RESEARCH ARTICLE

HOST MODULATORY THERAPY: A TREATMENT CONCEPT

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ABSTRACT

Host Modulation Therapy (HMT) is a treatment concept that reduces tissue destruction and stabilizes or even regenerates inflammatory tissue by modifying host response factors. It has been used for treating osteoporosis and arthritis for several decades. However, its use in dentistry has also been reported. The objective of this article is to present a review of the various literatures available on HMT and also its role as adjunct therapy in periodontics.

Key words: Periodontal disease, Non-surgical periodontal therapy, Host modulatory therapy.

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INTRODUCTION

Periodontitis is defined as, ‘an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific micro-organisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both.’ Host Modulatory 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. 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 scaling and root planing and surgery (Newman et al., 10th edition).

Historical background

The concept of host modulation was first introduced to dentistry by Williams (1990) and Golub et al. (1992) and then expanded on by many other scholars in the dental profession. In 1992, Golub and colleagues discussed “host modulation with tetracyclines and their chemically modified analogues.” Host modulation therapy (HMT) is a means of treating the host side of the host-bacteria interaction. Host modulation therapy offers the opportunity for modulating or reducing this destruction by treating aspects of the chronic inflammatory response.

Specific aspects of disease pathogenesis for modulation include (Academy Report, 2002),

1. Regulation of Immune and Inflammatory responses
2. Regulation of excessive production of matrix metalloproteinases
3. Regulation of arachidonic acid metabolites
4. Regulation of bone metabolism.

A. Regulation of immune and inflammatory responses

Immunization methods

Microbial plaque is recognized as the primary etiologic agent for periodontal disease initiation and progression (Brahn et al., 1998). Antigens used for active immunization have included bacterial whole cells, outer components (e.g., P. gingivalis fimbriae), and synthetic peptides (Evans et al., 1992).

Regulating reactive oxygen species

Neutrophils and macrophages subsequently release mediators including reactive oxygen species, which are antagonistic to plaque biofilms, but which in excess may initiate inflammation (Wahl et al., 1994). 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

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inflammatory conditions (Szabo, 1995) with important physiological functions, which include cardiovascular, nervous system and immune homeostasis.

C. Regulation of arachidonic acid metabolites

Goodson and colleagues, found a tenfold elevation of PGE2 levels in diseased gingival tissues when compared with healthy gingiva excised around the third molars. In the early 1970s, prostaglandins began to be implicated in the bone resorption of several osteolytic diseases in addition to periodontal disease.

Modulation of arachidonic acid metabolites with nonsteroidal anti-inflammatory drugs (nsaids)

NSAIDs can suppress alveolar bone resorption suggests that the synthesis of AA metabolites may represent a critical regulatory pathway for potentially blocking periodontal disease progression. Nonsteroidal anti-inflammatory drugs include analgesics such as ibuprofen and aspirin with multiple levels of anti-inflammatory effects (Salvi and Lang, 2005). Since many molecules in eicosanoid metabolism are associated with proinflammatory roles, blocking the actions of the arachidonic acid cascade has been realized to be an effective means of blocking the inflammation (Alpdogan Kantarci et al., 2006).

D. Regulation of bone metabolism

Osteoclast precursors express RANK (a receptor of RANKL) which recognizes RANKL expressed by osteoblasts through cell–cell interaction and differentiate into osteoclasts in the presence of macrophage colony-stimulating factor (Toshiyuki Nagasawa et al., 2007). Osteoprotegerin, produced mainly by osteoblasts, is a soluble decoy receptor for RANKL. Osteoprotegerin blocks osteoclastogenesis by inhibiting the RANKL–RANK interaction. Mature osteoclasts also express RANK and RANKL supports the survival and stimulates the bone-resorbing activity of osteoclasts.

Fig. 1. Potential adjunctive therapeutic approaches possible (Newman et al., 10th edition)

Regulating cytokines

Host cytokines are a second group of inflammatory mediators highly implicated in periodontal disease and intensely investigated as potential chemotherapeutic targets. Cytokines implicated in suppression of the destructive inflammatory response include IL-4, IL-10, IL-11, and Transforming Growth Factor-β. Both IL-4 and IL-10 can target macrophages and inhibit the release of IL-1, TNF, reactive oxygen intermediates, and nitrous oxide (Hayflick et al., 1998).

A. Inhibitors of mmp

The role of inhibitors is particularly important because it is the imbalance between the activated MMP and their endogenous inhibitors that leads to pathological breakdown of extracellular matrix in diseases such as periodontitis, arthritis, cancer invasion, etc. The therapeutic significance lies in the blockade or retarding the proteolytic destruction of connective tissues. Which can be achieved by use of drugs that can –Inhibit synthesis and/or release of these enzymes, block the activation of precursor (latent) forms of these MMP, inhibit the activity of mature MMP, stimulate the synthesis of endogenous tissue inhibitors of MMP, protect the host endogenous inhibitors from proteolytic inactivation (Ryan and Golub, 2000). Inhibitors of matrixmetall oproteinases are either Endogenous or Exogenous (synthetic).

Endogenous Inhibitors

Regulation of MMP functions involves activation of endogenous tissue inhibitors of MMP (TIMP) and α2 macroglobulin which bind in a non-covalent fashion to members of the MMP family. TIMP control MMP activities pericellularly, whereas α2 macroglobulin functions as a regulator of MMPs in body fluids (Ryan and Golub, 2000).

Exogenous Inhibitors

a. Phosphorus containing peptides – are potent inhibitors of metalloproteinases produced by the substitution of a tetrahedral phosphorus atom for the carbonyl carbon atom in a peptide substrate.

b. Sulphur based inhibitors – These were prepared by replacing the scissile (O)=NH bond of the peptide with various sulphur containing functional groups.

c. Peptidyl hydroxamic acid derivative – These are capable of inhibiting MMPs 1,2,3,7,8 and 9 in vitro with very low levels at which collagenase activity declines by 50%.

Host modulatory agents

Host modulatory agents are systemically or locally delivered pharmaceuticals that are prescribed as a part of periodontal therapy and are used as adjuncts to conventional periodontal treatments. Systemically administered agents are Nonsteroidal Antiinflammatory Drugs (NSAIDs), Bisphosphonates and Subantimicrobial Dose Doxycycline and locally administered agents are Nonsteroidal Antiinflammatory drugs (NSAIDs), tetracyclines, triclosan, enamel matrix proteins, growth factors and bone morphogenic proteins (Newman et al., 10th edition).

Non steroidal anti inflammatory drugs

NSAIDs can be both systemically and locally administered host modulatory agent. The basic rationale behind the use of NSAIDs is to block the arachidonic acid metabolites that are proinflammatory mediators implicated in a variety of bone resorptive and tissue degrading processes NSAIDs inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonic acid metabolism. They are used to used to reduce tissue inflammation and pain, and are indicated in a variety of chronic inflammatory diseases (Philip and Preshaw, 2008).
Side effects of nsaids

Associated with significant side effects are gastrointestinal problems, hemorrhage (from decreased platelet aggregation), renal and hepatic impairment (Newman et al., 10th edition). 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" (Williams et al., 1991).

Bisphosphonates

Bisphosphonates are 'bone-sparing' agents used in the management of various diseases with bone resorption. These compounds inhibit osteoclastic activity by blocking acidification by local release and represent a class of chemical structures related to pyrophosphate (Alpdogan Kantarci et al., 2006).

Bisphosphonate mechanism of action

Bisphosphonates inhibit bone resorption mainly on account of their effects on osteoclasts. Bisphosphonates mediate inhibition of the development of osteoclasts. Induce osteoclastic apoptosis, reduce the activity and prevent the development of osteoclasts from haematopoietic precursors, stimulate the production of an osteoclast inhibitory factor, inhibit matrix metalloproteinase enzyme (Newman et al., 10th edition).

Tetracyclines

Tetracyclines are the examples of agents with multiple matrix metalloproteinase targets. The ability of tetracyclines and doxycycline, in particular, to inhibit MMP activity was first identified in the early 1980s Golub et al. 1983. Tetracyclines have nonantimicrobial properties that appear to modulate host response.

Two therapeutic strategies based on the host modulating properties of tetracyclines are currently being developed:

1. The use of subantimicrobial dose doxycycline (the most potent anticollegenase of commercially available tetracyclines) formulations, which do not appear to result in tetracycline side effects.
2. The production of a family of chemically modified tetracyclines that have lost their anti-microbial activity but have retained their anti-collagenase activity.

Doxycycline: The lipophilic semi-synthetic tetracyclines, doxycycline and minocycline appeared more effective than tetracycline in reducing the collagenase activity in the gingival crevicular fluid. Doxycycline possesses the ability to downregulate MMP activity.

Subantimicrobial Dose Doxycycline

Subantimicrobial dose doxycycline remains, at present, the only systemic host response modulator specifically indicated as an adjunctive treatment for periodontitis. It is a 20-mg dose of doxycycline hyclate that is taken twice daily for periods of 3–9 months as an adjunct to root surface instrumentation in the treatment of periodontitis. The rationale for using doxycycline at subantimicrobial doses as a host response modulator is that it inhibits the activity of MMPs by a variety of synergistic mechanisms.

Chemically Modified Tetracyclines (CMTS)

In 1987, Golub et al. described a new use for the first chemically modified tetracycline (4-dimethylamino tetracycline or chemically modified tetracycline-1), which is devoid of antibacterial activity due to the removal of the dimethylamo group from the carbon-4 position of the "A" ring of the drug molecule, but which retains its anticollegenase activity (Golub et al., 1987). A series of 10 different chemically modified tetracyclines have since been identified, called chemically modified tetracyclines 1-10, nine of which were found to retain their anticollegenase but to have lost their antimicrobial properties.

Triclosan

Triclosan is a broad spectrum (bacteria, fungi, and viruses) bacteriostatic germicide, which can become bactericidal at high concentrations. Triclosan (2,4,4',-trichloro-2'-hydroxydiphenylether) is a well-known and widely used nonionic antibacterial agent which has recently been introduced in toothpastes and mouthrinses. Triclosan has the ability to inhibit both the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism (Gaffar et al., 1995).

Enamel Matrix Proteins

Enamel matrix proteins mainly amelogenin, are secreted by Hertwig’s epithelial root sheath during tooth development and induce acellular cementum formation. Based on these observations, these proteins are believed to favor periodontal regeneration.

Fibroblast Growth Factors (FGF)

There are nine different forms (isoforms) of this peptide, each with its own gene. The two major forms are FGF (acidic: aFGF) and FGF (basic: bFGF), each with quite different biological effects. FGF is also a potent inducer of angiogenesis and originally there was an 'angiogenic growth factor' described; this is now known to be the same molecule as bFGF. It was found that the effect of exogenous bFGF on skeletal muscle was negligible because of the endogenous growth factor in the vicinity of the lesion (John McGeechie and Marc Tennant, 1997).

Transforming growth factors

Transforming growth factor (TGF) occurs in at least six of the beta forms and a number of others in the alpha form, each with different properties. Its role in bone formation, either in embryonic osteogenesis or bone repair, is associated with the interaction between osteoblastic and osteoclastic activity.

Insulin like Growth Factors (IGF)

The term insulin like growth factor is used to describe growth-promoting activities that share structural homology with proinsulin. There are two different insulin like growth factors; insulin like growth factor -1 and insulin like growth factor-2. Insulin like growth factor-1 and insulin like growth factor-2 are independently regulated although they are functionally similar.
Bone Morphogenetic Proteins (BMPs)

Bone matrix is known to contain a large number of growth factors. These factors include basic and acidic fibroblast growth factor (bFGF, aFGF), insulin like growth factor-I and II, transforming growth factor beta (TGFβs), platelet derived growth factor (PDGFs), and bone morphogenetic proteins (BMPs) (Moon IL Cho et al., 1995). Bone morphogenetic proteins (BMPs) represent a unique set of differentiation factors that induce new bone formation at the sight of implantation instead of changing the growth rate of pre-existing bone.

Application for BMPs in dental and periodontal repair

The BMPs comprise a family of proteins with a unique activity, the ability to induce the formation of cartilage and bone tissues when implanted into a soft tissue site. Recombinant human bone morphogenetic protein-2 (rhBMP-2) may have tremendous therapeutic potential in dental and periodontal reconstruction.

Periodontal Vaccines

The concept that vaccination against periodontal pathogens can confer protection against periodontitis was first demonstrated in proof-of-principle rodent studies where whole bacterial cells or sonicates there of (e.g. P. gingivalis or E. corrodens) were used as immunogens. Subunit vaccine approaches have so far concentrated mainly on P. gingivalis virulence proteins, particularly its cysteine proteinases, as well as the fimbriae of both P. gingivalis and A. Actinomycetemcomitans (Moon IL Cho et al., 1995).

Anticytokine Drugs

Anticytokine therapy for periodontal diseases especially targets proinflammatory cytokines, that is, TNF-α, IL-1, and IL-6, because these are essential for the initiation of the inflammatory immune reaction and are produced for prolonged periods in periodontitis. This therapy aims to bind the cytokines with the receptors present on target cells such as the fibroblasts. This new therapy can act as a host response modulator in the control of inflammatory diseases of gums and may provide the basis for new molecular therapeutic approaches to the treatment of periodontitis (Yogesh Prakash Waykole et al., 2009).

Infliximab (Remicade) TNF-α is a special target molecule known for its neutralizing properties, therapeutics. Anti-TNF-α antibodies have effectively attenuated or prevented inflammation of arthritis in experiment models. Infliximab is a chimeric IgG monoclonal antibody.

Etanercept (Enbrel) TNF-α can also be neutralized with genetically engineered sTNF-α-RII. Etanercept (enbrel) is a fusion protein. It links human soluble TNF receptor to the Fc component of human IgG1.

Anakinra (Kineret)

It is an interleukin-1 (IL-1) receptor antagonist. It competitively inhibits the binding of IL-1 to the Interleukin-1 type receptor. Anakinra blocks the biological activity of naturally occurring IL-1, including inflammation and cartilage degradation (Yogesh Prakash Waykole et al., 2009).

Conclusion

The conventional methods aim at controlling one of the etiological factors. The best chance for clinical improvement may come from implementing complementary treatment strategies that target different aspects of the Periodontal Balance. The combination of reduction of bacterial load, risk factor modification and host response modification can lead to better clinical outcome as compared to conventional treatment modalities alone. However, this concept needs to be validated further in controlled clinical trials. As new mediators and pathways of periodontal tissue destruction are identified, so will new host modulating strategies for blocking tissue destruction evolve, which will lead to bright future of dental healthcare.

REFERENCES


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