HOST MODULATION-A NEW WAVE IN THE PHARMACOTHERAPY OF PERIODONTITIS.

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ABSTRACT

Periodontitis is a polymicrobial infectious disease of multifactorial origin. Plaque biofilm associated host responses are involved in the pathogenesis of periodontitis. In periodontal diseases, bacteria trigger inflammatory host responses, which along with the direct destructive effects of the bacteria, cause most of the tissue destruction. Host modulation therapy aims to reduce tissue destruction and stabilize or regenerate the periodontium by modifying host responses. The role of host modulation therapy in the inhibition of these inflammatory mediators and the potential application of host modulation as a therapeutic intervention for the management of periodontal disease has been discussed in this review.

KEYWORDS: Bisphosphonates, Host modulation, Periodontal disease, Sub - antimicrobial dose doxycycline, Tetracycline

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INTRODUCTION

Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganism resulting in progressive destruction of the periodontal ligament and alveolar bone with increased probing depth, recession or both”\(^1\). Chronic inflammatory periodontal disease is caused by host immune responses to periodontal microorganisms. The underlying biological mechanisms of the host response is characterized by the production of host-derived inflammatory mediators, including cytokines and lipids by neutrophils, monocytes, lymphocytes and fibroblasts.\(^2\) Several researchers have found out host-bacterial inter-relationship which led to the development of hostmodulatory therapy. This strategy was aimed to improve the therapeutic outcome and slow down the progression of the disease. Host modulation therapy is being proposed and developed to bring down excessive levels of enzymes, cytokines, prostanoids, as well as modulate osteoclast function.\(^3\)

MOUTH-SITE FOR MICROBIAL HABITAT

The mouth provides a warm and moist environment that suits the growth of many microorganisms. The mouth is the only site in the human body that normally provides non-shedding surfaces for microbial colonization; this facilitates the development of thick biofilms, particularly at stagnant sites. Up to 300 oral bacterial species can be cultured from oral plaque samples.\(^4\)

Host versus Periodontal disease

Host response in the periodontium is the defense mechanisms in periodontal tissues against bacterial infections. Bacteria, mainly Porphyromonasgingivalis, Aggregatibacteractinomycetemcomitans and others remain as a primary cause for periodontal disease.\(^5\) Immune response in the host is triggered as these bacteria predominate in the pathogenic flora which has a greatest risk of causing infections. These bacteria get colonized in the gingival margins and releases metabolic products and lipopolysaccharides which are the main factors to trigger the host response. The bacteria challenges the cells of the junctional epithelium and in turn the junctional epithelium releases inflammatory mediators like cytokines, prostaglandins E2 and matrix metalloproteinases. These mediators stimulate the immune responses and there is release of neutrophils to the site of infection. If these cells are able to resist the bacterial activity, the disease is confined only to the gingiva. If it fails, pathogens penetrate host tissues, hence it worsens the inflammation and progress to periodontitis.\(^6\) Infection can either be classic or opportunistic. Classic infection is noticed in Mycobacterium avium complex infections as “upper lobe cavitory form or cavitatory form”\(^7\). However, periodontitis is a chronic inflammatory multifactorial disease and it is an opportunistic infection.\(^8\) Opportunistic microorganisms are only pathogenic in a compromised host. They are regularly found in natural flora. They normally do not damage the host, but however in patients with reduced resistance, the existence of risk factors or immunosuppression, a selective increase in bacteria with weak virulence factors may occur, leading to an opportunistic infection.\(^8\)
HOST MODULATORY THERAPY-DEFINITIONS

"Host" can be defined as “the organism from which a parasite obtain its nourishment” or “in the transplantation of tissue” or “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 physical or chemical environment” (Taber’s Medical Dictionary 2004). However, the concept of host modulation was first introduced in dentistry by Williams & Golub et al in 1990 states that “There are compelling data from studies in animals and humans indicating that pharmacologic agents that modulate host response may be efficacious in slowing down the progression of periodontitis”

Host modulatory therapy is an adjunctive therapy which aims at reducing the 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. Host modulatory therapy treats the host side of the host bacterial interactions.

TREATMENT STRATEGIES FOR PERIODONTITIS

Since periodontitis is a multifactorial disease, various treatment options are involved. Complementary treatment strategies includes the reduction in the bacterial burden by root surface instrumentation and hygiene therapy, risk factor modification by smoking cessation and improved diabetes control and host response modulation(Fig. 2). This can be achieved by ensuring that patients are aware of the importance of their own self management, and we as clinicians facilitate this through education, motivation, empowerment, and the provision of excellent clinical care.
COMPLEMENTARY TREATMENT STRATEGIES

CLASSIFICATION OF HOST MODULATORY AGENTS

The host modulatory agents can be broadly classified as

Agents preventing destruction (those which downregulate the destructive aspects of host response) and as agents promoting resolution & healing (those which upregulate the protective or regenerative responses)

AGENTS PREVENTING DESTRUCTION

(i) MATRIX METALLOPROTEINASE INHIBITORS

Matrix Metalloproteinases (MMP) are zinc and calcium dependent endopeptidases secreted by polymorphonuclear neutrophils, macrophages, fibroblasts, epithelial cells, osteoblasts and osteoclasts. MMP’s destroy extracellular components like collagen, gelatin, laminin, fibronectin and proteoglycans. The activity of MMP’s increases in chronic inflammatory conditions like periodontitis, rheumatoid arthritis. In pathological conditions, macrophage derived tumor necrosis factor-α, interleukin-1β and interleukin-6 markedly increases the local production of various matrix metalloproteinases in periodontal tissues. MMP’s inhibitors act by inhibiting the release or synthesis of these enzymes by blocking the activation of precursor forms of these MMP’s (pro- MMPs). This pro-MMP inhibits the activity of mature MMP’s and stimulates the synthesis of endogenous tissue inhibitors of MMP’s thereby protecting the host's endogenous inhibitors from proteolytic inactivation. The endogenous MMP inhibitors are TIMP(tissue inhibitor of metalloproteinase) and alpha-2 macroglobulin. Exogenous inhibitors are present that includes zinc and calcium chelating agents, phosphorous containing peptides, sulfur based inhibitors, hydroxamic acid inhibitors. Hydroxamic acid inhibitors, where the hydroxamate group binds to the zinc at the active site of enzymes and they are capable of inhibiting MMP’s 1,2,3,7,8 and with very low levels of inhibitors. They are commercially available as; Galardin™, Batimastat™, Marimastat™. The enzyme inhibitory spectrum of Marimastat™ and Batimastat™ reveals that it is capable of inhibiting MMP 1,2,3,7 & 9.

a) TETRACYCLINES

Tetracyclines are a group of broad spectrum antimicrobial agents which, apart from their antimicrobial activity also exhibit anti-collagenase activity by inhibiting matrix metalloproteinases. Tetracyclines inhibit the
connective tissue breakdown which is mediated by -Extracellular mechanism -Pro-anabolic effects -Cellular regulation In extracellular mechanism, there is a direct inhibition of active MMP’s thereby the oxidative activation of pro-MMP’s is inhibited. Tetracycline disrupts the activation of pro-MMP’s thereby promoting proteolysis of pro-MMP’s into enzymatically inactive fragments. Hence the Inhibition of MMP’s, protects α1-proteinase inhibitor thus indirectly decreases serine proteinase activity i.e elastase. This causes reduction in the breakdown of connective tissue. In cellular regulation, tetracyclines decreases the activity of cytokines, inducible nitric oxide synthase, phospholipase A2, prostaglandin synthase, which causes direct effects on protein kinase C and calmodulin. Pro-anabolic effects includes tetracyclines where collagen production and osteoblasts activity is increased thereby resulting in bone formation.15

CHEMICALLY MODIFIED TETRACYCLINES
Tetracyclines are a group of broad spectrum antibiotics and are also the major antiproteinases used in periodontal treatment. Chemically modified tetracyclines are derivatives of tetracycline group of drugs, which lack antimicrobial action, but have potent host modulatory effects. They inhibit pathologically elevated MMP’s, pro-inflammatory cytokines, and other destructive mediators. It is devoid of antibacterial activity due to the removal of dimethylamino group from the carbon 4 position of the“A” ring of the drug molecule, but retains its anti-collagenase activity.15 A series of 10 different chemically modified tetracyclines have since been identified called chemically modified tetracyclines 1–10. C MT-5, or the pyrazole analogue, in which the carbon-11 carbonyl oxygen and carbon-12 hydroxyl groups were replaced by nitrogen atoms, which eliminated Zn2+ or Ca2+ binding site has no anti-collagenase activity.

b)DOXYCYCLINE
Doxycycline is an antimicrobial agent belonging to the tetracycline group. It is the most potent collagenase inhibitor amongst the tetracyclines. Doxycycline has a low minimum inhibitory concentration, highly concentrated in GCFand has substantivity to bind to the tooth structure, which makes it highly advantageous to use doxycycline as a host modulatory agent.

SUB-ANTIMICROBIAL DOSE OF DOXYCYCLINE
Subantimicrobial dose doxycycline (SDD) remains, at present, the only systemic host response modulator specifically indicated as an adjunctive treatment for periodontitis. Subantimicrobial dose doxycycline is approved by the US Food and Drug Administration, 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 doxycyclinehyclate that is taken twice daily for periods of 3–9 months as an adjunct to root surface instrumentation in the treatment of periodontitis.16 Doxycycline, similarly to other members of the tetracycline family, has the ability to downregulate MMPs, a family of zinc-dependent enzymes that are capable of degrading a variety of extracellular matrix molecules, including collagens. SDD acts by following mechanisms, 1) Direct inhibition of active MMPs by cation chelation (dependent on calcium & zinc 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-α) and prostaglandins E2.4) Scavenges and inhibits production of reactive oxygen species produced by neutrophils. 5) Inhibits MMPs and reactive oxygen species thereby protecting α1-proteinase inhibitor, and thus indirectly reducing tissue proteinase activity 6) Stimulates fibroblast collagen production 7) Reduces osteoclast activity and bone resorption 8) Inhibits osteoclast MMPs.

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**INDICATIONS FOR SDD**

SDD can be prescribed for patients with chronic periodontitis, aggressive periodontitis, smokers and patient with systemic diseases like diabetes.

**CONTRAINDICATIONS FOR SDD**

SDD is contraindicated in patients who has a previous history of allergy, pregnant or lactating women, children under 12 years of age and patients under oral contraceptives as SDD may reduce its effectiveness.\(^{17}\)

**ii) NONSTEROIDAL ANTIINFLAMMATORY DRUGS**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are those drugs that inhibit the formation of prostaglandins, including prostaglandin E2, which is produced by a variety of resident and infiltrating cell types in the periodontium (including neutrophils, macrophages, fibroblasts and epithelial cells) in response to lipopolysaccharide\(^{18}\). Prostaglandin E2 is a key inflammatory mediator in periodontal disease as it upregulate osteoclastic bone resorption and prostaglandin E2 levels are significantly increased in the tissue and gingival crevicular fluid of patients with periodontal disease compared to healthy controls. Nonsteroidal anti-inflammatory drugs act by inhibiting the formation of prostaglandins by blocking the cyclo-oxygenase (COX) pathway of arachidonic acid metabolism. They are used to reduce tissue inflammation and pain and inhibiting osteoclast activity, in patients with periodontal disease. Systemic flurbiprofen, indomethacin, naproxen and others are administered daily for periods of up to 3 years, significantly slowed the rate of alveolar bone loss\(^{18}\). However there are several disadvantages associated with NSAIDs which include gastrointestinal upset, gastrointestinal hemorrhage, renal impairment, hepatic impairment and rebound phenomenon. Selective COX-2 inhibitors are a form of NSAIDs, that directly target COX-2, an enzyme responsible for pain and inflammation. The selective cyclo-oxygenase-2 inhibitors were investigated in the anticipation that they could offer potential in the treatment of periodontitis\(^{19}\). Induction of cyclo-oxygenase-2 results in the production of elevated quantities of prostaglandins, and therefore inhibition of cyclo-oxygenase-2 by selective inhibitors results in a reduction of inflammation without the unwanted effects commonly seen after long-term non-steroidal anti-inflammatory drug use. COX-2 inhibitors include meloxicam, etodolac, nimesulide, celecoxib, rofecoxib, valdecoxib. However, they are not approved by the US FDA as host modulatory agent for the management of periodontitis.

**iii) BISPHOSPHONATES**

Bisphosphonates are bone-seeking agents that inhibit bone resorption by disrupting osteoclast activity. These are analogs of pyrophosphate (P-O-P) in which the oxygen is replaced by carbon with various side chains. It binds to the hydroxyapatite crystals of bone preventing their growth and dissolution, thereby has the ability to increase osteoblast differentiation and inhibit osteoclast recruitment an activity known as “bone sparing agents”. The anti-resorptive properties of bisphosphonates change according to their side chains and their potency increases from first to third generation. First generation (alkyl side chain)-Etidronate. Second generation (amino terminalgroup)-Alendronate&Pamidronate Third generation (cyclic side chains)-Risedronate. Activities of bisphosphonates on osteoclast function can be described at a tissue level, cellular level and molecular level.

**Tissue Level**

* Decreased bone turnover due to decreased bone resorption
* Decreased number of new bone multicellular units
* Net positive whole body bone balance

**Cellular level**

* Decreased osteoclast recruitment
* Increased osteoclast apoptosis
* Decreased osteoclast adhesion
* Decreased depth of resorption site
* Decreased release of cytokines by macrophages
Increased osteoblast differentiation and number

**Molecular level**
- Inhibit mevalonate pathway (can result in perturbed cell activity and induce apoptosis)
- Decreased post-translational prenylation of GTP-binding proteins.

Bisphosphonates are used as an adjunct to scaling and root planing, probing depth reduction, clinical attachment gain, alveolar bone gain, and increase in bone mineral density. Long-term use of bisphosphonates results in osteonecrosis of the jaw.

**RANK / RANKL / OSTEOPROTEGERIN**

RANK (Receptor Activator of Nuclear Factor κB) / RANKL (Receptor Activator for Nuclear Factor κB Ligand) interaction is responsible for differentiation & maturation of osteoclast precursor cells to activate osteoclast. Osteoprotegerin (OPG) acts as a decoy receptor expressed by osteoblastic cells which binds to RANKL & inhibits osteoclast development. OPG prevents the binding of RANKL to specific membrane bound receptors expressed in osteoclast precursor cells. Expression of the RANKL gene in osteoblasts/stromal cells is enhanced by Vitamin D3, PTH, IL-1, IL-6, IL-17, TNF-α, BMP, PGE2. Denosumab, a fully human monoclonal antibody targets RANKL and this could be a potential host modulatory therapy.

OPG is the natural inhibitor of RANKL, produced by human PDL cells, gingival fibroblasts and epithelial cells. OPG as a therapeutic agent was described by Simon et al 1997. Interference with the RANK–RANKL–OPG axis had a protective effect on osteoclastogenesis and alveolar bone loss in animal studies.

**v) CATHEPSIN K INHIBITORS**

Cathepsin K is a cysteine proteinase of the papain superfamily. It is selectively expressed in osteoclasts and plays pivotal role in degradation of bone matrix. It is the only known mammalian proteinase that can solubilize both types I and II collagens increased in gingival crevicular fluid in patients with periodontitis, which correlated with an increased concentration of RANKL. Cathepsin K has been viewed as an attractive target for modulating bone resorption. Stroup et al in 2001 stated that cathepsin K inhibitors causes inhibition of human cathepsin k which in turn induces a reduction in bone in non human primates whereas Deal et al in 2009 states that a number of prototype cathepsin inhibitors have now entered clinical trials for the management of osteoporosis. However none have yet been made available for use as host modulation therapy for periodontitis.

**vi) VITAMIN D**

Vitamin D is crucial for a wide variety of organ systems; nevertheless, its deficiency is highly prevalent, present in 30-50% of the general population. Evidence has demonstrated that vitamin D deficiency may place subjects at risk for not only low mineral bone density/osteoporosis and osteopenia, but also infectious and chronic inflammatory diseases. Due its effect on bone and mineral metabolism, innate immunity, and several vitamin D receptor gene polymorphisms, vitamin D has been reported to be associated with the periodontal disease. More recent studies showed significant associations between periodontal health and intake of vitamin D and calcium, and that dietary supplementation with calcium and vitamin D results. Hormone replacement therapy in post menopausal women shows a slight improvement in periodontal condition but generally such improvements appear to be small and of debatable value. Potentially large number of significant side effects is present. Although this strategy has been not recommended for proposed management of periodontitis.

**iv) HORMONE REPLACEMENT THERAPY**

Hormone replacement therapy refers to any form of hormone therapy where in the patient, in the course of treatment receives hormones either to supplement a lack of naturally occurring hormones. Use of hormone replacement therapy in the management of rheumatoid arthritis has produced conflicting
may improve periodontal health, increase bone mineral density in the mandible and inhibit alveolar bone resorption. In a recently published longitudinal study, Garcia et al reported that calcium and vitamin D supplementation may reduce the severity of periodontal disease if used at doses higher than 800-1,000 IU daily. They also noted that vitamin D, in addition to its role in bone and calcium homeostasis, acts as an anti-inflammatory agent because it inhibits immune cell cytokine expression and causes monocyte/macrophages to secrete molecules that have a strong antibiotic effect. 1,25-Dihydroxy vitamin D3 plays a role in prevention of periodontal disease.

vii) STATINS
Statins, 3-hydroxy-3-methylglutarylcoenzyme A (HMG CoA) reductase inhibitors, can be fermentation derived statins include simvastatin, pravastatin whereas atorvastatin, cerivastatin, fluvasatin, pitavastatin and rosuvastatin are synthetic stains. Synthetic statins have a higher potency as compared to the fermented statins. Also statins influence the production of receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegrin by human gingival fibroblasts to favour bone catabolism under non-inflammatory conditions. Clinical trial on patients with chronic periodontitis showed that there was a greater decrease in gingival index (GI) and probing depth (PD) and more clinical attachment level gain with significant intrabony defect fills at sites treated with scaling and root planing (SRP) plus locally delivered simvastatin than with SRP alone. Beneficial effect of atorvastatin on bone alveolar loss and tooth mobility in subjects with periodontal disease have also been identified.

viii) Wnt pathway
Wnt canonical pathway and the transcription factor activator protein – 1 are important for the regulation of osteoprotegerin production in osteoblasts. Within this process beta-cateninplays an important role in the Wntsignaling pathway and bone remodeling. Beta catenin could enhance IL -1 α induced OPG production. Wntpathway has an important link between inflammation and bone metabolism and has novel target for treating bone erosive conditions. DICKKOPF-1(DKK-1), a glycoprotein that can inhibit the Wnt pathway. Pinzone et al in 2009, states that use of a DKK1, led to an increase in the amount of trabecular bone, an increased number of osteoblasts and increased osteocalcin levels.

ix) PROTEASE ACTIVATED RECEPTOR 2 AGONISTS & ANTAGONISTS
Protease activated receptor 2 (PAR2) also known as coagulation factor II (thrombin) receptor-like 1 (F2RL1) or G-protein coupled receptor 11 (GPR11) is a protein that in humans is encoded by the F2RL1 gene. PAR2 modulates inflammatory responses and acts as a sensor for proteolytic enzymes generated during infection. 4 PAR has been identified. Smith et al in 2004, states that PAR 2 activation inhibits bone resorption by Inhibiting osteoclasts differentiation. Uehara et al in 2003 states that PAR 2 activation is associated with increased production of IL-6 and associated periodontal destruction which leads to production of IL -8 which also led to periodontal destruction.

x) HISTONE DEACETYLASE INHIBITORS
This acts by inhibiting angiogenesis,causing a protective effect on bone thereby inhibits the production of proinflammatory cytokines. Lin et al in 2007 described the action of Histone deacetylase inhibitors in animal models of rheumatoid arthritis where there is decrease in bone destruction. However this strategy has not been applied for the management of periodontitis.

xi) ANTICYTOKINE THERAPY
Anticytokine therapy for periodontal diseases especially targets proinflammatory cytokines, that is, TNF-α, IL-1, and IL-6, because these are essential for the initiation of the inflammatory immune reaction and are produced for prolonged periods in periodontitis. This therapy aims to bind the cytokines with the receptors present on target
cells such as the fibroblasts. The three basic treatment strategies are:
1. Neutralization of cytokines,
2. Blockade of cytokine receptors, and
3. Activation of anti-inflammatory pathways, such as, immune-suppressive pathways.

Anticytokine therapy can be initiated by use of receptor antagonist, neutralizing antibodies, and soluble receptors. Drugs for anticytokine therapy includes:
- TNF-α antagonist adalimumab, cetrolizumbpegol, entanercept, Golimumab, infliximab.
- IL-1 antagonists – Rilonacept
- Recombinant IL-1 ra – Anakinra
- IL-1 monoclonal antibody – canakinumab
- IL-15 monoclonal antibody - AMG714
- IL -12 & IL -23 monoclonal antibody - Ustekinumab
- IL - 6 monoclonal antibody – Tocilizumab


xiii) NITRIC OXIDE SYNTHASE INHIBITORS
Nitric oxide (NO) is not only important in host defense and homeostasis but it is also regarded as harmful and has been implicated in the pathogenesis of a wide variety of inflammatory and autoimmune diseases. The presence of NO in periodontal disease may reflect the participation of an additional mediator of bone resorption responsible for disease progression. Nitric oxide may activate proinflammatory enzymes such as cyclooxygenase and metalloproteinases, which, in turn, may also contribute to periodontal tissue damage. The most commonly used drug is mercapto ethyl guanidine which blocks inducible Nitric oxide synthase (iNOS), which in turn inhibits COX and scavenges peroxynitrate. Lohinai et al 1998 - found a reduction of alveolar bone loss and gingival inflammation after the use of a selective iNOS inhibitor – mercaptoethylguanidine.

xiv) ANTAGONISTS FOR ADHESION MOLECULES
Studies have proven that there are increasing levels of ICAM-1(Intercellular Adhesion molecule-1), LECAM-1(Neutrophil Lectin Adhesion molecule-1) and PECAM-1(Platelet/Endothelial cell adhesion molecule-1) expression with increasing degrees of inflammation in cases of both gingivitis and periodontitis. ICAM – 1 & E – selectin inhibitors
- Tepoxalin
- Sodium Cromoglycate,
- BMS-190394

xv) CELL SIGNALLING PATHWAY DESTRUCTION
As soon as the bacterial biofilm accumulates in the gingival margin, an inflammatory process is initiated, triggering a dynamic cascade of events. The main purpose of these events is the combat of microbial invades through pro-inflammatory actions. These pro-inflammatory actions depends on the recognition of external antigenic stimuli by host leukocyte of the innate immune response. Eg: Neutrophils, macrophages, dendritic cells, natural killer cells and others. This recognition of the external stimuli triggers a signal that travels through cytoplasm and then reaches nucleus altering the pattern of gene expression. In a periodontal disease, the most important pathways includes the NF-κB, p38, ERK, JNK pathways. The cell signalling pathway can be described by:
- Nuclear factor-kappa B (NF-κB) inhibitors
- IKK-B inhibitors (Inhibitor of IKappa-B kinase)
- Extracellular signal-regulated kinases (ERK) 1/2inhibitors
- Jun N-terminal kinases (JNK) inhibitors
- p-38 inhibitors
- NF-kB Inhibitors- Proteasome inhibitors block NF-kB activation.

Bortezomib (Velcade) was tested in multiple myeloma with highly promising results.
- IKK – β inhibition-IKK – β is activated following the binding of RANK to RANKL. And this inhibition is a target for the inactivation of nuclear factor – kappa B.
BMS-345541 – first IKK inhibitor. Oral administration of a selective potent inhibitor of IKKβ has demonstrated both anti-inflammatory and anti bone resorbing effects in an animal model by Schopf et al 2006. Activation of p38 induces synthesis of TNF-α, IL-1, IL-6 and IL-8. Hence p38 inhibitors are used. p38 inhibitors are known cytokine suppressive anti-inflammatory drugs (CSAIDs). It includes BIRB-796, SCIOS-469.

**xv) MODULATION OF TOLL LIKE RECEPTORS (TLR)**

Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system. They are single, membrane-spanning, non-catalytic receptors usually expressed in sentinel cells such as macrophages and dendritic cells, that recognize structurally conserved molecules derived from microbes. Strategies for inhibition of Toll Like Receptors function (TLR) and signaling includes;
- Natural or synthetic agonists blocks ligand binding
- Monoclonal antibodies blocks ligand binding
- Soluble decoy toll like receptors inhibits TLR or co-receptor interactions
- Kinase inhibitors brings about a negative regulation of toll like receptors downstream signalling.
- Anticytokine agents neutralize toll like receptors thereby induce proinflammatory cytokines.

**xvi) PERIODONTAL VACCINES**

Vaccination is a process that induces specific immune resistance to a bacterial or viral infection. In the early twentieth century, three periodontal vaccines were employed, which includes; *Pure cultures of streptococcus and other organisms
* Autogenous vaccines
* Stock vaccines.
Example includes Vancott's vaccine and Inava endocarp vaccine. There are 3 types of periodontal immunization. This includes;

**Active immunization**
- Whole bacterial cells
- Sub unit vaccines

*Synthetic peptides as antigens

**Passive immunization**
- Murine monoclonal antibody
- Plantibodies

**Genetic immunization**
- Plasmid vaccines
- Live, viral vector vaccines

Antigens used for active immunization includes:
- Bacterial whole cells
- P. gingivalis fimbiae
- P. gingivalis cysteine protease
- Synthetic peptides

**AGENTS PROMOTING RESOLUTION AND HEALING**

**i) PRO RESOLUTION MEDIATORS**

Resolution is an active process involving biochemical circuits that actively biosynthesize local mediators within the resolution phase target resolution rather than inhibiting inflammation by the role of stromal cells where there is withdrawal of survival signals, normalization of chemokine gradients, induction of resolution programs that allow infiltrating cells to undergo apoptosis or exit the inflamed tissue through draining lymphatics. Anti inflammatory & pro resolving molecules
- Lipoxins (LX)
- Resolvins of the E Series (RvE)
- Resolvins of the D Series (RvD)
- Aspirin Triggered Epimeric Forms from DHA
- The Neuroprotectins /Protectins
- Aspirin Triggered Lipoxins (ATL)
- Glucocorticoid induced annexin -1
- Melanocortins /nuclear receptor agonists
- Hemeoxygenase 1.

**Lipoxins**

Lipoxins are members of the Eicosanoid family produced by lipoxygenase mediated metabolism of Arachidonic Acid (AA). They are generated by cell to cell interactions (transcellular biosynthesis). Crevicular fluid samples from localized aggressive periodontitis (LAP) patients were examined and found to contain PGE2 (prostaglandins E2), LTB4 (leukotriene B4), and LXA4 (lipoxin...
A4). Neutrophils from peripheral blood of LAP patients, but not from healthy volunteers, also generated LXA4, suggesting that it may also have a role in periodontal diseases (Pouliot et al 2000).46

**Resolvins**

Lipid mediators that are induced in the resolution phase following inflammation. Resolvins are synthesized from omega 3 PUFA (Poly unsaturated fatty acid) – EPA (Eicosapantaenoic acid) & DHA (Docosahexaenoic acid). They demonstrate potent anti inflammatory and immunomodulatory actions in the nanogram dose range in-vivo.

**RvE1(ResolvinE1)**

Topical application of RvE1 in experimental model of periodontitis in rabbits prevented the progression of periodontitis. There was no neutrophils and tissue damage and lack of osteoclast proliferation. A radiographic evidence of decreased percentage of bone loss is also seen.

**Protectins**

Endogenous DHA is converted in to another family of lipid mediators called as protectins, that is owing to its present protective activity in inflammatory and neural system, known as protectinD1 (Hong et al 2003)47. Protectin D1 is also known as neuroprotectin D1, when produced by neural tissues (Serhan et al).47 However, none of these pro-resolution strategies have been approved for the management of periodontal disease.

**iii) GROWTH AND DIFFERENTIATION FACTORS**

**Growth differentiation factors**

(GDFs) are a subfamily of proteins belonging to the transforming growth factor β superfamily that have functions predominantly in development.49

- Platelet derived growth factor plays a significant role in angiogenesis. It is a element in cellular division for fibroblast.
- Insulin like growth factors are proteins that resembles insulin.

Bone morphogenetic proteins are group of growth factors also known as cytokines and metabologens. BMP-2 & BMP-7 are involved in promoting resolution & healing. Among the other bone morphogenetic proteins, BMP-2 & BMP-7 belong to Transforming Growth Factor-β. BMP-2 & BMP-7 plays a key role in osteoblast differentiation.50

**CONCLUSION**

Host response modulation has emerged as a valid treatment concept for the management of periodontal disease and represents a significant step forward for clinicians and patients. SDD (Sub antimicrobial-dose doxycycline) is the only host modulatory agent currently approved and indicated as an adjunct to SRP (scaling and root planning) for treating periodontitis. The most numerous of the strategies those have been proposed are in the trial phase and awaiting approval for the management of inflammatory condition like periodontitis. Host response modulators must be viewed as comprising part of the overall management strategy for patients with periodontitis. They should form part of an integrated treatment approach, together with hygiene therapy, plaque control, root surface instrumentation, maintenance care and risk factor modification. Therefore, it is appropriate that host modulatory agents present the next wave in the pharmacotherapy in the management of periodontal disease.
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