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Host Modulation Therapy In The Management Of Periodontal Diseases

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Abstract
Traditionally, only antimicrobials have been used as the chemotherapeutic modality for the treatment of periodontitis. Though bacteria are the primary etiologic factors of periodontal diseases, yet the extent and severity of tissue destruction seen in periodontitis is determined by the host immuno-inflammatory response to these bacteria. 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 parmacotherapeutic 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. In this article the host modulating role of various systemically and locally delivered perioceutic agents will be reviewed.

Key Words
bisphosphonates, host modulation, nonsteroidal anti inflammatory drugs, perioceutics, tetracycline

Introduction

Host can be defined as "the organism from which a parasite obtains its nourishment" 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 chemical or physical environment".[1] In diseases of the periodontium that are initiated by bacteria, the "host" clearly is the individual who harbors these pathogens.Host modulation with chemotherapeutic therapy or drugs is a promising new adjunctive therapeutic option for the management of periodontal diseases. So, here an attempt has been made to review various host modulation therapies and ongoing development of safe, effective pharmacotherapies that specially target host response mechanism, as an adjunct to traditional, antimicrobial interventions, representing a new integrated approach in the long term management of periodontal diseases.

Discussion

Until the 1970s, periodontists believed that periodontal disease was an inevitable consequence of ageing and was uniformly distributed in the population.They thought that disease severity was directly correlated with plaque levels (i.e. worse the oral hygiene, worse the periodontal disease) and that disease progression occurred in a continous, linear manner throughout life. But the recent observation led researchers to realize that host response to the bacterial challenge presented by subgingival plaque is the important determinant of disease severity[1].

Although plaque bacteria are capable of causing direct damage to the periodontal tissues (e.g., by release of H2S, butyric acid, and other enzymes and mediators), it is now recognized that the great majority of the destructive events occurring in the periodontal tissues result from activation of destructive processes that occur as a part of the host immune-inflammatory response to plaque bacteria. The host response is essentially protective by intent but paradoxically can also result in tissue damage, including breakdown of connective tissue fibers in the periodontal ligament and resorption of the alveolar bone1. The concept of host modulation was first introduced to dentistry by Williams (1990)[2] and Golub et al (1992)[3].

Host Modulation Therapy (HMT) is a means of treating the host side of the host bacteria interaction. Host Modulation Therapies do not "switch off" normal defense mechanisms or inflammation; instead, they ameliorate excessive or pathologically elevated inflammatory processes to enhance the oppurtunities for wound healing and periodontal stability. Host Modulation Therapeutic agents are systemically or locally delivered pharmaceuticals that are prescribed as a part of periodontal therapy and are used as adjuncts to the conventional periodontal treatments, such as scaling root planing (SRP) and surgery1.Various Host Modulation Therapeutic agents have been developed or proposed to block pathways responsible for periodontal tissue break down.Now a days, the field of 'Perioceutics' i.e., use of pharmacological agents specifically developed to better manage periodontitis, is emerging to aid in the management of susceptible patients who develop periodontal disease. It includesantimicrobial therapies that can be used to address changes in the microflora andhost modulatory therapy that can be used to address a host response consisting of excessive levels of enzymes, cytokines, prostanoids & excessive osteoclast function that may be related to risk factors[4].

Host Modulation Therapy (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. It includes systemically or locally delivered pharmaceuticals that are prescribed as adjuncts to other forms of periodontal treatment[5].

A. Systemically administered host modulating agents:

I) Modulation of arachidonic acid (AA)metabolites

Over decades, Arachidonic Acid metabolites have been established as mediators of tissue destruction in various inflammatory diseases including rheumatoid arthritis and periodontal diseases[6]. Free Arachidonic acid is metabolized via either the cyclooxygenase (COX) or the Lipooxygenase (LO) pathways. Arachidonic acid is enzymatically oxidized by either cyclooxygenase for unstable cycloendoperoxide intermediated (PGG2 and PGH2) leading to prostanoid synthesis (prostaglandins, prostacyclin and thromboxane) or by the action of lipooxygenase to form the Leukotrienes (LTs) and other monohydroxy-eicosatetraenoic acids[3].

i. Modulation of Arachidonic acid metabolites with NSAIDS

The majority of NSAIDs are weak organic acids that selectively (COX-2) and non-selectively (COX-1) inhibit the synthesis of arachidonic acid metabolites, thereby blocking the production of prostaglandins, thromboxane and prostacyclin[3].

- NSAIDs inhibit prostaglandins and therefore reduce tissue inflammation.
- These are used to treat pain, acute inflammation, and a variety of chronic inflammatory conditions.

NSAIDs include salicylates (e.g., aspirin), indomethacin and propionic acid derivatives (e.g., ibuprofen, flurbiprofen, naproxen). Studies have shown that systemic NSAIDs such as indomethacin, flurbiprofen and naproxen admin¬istered daily for up to 3 years significantly slowed the rate of alveolar bone loss compared with placebo. But disadvantages have been associated with long term use of NSAIDS. These include; Gastrointestinal problems, Hemorrhage (from decreased platelet aggregation), Renal and hepatic impairment. Research shows that the periodontal benefits of taking long term NSAIDs are lost when patients stop taking the drugs, with a return to, or even an acceleration of the rate of bone loss seen before NSAID therapy, often referred to as a "rebound effect"[43]. Long-term use of NSAIDs as an adjunctive treatment for periodontitis has never really developed beyond research studies.

ii. Omega-3 Fatty Acids

Omega-3 fatty acids such as dietary fish oil has beendemonstrated to protect mice against infection with numerous extra cellular bacterial pathogens that regulate the serum triglycerides and cholesterollevels, inhibit synthesis of lipid mediators of inflammation(PGE2, arachidonic acid, cyclo-oxygenase, 5-lipoxygenase), alter cellular functions of polymorphonuclear leukocytes, modulate lymphocyte proliferation and cytokine production, and increase endogenous host anti-oxidant capacity, e.g., SOD and catalase [7].

iii. Lipoxins (endogenous modulators of inflammation)

Lipoxins and aspirin-triggered lipoxin (AXL) are bioactive lipid mediators involved in the Arachidonic Acid cascade and are formed by the interaction of 5- and 15- Los[8]. Like most lipid mediators, lipoxins are rapidly synthesized, act within a local environment and are rapidly degraded enzymatically. The lipoxins (LX) , were the first to be identified and recognized as endogenous anti-inflammatory lipid mediators of resolution that function as “braking signals” for neutrophils in inflammation[9]. Thus, it is of particular interest that aspirin ,a widely used NSAID with many beneficial properties in addition to its well-appreciated action to inhibit prostaglandins also triggers the endogenous generation of 15- epimeric LX via acetylation of cyclooxygenase 2 (COX-2) that have both anti-inflammatory and antiproliferative properties at sites of inflammation in vivo[10],[11],[12].

iv. Steroids

Steroids inhibit PLA2 (phospholipase2) by stimulating the production of annexins/lipocortins. They stabilize the lysosomal membranes and suppress the cellular degranulation. Steroids like dexamethasone cause degradation of pre-existing mRNAs for IL-1b, TNF-a thereby dampening PGE release[48].

v. Antioxidants

They serve to prevent oxidation of arachidonic acid by molecular oxygen and subsequent hydrolysis to form PGE2. Nutrients, which include major extracellular antioxidants, like vitamin C, vitamin E, carotenoids, reduced glutathione can also act as modulators of inflammation by scavenging free radicals as they are formed, sequestering transition metal ions and catalyzing formation of other molecules[13] .

II) Modulation of Matrix Metalloproteinases(MMPs)

MMPs endopeptidases which are secreted by a variety of host cells, play key roles in the degradation of the extracellular matrix, basement membrane and modify the action of cytokines as well as activation of osteoclasts[14]. During active periodontal diseases, microbial attack leads to excessive production as well as activity of these MMPs which, if not adequately controlled by the endogenous metalloproteinases inhibitors, results in enormous tissue destruction. To impede this destruction of host tissues synthetic inhibitors of Matrix metalloproteinase as host modulating agents have been developed which generally contain a chelating group, inhibiting MMPs by binding to the catalytic zinc atom at its active site.

i.Tetracycline analogues as host modulating agents

The ability of tetracyclines and doxycycline, in particular, to inhibit MMP activity was first identified in the early 1980s[3]. In addition to its antimicrobial activity, this group of compounds has the capability of inhibiting the activities of neutrophils, osteoclasts, and matrix metalloproteinase (specifically matrix metalloproteinase-8), thereby working as an ‘anti-inflammatory’ agent that inhibits bone destruction[15].Tetracyclines are considered to be bacteriostatic agents but may have a bactericidal effect in high concentrations[16]. Tetracyclines have non antimicrobial properties that appear to modulate host response. The mechanism by which tetracyclines affect and, possibly, diminish bone resorption are:

- Direct inhibition of the activity of extracellular collagenase and other matrix metalloproteinases such as gelatinase;
- Prevention of the activation of its proenzyme by scavenging reactive oxygen species generated by other

cell types (e.g. neutrophils, osteoclasts);
- Inhibition of the secretion of other collagenolytic enzymes(i.e. lysosomal cathepsins);
- Direct effect on other aspects of osteoclast structure and function.

Chemically Modified Tetracyclines (CMTS)

Golub and McNamara et al. synthesized a chemically modified tetracycline (CMT) by removing the dimethylamino group from the carbon-4 position of the "A" ring, resulting in the 4-dedimethylaminotetracycline, i.e. CMT, which eliminated the drug's antimicrobial efficacy but did not reduce the ability of the drug to block the activity of collagenases[17],[18]. Certain chemically modified tetracyclines have advantages over commercially available tetracyclines because,

- They are absorbed more rapidly,
- Can reach higher levels in the blood ,
- Have longer serum half lives,
- More potent inhibitors of matrix metalloproteinases [2].

Their long-term systemic administration does not result in gastrointestinal toxicity, Higher plasma concentrations can be reached for prolonged time period àless frequent administration regimens.

Subantimicrobial Dose Doxycycline

Though numerous MMP inhibitors have been investigated, only tetracycline based host modulating agent, i.e. SDD – subantimicrobial dose of doxycycline (Doxycycline hyclate 20 mg; Periostat, CollaGenex, Pharmaceuticals Newton PA) has been approved by Food and drug administration (FDA) to be used as an adjunct to periodontal treatment[19]. A typical prescription for Periostat (20 mg doxycycline tablets) is for at least 3 months (180 tablets, 1 tablet twice a day until complete), and refills may be provided for longer courses of therapy[20]. Doxycycline has the ability to downregulate matrix metalloproteinases (MMPs), a family of zinc-dependant enzymes that are capable of degrading extracellular matrix molecules, including collagen.

ii. Antiproteinases (Tranilast, Seletinoid G, S-3304)

The effect of tranilast, which suppresses collagen synthesis and cell proliferation, on matrix metalloproteinase-1 secretion from human gingival fibroblasts, significantly decreased the activity of matrix metalloproteinase at higher doses[21]. A novel synthetic retinoid, seletinoid G, designed by using computer aided molecular modeling, has potential anti matrix metalloproteinase activity. A novel sulfonamide derivative, S- 3304, was discovered to be a potent matrix metalloproteinase inhibitor. This derivative is a more specific inhibitor of matrix metalloproteinase - 2 and matrix metalloproteinase – 9[21].

III) Modulation of Bone Remodelling

i.Bisphosphonates

Bisphosphonates are 'bone sparing' agents used in the management of various diseases associated with bone resorption. These compounds inhibit osteoclastic activity by blocking acidification by local release and represent a class of chemical structures related to pyrophosphate. Pyrophosphate regulates mineralization by binding to hydroxyapatite crystals in vitro but it is not stable in vivo, undergoing rapid hydrolysis of its labile P–O–P bond as a result of pyrophosphatase activity.The replacement of the linking oxygen atom with a carbon atom (e.g. P–C–P) results in the formation of a bisphosphonate molecule. This compound is chemically stable and completely resistant to enzymatic hydrolysis via pyrophosphatase and alkaline phosphatase.

Given their affinity to bind to hydroxyapatite crystals and prevent their growth and dissolution and to their ability to increase osteoblast differentiation and inhibit osteoclast recruitment and activity, bisphosphonates are widely used in the management of systemic metabolic bone disorders such as tumour-induced hypercalcemia, osteoporosis and Paget's disease . The ability of bisphosphonates to modulate osteoclast activity clearly may be useful in the treatment of periodontitis.Bisphosphonates appear to inhibit Matrix metalloproteinase activity through a mechanism that involves the chelation of cations.

IV) Modulation of Host Cell Receptors

Cytokines are defined as regulatory proteins controlling the survival, growth, differentiation and functions of cells. Cytokines are produced transiently at generally low concentrations, act and are degraded in a local environment. Based upon the increased expression of IL-1 and TNF in inflamed gingiva and high levels in the GCF of periodontitis patients, several studies have suggested that increased production of these cytokines may play an important role in periodontal tissue destruction[22]. To counteract tissue destruction and maintain homeostasis, cytokine antagonists such as IL-1 receptor antagonist (IL-1Ra) or soluble TNF receptors can competitively inhibit receptor-mediated signal transduction. To prevent an uncontrolled inflammatory response with rapid tissue destruction, the activities of IL- 1 and TNF – α are naturally counteracted by the production of cytokines such as IL-4, IL-10 and IL-11[22].

V) Tumor necrosis factor blocking agents

Tumor necrosis factor-α, an inflammatory cytokine that is released by activated monocytes, macrophages and T lymphocytes , promotes inflammatory responses that are important in the pathogenesis of rheumatoid arthiritis and periodontal diseases[23]. Tumor necrosis factor – α binds to two receptors that are expressed by a variety of cells :Type I tumor necrosis factor receptor (p 55); andType 2 tumor necrosis factor receptor (p75). Activation of tumor necrosis factor-R1 upregulates the inflammatory response, while tumor necrosis factor-R2 appears to dampen the response[21]. Patients with periodontal disease have high concentrations of tumor necrosis factor in the gingival crevice fluid . Studies have shown a very strong association of active bone resorption coincident with high local levels of tumor necrosis factor at the diseased sites. Interleukin-1, interleukin-6 and tumor necrosis factor have all been found to be significantly elevated in diseased periodontal sites compared with healthy or inactive sites .

VI) Modulation of nitric oxide synthase (NOS) activity

Nitric oxide is a free radical with important physiological functions of maintaining homeostasis. While homeostasis requires low nitric oxide tissue levels, proR09;inflammatory stimuli such as endotoxins leads to increased expression of the inducible nitric oxide synthase enzyme (iNOS) that produces a large amount of nitric oxide (NO) and peroxynitrite, which acts beneficially for the host as a cytotoxic

molecule against the invading microorganism, yet, it may also cause deleterious effects to host such as DNA damage, lipid peroxidation, protein damage, and stimulation of inflammatory cytokine release[24],[25],[26]. Lohinai et al.[27] demonstrated the protective effects of mercaptoethylguanidine (MEG), which is a selective inhibitor of iNOS, against bone destruction in ligature induced periodontitis in the rat. Leitao et al. (2005) also proved that NOS inhibitors prevent alveolar bone resorption in experimental periodontitis[28].

B. Local agents

I. Triclosan

A compound which has received interest as both an antibacterial and anti-inflammatory agent is triclosan. Triclosan (2, 4, 41-trichloro-2-hydroxy-diphenyl ether) is a non-ionic antimicrobial agent. Tri¬closan also inhibits CO and LO and thus may interfere with the production of AA metabolites[49].

ii. Enamel matrix proteins

It is believed that during development of root and attachment apparatus, there is a secretory phase in which Hertwig's epithelial root sheaths secretes enamel related matrix proteins[29]. Enamel matrix derivative is now commercially available forthe treatment of periodontal defects as Emdogain® (Biora AB, Malmo, Sweden) which has received FDA approval[30].The basic rationale behind using Emdogain is that it will act as a tissue healing modulator that would mimic the events thatoccur during root development and help stimulate periodontal regeneration[30],[31],[32]. Enamel matrix proteins (EMD) initiates periodontal regeneration through recruitment of cementoblasts to the root surface and stimulates these to form root cementum, which will thereafter secondarily lead to regeneration of periodontal fibers and alveolar bone[33].The above mentioned actions of EMD justify its role as a host modulating agent.

iii. Bone morphogenetic proteins

Bone morphogenetic protein (BMP) guides modulationand differentiation of mesenchymal cells into bone andbone marrow cells[34]. Absorbable collagen sponge (ACS)containing recombinant human BMP-2 has been approved for clinical use in certain oral surgery procedures, including localized alveolar ridge augmentation, under the name INFUSE® Bone Graft (Medtronic, Minneapolis, MN, USA)and Induct OS™ (Wyeth, Maidenhead, UK). These ACS releasethe protein over time in the location where it is implanted and provides a scaffold on which new bone can grow. As the graft site heals, the ACS is absorbed and replaced by bone[35].

iv.Platelet derived growth factor

FDA has approved GrowthR09;factor Enhanced Matrix, GEM 21S® (Osteohealth, Shirley, NY) which is a combination of a bioactive highly purified recombinant human PDGFR-BB with an osteoconductive bone matrix[35]. Platelet derivedgrowth factor (PDGF), as a host modulating agent canincrease chemotaxis of neutrophils and monocytes, stimulate fibroblasts proliferation and extracellular matrix synthesis, increase proliferation and differentiation of endothelial cells, stimulate proliferation of mesenchymal progenitor cells and differentiation of fibroblasts. Nevins et al. demonstrated that the purified rhPDGFR-BB mixed with bone allograft results in robust periodontal regeneration in both Class II furcations and interproximal intrabony defects[36].

v.Hypochlorous Acid and Taurine N Monochloramine

It has been reported that hypochlorous acid (HOCl) and taurine-N-monochloramine (TauCl) which are the end products of the neutrophilic respiratory burst, modulate the host inflammatory response by inhibiting the production of interleukin-6, prostaglandins, and other proinflammatory substances. Thus, HOCl and TauCl, playing a crucial role in the periodontal inflammatory process offer opportunities for the development of novel host modulating therapies for the treatment of periodontitis[37]. Lorenz et al.assessed the influence of 2 and 3% N-chlorotaurine mouth rinse on dental plaque and demonstrated that rinsing with 10 mL of the test solution two times daily for 4 days reduced the plaque vitality[38].

vi. Cimetidine

Cimetidine is a powerful H2 (Histamine) receptor antagonist, and hence eliminates histamine's inhibitory effects on immune response, thereby acting as a modulator of inflammation and immunity by inhibiting neutrophil chemotaxis and superoxide production, increasing cyclic adenosine monophosphate (cAMP) levels and down regulating cytokines.Hasturk et al. (2006) provided morphological and histological evidence to prove that topically active cimetidine is a potent inhibitor of P. gingivalis ;elicited periodontal inflammation and can arrest and/or prevent tissue destruction and influence cell populations present in the inflammatory cell infiltrate[50].

vii. Bisphosphonates

Role and action of BPs have already being discussed above. Due to serious side effects of systemically administered BPs leading to osteonecrosis of the jaws (ONJ) additional studies using topically administered bisphosphonates have been carried out which have reported a significant increase in the postoperative percentage of bone defect fill, prevention of bone resorption as well as the boosting effect of locally delivered BPs on the osteoconductive and regenerative potential of bone grafts used in periodontal therapy[39],[40],[41].

viii. NSAIDS

Role of NSAIDs as a host modulating agent has also been discussed above. Since NSAIDs are lipophilic and are well absorbed into gingival tissues, its topical application is possible. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine rinse and S-ketoprofen dentifrice[42], piroxicam[43] and meclofenamic acid[44] in inhibiting gingivitis and progression of periodontitis.

C. 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[45]. 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[47].

ii.Periodontal Vaccine

George Hajishengallis reported that toll like receptors (TLRs) may offer novel targets for hostR09;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[46].

Summary & 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 periodon¬titis. 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 develop¬ment 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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