Host modulation therapy – a promising new concept in treating periodontal diseases
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Abstract
The primary etiology of periodontal diseases is a bacterial infection, but not sufficient to induce periodontal disease initiation or progression. The host’s reactions to the presence of the bacteria are the one which mediates the tissue destruction. The destruction of periodontal tissue is believed to be due to the host response, it is logical to consider therapeutic approaches that modulate the host response in addition to antibacterial approaches in the management of periodontitis. A number of host modulatory agents like non-steroidal anti-inflammatory drugs, sub-antimicrobial dose doxycycline (SDD), and bisphosphonates were effective in treating periodontal disease in experimental animal studies and human trials when used as host modulating agents. This paper review the Host Modulatory Therapy which in future will be the effective tool dental practitioners when used as adjunct to mechanical therapy in treating periodontal diseases.

Key Words Periodontal disease; Host modulation; Non-steroidal inflammatory drugs; Bisphophonates; Sub-antimicrobial dose Doxycycline

Received on: 13/08/2010 Accepted on: 13/11/2010

Periodontitis is a health concern for centuries and are the most important causes of pain, discomfort, and tooth loss in adults. While a significant portion of the population is susceptible to periodontitis, there are those that are relatively resistant to the severe forms of periodontal disease. This leads to the hypothesis that, there are susceptibility factors or risk factors that modulate susceptibility or resistance of individuals to destructive periodontal disease.

The progression of periodontal disease is adversely influenced by a number of risk factors and risk indicators like diabetes, gender, age, hereditary and smoking. Once it was thought that the presence of pathogenic bacteria in the gingival sulcus was solely responsible for tissue destruction, traditional treatments focused on reducing the bacterial load through scaling and root planning, systemic and locally delivered antimicrobial drugs and antiseptics, however these treatment modalities were ineffective or less effective in all patients affected by periodontal disease.

Many individuals harbor the putative pathogens associated with periodontal disease but they do not develop the disease. Study by Loe in migratory srilankan tea laborers, Patients with poor oral hygiene with no access to basic oral hygiene measures, two types of response were observed, Rapid progression of periodontal disease and No or little progression giving rise to the speculation that two population categories may exist, one disease susceptible and another disease resistant.

Clinical evidence has demonstrated that not all individuals have the same response to similar amounts of plaque accumulation. There are patients with moderate and advanced disease who have very little plaque while other patients with little disease have large amounts of plaque. Most importantly, the plaque quantity, as well as the presence of specific bacteria, to the severity of periodontitis indicates that a substantial part of the variation in clinical severity of disease may be explained by factors other than the bacterial challenge. It should be emphasized that this statement in no way means that bacterial plaque is unimportant- in fact, it is quite the contrary.

Bacterial plaque is absolutely essential for the initiation and progression of periodontitis. However, it now appears that once the bacteria are present, the amount of periodontitis that a patient develops is due to factors related to the body's response to the bacterial challenge. It is in these disease susceptible individuals, the excessive host response leads to destruction of periodontal structures.

Mechanism of host induced periodontal destruction: Concepts of the etiology of periodontal disease have changed markedly in the last four decades. In 1985 research began focus to on bacterial- host interactions. Several specific subgingival oral bacteria including porphyromonous gingivalis, actinobacillus actino mycetemcomitans, prevotela intermedia, bacteroides forsythus and perhaps others such as campylobacter rectus, fusobacterium nucleatum, and spirochetes are associated with severe forms of periodontal disease. The microbial challenge consisting of antigens, lipopolysaccharide (LPS), and other virulence factors stimulates host responses which result in disease limited to the gingiva (i.e., gingivitis) or initiation of periodontitis. 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. Perpetuation of the host response due to a persistent bacterial challenge disrupts homeostatic mechanisms and results in release of mediators including proinflammatory cytokines (e.g., IL-1, IL-6, tumor necrosis factor (TNF-α), proteases (e.g., Matrix Metallo proteinase’s), and prostanooids (e.g., prostaglandin E2 [PGE2]), which can promote extracellular matrix destruction in the gingiva and stimulate bone resorption.

The production of collagenase from infiltrating neutrophils and resident periodontal tissue cells is part of the natural host response to infection, in periodontal disease and other chronic inflammatory diseases. There is an imbalance between the level of activated tissue destroying matrix metallo proteinases (MMPs) and their endogenous inhibitors. These cascades of events from inflammation collectively lead to gingival recession, pocket formation, tooth mobility and tooth loss. It is clear that host factors play a major role in the pathogenesis of periodontal disease. (7)

Host response modulation: The concept of host modulation is fairly new to the field of dentistry but is universally understood by most physicians who routinely apply the principles of host modulation to the no of chronic disorders such as arthritis and osteoporosis. This concept to dentistry was introduced by Williams and Golub. (5) Williams in 1990 concluded that, “There are compelling data from animal and human trials indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be effective in slowing progression of periodontal disease”. (1)

Various host modulatory therapies (HMT) have been developed or proposed to block pathways responsible for periodontal tissue breakdown. Specific aspects of disease pathogenesis which have been investigated for modulation include regulation of immune and inflammatory responses, excessive production of matrix metallo proteinase’s and arachidonic acid metabolites, and regulation of bone metabolism. Currently, one systemically administered agent that modifies the host response is commercially available (i.e., subantimicrobial dose doxycycline) for the adjunctive treatment of chronic periodontitis. (8)

**Host Modulation Therapy:** It is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of host response and up regulating protective or regenerative responses. The purpose of host modulatory therapy is to restore balance between on the one hand, proinflammatory mediators and destructive enzymes and on the other hand anti-inflammatory mediators and enzyme inhibitors. They can be systemically administered or locally delivered and used as adjuncts to scaling and root planning. (8)

**Host Modulation Agents:** New strategies of managing periodontitis are to reduce bacterial load while simultaneously suppressing destructive host response. Host modulation with chemotherapeutics or drugs is an exciting new adjunctive therapeutic option for the management of periodontal diseases. These agents have included the systemic (flurbiprofen) and topical (ketoprofen) use of Nonsteroidal anti-inflammatory drugs, the systemic use of subantimicrobial-dose doxycycline (SDD; Periostat [Cola-Genex Pharmaceuticals, Newtown, Pennsylvania]), and the systemic use of Bisphosphonates (Fosamax). 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 on wound healing but also to stimulate regeneration of lost bone, periodontal ligament, and cementum, restoring the complete periodontal attachment apparatus. These agents have included enamel matrix proteins (Endogain), bone morphogenetic proteins 2 and 7, growth factors (platelet-derived growth factor and insulin-like growth factor), and tetracyclines. (9)

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)** have been used to treat pain of acute or chronic inflammation. They are effective in inhibition of prostaglandin synthesis. They limit the progression of periodontitis through their ability to reduce inflammation and bone resorption. A pathway involved in periodontal disease pathogenesis involves the synthesis and release of prostaglandins and other arachidonic acid metabolites within periodontal tissues. Both bacterial and host factors initiate tissue damage. (10)

This damage allows phospholipids in plasma membranes of cells to become available for action by phospholipase A2 and thereby results in production of free arachidonic acid (AA). AA can be metabolized via the cyclooxygenase (CO) or lipoxygenase (LO) pathways. The final products of the CO pathway include prostaglandins,
Bisphosphonates have been reported in gingival crevicular fluid (GCF) and periodontal tissues in patients exhibiting gingivitis, periodontitis, and peri-implantitis. Mean crevicular PGE2 concentrations are also significantly elevated in patients who exhibit disease progression compared to periodontally stable individuals. One proposed approach to modulate the host response is inhibition of enzymes responsible for the release of these destructive products. NSAIDs currently under investigation are Flurbiprofen, Naproxen, Meclofenamate and Ketorolac.(11)

The topical administration of NSAIDs is a method to deliver these agents. In general, topical application of NSAIDs is possible because these drugs are lipophilic and are absorbed into gingival tissues. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine rinse and S-ketoprofen dentifrice. However, adverse effects associated with prolonged systemic administration of non-selective NSAIDs that possess both Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) inhibitory activity include gastrointestinal upset and hemorrhage, renal and hepatic impairment. These adverse events associated with systemic use of NSAIDs have precluded their incorporation into treatment regimens. (10, 12)

Recently, selective NSAIDs called coxibs (COX-2 inhibitors, Nimesulide) have been developed that selectively block the isoenzyme associated with inflammation (COX-2). Clinical trials have demonstrated that use of these agents cause significantly fewer serious gastrointestinal adverse events than does treatment with non-selective NSAIDs. More recently, a selective COX-2 inhibitor (nimesulide), scaling and root planning therapy was compared with a non-selective COX inhibitor (naproxen), scaling and root planning on periodontal clinical parameters and on gingival tissues levels of prostaglandin E2 and prostaglandin F2a. No additional increase was observed in clinical attachment levels and probing depth reduction after both adjunctive therapies when compared with a placebo/ scaling and root planning group. Nevertheless, NSAID groups showed significant reduction of prostaglandin E2 (only naproxen) levels, while the placebo group showed an increase of these levels after 10 days of treatment. (13)

A compound which has received interest as both an antibacterial and anti-inflammatory agent is triclosan. Triclosan (2,4,4’trichloro-2’-hydroxydiphenyl ether) is a non-ionic antimicrobial agent. Triclosan also inhibits Cyclooxygenase and Lipoxygenase and thus may interfere with the production of AA metabolites (45). Use of a dentifrice containing sodium fluoride (0.243%) and triclosan (0.3%) with 2.0% PVM/MA copolymer (the non-proprietary designation for a polyvinylmethyl ether maleic acid copolymer) reduced the frequency of deep periodontal pockets and the number of sites exhibiting attachment and bone loss in patients deemed highly susceptible to periodontitis. Additional studies are warranted to examine the effect of this combination of drugs on periodontitis. At this time, the triclosan / copolymer dentifrice is indicated for the reduction of plaque, calculus, gingivitis, and caries. Safety and efficacy evaluations continue for these drugs. However, at this time no NSAID formulation is FDA approved for the management of periodontal diseases.(8)

Bisphosphonates: (Alendronate, Residronate, Zoledronic Acid, Pamidronate, Ibadronate): Bisphosphonates were introduced in 1990 for treatment of osteoporosis and osteolytic tumors. They are second group of drugs under investigation for their ability to modulate the bone loss and prevent bone resorption. They are primarily used to treat hypercalcemia, pagets disease and osteoporosis. Bisphosphonates are non-biodegradable analogs of pyrophosphate that have a high affinity for calcium phosphate crystals and that inhibit osteoclast activity. Bisphosphonates bind to and accumulate in bone and remain there for months. They inhibit osteoclast attachment to bone, induce apoptosis of osteoclasts, and inhibit differentiation of bone marrow precursor cells into osteoclasts, thus contributing to inhibition of bone resorption and increased bone mass. These compounds also appear to inhibit matrix metalloproteinase activity through a mechanism that involves chelation of cations.(14)

One of these drugs, alendronate, has been evaluated in ligation induced periodontitis models and assessed for changes in bone density. Alendronate inhibited the loss of bone density in these models. However, minimal effects were demonstrated on clinical parameters. A pilot human clinical study was performed to assess the efficacy of alendronate in slowing alveolar bone loss associated with periodontitis. Limitations of these drugs on prolonged use may lead to inhibition of bone mineralization and subsequent osteomalacia, change in white blood cell counts and jaw necrosis. However newer generation of bisphophonates appear to minimize this activity. Currently they are still under investigation and may be soon available for treatment of periodontitis.(14)
Tetracyclines and their chemically modified analogues: Tetracyclines are broad-spectrum antibiotics and have been widely used in the treatment of periodontal diseases. They are effective in treating periodontal diseases because their concentration in the gingival crevice is 2 to 10 times higher than in serum. Tetracyclines at low GCF concentration 2-4 μg/ml and their ability to bind to tooth surface and bone enhance their activity at site of infection and are effective against many periodontal pathogens. However, it is not the antibacterial property but their ability to prevent connective tissue breakdown (anticollagenase) and bone loss (osteoclast inhibition) independent of their antibacterial property has found much interest in host modulatory therapy. One important group of proteolytic enzymes present in the periodontal tissues is formed by the matrix metalloproteinases (MMPs), which include collagenases, gelatinases and metallo elastases. Matrix metalloproteinases are produced by fibroblasts, keratinocytes, macrophages, neutrophils and endothelial cells, and are responsible for remodeling the extracellular matrix. 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. In 1985, tetracycline had been discovered to have anticollagenolytic activity and was proposed as a host-modulating agent for periodontal treatment. Tetracycline appear to inhibit MMP activity and extracellular matrix destruction by multiple non-antimicrobial mechanisms (e.g., chelation, inhibition of activation of pro-MMP molecules). (15)

Long term use of antimicrobial doses is limited by potential development of resistant microorganisms. In an attempt to bypass this problem while maintaining host modulatory properties researchers have evaluated the efficacy and safety of subantimicrobial doses of tetracycline in conjunction with mechanical procedures in the treatment of periodontitis. Recently a formulation containing a sub antimicrobial dose of Doxycycline (SDD) (Doxycycline hyclate 20 mg; Periostat, CollaGenex, Pharmaceuticals Newton PA) is FDA approved and ADA accepted. It is indicated as an adjunct to scaling and root planning in the treatment of chronic periodontitis. It has been evaluated as 20mg taken twice daily for up to 9 months of continuous dosing in clinical trials. The 20mg twice per day dose exerts its therapeutic effect by enzyme, cytokine, and osteoclast inhibition, rather than by any antibiotic effect (15).

At the present time, SDD is the only FDA-approved, ADA-accepted host modulatory therapy specifically indicated for the treatment of chronic periodontitis. SDD works so well as a host modulatory agent because of its pleiotropic effects on multiple components of the host responses. The only enzyme (MMP- Matrix Metalloproteinases) inhibitors that have been tested for the treatment of periodontitis are members of the tetracycline family compounds. In an early study using these different tetracyclines reported that the semi synthetic compounds (ie, doxycycline) were more effective than tetracycline in reducing excessive collagenase activity in the GCF of adult periodontitis patients. Recent clinical trials have focused on doxycycline because it was found to be a more effective inhibitor of collagenase than minocycline or tetracycline and because of its safety profile, pharmacokinetic properties, and systemic absorption. (16)

With regard to the issue that low dose antibiotics could result in microbial resistance, several in vivo human studies have indicated that long-term (i.e., 9 to 18 months) administration of SDD does not result in emergence of resistant organisms or alteration of the sub gingival micro flora. Whether continuous administration or multiple applications to the same individual over longer time intervals result in microbial resistance or the emergence of resistant strains has not been determined. The adjunctive use of SDD might prove beneficial in patients with increased susceptibility to disease progression. In this respect, a recent study compared the efficacy of scaling for 30 minutes with and without adjunctive SDD among patients who consistently exhibited elevated GCF collagenase levels prior to treatment. It was determined that patients who received periodically administered SDD (12 weeks on, 12 weeks off, 12 weeks on) demonstrated less clinical attachment loss than individuals who received scaling alone during a 36-week period (0.15mm versus 0.8mm). (15)

Future Host Modulation Therapy: Initial host responses to bacterial infections include activation and recruitment of neutrophils and macrophages. These cells subsequently release mediators including reactive oxygen species, which are antagonistic to plaque biofilms, but which in excess may initiate inflammation. For example, nitric oxide (NO) is a free radical involved in host defense that can be toxic when present at high levels and it has been implicated in a variety of inflammatory conditions. In this regard, a study utilizing a ligature induced periodontitis rat model demonstrated that administration of an NO inhibitor (mercapto ethyl guanidine) resulted in decreased bone loss. Further preclinical studies are
warranted to evaluate the effect of this agent on periodontal disease progression. Other host inflammatory mediators being investigated for modulation include nuclear factor kappa B and endothelial cell adhesion molecules. However, the role of these inflammatory mediators in periodontitis needs to be elucidated. (17)

Constituents of the biofilm also stimulate host cells to produce proinflammatory cytokines including IL-1β and TNF-α, which can induce connective tissue and alveolar bone destruction. These cytokines are present in diseased periodontal tissues and gingival crevicular fluid (GCF). (7) The catabolic activities of these cytokines are controlled by endogenous inhibitors that include IL-1 and TNF receptor antagonists. When administered for therapeutic purposes, these antagonists can reduce inflammation. The use of cytokine receptor antagonists to inhibit periodontal disease progression has been investigated in a ligature induced periodontitis non-human primate model. It was demonstrated that IL-1/TNF blockers partially inhibited disease progression. However, the use of cytokine antagonists to treat human periodontal disease needs to be evaluated. (11)

Cytokines implicated in suppression of the destructive inflammatory response include IL-4, IL-10, IL-11, and TGF-β. Both IL-4 and IL-10 can target macrophages and inhibit the release of IL-1, TNF, reactive oxygen intermediates, and nitrous oxide. IL-4 also induces programmed cell death (apoptosis), which reduces the number of infiltrating inflammatory macrophages. It can also up regulate the production of IL-1 receptor antagonists. The evidence that IL-4 is deficient in diseased periodontal tissues and the finding that exogenous IL-4 administration in experimental arthritis reduces inflammation, suggest that use of this cytokine may provide a therapeutic benefit in the treatment of periodontal diseases. (18) Recently, recombinant human IL-11, which inhibits production of TNF-α, IL-1 and nitrous oxide was also shown to reduce disease progression in a ligature-induced periodontitis canine model.

In addition to use of SDD in host modulatory therapy, 10 different chemically modified tetracyclines (CMTs) have been developed, 9 of which inhibit MMPs and do not possess antimicrobial properties. CMTs have been reported to reduce the progression of experimentally induced periodontitis in animal models. The development of recombinant Tissue inhibitor of matrix metalloproteinase (TIMP) and synthetic MMP inhibitors offers promising therapeutic approaches for the treatment of conditions characterized by excessive MMP activity. (19)

Conclusion

Because periodontopathic microorganisms and destructive host response are involved in the initiation and progression of periodontal disease and there are situations in which conventional therapy does not always achieve the desired clinical outcome, for example, certain patients possess non-microbial risk factors which are difficult to reduce or eliminate (e.g., smoking, diabetes) or are beyond the clinician’s ability to control (e.g., genetic predisposition), cases which are refractory to conventional treatment and patients in whom surgical approach is not possible because of medical risk factors or age, dual approach like host modulatory therapy in conjunction with anti-biofilm therapy as adjunct to mechanical therapy may prove to be advantageous. With the approval of Periostat and anticipated future approval of many additional agents, dental professionals now have novel treatment options that can be used together with traditional therapies for successful long term management of periodontitis.

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Source of Support: Nil, Conflict of Interest: None Declared