Host Modulation Therapy: A Novel Approach In The Treatment Of Periodontal Diseases

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Abstract

The primary etiology of periodontal diseases and chronic inflammation around dental implants is a bacterial infection.

In essence, a gram negative infection of the pocket is necessary, but not sufficient to induce periodontal disease initiation or progression.

Ultimately, it is the host's reaction to the presence of the bacteria that mediates tissue destruction. Since 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 and peri-implant disease. A number of host modulatory agents have been investigated which include the nonsteroidal anti-inflammatory drugs, subantimicrobial-dose doxycycline (SDD), and bisphosphonates.

INTRODUCTION

The primary etiology of periodontal diseases and chronic inflammation around dental implants is a bacterial infection.(1) In essence, a gram negative infection of the pocket is necessary, but not sufficient to induce periodontal disease initiation or progression. Ultimately, it is the host's reaction to the presence of the bacteria that mediates tissue destruction. This response can be influenced by environmental (e.g., tobacco use), acquired (e.g., systemic disease), and genetic risk factors.

Since the destruction of periodontal tissue is believed to be due to the host response, it is logical to consider therapeutic approaches that manipulate the host response in addition to antibacterial approaches in the management of periodontitis and peri-implant disease.

Host response modulation is a term which has been introduced to the dental profession relatively recently.(2) The rationale behind this approach is to aid the host in its fight against infectious agents by supplementing the natural inherent defense mechanisms or to modify its response by changing the course of inflammatory systems. Compared to other weapons against infection, host response modulation potentially has fewer side-effects, is not invasive, and does not require complicated application methods.(3)

Host response modulation is routinely practiced by our medical colleagues, who use host modulation strategies in the treatment of disorders such as rheumatoid arthritis and osteoporosis. (2) Over the last two decades, a variety of pharmacological agents have been studied for a possible role as host modulators in the management of periodontal disease. These include nonsteroidal anti-inflammatory drugs, bisphosphonates and the tetracycline family (and their chemically modified analogues(4)). Newer agents that have the potential to be of benefit in periodontal treatment include anti-cytokine drugs e.g. infliximab (5) (which have successfully been used in the treatment of rheumatoid arthritis), soluble cytokine blockers and lipoxins.(6)

PATHOGENESIS OF PERIODONTAL DISEASE

Periodontitis, initiated by plaque bacteria is characterized by destruction of the periodontal ligament and bone. Alveolar bone resorption occurs as a result of uncoupling of the normally balanced processes of bone resorption and bone formation. Cytokines, chemokines and prostaglandins have been identified as regulators of the immune-inflammatory process in periodontitis. Cytokines (especially interleukin-1 and tumor necrosis factor-⍺) can induce bone resorption indirectly by promoting the differentiation of osteoclast precursors and by activating osteoclasts.(6)

The purpose of host modulatory therapy is to restore balance between, on the one hand, pro-inflammatory mediators and destructive enzymes, and, on the other hand, anti-inflammatory mediators and enzyme inhibitors. (Fig. 1)

Figure 1

Fig. 1: Points of intervention for nonsurgical therapy. CAL, clinical attachment loss; IL, interleukin; NSAIDS, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor. Ryan ME, Preshaw PM. In Newman MG, Takei H, Klokkevold PR, Carranza FA. Host modulation. CarranzaÂ's Clinical periodontology, 10th Ed., St. Louis: Elseveir, 2009:275-282. (7)
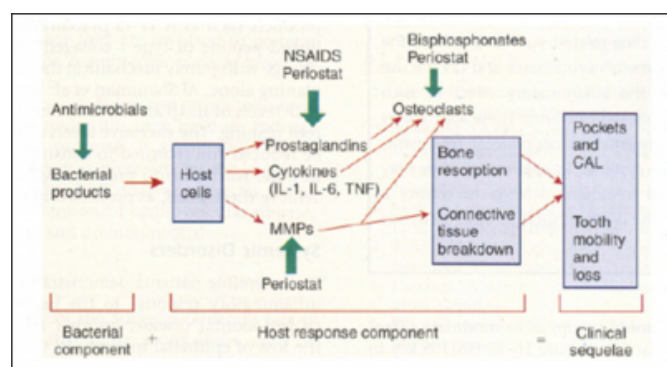
CONVENTIONAL TREATMENT MODALITIES

The mechanical removal of plaque and calculus is considered as the standard treatment for periodontitis. The objective of this treatment is to reduce the chronic challenge presented by the subgingival plaque bacteria, such that inflammatory responses in the periodontal tissues are reduced, leading to resolution of inflammation and shrinkage of the gingival tissues.

In many patients, nonsurgical management alone (comprising oral hygiene instruction, root surface instrumentation and periodontal maintenance care) may be sufficient to result in clinical improvements and control of periodontal disease. However, there are many patients in whom treatment responses following conventional treatment are more limited and both patient and clinician may ask if anything further can be done.

Our improved understanding of the pathogenesis of periodontal disease has led to the development of host modulation as a treatment strategy that can be used in addition to conventional treatment approaches. Thus, a combination of therapeutic approaches may offer the best chance for clinical improvements,(8) and this could include:

- Reduction in the bacterial burden (by root surface instrumentation and hygiene therapy).

- Risk factor modification (by smoking cessation and improved diabetes control).

- Host Response Modulation

Host response modulation offers the potential for downregulating destructive aspects of the host response so that, in combination with conventional treatments to reduce the bacterial burden, the balance between health and disease progression is tipped in the direction of a healing response.

Various host modulatory therapies 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 metalloproteinases and arachidonic acid metabolites, and regulation of bone metabolism.

IMMUNE MODULATION THERAPY PRO-INFLAMMATORY CYTOKINE INHIBITION

The immune system is in a dynamic equilibrium, with inflammatory responses (mediated by T-helper type 1 cells, interleukin (IL)-1b, interferon-c (IFN-c), and tumor necrosis factor-⬜ (TNF- ⬜) being counterbalanced by endogenous anti-inflammatory responses (mediated by T regulatory type 1 cell, T-helper type 3 cells, IL-4, IL-10, and transforming growth factor-b

(TGF-b).(9) These pathways regulate homeostatic stability of immune system. The inflammatory disease process is characterized by domination of pro-inflammatory cytokine mediators. Therefore, external neutralization of inappropriate inflammatory cytokines is a therapeutic strategy that has been attempted in many chronic inflammatory conditions.

Currently, anti-cytokine therapy using anti-IL-1 or anti-tumor necrosis factor- ⬜ monoclonal antibodies and soluble tumor necrosis factor receptors have been approved for the treatment of rheumatoid arthritis,(10) Crohn's disease, juvenile arthritis and psoriatic arthritis with research continuing on periodontal disease .

In periodontal research, the effects of soluble receptors and receptor antagonists of IL-1 and TNF- ⬜ have been studied during experimentally induced periodontitis in a non-human primate model (e.g. Macaca fascicularis).(11) The clinical, radiographic and biochemical findings of these experiments

showed that IL-1 and TNF- ⬚ antagonists blocked i) the progression of the inflammatory cell infiltrate towards the alveolar crest, ii) the recruitment of osteoclasts and (iii) periodontal attachment and bone loss. Compared with control animals, intra-papillary injection of soluble receptor antagonists of IL-1 and TNF- ⬚ reduced the pattern of bone loss by approximately 50% as assessed by computer assisted densitometric image analysis (CADIA).

However, the harsh enzymatic environment in periodontal lesions may destroy the soluble cytokine antagonists prior to their peak activity, which may necessitate more frequent administration of the active agents to the defects.

MODULATION OF MATRIX METALLOPROTEINASE (MMP) ACTIVITIES

Matrix metalloproteinases are a family of zinc dependent and calcium-requiring endopeptidase enzymes that are responsible for the degradation of most extracellular matrix proteins during organogenesis, growth, and normal tissue turnover.(12) These enzymes can be produced by several different types of cells such as fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils and their activity can be specifically inhibited by tissue inhibitors of metalloproteinases (TIMPs).

Tissue inhibitors of metalloproteinases are important controlling factors in the actions of matrix metalloproteinases, and tissue destruction in disease processes often correlates with an imbalance of matrix metalloproteinases over tissue inhibitors of metalloproteinases.

The expression and activity of matrix metalloproteinases in adult tissues is normally quite low, but increases significantly in various pathologic conditions that may lead to unwanted tissue destruction, such as inflammatory diseases, tumor growth, and metastasis.

Treatment of periodontitis with medications and down-regulators (such as doxycycline, chemically modified nonantimicrobial tetracycline-derivates, bisphosphonates, and their combinations) and therapeutic applications of anticollagenase drugs (such as synthetic matrix metalloproteinase inhibitors) in endotoxin-induced tissue-destructive periodontitis model in rats have been shown to result in reduced levels of matrix metalloproteinase and in activity that is associated with clinically beneficial outcomes.(13)

The major anti-proteinase used in periodontal treatment is tetracycline. In addition to its antimicrobial activity, this group of compounds has the capability of inhibiting the activities of neutrophils, osteoclasts, and matrix metalloproteinases (specifically matrix metalloproteinase-8), thereby working as an anti-inflammatory agent that inhibits bone destruction.(14)

Identification of the site on the tetracycline molecule responsible for its matrix metalloproteinase-inhibitory activity led to the development of a series of chemically modified nonantimicrobial analogs, called chemically modified tetracyclines, which also have therapeutic potential but which do not appear to induce antibiotic side-effects.

Thus far, one approved host modulation therapy (HMT) prescribed as systemic subantimicrobial-dose doxycycline (SDD) in conjunction with mechanical periodontal therapy is available in some countries.

Thus, anti-matrix metalloproteinase treatment through tetracyclines or their derivatives or numerous novel medications presents an exciting and promising field of research in the context of modulation of host response.

MODULATION OF ARACHIDONIC ACID METABOLITES
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The basic rationale behind the use of nonsteroidal anti-inflammatory drugs is to block the arachidonic acid metabolites that are pro-inflammatory mediators implicated in a variety of bone resorptive and tissue degrading processes. Nonsteroidal anti-inflammatory drugs include analgesics such as ibuprofen and aspirin with multiple levels of anti-inflammatory effects.(15) These compounds block platelet activity through thromboxane inhibition, inhibit cyclooxygenase, and prevent the production of arachidonic acid metabolites.

Arachidonic acid is an important component of phospholipids' metabolism in animals through which biosynthesis of most eicosanoids such as prostanoids (further grouped as prostaglandins and thromboxanes) and leukotrienes starts. Arachidonic acid derivatives and lipid mediators of inflammation play critical roles in health and disease. They can initiate and take part in the progression of inflammation and thus are named pro-inflammatory mediators.(15)

The ability of nonsteroidal anti-inflammatory drugs to block

prostaglandin E2 production, thereby reducing inflammation and inhibiting osteoclast activity, has been investigated in patients with periodontal disease. Studies have shown that systemic flurbiprofen, indomethacin, naproxen and others, administered daily for periods of up to 3 years, significantly slowed the rate of alveolar bone loss compared to patients treated with placebo.(16)

However, the nonsteroidal anti-inflammatory drugs have some serious disadvantages that essentially preclude their use as an adjunctive treatment for periodontal disease.(17) Daily administration for extended periods of time (years rather than months) is necessary for periodontal benefits to become apparent, and the nonsteroidal anti-inflammatory drugs are associated with significant unwanted effects, including gastrointestinal problems, hemorrhage (as a result of decreased platelet aggregation), and renal and hepatic impairment. Also, once patients cease taking nonsteroidal anti-inflammatory drugs, a return to, or even acceleration of, the rate of bone loss seen prior to drug therapy occurs, sometimes referred to as a rebound effect.

LIPOXINS AND RESOLVINS

Neutrophils are within the first line of host defense, and, by their ability to phagocytose microbes; they can protect the host from infection. They can also give rise to neutrophil-dependent vascular injury and contribute to increased vascular permeability, edema, and further release of chemoattractants, with a net pro-inflammatory effect. The involvement of the inducible cyclooxygenase isoform (COX-2) and the role of novel lipid mediators in the pathogenesis of periodontal disease are under study, and data derived from these observations have showed that periodontitis represents an important inflammatory model for the investigation of lipid mediators. The working hypothesis is that COX-2 could have multiple roles in the development and progression of the periodontal disease.(18) First, crevicular fluid samples from localized aggressive periodontitis (LAP) patients were examined and found to contain prostaglandin PGE_2 and lipoxygenase derived products. Neutrophils were found to generate considerable arachidonic acid metabolites in this study.(18) This finding suggests that neutrophils contribute to the pathogenesis of periodontal disease in ways that were not previously anticipated. Furthermore, neutrophils from peripheral blood of LAP patients, but not from healthy volunteers, also generated lipoxin A_4, suggesting that this immunomodulatory molecule may also have a role in periodontal disease.(18)

The role of lipid mediators in the neutrophils' response to Porphyromonas gingivalis was also characterized in an animal model. When P. gingivalis was introduced into murine dorsal air pouches, leukocyte infiltration was initiated. The administration of metabolically stable analogues of lipoxin and of aspirin-triggered lipoxin potently blocked neutrophil traffic into the dorsal pouch cavity and lowered PGE2 levels within exudates without allowing infection to spread. These results show that neutrophils can provide an important source of PGE2 in periodontal tissues. Moreover, they provide strong support for the notion that lipoxin can have a protective role in periodontitis, limiting further neutrophil recruitment and neutrophil-mediated tissue injury that can lead to loss of inflammatory barriers that prevent tissue invasion by oral microbial pathogens.(18)

These results support the concept that lipoxins may be involved in the regulation of local acute inflammatory responses in periodontal disease. However, additional studies are needed to elucidate the role of lipoxins in the pathogenesis of periodontitis.

MODULATION OF BONE REMODELLING

Destruction of the osseous support of the dentition is a hallmark of periodontal diseases. This localized bone resorptive process has been the target of therapeutic intervention and preventive strategies

PHARMACOLOGICAL STRATEGIES FOR TREATING PERIODONTAL BONE LOSS

Pharmacologic strategies designed to treat periodontal bone destruction generally either target the bacteria in the lesion or the host response to the bacteria. Historically, most strategies have focused on the bacteria, whereas pharmacologic strategies that specifically inhibit the formation or activity of osteoclasts have been less intensively utilized. Still, many of these osteoclastic pathway inhibitors have proved valuable for treating systemic diseases associated with bone loss such as osteoporosis and Paget's disease.(19) Targeting the host response via inhibition of bone resorption may be accomplished by altering the differentiation of osteoclasts, the specific components necessary for the process of resorption, or the duration of their activity via reducing their lifespan.

ANTI-INFLAMMATORY AGENTS

Agents that block cytokine production or activity are the early strategies to inhibit bone resorption. Historically, non-steroidal anti-inflammatory agents (NSAIDs) have provided

promising results in slowing periodontal destruction.(20) Adverse reactions, however, have limited their widespread use.

CHEMICALLY MODIFIED OR LOW-DOSE TETRACYCLINES

Tetracyclines, broad-spectrum antibiotics, are used extensively in the management of periodontal disease because of their ability to inhibit bacterial protein synthesis. However, newer applications of tetracyclines have focused on the ability of these agents to block tissue-destructive enzymes, such as the matrix metalloproteinases.(21) A group of tetracyclines including chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline, and minocycline chelate the cations of metalloproteinases that are required for action. The mechanism by which tetracyclines inhibit matrix metalloproteinases appears to be independent of their antibacterial activity.

BISPHOSPHONATES

Bisphosphonates are widely used in the management of systemic metabolic bone disorders such as osteoporosis and Paget's disease. They are also indicated in cancer-related diseases such as neoplastic hypercalcemia, multiple myeloma, and bone metastases secondary to breast and prostate cancer, suggesting a direct antitumor effect of bisphosphonates at different levels of action. These compounds inhibit osteoclastic activity by blocking acidification by local release and represent a class of chemical structures related to pyrophosphate.(22)

Given their known affinity to bone and their ability to decrease osteoblastic differentiation and inhibit osteoclast recruitment and activity, there exists a possible use for bisphosphonates in the management of periodontal diseases. Bisphosphonates downregulate levels of several matrix metalloproteinases including matrix metalloproteinase-3, matrix metalloproteinase-8, and matrix metalloproteinase-13 from human periodontal ligament cells.(23) These bone-specific properties also provide an interesting management strategy to stimulate osteogenesis in conjunction with regenerative materials around osseous defects and may result in the promotion of bone formation around endosseous implants. (Table 1)

Early trials showed that alendronate, an aminobisphosphonate, may inhibit bone loss in osteolytic diseases by altering osteoclast activity. A very recent clinical trial evaluated the effect of bisphosphonate therapy as an adjunct to nonsurgical periodontal treatment in patients with moderate to severe chronic periodontitis.(23) Bisphosphonate therapy significantly improved clinical measures of periodontal therapy during the 6- to 12-month period but there was no difference in periodontal bone mass change between the bisphosphonate and placebo groups. These data suggest that bisphosphonate treatment improves the clinical outcome of nonsurgical periodontal therapy and may be an appropriate adjunctive treatment to preserve periodontal bone mass. However, there were no effects on clinical parameters of periodontal inflammation, necessitating further and more extensive analyses.

Figure 2

Table 1: Bisphosphonate Modulation of Bone Metabolism

Tissue level	Cellular level	Molecular level
↓ Bone turnover due to ↓ Bone resorption	↓Osteoclast recruitment	Inhibit mevalonate pathway (an result in perturbed cell activity and induction of apoptosis)
↓ Number of new bone multicellular units	↑Osteoclast apoptosis	
	↓Osteoclast adhesion	↓Post-translational prenylation of GTP − binding proteins
Net positive whole body bone balance	↓Depth of resorption site	
	↓Release of cytokines by macrophages	
	↑Osteoblast differentiation and number	

MODULATION OF NITRIC OXIDE SYNTHASE (NOS) ACTIVITY

Nitric Oxide (NO) is a short-lived molecule implicated in a wide range of biological processes ranging from immune homeostasis to cancer.(24) It is synthesized in vivo from the substrate L-arginine by three isoenzymes called NOSs. While low levels of NO are present in tissue homeostasis, NO is produced at higher concentrations in response to inflammatory stimuli such as bacterial lipopolysacharides via inducible forms of NOS (iNOS). NO is a highly reactive free radical reacting with metal and thiol residues leading to lipid peroxidation, protein and DNA damages and stimulation of cytokine release. An exaggerated production of NO has been implicated in the pathophysiology of several inflammatory processes such as arthritis, colitis and ileitis.

Animal experiments have shown that pharmacological inhibition of iNOS with mercaptoalkylguanidines was associated with decreased inflammation, haemorrhagic shock and arthritis scores.(25) This may be explained by the fact that this class of drugs (e.g. mercaptoethylguanidines (MEGs) is able to (i) inhibit COX(24) (ii) scavenge peroxinitrite (i.e. the product of NO and superoxide) and (iii) block iNOS. However further studies are needed to substantiate its therapeutic effects in periodontal diseases.

Combinations of host response modulators

Host modulating drugs that target different aspects of the pathogenic processes in periodontitis have been combined to maximize therapeutic outcomes. Statistically significant results have been obtained when patients were treated using subantimicrobial dose doxycycline, flurbiprofen. These drugs synergistically suppressed MMPs and other neutral proteinases in the gingiva of patients with chronic periodontitis. Similarly, CMT-8 (a nonantimicrobial chemically modified doxycycline), has been combined with a bisphosphonate (clodronate) in rats with experimental periodontitis.(4) After 1 week of treatment with either CMT-8 alone or the bisphosphonate alone, there were slight reductions in the levels of MMP-8 and MMP-9 in the gingival tissues. However, combination of these agents normalized the pathologically elevated levels of these MMPs, indicating a synergistic inhibition in this animal model.(4)

Subantimicrobial dose doxycycline has also been combined with the locally delivered doxycycline gel, placed into pockets of ±5 mm, in combination with root surface instrumentation in a placebo-controlled study.(26) This combination therapy resulted in significantly greater clinical improvements than instrumentation alone, with mean probing depth reductions of 2.4 mm in the combination group compared with 1.7 mm in the control group (P < 0.01)

The Future of Host Response Modulation

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 (Fig. 2).(27) To date, only subantimicrobial dose doxycycline has been approved specifically as a host response modulator. Further research is necessary to evaluate the efficacy of subantimicrobial dose doxycycline in primary care, and also to focus on very long-term outcomes, such as prevention of tooth loss.

Given the huge and ever-expanding range of pathogenic pathways that play a role in periodontal tissue destruction blocking one single inflammatory pathway may not achieve the desired outcome because receptor mediated responses could be activated by alternate pathways. Thus, poly-pharmaceutical approaches may be developed that modify a number of different pathways associated with inflammation and tissue destruction. Alternatively, targeting of mediators that play a particularly important role in periodontal

pathogenesis, such as interleukin-1b or tumor necrosis factor-⬚, may constitute a rational therapeutic strategy.

However, it should be remembered that these pathways are important in physiological processes and therefore their inhibition could also result in adverse effects, such as increased susceptibility to infection, and the development and investigation of such agents require careful monitoring.

Figure 3

Fig. 2: Complementary strategies for treating periodontitis patients. SRP, scaling and root planing; MMP, matrix metalloproteinase Novak MJ, Dawson DR, Magnusson I, Karpinia K, Polson A, Polson A, Ryan ME, Ciancio S, Drisko CH, Kinane DF, Powala CV, Bradshaw MH. Combining host modulation and antimicrobial therapy in the management of moderate to severe periodontitis: a randomized, multi-center trial. J Periodontol 2008: 79: 33Â–41. (27)
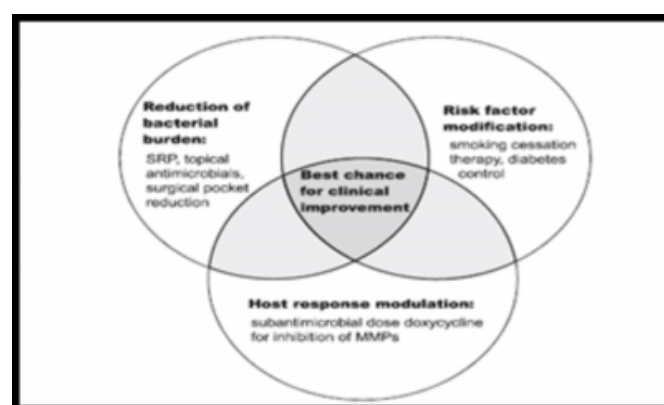
SUMMARY AND CONCLUSION

With the paradigm rapidly changing, the focus in periodontics is shifting from diagnosis and treatment to prevention and health promotion. Identifying and managing the risk factors for periodontitis is of utmost importance. Environmental risk factors, such as tobacco use and diabetes, can be significantly reduced or eliminated by smoking-cessation programs and metabolic control, respectively. Future diagnostic and preventive approaches appear to be in the application of the genetic information to determine the inherent susceptibility of individuals to periodontal disease.

It is likely in the future that more effective therapeutic approaches will include multiple, synergistic host modulation therapies combined with treatments that target the microbial etiology. This new awareness has resulted in the recognition of periodontal etiology as being a chronic microbial challenge in a susceptible host. With respect to the extensive immunological, microbiological, and diagnostic and tissue regeneration research efforts, we are unfortunately

still some way from elucidating accurately the disease and healing processes but in time we will undoubtedly utilize these to develop better diagnostic and therapeutic management of patients.

It is the responsibility of the dentist to select and provide appropriate treatments on an individual basis, following discussion and informed decision making by the patient. Ultimately, practitioners will need to determine the utility of Host Modulation Therapies as they emerge, based on the specific needs of each individual patient.

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