Recent Host Modulation Therapy: A Mini Review

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Abstract

Periodontitis is one of the most ubiquitous diseases and is characterized by the destruction of connective tissue and dental bone support following an inflammatory host response secondary to infection by periodontal bacteria.1 The first clinical manifestation of periodontal disease is the appearance of periodontal pockets, which offer a favorable niche for bacterial colonization. It can be diagnosed by clinical examination with periodontal probe to determine pocket depths in combination with X-ray imaging, using microbiological techniques for a precise analysis of the infectious agents.2 According to current concepts of the multifactorial etiology of periodontal disease, it is caused by the interaction among single or multiple microbial agents, a host with some degree of susceptibility, and environmental factors with an influence on both. Although a single model of the etiopathogeny of periodontal disease has yet to be validated, it is broadly accepted that periodontal disease results from action of the bacterial biofilm on the periodontium of the susceptible individual. Bacteria are able to survive and grow in the complex ecosystem of this biofilm because of their production of virulence factors. These factors also confer a greater resistance to host defense mechanisms, i.e., they increase the capacity of the bacteria to overcome the inflammatory reaction and immune response to antigen presentation.3 RecentHostModulationTherapyAMiniReviewStrictly as per the compliance and regulations of:

Index terms—

1 Introduction

eriodontitis is one of the most ubiquitous diseases and is characterized by the destruction of connective tissue and dental bone support following an inflammatory host response secondary to infection by periodontal bacteria. 1 The first clinical manifestation of periodontal disease is the appearance of periodontal pockets, which offer a favorable niche for bacterial colonization. It can be diagnosed by clinical examination with periodontal probe to determine pocket depths in combination with X-ray imaging, using microbiological techniques for a precise analysis of the infectious agents. 2 According to current concepts of the multifactorial etiology of periodontal disease, it is caused by the interaction among single or multiple microbial agents, a host with some degree of susceptibility, and environmental factors with an influence on both. Although a single model of the etiopathogeny of periodontal disease has yet to be validated, it is broadly accepted that periodontal disease results from action of the bacterial biofilm on the periodontium of the susceptible individual. Bacteria are able to survive and grow in the complex ecosystem of this biofilm because of their production of virulence factors. These factors also confer a greater resistance to host defense mechanisms, i.e., they increase the capacity of the bacteria to overcome the inflammatory reaction and immune response to antigen presentation. 3 According to a review by Offenbacher in 1996, the presence of bacteria in the periodontal pocket triggers a reaction that starts with intervention of the neutrophilantibody-complement axis, stimulating different cell types. 4 Host modulatory therapy is a new treatment modality that has been incorporated into the dental therapeutics but it has not been well implemented in the dental practice due to the easy unavailability of host modulatory agents in India. Host can be defined as

"the organism from which a parasite obtains nourishment," or in the transplantation of tissue, "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". Host modulation with chemotherapeutic agents or drugs is a promising new adjunctive therapeutic opportunity for the management of periodontal diseases. The concept of host modulatory therapy was first introduced to dentistry by Williams and Golub et. al. and then expanded by many other researchers in the dental profession. Golub and colleagues discussed "host modulation with tetracyclines and their chemically modified analogues". 5 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 osteoclasts with bone-sparing agents. 6 II.

2 Host Response

Concepts of the etiology of periodontal disease have changed noticeably in the last four decades. In 1985 research began to focus on bacterial-host interactions. Several specific subgingival oral bacteria including porphyromonus gingivalis, actinobacillus aggregatibater, prevotela intermedia, bacteroides forsythus and perhaps others such as campylobacter rectus, fusobacterium nucleatum, and spirochetes are associated with severe type of periodontal diseases. 7 Protective aspects of the host response include recruitment of neutrophils, production of protective antibodies, and possibly the release of antiinflammatory cytokines including transforming growth factor (TGF-?), interleukin-4 (IL-4), IL-10, and IL-12. Persistent bacterial aggression disrupts homeostatic mechanisms and results in release of proinflammatory cytokines (e.g., IL-1, IL-6, tumor necrosis factor? (TNF-?), proteases (e.g., Matrix Metallo proteinase's), and prostanoids (e.g., prostaglandin E2 [PGE2]), which can endorse extracellular matrix destruction in the periodontium and stimulate bone resorption, tooth mobility and tooth loss. 8 III.

3 Host Modulation

The therapeutical agents or perioceutics that are mainly used to control periodontitis is a rising branch in the treatment of periodontal diseases along with mechanical debridement. To lower excessive levels of enzymes, cytokines, prostanoids (prostaglandin E2 [PGE2]), as well to modulate osteoclast functions, host modulation therapy (HMT) are being used, but it should not reduce below constitutive levels. Nonsteroidal antiinflammatory drugs (NSAIDS), subantimicrobial dose doxycycline (Periostat), systemic bisphosphonates (BP), are few host modulating agents that are being recommended. Systemic flurbiprofen and topical ketoprofen are NSAIDS that act by inhibiting PGE2. Bisphosphonates modulates the osteoclast function, and subantimicrobial dose doxycycline uses the anticollagenase properties of tetracycline (TC), which is lone permitted drug by FDA. Future prospect lies for chemically modified tetracycline (CMT's), bone resorption uncouplers, anti cytokine drugs, antimetabolites, and lipoxins (LXs). This provides clinician with supplementary equipment to conventional mechanical debridement, which could improve and make the clinical therapeutic outcome more predictable, in a susceptible host. 9 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 upon wound healing but also to stimulate regeneration of lost bone, periodontal ligament, and cementum, restoring the complete periodontal attachment apparatus. These have included enamel matrix proteins (Emdogain), bone morphogenetic proteins (BMP-2 and BMP-7), growth factors (platelet-derived growth factor and insulin-like growth factor), and tetracyclines. The only host modulatory agent currently approved by the FDA for adjunctive use during surgery is Emdogain.

4 v. Chemically Modified Tetracyclines

Tetracyclines were first introduced in 1948 and were soon recognized as highly effective against Rickettsiae, several Gram-positive and Gram-negative bacteria, and other organisms. These nonantibiotic tetracyclines analogs are nothing but the tetracycline molecules which have been modified to eliminate the antimicrobial property, but retain the host modulatory, anticollagenolytic property. Furthermore, these drugs, known as broad spectrum antibiotics. 15 Chemically Modified Tetracyclines are used as Host Modulating agents in the management of periodontitis by inhibition of Matrix Metalloproteinases, inhibition of proinflammatory cytokines, inducible nitric oxide synthase (iNOS) and inhibition of bone resorption, enhancement of the attachment of fibroblasts and connective tissues to the tooth surface. 16 The anti-Matrix Metalloproteinases actions of Chemically Modified Tetracyclines include direct inhibition of the active MMPs by the virtue of Ca2+ and Zn2+-binding sites, inhibition of reactive oxygen species-mediated activation of pro-MMPs, proteolysis of pro-MMPs into enzymatically inactive fragments, protection of ?-1 proteinase inhibitor from MMPs, reduction in the activity of serine proteinases. Polymorphonuclear leucocytes (PMNs) provide the major source of collagenases that mediate the connective tissue breakdown during inflammatory periodontal disease, while the fibroblasts contribute the collagenase required for connective tissue remodeling in normal gingiva. The anti-collagenase activity of CMTs is specific against the collagenase produced from neutrophils but not the fibroblasts. 16 a) SDD-Sub antimicrobial dose of Doxycycline SDD is the only systemic host response modulator specifically indicated as adjunctive treatment for periodontitis and it is approved by USFDA and UK medicines and health care products regulatory agency. It is marketed as periostat, 20mg dose of doxycycline hyclate BD for 3-9 months has the ability to down

regulate MMPs. 17 Mechanism of Action. 11 1. In junctional epithelium inhibition of production of epithelial derived MMPs by inhibiting cellular expression and synthesis.

5 In connective tissue -Direct inhibition of active

MMPs by cation chelation Inhibition of oxidative activation of latent MMPs, down regulates the expression of key inflammatory cytokines including interleukin IL1,IL6, and tumor necrosis factor (TNF)?, as well as prostaglandin E2 (PGE2)Scavenges and inhibits production of reactive oxygen species (ROS) produced by PMNs (e.g. HOCl, which activates latent MMPs),Inhibition of MMPs and ROS protects ?1 proteinase inhibitor (?1PI) thereby indirectly reducing tissue proteinase activity, Stimulates fibroblast collagen production. 3. Alveolar bone-Reduces osteoclast activity and bone resorption, blocks osteoclast MMPs, Stimulates osteoblast activity and bone formation. Crout et al. 1996 -In a study of 14 patients with chronic periodontitis, after removal of subgingival plaque and calculus, patients were randomised to receive either SDD for 2 months, then no drug for 2 months, then SDD for 2 months or placebo for 2 months, then no drug for 2 months, then placebo for 2 months SDD resulted in significantly improved probing depths and attachment levels compared with placebo, but did not affect plaque index or gingival inflammation. 18 Al-Shammari et al. 2001 -SDD was given to 12 patients with chronic periodontitis for 2 months following a course of subgingival instrumentation. Six patients were prescribed placebo. At baseline, months 1 and 2, GCF samples were collected and analysed for MMP-8, MMP-13 and ICTP (carboxyterminal peptide, a pyridinoline-containing fragment of type-1 collagen). The 2-month regime of SDD resulted in statistically significant reductions in GCF concentrations of ICTP, MMP-8 and MMP-13 compared with placebo. This was the first study that demonstrated in human subjects that SDD results in a simultaneous reduction of elevated MMP activity with a concomitant reduction in levels of collagen degradation fragments. SRP alone has no effect on GCF ICTP levels. 18 VI.

6 Bisphosphonates

The bisphosphonates are bone-seeking agents that inhibit bone resorption by disrupting osteoclast activity. 11

7 Mechanism of action

Bisphosphonates acts on osteoclast function at Tissue, Cellular and molecular levels 20 Pradeep AR et al. used Alendronate as local drug delivery as 1% gel and found that there is increase percentage of bone fill, decreased probing depth and clinical attachment level. 21 Other host modulatory agents

8 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. 22 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. 23 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. 24 VII.

9 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 periodontitis. 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 development 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.

Figure 1:

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