HOST MODULATORY THERAPY IN AGGRESSIVE PERIODONTITIS

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Abstract

Host modulatory therapy (HMTs) ia a treatment concept that goal to reduce tissue destruction and stabilize or even regenerate the periodontium. The aggressive periodontitis result in rapid destruction of the periodontium and can lead to early bone destruction, until tooth loss. HMTs modifying or downregulating dectructive aspects and upregulating protective aspectc of the host response, 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. Many aspects of the host response can be affected, including modification of proteolytic enzymes such as matrix metalloproteinases, stimulation of cellular activity, and alteration of the extracellular matrix, all these aspects can be considered as host modulation. HMTs are systemically or locally delivered pharmacheuticals that are prescribed as part of periodontal therapy and are used as adjuncts to conventional periodontal treatments. A variety of different drug classes have been evaluated as host modulation agents, including the nonsteroidal antiinflammatory drugs (NSAIDs), biphosphonates, chemically modified tetracyclines (CMTs) or subantimicrobial-dose doxycycline (SDD).
The concept of periodontal medicine is not only the bacterial challenge by scaling and rootplaning (SRP) but also the host side of the host-bacterial interactions. Subantimicrobial-dose doxycycline (SDD) is the only HMTs currently approved and indicated as an adjunct to SRP for treating aggressive periodontitis.

Keywords : host modulatory agents, respon host, periodontitis

Introduction

Aggressive periodontitis, as the name implies is a type of periodontitis where there is rapid destruction of periodontitis where there is rapid destruction of periodontal ligament and alveolar bone which occurs in otherwhise systematically healthy individuals generally of a younger age group but patients may be older.[1] Aggressive periodontitis, by definition, causes rapid destruction of the periodontal attachment apparatus and the supporting alveolar bone. The responsiveness of aggressive periodontitis to conventional periodontal treatment is unpredictable, and the overall prognosis for these patients is poorer than for patients with chronic periodontitis. Because these patients do not respond "normally" to conventional methods and their disease progresses unusually fast, the logical question is whether there are problems associated with an impaired host immune response that may contribute to such a different disease and result in a limited response to the usual therapeutic measures. Indeed, defects in polymorphonuclear leukocyte (PMN, neutrophil) function have been identified in some patients with aggressive periodontitis.[2] It is well know that certain periodontopathogenic bacterial species are responsible for periodontal breakdown and the prevention of periodontitis is based on suppresion or elimination of periodontopathogenic bacteria. Apart from the conventional mechanical non surgical and surgical therapy methods, various adjunctive anti infectious therapeutic possibilities are available.[3]

For these reasons, alternatives that might offer the possibility the use of modulating agents. In 1985, research began to focus very closely onbacterial-host interaction, leading to "host-bacterial interrelationship era. During this era it was recognized that although there is evidence that specific bacterial pathogens initiate pathogenesis of disease, the host response to these pathogens is equally important in mediating connective tissue breakdown and bone loss. It has

become clear that it is the host derived enzymes and mediators like matrix metalloproteases (MMPS), cytokines, and other inflammatory mediators like PGE2 that cause the majority of tissue destruction in the periodontium. This shift in paradigm of concentration on host response has led to the development of Host Modulatory Therapies (HMT) which could improve therapeutic outcomes, slow the progression of disease, allow for more predictable management of patients, and possibly es.ven work as preventive agents against the development of periodontitis.[4]

Some patients present with either a significant amount of periodontal tissue loss at a young age or a significant amount of tissue loss over a short period. These cases are reffered to as aggressive periodontitis. The tissue loss can occur around selected teeth, first molars and incisors or in a more generalized manner. The exact etiology for these aggressive forms of periodontitis is not known, although some patients have decreased function of polymorphonuclear leukocytes (PMNs). Several microorganisms also are suspected as playing a role, particularly *Actinobacillus actinomycetemcomitans,* and an as-yet undetected genetic predispoposition may exist as well.[2]

Discussion

The determination that periodontal tissue destruction is primarily due to the host response has created areas of research directed at altering an individual's reaction to the bacterial challenge. 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 metalloproteinases and arachidonic acid metabolites, and regulation of bone metabolism. Currently, one systemically administered agent that modifies the host response is commercially available for the adjunctive treatment of periodontitis.[5] This treatment and other therapeutic methods under investigation will be discussed.

Periodontitis is multifactorial infectious disease of the supporting structures of the teeth, characterized by destruction of the bone and connective tissue. Specific periodontopathic bacteria and their virulence factors are the primary etiologic agents. However interaction of host defense mechanisms and these etiological agents plays an important role in the onset and progression of the disease.[4]

Antimicrobial therapies both local and systemic administration along with mechanical debridement is one of the mainstay in periodontal treatment strategies, which answered microbial etiology of periodontal diseases, in a complex chain of events leading to periodontal tissue destruction. These treatment strategies however, failed to block or inhibit the host response mediated tissue destruction to continued bacterial challenge.[4] Periodontal disease is a multifactorial, complex disease, and an upregulated or maladapted immune-inflammatory response to bacterial plaque predisposes patients to periodontal breakdown. The importance of the host response as a determinant of disease susceptibility is now driving researches to identify genetic traits that characterize individuals as disease susceptible. Researchers are also investigating host modulatory therapies (HMTs), which aim to modify or reduce destructive aspects of the host response so that the immune-inflammatory response to plaque is less damaging to the periodontal tissues. A range of pharmaceuticals will likely be develop. HMTs targetting different aspects of the host response as adjunctive treatments for the periodontal disease.[2]

Periodontal pathogenesis

The immune system provides the body with a strong defense against invading microorganisms. Bacterial plaque in the oral cavity triggers the immune response. In many cases, the host response is still able to contain the bacterial challenge. Insome individuals, however, the host resistance is insufficient to contain the bacterial challenge. Mediators of inflammation produced by macrophage are largely responsible for the tissue destruction seen in periodontitis, with the charactirized by high levels of cytokines, MMPs, and PGE_2, that destroy yhe connective tissue of the gingiva and periodontal ligament and resorb the alveolar bone.[6] Proteolytic enzymes are implicated in a number of processes in normal bone remodeling,including bone resorption and bone formation. The activity of osteoclast-secreted proteolytic enzymes, such as the MMPs, is essential to normal bone homeostasis. Such MMPs are responsible for the destruction of mineralized tissue during bone resorption. In contrast, osteoblasts also secrete MMPs that degrade the nonmineralized osteoid layer on the surface of bone.[7]

Host modulatory therapy

Host modulatory therapy (HMTs) is a treatment concept that aim to reduce tissue destructionand stabilize or even regenerate the periodontium by modifying or downregulating destructive aspects of the host response and upregulating protective or regenerative responses. HMTs are systemically or locally delivered pharmaceuticals that are prescribed as part of periodontal therapy and are used as adjuncts to conventional periodontal treatments, such as scalling and root planing (SRP) and surgery. Removal of plaque by SRP targets one aspect of the pathogenic process by reducing the bacterial burden and therefore the antigenic clallenge that drives the inflammatory response in host

tissue. However, the bacterial challenge is never completely eliminated after SRP, and recolonization by bacterial species occurs. HMTs offer the potential for downregulating destructive aspects and upregulating protective aspects of the host response so that, in combination with conventional treatments to reduce the bacterial burden, the balance between health (resolution of inflammation and wound healing) and disease progression is tipped in the direction of a healing response.[2]

Three potential approaches to host modulation have been considered : 1) inhibition of matrix metalloproteinases (MMPs) with antiproteinases, 2) blocking production of proinflammatory cytokines and prostaglandins with antiinflammatory drugs, and 3) inhibiting activation of osteoclast with bone-sparing agents.[8]

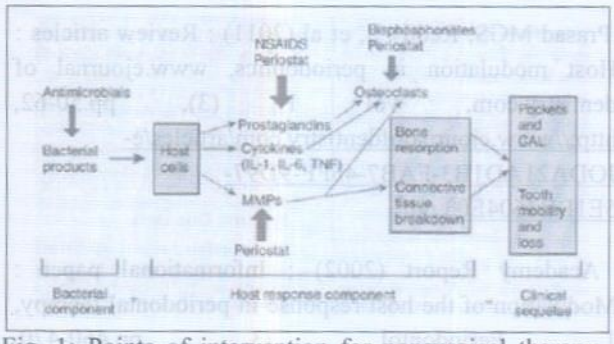

Fig. 1: Points of intervention for nonsurgical therapy. CAL, clinical attachment loss; IL, interleukin; NSAIDS, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.[7]

Nonsteroidal anti-inflammatory Drugs (NSAID)

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, naproxen, are analgesic, anti-platelet, anti-thrombocytic and aspirin with multiple levels of anti-inflammatory effects. 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. 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.[7,8] Topical NSAIDs have shown benefit in the treatment of periodontitis. Locally administered ketoprofen has been investigated. To date, topically administered NSAIDs have not beenapproved as local HMTs for the management of periodontitis.[2]

Chemically Modified Tetracyclines (CMTs)

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. 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.[2,7]

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.[7]

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. 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.[2,7,8]

Subantimicrobial-Dose Doxycycline (SDD)

Subantimicrobial-Dose Doxycycline (SDD) is a 20-mg dose of doxycycline that is approved and indicated as an adjunct to SRP in the treatment of periodontitis. It is taken twice daily for 3 months, up to a maximum of 9 months of continuous dosing. The 20 mg dose exerts its therapeutic effect by enzyme, cytokines, and osteoclast inhibition rather than by any antibiotic effect. Research studies have found no detectable antimicrobial effect on the oral flora or the bacterialflora in other regions of the body and have identified clinical benefit when used as an adjunct to SRP. At present, SDD is the only HMT specifically indicated for the treatment of periodontitis.[2]

Conclusions

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. Thus, polypharmaceutical approaches may be developed that modify a number of different pathways associated with inflammation and tissue destruction. Recently, only sub antimicrobial dose doxycycline has been approved specifically as a host response modulator. Further research is necessary to evaluate the efficacy of sub antimicrobial 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 achievethe desired outcome because receptor mediated responses could be activated by alternate pathways. Alternatively,targeting of mediators that play a particularly important role in periodontal pathogenesis, such as matrix metalloproteinases, prostagland and cytokines may constitute a rational therapeutic strategy.

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Widyastuti

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