Review Article

Pharmacotherapy for host modulation in periodontal disease: A review

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ABSTRACT

Recent research works in the field of periodontics have elaborated on a wide range of treatment modalities for the treatment of periodontal disease. One such approach for controlling the host-mediated periodontal tissue destruction is host modulation therapy (HMT). Used as an adjunct to standard periodontal therapy HMT is proved as a valid treatment option. The present article reviews different pharmacotherapeutic agents used for host modulation.

Key words: Bisphosphonates, chemically modified tetracycline (CMT), nonsteroidal anti-inflammatory drug (NSAID), subantimicrobial dose of doxycycline (SDD)

INTRODUCTION

Microbial plaque is recognized as the primary causative agent of periodontal disease, and the treatment strategies were based on the understanding that plaque microbes and their by-products mediated the periodontal tissue destruction. The host response to the invading microorganism is the prime reason behind periodontal destruction. 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).

DEFINITION[1]

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.

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RATIONALE[2]

- To improve the therapeutic outcomes.
- To slow the progression of the disease.
- To allow for more predictable management of patients.
- Possibly even work as agents that prevent the development of periodontitis.

CLASSIFICATION OF HOST MODULATION AGENTS BASED ON THE MODE OF REGULATION[3]

Inhibition of matrix metalloproteinase (MMPs):
- Chemically modified tetracyclines (CMTs).

Inhibition of arachidonic acid (AA) metabolite:
- Cyclooxygenase (COX)-1 inhibitors: Indomethacin, flurbiprofen, and naproxen.
- COX-2 inhibitors: Rofecoxib.
- COX and lipoxygenase (LOX) inhibitors: Triclosan and topical ketoprofen.
- LOX inhibitors: Lipoxins.

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Modulation of bone metabolism:
- Bisphosphonates.
- Hormone replacement therapy (HRT).
- Calcium supplementation.

Regulation of immune and inflammatory response:
- Suppressing proinflammatory cytokines: Interleukin-1 (IL-1) and tumor necrosis factor (TNF)-α receptor antagonist.
- Nitric oxide inhibition.
- Generation of protective antibodies through vaccination.
- Infusion/supplementary anti-inflammatory cytokines: IL-4 and IL-10.

MODULATION OF MMP

Chemically modified tetracyclines (CMTs) are considered as one of the most important host modulatory agents. CMTs possess antibacterial property, anticollagenase, and osteoclast inhibition activity. Currently, there is a new formulation of subantimicrobial dose of doxycycline (SDD) (doxycycline hyclate 20 mg; Periostat) that is accepted by American Dental Association (ADA) and approved by Food and Drug Administration (FDA).[4-6]

The effects of CMT can be summarized as:[5,7-9]
1. Direct inhibition of active MMPs by cation chelation.
2. Inhibits oxidative activation of latent MMPs.
3. Downregulates the expression of the key inflammatory cytokine production.
4. Inhibition of reactive oxygen species (ROS) activation of pro-MMPs.
5. Protection of α-1 proteinase inhibitor from MMPs.
6. Reduction of serine proteinase activity.
7. Reduces osteoclast activity and bone resorption.
8. Inhibits osteoclast MMPs.

Table 1 describes study reports on MMP regulation.

MODULATION OF ARACHIDONIC ACID METABOLITE

The AA metabolites are enzymatically produced and released in response to a local tissue injury. Both bacterial and host factors initiate tissue damage that allows phospholipids in plasma membranes to become available for action by phospholipase A_2 and thereby results in the production of free AA. Free AA can then be metabolized *via* COX or LOX enzyme pathways.

COX 1 is constituently expressed and thought to maintain housekeeping function such as gastric cytoprotection and vascular and renal homeostasis. In contrast, COX 2 is inducible and plays a role in inflammatory cellular differentiation and mitogenesis. COX 1 and 2 produce prostaglandins, prostacyclin, and thromboxane, whereas the enzyme LOX produces leukotrienes and other hydroxyeicosatetraeonic acids.[15]

There are three major approaches to inhibit prostaglandin E_2 (PGE_2) synthesis:
1. Steroids reduce the availability of free ARA for CO enzymatic activity by stabilizing lysosomal membranes, inhibiting PLA_2 production and by inhibiting cellular degranulation. It also causes degradation of preexisting mRNAs for IL-1α and TNF-α thereby dampening the secondary PGE_2 response.
2. The use of antioxidants serves to prevent the oxidation of ARA and the subsequent hydrolysis to form PGE_2.
3. Inhibiting the COX directly by NSAIDs can suppress alveolar bone resorption.[16]

Table 2 describes study reports on regulation of prostaglandin.

MODULATION OF BONE METABOLISM

The use of bone sparing agents that inhibit the alveolar bone resorption that is the principal sequelae of periodontal disease is another field in HMT.

Bisphosphonates were introduced in 1990, primarily for hypercalcemia, Paget's disease, and osteoporosis.[15]

There are mainly two modes of action:
1. Indirect.
2. Direct.

INDIRECT ACTION

- Indirect mode of action suggests that following exposure to bisphosphonates, an osteoclast inhibitory factor is secreted by osteoblasts that can inhibit the function of osteoclast.

DIRECT ACTION

- Bisphosphonate mediated inhibition of osteoclast development.
- Induction of osteoclastic apoptosis.
- Reduction of activity of osteoclasts.
- Inhibiting the development of osteoclasts from hematopoietic precursors.
- Downregulation of bone resorption by bisphosphonate that correlated with MMP inhibition.[22]

After their systemic administration, BPs are absorbed selectively on bone surfaces and are present in all areas of high bone resorption activity. Once released during the bone resorption activity, they are endocytosed in the osteoclasts altering the normal intracellular biochemical processes.

Table 1: Study reports on MMP regulation

Author	Mode of interception	Key conclusion
Caton *et al*. (2003)[10]	SRP+SDD (20 mg)	SDD 20 mg bid for a period of 9 months showed significant clinical outcome and is not associated with any rebound effects or delayed or negative effects for a 3-month posttreatment period
Lee *et al*. (2004)[11]	SRP+SDD (20 mg)	SRP+SDD might be safe and effective in the management of chronic periodontitis
Novak *et al*. (2008)[12]	Combination therapy of SRP+SDD –20 mg + locally delivered doxycycline 10%	Combination therapy provided significantly greater clinical benefits than SRP alone
Preshow *et al*. (2008)[13]	Modified release sub-antimicrobial dose doxycycline (40 mg doxycycline)	SDD-40+SRP resulted in significant clinical benefits than SRP alone
Javali *et al*. (2012)[14]	Atridox delivery system (10% doxycycline hyclate)	Atridox is effective as SRP in reducing the clinical signs of periodontitis

Table 2: Study reports on regulation of prostaglandin

Author	Mode of interception	Key conclusion
Srinivas *et al*. (2011)[17]	SRP+1.5% ketoprofen (local drug delivery)	LDD+SRP were more effective in controlling periodontal disease than SRP alone
Yen *et al*. (2008)[18]	SRP+celecoxib (cyclooxygenase –2 inhibitor) 200 mg for 6 months	Celecoxib can be an effective adjunct to SRP to reduce progressive attachment loss in patients with chronic periodontitis
Azoubel *et al*. (2008)[19]	SRP+Etoricoxib 120 mg/day for 7 days	Etoricoxib did not produce any clinical improvements but reduced PGE_2 levels in GCF that could be related to the improvement in the bone condition
Zeren *et al*. (2006)[20]	SRP+Ibuprofen (800 mg/day for 2 weeks)	Adjunctive use of ibuprofen demonstrated no beneficial effect on the outcome of periodontal treatment of chronic periodontitis
Heasman *et al*. (1993)[21]	1% w/w flurbiprofen tooth paste (b.i.d for 12 months)	Even though 1% w/w flurbiprofen toothpaste showed no apparent effect on clinical parameters, it exerts a small yet significant effect on bone metabolism

The nonnitrogen containing BPs (e.g. clodronate and etidronate) cause osteoclast apoptosis through activation of caspase pathway. It may inhibit ATP-dependent intracellular enzyme osteoclast proton-pumping vacuolar ATPase (V-ATPase), which plays a crucial role in the bone resorption by pumping protons in the resorption lacunae.

The nitrogen-containing BPs (e.g. zoledronate and pamidronate) blocks the key enzyme farnesyl pyrophosphate synthase of the mevalonate pathway. This prevents the biosynthesis of isoprenoid compounds that modify guanosine triphosphate (GTP)-binding proteins (prenylation). This causes the loss of the ruffled border, alteration of the cell morphology, the integrin signaling, or endosome trafficking of osteoclasts. The inhibition of protein prenylation and disruption of the function of regulatory proteins finally leads to the loss of osteoclastic activity. It was also demonstrated that different groups of BPs have the potential to induce apoptosis of osteoclasts and in inhibiting the differentiation and maturation of osteoclasts.

In addition, BPs have an osteogenic action *in vitro* and *in vivo* by promoting the osteoblast differentiation and maturation. This is done by increasing the matrix formation and collagen synthesis.[23]

Table 3 describes study reports on modulation of bone metabolism.

REGULATION OF IMMUNE AND INFLAMMATORY RESPONSE

Host cell recognizes microbial components as danger signals and produces inflammatory mediators. Binding of the bacterial components with the toll-like receptors expressed by leukocytes and resident cells in the periodontal environment activates the innate immune response. Toll-like receptor (TLR) activation of transcription factors results in subsequent inflammatory cytokine expression. Innate immunity cytokines, such as TNF-α, IL-1, and IL-6, produced after microbial recognition were the first to have their role in periodontal disease pathogenesis unraveled. Activation of cytokine gene results in the production of cytokines that binds to the receptor present in the target cell. This binding results in gene activation of the target cell. Activated target cell then releases secondary mediators (MMPs and PGE2), these mediators are responsible for loss of connective tissue and bone resorption.[29]

The balance between the pro-inflammatory (e.g. IL-1α, IL-1β, IL-6, TNF-α, IFN-γ, etc.) and anti-inflammatory cytokines (IL-4, IL-10, etc.) is required to maintain the health of the periodontium.

HMT targeted against cytokines (cytokine therapy) can be an effective treatment modality for periodontal diseases. These therapies aim at:

1. Antagonizing the pro-inflammatory cytokines.
2. Disrupting inflammatory cell-signaling pathways.
3. Recombinant anti-inflammatory cytokine administration.[30]

Table 4 describes study report on regulation of immune and inflammatory response.

Table 3: Study reports on modulation of bone metabolism

Author	Mode of interception	Key conclusion
Pradeep *et al*. (2012)[24]	Local drug delivery of 1% alendronate gel	1% alendronate gel resulted in significant reduction of PD, CAL gain, and improved bone fill
Goya *et al*. (2006)[25]	Topical administration of 100 μL 150 mM monosodium olpadronate	Drug effectively prevented bone loss and caused marked morphologic changes in osteoclasts
Yaffe *et al*. (2003)[26]	Combined application of alendronate + tetracycline hydrochloride 1%	Combined treatment reduced alveolar bone loss that might be due to the synergistic effect
Ishii *et al*. (2003)[27]	Oral administration of incadronate (YM 175) 2 mg/kg in rats with experimental periodontitis	Results revealed that incadronate inhibits bone resorption and PMN migration periodontitis induced by *P. gingivalis*
Alencar *et al*. (2002)[28]	Oral administration of Disodium clodronate 2 mg/kg in experimental periodontitis in rat model	Disodium clodronate decreases inflammatory changes and bone resorption in a periodontitis model in rats

Table 4: Study report on regulation of immune and inflammatory response

Author	Agents evaluated	Key conclusion
Martuscelli *et al*. (2000)[31]	Recombinant human IL-11	Subcutaneous injection of rhIL-11 was able to slow the progression of attachment and radiographic alveolar bone loss in ligature induced beagle dog model

DRAWBACKS

1. Immune system is downregulated with anti-cytokine therapy.
2. Latent infectious disease, such as tuberculosis, should be screened before the anti-cytokine therapy.
3. For patients under anti-cytokine therapy, antimicrobials must be used with caution to prevent an inapparent infection without inflammatory symptoms. If anti-cytokine therapy is performed for periodontal treatment use of chemical plaque control agents is recommended in addition to mechanical plaque control.[32]

CONCLUSION

At present, HMT is one of the main focuses of interest for many of the investigators. Even though HMT is not in use in routine periodontal therapy, the invention of newer agents with lesser side effects will validate it as a treatment option for periodontal disease. At the same time, host response modulation by therapeutic agents should not be considered a stand-alone procedure but as an adjunct to the conventional treatment approaches.

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Conflicts of interest
There are no conflicts of interest.

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