2 inhibitors: Rofecoxib
- 3.COX and LOX inhibitors: Triclosan, Tropical Ketoprofen
- 4.LOX inhibitors: Lipoxins

### 3. Modulation of Bone metabolism

- 1.Bisphosphonates
2. Hormone Replacement Therapy

### 4. Regulation of immune and inflammatory responses

- 1.Suppressing proinflammatory cytokines (IL-1 and TNF-  $\alpha$  receptor antagonists)
- 2.Nitric Oxide inhibition
- 3.Generation of protective antibodies through vaccine
- 4.Infusion/ supplementary anti-inflammatory cytokines IL-4 and IL-10.

### 5. Miscellaneous Host Modulatory agents

- 1.Aloe vera
- 2.Probiotics
- 3.Hypochlorous acid and taurine-N-monochloramine
- 4.Azithromycin's

## Uses

These therapeutic agents are particularly useful in susceptible, high-risk patients such as smokers, diabetics, genetic predisposition. FDA has recommended the approved use of Periostat for systemic administration as an adjunct to scaling to root planning, in the treatment of chronic periodontitis.

### A. Chemically Modified Tetracyclines (CMTs)

Tetracyclines have been used as an antibiotic from a very long time. Periodontal pathogens (*P. gingivalis* and *A. actinomycetemcomitans*) produce MMPs. However, it is believed that endogenous MMPs are not the bacterial proteinases that are primarily responsible for tissue destruction. This further state the importance of the role of host modulatory approaches in periodontal therapy. Chemically modified tetracyclines are tetracyclines that lack dimethylamino group on the 4<sup>th</sup> carbon atom.

### Mechanism of Action of Chemically modified tetracyclines

- 1.Inhibits or chelated the calcium atoms that Matrix metalloproteins require for their action
- 2.Inhibits already active MMPs
- 3.Decreases MMPs expression
- 4.Scavengers reactive oxygen species
- 5.Modulates the osteoclast functions

### Side effects of CMTs

- 1.Photosensation property
- 2.Neurotoxicity
- 3.Cytotoxic effects at higher concentration.
- 4.Rapid emergence of resistant microorganisms.

**Periostat ( Subantimicrobial dose of doxycycline)**

It is a subantimicrobial dose of doxycycline hyclate capsule of 20 mg that uses anticollagenase properties of tetracycline. It is prescribed to patients with chronic periodontitis twice daily. Administration of drug for only 2 weeks. This can inhibit collagen activity by 60%-80% in the gingival tissue of chronic periodontitis patients. However, collagen activity also decreases in GCF. Prescription of the drug for a smaller duration decreases the chance for drug resistant. It is an effective tool adjunct to mechanical therapy in treating periodontal diseases<sup>4</sup>.

**Mechanism of Action**

It acts as a host modulator by directly inhibiting MMPs (secreted by plaque biofilm) which indirectly reduces osteoclast activity and bone resorption. It stimulates osteoblast activity and hence promotes bone absorption. It also stimulates fibroblast collagen production.

**Indications**

1. Patients who have not responded to non-surgical therapy.
2. Patients with generalized recurrent sites of 5mm or greater pocket depth that bleed on probing.
3. Patients with mild to moderate chronic periodontitis but have a high susceptibility to rapid periodontal disease progression.
4. Patient who has aggressive periodontitis
5. Patient with periodontitis associated with genotype (PAG), has specific variation in genes that regulates IL- 1.

**Contraindications**

1. The patient who are allergy to tetracycline.
2. Pregnant women, Lactating women, and children below 12 years of age.
3. Patient in whom antibiotic regimen is necessary.
4. May reduce the effectiveness of oral contraceptives.

**Side effects**

1. Photosensitivity
2. Hypersensitivity reactions
3. Nausea and vomiting
4. Esophageal irritation

The administration of doxycycline in human osteoarthritis produces benefits in association with the suppression of matrix metalloproteinases.

**B. NSAIDS ( Non-Steroidal Anti-inflammatory Drugs)****Inhibition of Arachidonic Acid metabolites**

In periodontal diseases destructive pathways are initiated as arachidonic acid is activated which gets metabolized by cyclooxygenase, and releases prostaglandins, prostacyclin's and thromboxane whereas the end product of the Lipoxygenase pathway releases Leukotrienes and hydroxy eicosatetraenoic acid<sup>5</sup>. So, an approach to modulate the host response is inhibition of enzymes responsible for the release of these destructive products can be adopted. These include:

1. Systemically administered NSAIDS
2. Locally administered NSAIDS
3. Triclosan

**Systemically administered NSAIDS**

Nonsteroidal anti-inflammatory drugs act by inhibiting cyclooxygenase in an arachidonic acid pathway. Thereby reducing prostaglandins (PGE<sub>2</sub>) which are responsible for bone loss. These include ibuprofen, indomethacin<sup>6</sup>.

**Locally administered NSAIDS**

Topical administration is another method to deliver these agents. It is possible as these drugs are lipophilic and are absorbed into gingival tissues. These include Ketoprofen that inhibits both cyclooxygenase and lipoxygenase pathway. Besides these, Ketorolac trimethamine rinse and S-ketoprofen dentifrices<sup>7</sup> can also be used.

Topical use of lipoxins which blocks neutrophil infiltration induced by *P. gingivalis* and reduced in PGE<sub>2</sub> levels can be used as an adjunct in scaling and root planing.

### **Triclosan**

It has both anti-bacterial and anti-inflammatory properties. It is a non-ionic antibacterial agent that also inhibits both cyclooxygenase and lipoxygenase pathways and thus interferes in the arachidonic acid pathway<sup>8</sup>. Dentifrice containing sodium fluoride and triclosan and a copolymer has been tested and shows positive results in the treatment of Periodontitis.

### **Side effects**

1. Hemorrhage
2. Gastric ulceration
3. Renal failure
4. Rebound effect
5. Liver Failure

### **C. Bisphosphonates**

Bisphosphonates are drugs that are non-biodegradable analogs of pyrophosphate with a high affinity for calcium phosphate crystals and that inhibit osteoclast activity. These bisphosphonates appear to inhibit MMP activity through a mechanism that involves the chelation of cations.

Alkyl side chains characterize.

1. **First generation bisphosphonates:** eg. Etidronic acid and Clodronic acid
2. **Second generation Bisphosphonates** includes an amino-terminal group along with an aminobisphosphonates. eg. Alendronate and Pamidronate.
3. **Third generation Bisphosphonates-** have cyclic side chains For example: risedronate<sup>9</sup>.

### **Mechanism of Action**

1. Inhibition of the development of osteoclasts
2. Induction of osteoclastic apoptosis
3. Reduction of the activity of osteoclast
4. Prevention of the development of osteoclasts from hematopoietic
5. Initiates the production of an osteoclast inhibitory factor.
6. Stimulate production of osteoclast inhibitory factor.
7. Decreasing bone resorption by inhibiting MMPs.

### **Disadvantages**

1. Long term use can compromise healing of even micro-injuries within bone
2. Can lead to osteonecrosis of jaw following dental extraction.
3. Inhibit bone calcification

### **Contraindications**

The contraindication for use of bisphosphonates is the sensitivity to phosphates and gastrointestinal upset.

### **D. Osteoprotegerin (OPG)**

The discovery of a novel receptor called osteoprotegerin revealed a key regulatory mechanism in osteoclast differentiation and activity. OPG and receptor activator of NF- $\kappa$ B (RANKL) ligand are two molecules that regulate osteoclast formation and bone resorption. RANKL has the effects on osteoclasts as they induce osteoclast differentiation followed by activation, whereas OPG blocks this process by acting as a decoy receptor for RANKL.

### **E. Statins**

These are the drugs that lower the lipid level in the body and are hence used to treat hyperlipidaemia. These drugs have pleiotropic effects such as antithrombotic, antioxidant, anti-inflammatory, vasodilative<sup>10</sup>. They inhibit the activity of enzyme 3-hydroxy-3-methyl glutaryl coenzyme.

## Mechanism of Action

They act by inhibiting the release of proinflammatory mediators such as cytokines and MMP and this inhibit osteoclast activity.

### F. Regulation of immune and inflammatory responses

**1. Modulation of Nitric Oxide activity:** Nitric oxide (NO) is a molecule that has a wide range of biological processes. It is a highly reactive free radical reacting with metal and thiol residues that results to lipid peroxidation, protein damage, DNA damage and stimulation of cytokine release. Nuclear Poly ADP-ribose polymerase enzyme decreases NO toxicity<sup>11</sup>.

**2. Suppressing proinflammatory cytokines:** Cytokines are defined as regulatory proteins controlling the survival, growth, differentiation, and function of cells. They function as a network and are produced by different cell types and share overlapping features. This phenomenon is called Biological redundancy. To avoid tissue damage and maintain homeostasis, cytokines antagonists such as IL-1receptor antagonist or soluble TNF receptors can competitively inhibit receptor mediated signal transduction<sup>12</sup>.

**3. Other Locally administered agents:** These include agents such as enamel matrix proteins, growth factors, and bone morphogenic proteins have been investigated for potential use as adjuncts to surgical procedures. It improves wound healing as well as stimulate regeneration of lost bone, periodontal ligament, and cementum and thus, restoring the complete periodontal attachment apparatus. The only local host modulatory agent currently approved by the FDA for adjunctive use during surgery is Emdogain<sup>13</sup>. It affects early stages of osteoblast maturation. They are believed to regulate the initiation, propagation, termination, and maturation of enamel hydroxyapatite crystals. They also take part in cementogenesis.

### G. Miscellaneous Host Modulatory agents

#### 1. Aloe vera

It is a herbal product with many advantages that can be used in various phases. They are antioxidant, anti-inflammatory, anti-microbial, immune boosting, healing properties. Aloe vera gel is used as an adjunct to mechanical debridement that is scaling and root planning in the treatment with Type-II Diabetes Mellitus. A study conducted by Pradeep et.al 2016 evaluated that aloe vera show greater improvement in clinical parameter<sup>14</sup>.

#### 2. Probiotics

The use of probiotics administered orally has proven to be beneficial for periodontitis patients. They lowered the periodontal pathogens such as *Candida Albicans*, *Staphylococcus intermedius*, *Bacteroides*, *Actinomyces* either by direct microbiological interaction or by immunomodulatory interaction. They are used in periodontal dressings<sup>15</sup>.

#### 3. Hypochlorous acid and taurine-N-monochloramine

They play an important role in controlling the periodontal inflammatory process. They act together to differ the inflammatory responses by inhibiting the production of Prostaglandins, IL-6, and other proinflammatory substances<sup>16</sup>. It is used 10 ml daily as a mouth rinse and within 4 days it reduces plaque vitality.

#### 4. Azithromycin's

Azithromycin is an antibiotic that is taken up readily into inflamed tissues by neutrophils, macrophages through chemotaxis. It is given per tablet of 500 mg for 3 consecutive days. It is effectively useful in the treatment of moderate to advanced periodontitis as it has the ability to penetrate biofilm and has a long anti-bacterial half-life. It is effective against gram negative bacteria and the short course of the drug makes it a great option of treatment along with mechanical debridement<sup>17</sup>. It decreases the proinflammatory cytokine production and increase the production of anti-inflammatory cytokines. However, it has been considered as a better mode of treatment than low dose doxycycline.

#### 5. Cimetidine

It is a histamine receptor antagonist that eliminates the inhibitory effects on immune response thereby acting as a modulator of inflammation and immunity, the neutrophil chemotaxis, and superoxide production. They increase cyclic adenosine monophosphate levels and decrease the level of cytokines.

## Futuristic Approaches

Host modulatory therapy has proven to be very useful for the health of the periodontium. Various new host modulating agents has also been introduced such as lipoxins, resolvins and probiotics (lactobacilli and bifidobacteria). Besides these, Immunoglobulin Y(IgY), Glycoproteins (GP) are also recommended to be effective agents in the treatment of Chronic Periodontitis. Glycoproteins along with Immunoglobulin Y are pretreated to form ImmunoGlycoprotein (IgYGP) to prevent antibody against Glycoprotein activity<sup>18</sup>. The introduction of Periodontal vaccines against the serious infectious diseases that do not have an effective treatment can also be used. They have shown positive result in controlling the infection or regulation of inflammation. Moreover, the use of nutrients which include major antioxidants such as Vitamin C, Vitamin E, omega 3 Fatty acids act as a modulator of inflammation by scavenging free radicals and sequestering transition of metal ions and catalyzing formation of other molecules.

Recently, the use of hypoglycemic drug known as Glitazone suppress P.Gingivalis by inducing IL-6 production. The continues advancements in chemically modified tetracyclines such as combination of CMT and Fluriprofem, seems to be promising in improving the most modulation therapy.

## Conclusion

Host modulatory therapy is considered as a bench mark in the treatment of patients with periodontal diseases. They are used in patients with diabetes and immunocompromised situations. They have been beneficial in peri-implant disease where local and systemic efficiency of host modulatory therapy are used as an adjunct to conventional local disinfection treatment. Although the efficacy and usefulness of host modulating agents have improved the treatment in several folds still, more research is required to make treatment response faster and to increase periodontal stability.

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