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Host modulation therapy: A review

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Abstract

Periodontitis is a multi-factorial disease. The periodontal tissue destruction is a result of both microbial activity as well as host response. 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. This has led to the emergence of the field of "Perioceutics" i.e. the use of pharmacotherapeutic agents including antimicrobial therapy as well as host modulatory therapy for the management of periodontitis. Host modulation therapy 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. This review article discussed the host-modulation and role of various systemically and locally delivered host modulation agents.

Keywords: Host modulation, Nonsteroidal anti-inflammatory drugs, Perioceutics, Bisphosphonate, Tetracycline, Matrix Metalloproteinases.

Introduction

Chronic periodontitis has been defined as "an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss and bone loss." The progression of the disease and destruction of periodontal tissues is due to series of complex interactions between micro biota and host immune responses. Host immune-inflammatory response in the periodontal tissues characterized by the production of inflammatory cytokines., Environmental, genetic and acquired risk factors can accentuate the host inflammatory response and create an imbalance between the pro inflammatory and anti inflammatory activities in the periodontal tissues that result in the tissue destruction.9The host immune inflammatory response against bacterial plaque is protective by intent, yet in susceptible patients who exhibit exaggerated inflammatory response to plaque. It is ultimately responsible for perpetuating destruction of

periodontium.8Host modulation therapy 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 concept of host modulation was first introduced to dentistry by Williams in 1990 and Golub et al in 1992 .HMT's are systemically or locally delivered pharmaceuticals that are prescribed as a part of periodontal therapy and are used as adjuncts to conventional periodontal treatments, such as scaling and root planning (SRP) and surgery.9

Potential Targets of Host Modulation Therapy: [5]

- Matrix metalloproteinases: eg. TIMPs, Tetracylines
- Arachidonic acid metabolites: eg. NSAIDs
- Bone metabolism:eg. Bisphosphonates
- Pro-inflammatory Cytokines: eg. blockade of receptors for IL-1, TNF
- Other inflammatory mediators such as Nitric oxide (NOS) syntase activity (eg. mercapto ethyl guanidine),Nuclear factor kappa β, Endothelial cell adhesion molecules, Disruption of cell signaling pathways such as RANK /RANKL /osteoprotegerin axis.

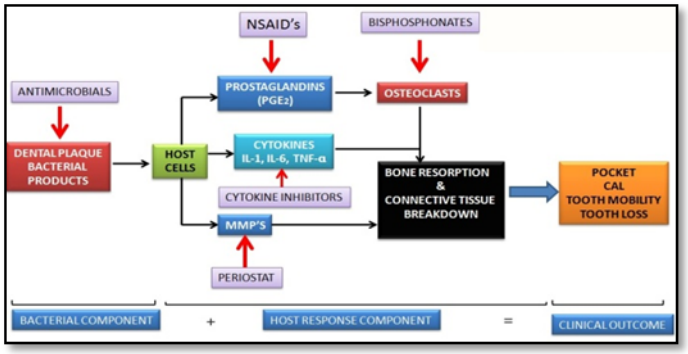

Figure1: Potential adjunctive therapeutic approaches

Classification of The Host Modulating Agents: Carranza, Newman, Takei, Klokkevold (2009)Error! Bookmark not defined.

Systemically administered agents: NSAIDs, Bisphophonates, Sub antimicrobial-dose doxycycline (SDD).

Locally administerd agents : NSAIDs, Enamel matrix proteins (EMP), Growth factors, Bone morphogenic proteins (BMPs)

Host Modulatory Therapy

Modulation of Host Matrix Metalloproteinases

MMPs are enzymes which belong to the family of zinc and calcium dependent endopeptidases secreted or released by a variety of host cells such as polymorph nuclear leucocytes, macrophages, fibroblasts, bone, epithelial and endothelial cells found in periodontium.[i]MMPs function at neutral pH to degrade various constituents of extracellular matrix (e.g. collagen, gelatin, laminin, fibronectin & proteoglycan) as their substrate.[1]This imbalance between the activated MMP and their endogenous inhibitors that leads to pathological breakdown of extracellular matrix in diseases such as periodontitis, arthritis and cancer invasion etc.This rationale has led to the development of number of synthetic MMP inhibitors.

Inhibitors of MMPs are either

A. **Endogenous eg.** α_2 macroglobulin, Tissue inhibitors of MMP (TIMP)
B. **Exogenous (synthetic)** eg. Tetracycline, CMT,SDD

A. Endogenous Inhibitors: Regulation of MMP functions involves activation of endogenous α_2 macroglobulin and tissue inhibitors of MMP (TIMP) which bind in a non-covalent fashion to members of the MMP family.

α2 macroglobulin: functions as a regulator of MMPs in body fluids. During inflammation, α2 macroglobulin, which is a high molecular protein, may escape vasculature

and also function on the extra cellular matrix.[i2] α2 - macroglobulins, particularly α2-M play an important role in the regulation of MMP activity at bond cleavage region.

Tissue inhibitors of MMP (TIMP)

The inhibitory activity of TIMP-1 was discovered in the early 1970s in the form of a collagens inhibitor in the media of cultured human skin fibroblasts[2], human serum[3], and in extracts of bovine cartilage and aorta.[4] It was later designated "tissue inhibitor of metalloproteinases" as it inhibited not only collagenases, but also gelatinases and proteoglycanase (now called matrix metalloproteinase 3)[5]. In addition TIMPs have various biological activities such as promoting cell proliferation, anti-angiogenic, pro- and anti-apoptotic and synaptic plasticity activities, many of which are independent of metalloprotease inhabitation.[17]

B. B.Exogenous Inhibitors: Zn2+ and Ca2+ chelating agents (EDTA and 1, 10 Phenanthroline) are potent inhibitors of MMP enzyme activity in vitro but are toxic and not used in vivo as therapeutic agents. Multiple synthetic peptides have been formulated to synthesize more specific chelators such as Phosphorus containing peptides, Sulphur based inhibitors and Peptidyl hydroxamic acid derivative.

- **Tetracyclines:** The tetracycline analogues are currently the only MMP inhibitors approved by the US Food and Drug Administration to be used clinically and are the only proteinase inhibitors that have been clinically tested in humans for efficacy in periodontal therapy. The ability of tetracyclines and doxycycline, in particular, to inhibit MMP activity was first identified in the early 1980s **(Golub et al. 1983)**.[6]

Two therapeutic strategies based on the host modulating properties of tetracycline's are currently being developed:

1. Doxycycline

Research focused on doxycycline, as it possesses the most potent anticollagenase properties of commercially available tetracycline's. Doxycycline has a much lower inhibitory concentration (IC_{50}=15 μM) than minocycline (IC_{50}=190 μM) or tetracycline (IC_{50}= 350 μM), indicating that a much lower dose of doxycycline is necessary to reduce a given collagenase level by 50% compared with minocycline or tetracycline.[7]

A major concern, however, was that the long-term administration of doxycycline might be associated with the development of antibiotic resistance. Indeed, when antibiotic doses of tetracycline (250 mg daily for 2–7 years) had previously been given to patients with refractory periodontitis, up to 77% of the patients cultivable subgingival microflora exhibited tetracycline resistance**. (Kornman & Karl 1982)**[8]In light of this concern, a low, SDD (Sub antimicrobial Dose of Doxycycline) preparation was introduced, containing 20 mg doxycycline, as opposed to the 50 or 100 mg dose that is available for antibiotic purposes **(Golub et al 1990)**.[9]One of the preliminary experiments to be conducted with this new formulation demonstrated clearly that SDD (20 mg twice daily) administered for just 2 weeks inhibited collagenase activity by 60–80% in the

gingival tissues of patients with chronic periodontitis.[10]Subsequent studies of relatively short duration (1–3 months) indicated that this dosing regimen could prevent periodontitis progression without the emergence of doxycycline-resistant microorganisms or other typical antibiotic side- effects.[11]Thus, the concept was born that SDD could be used as an adjunct for treatment of chronic periodontitis.

Sub antimicrobial Dose Doxycycline (SDD)

SDD at present, the only systemic host response modulator is approved by the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency, and by similar agencies in other countries throughout the world, and was introduced under the trade name Periostat (CollaGenex Pharmaceuticals Inc., Newtown, PA). 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 SDD as a host response modulator is that it inhibits the activity of MMPs by a variety of synergistic mechanisms independent of any antibiotic properties like

- Direct inhibition of active MMPs by cation chelation (dependent on Ca2+- and Zn2+-binding properties)
- Inhibits oxidative activation of latent MMPs (independent of cation-binding properties)
- Downregulates expression of key inflammatory cytokines (interleukin-1, interleukin-6 and tumor necrosis factor-α) and prostaglandin E2
- Scavenges and inhibits production of reactive oxygen species produced by Neutrophils
- Inhibits MMPs and reactive oxygen species thereby protecting a1-proteinase inhibitor, and thus indirectly reducing tissue proteinase activity
- Stimulates fibroblast collagen production
- Reduces osteoclast activity and bone resorption
- Inhibits osteoclast MMPs[12]

The results have been positive with tetracycline analogues with fewer side effects. Further studies are required to establish MMP modulators as therapeutic interventions in periodontal disease.

1.**Chemically modified tetracycline's (CMTs)**

In 1987, Golub et al[24] described a new use for the first CMT (4-dedimethylamino tetracycline or CMT-1), which is devoid of antibacterial activity due to the removal of the dimethylamino group from the carbon-4 position of the "A" ring of the drug molecule, but which retains its anticollagenase activity. A series of 10 different chemically modified tetracyclines have since been identified, called chemically modified tetracycline's 1-10, nine of which were found to retain their anticollagenase but to have lost their antimicrobial properties. The one chemically modified tetracycline found to have lost its anti-collagen's property was chemically modified tetracycline-5. Certain CMTs have advantages over commercially available tetracycline's because, they are absorbed more rapidly, can reach higher levels in the blood, have longer serum half-lives, more potent inhibitors of MMPs.

A significant advantage of the low-dose doxycycline and the CMTs, is that both regimens lack antimicrobial

efficacy and can be administered for long periods of time (such as 18 months) without the emergence of antibiotic resistant microorganisms. Therapeutically observations indicate that anti-microbial regimens of tetracyclines may be required for successful use of these drugs in localized aggressive periodontitis.

Marimastat and Batimstat

Batimastat (BB-94) and marimastat (BB-2516) are synthetic, low-molecular weight MMP inhibitors. They have a collagen-mimicking hydroxamate structure, which facilitates chelation of the zinc ion in the active site of the MMPs. Batimastat was the first synthetic MMP inhibitor studied in humans with advanced malignancies, but its usefulness has been limited by extremely poor water solubility, which required intraperitoneal administration of the drug as a detergent emulsion. Marimastat belongs to a second generation of MMP inhibitors. In contrast to batimastat, marimastat is orally available. Both of these agents are currently in Phase I/II trials in US, Europe and Canada.[13]

Modulation of Arachidonic Acid Metabolites: Over decades, arachidonic acid metabolites have been established as mediators of tissue destruction in various inflammatory diseases including rheumatoid arthritis and periodontal diseases **(Offenbacher et al 1993, O'Dell 2004).**[14]

Modulation of arachidonic acid metabolites can be done with

1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

The fact that 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. These compounds block platelet activity through thromboxane inhibition, inhibit cyclooxygenase, and prevent the production of arachidonic acid metabolites. Based on this principle, several drugs have been developed to arrest or modify inflammation by blocking the enzymatic pathways that lead to the generation of lipid mediators, including flurbiprofen, meclofenamate, ibuprofen, ketorolac, naproxen and aspirin, administered systemically or locally.

Role of NSAIDs in the control of periodontal disease progression

NSAIDs inhibit the formation of prostaglandins (PGE2), which is produced by Neutrophils, macrophages, fibroblasts, and gingival epithelial cells in response to the presence of lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria. The majority of NSAIDs are weak organic acids that selectively (COX-2) and non-selectively (COX-1) inhibit the synthesis of Arachidonic acid metabolites, thereby blocking the production of prostaglandins, thromboxane and prostacyclin.

Vane and co-workers 1971[15]discovered that aspirin and other aspirin like drugs (NSAIDS) inhibited the products of arachidonic acid metabolism. Much of the research of NSAIDS has concentrated on three major groups. They are:

- Pyrazolone compounds - indomethacin, phenyl butazone and tolmetin.
- Phenylpropionic acid derivatives - ibuprofen, fenoprofen, ketoprofen, flurbiprofen and naproxen.
- Oxicams - Specifically piroxicam.

The evidence available so far those NSAIDs can inhibit the periodontal disease process has come from animal

model studies using both ligature induced and naturally occurring periodontal disease. There have also been studies in humans indicating that NSAIDS may reduce periodontal disease process.[16]

Side effects of NSAIDs

- **Rebound effect:** 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.[17]
- Gastrointestinal problems
- Hemorrhage (from decreased platelet aggregation).
- Renal and hepatic impairment.

2. Triclosan

Triclosan has the ability to inhibit both the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism.[18]Triclosan is a broad spectrum (bacteria, fungi, and viruses) bacteriostatic germicide, which can become bactericidal at high concentrations. Its activity depends on the concentration and on the formulation.[19]Several studies have demonstrated that triclosan, the lipid soluble compound added to toothpastes and mouthrinses for its antibacterial properties, also may act as an anti-inflammatory agent.

3. Omega3 fatty acid

The administration of ω-3 PUFAs demonstrated an increased level of circulating resolvins.[20]The prevention and treatment of periodontitis with resolvins and lipoxins were described in animal studies.[21]These molecules are not available for human use; however, dietary supplementation with ω-3 PUFAs in humans is known to increase the circulating level of resolvins which suggests a potential therapeutic modality.

Vardar et al (2005) evaluated the use of omega3 fatty acids with the purpose of blocking arachidonic acid cascade in induced periodontal disease in rats. The authors also combined omega3 fatty acid with celecoxib, looking for a synergism of the antiinflammatory effects of these two agents. The associated therapy resulted in significant superior reductions on periodontal tissue levels of prostaglandins, leukotriene B4, and platelet activating factor, which is also a proinflammatory mediator.[22]

Modulation Of Host Cytokines

Host cytokines are a group of inflammatory mediators highly implicated in periodontal disease and intensely investigated as potential chemotherapeutic targets. These cytokines are present in diseased periodontal tissues and gingival crevicular fluid (GCF)[23].

The catabolic activities of these cytokines are controlled by endogenous inhibitors that include IL-1 and TNF receptor antagonists. The use of cytokine receptor antagonists to inhibit periodontal disease progression has been investigated in a ligature induced periodontitis non-human primate model.[24.] It was demonstrated that IL-1/TNF blockers partially inhibited disease progression.[25] However, the use of cytokine antagonists to treat human periodontal disease needs to be evaluated.

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. IL-4 also induces programmed cell death (apoptosis), which reduces the number of infiltrating inflammatory macrophages.[26] It can also up regulate the production of IL-1 receptor antagonists.[27]The evidence that IL-4 is deficient in diseased periodontal tissues[28]and the finding that exogenous IL-4 administration in experimental arthritis reduces inflammation,[29] suggest that use of this cytokine may provide a therapeutic benefit in the treatment of periodontal diseases.

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. Thus, gene transfer of TNF antagonists may offer a more efficient mode of delivery of disease-controlling agents to the periodontal structures.

Anticytokine Drugs

Anticytokine therapy for periodontal diseases especially targets proinflammatory cytokines, that is, TNF-α, IL-1β, and IL-6[30]this therapy aims to bind the cytokines with the receptors present on target cells such as the fibroblasts. The three basic treatment strategies are:

- Neutralization of cytokines,
- Blockage of cytokine receptors, and
- Activation of anti-inflammatory pathways, such as, immune-suppressive pathways.

Infliximab (Remicade)

Infliximab is a chimeric IgG monoclonal antibody. It works by binding to TNF-α. TNF-α is a chemical messenger (cytokine) and a key part of auto-immune reaction. It seems to work by preventing TNF-α from binding to its receptor in the cell.[41]

Etanercept (Enbrel)

It is a biopharmaceutical that treats autoimmune diseases by interfering with tumor necrosis factor. Etanercept (enbrel) is a fusion protein. It links human soluble TNF receptor to the Fc component of human IgG1 antibody. [41]

Anakinra (Kineret)

Anakinra competitively inhibits the binding of IL-1 to the IL-1 type receptor. It blocks the biological activity of naturally occurring IL-1, including inflammation and cartilage degradation.The researchers applied exogenous sIL-1RI and sTNF-RII to the gingival tissues of non-human primates with experimental periodontitis and found inhibition of inflammatory cell infiltration, alveolar bone loss and loss of tissue attachment.[41]

Currently, anticytokine therapy using **anti-IL-1** or **anti-TNF-α monoclonal antibodies** and **soluble TNFreceptors** have been approved for the treatment of rheumatoid arthritis, crohn's disease, juvenile arthritis and psoriatic arthritis with research continuing on periodontal disease.[31]

There are certain pharmacological agents with potential host modulation action such as Recombinant human interleukin-11 (rhIL-11), Cytokine suppressive anti-

inflammatory drugs (CSAIDS) / p38 inhibitors, JNK inhibitors and Resolvins; but more studies are yet required toward their therapeutic use in treatment of periodontal diseases.

Regulation of Bone Remodeling

It has long been accepted that bone formation and bone resorption are processes that are "coupled," although periodically there is evidence suggesting they can act independently. This coupling process entails that osteoclasts resorb an area of bone, and osteoblasts are signalled to come in and replace the lost bone. There are 2 molecules considered essential and sufficient to support osteoclastogenesis:

A. **Macrophage colony stimulating factor (M-CSF)** was one of the earliest signalling molecules identified to play a role in osteoclast development and activation. M-CSF is produced mainly by osteoblasts or bone marrow stromal cells and binds to a receptor on pre-osteoclasts known as cFMS, a member of the tyrosine kinase receptor super family. The binding of M-CSF to cFMS results in the activation of several transcription factors, which ultimately results in the initiation of osteoclastogenesis.[32]

B. **Receptor Activator of Nuclear Factor kappa B Ligand (RANKL)** is a key mediator in the process of osteoclast formation. This membrane-bound protein is a member of TNF super family and is expressed by a variety of cells, including osteoblasts, fibroblasts and T-cells. The binding of RANKL to its receptor RANK on the surface of pre-osteoblasts results in the activation of terminal kinase and the subsequent activation of nuclear factor-kappaB, leading to osteoclast formation. The production of RANKL is regulated in response to the presence of inflammatory cytokines such as TNF-α and IL-1.A number of studies has confirmed a role for RANKL in periodontal bone resorption. Elevated expression of RANKL has been noted in inflamed periodontal tissues.[49]

Osteoprotegerin (OPG) is a natural inhibitor of RANKL. It is a soluble TNF receptor-like molecule that acts as a decoy and blocks the binding of RANKL to RANK and thus prevents osteoclastogenesis. Hence, it has been suggested that the balance between RANKL levels and osteoprotegerin levels regulates the bone destruction observed in periodontitis.[49]

Based on these pre-clinical animal studies and on preliminary human clinical studies, the osteoprotegerin (RANK), RANKL axis is a new target for the treatment of destructive periodontal disease. Further studies are necessary to determine the most efficacious therapeutic approach on this molecular interaction.

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.**Error! Bookmark not defined.** Bisphosphonates are structurally similar to pyrophosphate, which is a normal product of human metabolism present in serum and urine that has calcium chelating properties. If a carbon atom replaces the linking

oxygen atom in the pyrophosphatase molecule, a bispophanate is formed. These analogues are completely resistant to enzymatic hydrolysis and are extremely stable from a chemical perspective. Like pyrophosphate, bisphosphanates bind to the hydroxyapatite crystals of

bone and prevent both their growth and dissolution.**Error! Bookmark not defined.**

Classification

A. According to the nature of side chains, bisphosphonates are divided into-

- **First generation** – Alkyl side chains (e.g. Etidronate)
- **Second generation** –Aminobisphosphonates with an amino-terminal group (e.g. Alendronate and Pamidronate)
- **Third generation** - cyclic side chains (e.g. Risedronate)

The anti-resorptive property of bisphosphonates increases approximately 10-fold between generations.**Error! Bookmark not defined.**

B. On their basis of their effects on macrophages, bisphosphonates can be sub grouped into -

- **Aminobisphonates** – which sensitize macrophages to an inflammatory stimulus, inducing an acute-phase response.
- **Nonaminobisphosphonates** - which can be metabolized by macrophages and which may inhibit the inflammatory response of macrophages.**Error! Bookmark not defined.**

Several in vivo studies have demonstrated an acute-phase reaction after the first administration of aminobisphosphonates, with a significant increase in the main proinflammatory cytokines. However, nonaminobisphosphonates seem to have anti-inflammatory activity caused by the inhibition of the release of inflammatory mediators from activated macrophages, such as IL-6, tumor necrosis factor-α and IL-1β.[33,34]

Bisphosphonate Mechanism of Action

1. Bisphosphonates inhibit bone resorption mainly on account of their effects on osteoclasts.
2. Bisphosphonates mediate inhibition of the development of osteoclasts.
3. Induce osteoclastic apoptosis.
4. Reduce the activity and prevent the development of osteoclasts from hematopoietic precursors.
5. Stimulate the production of an osteoclast inhibitory factor.
6. Inhibit matrix metalloproteinase enzyme.**Error! Bookmark not defined.**

It has been shown that the bisphosphonate Alendronate caused a rise in intracellular calcium in an osteoclast. This may suggest presence of receptor for bisphosphonates on osteoclasts. Several animal studies have examined the effects of local or systemic bisphosphonate delivery on alveolar bone resorption by using the experimental periodontitis model with the observation period in different studies ranged between 7 days to 25 weeks. They have reported significant reduction in bone density changes by using Alendronate, however they did not find changes in clinical parameters (Schweitzer et al1995).[35]

Palmo L et al (2007)[36] in a review of bisphosphonate therapy stated that bisphosphonate drugs used for systemic bone loss affect the maxilla and mandible. Alveolar bone loss in periodontitis and skeletal bone loss share common mechanisms. In fact,

periodontal therapy using bisphosphonates to modulate host response to bacterial insult may develop into a potential strategy in populations in which periodontal therapy is not convenient. Developing bisphosphonates to

slow the progression of periodontal disease depends on identifying an effective dosage regimen and delivery system that would reach the target site in the periodontium, while limiting unwanted side effects. Therefore, the use of bisphosphonate to prevent and/or treat periodontitis must be considered very carefully at this time.

Bisphosphonates: Uses

1. **Osteoporosis -** Alendronate and etidronate have been approved in many countries and have been shown to increase bone mass and reduce fracture rates at the spine, hip and other osseous sites in postmenopausal women.
2. Treatment of **Pagets disease**
3. Treatment of **tumour-induced hypercalcemia** - These can decrease hypercalcaemia of malignancy, normalising calcium concentrations within 48 hrs of administration and the subsequent risk of pathological or tumour related fractures.
4. **Pain alleviation** - They are used as inhibitors of osteoclast activity to alleviate bone pain that results from the release of bio-chemical mediators in metastatic disease.[48]

Potential drawbacks

1. Some of these agents have unwanted effects of inhibiting bone calcification and inducing changes in white blood cell counts.
2. Long term bisphosphonate therapy leads to Avascular jaw necrosis.

Contraindications

1. Sensitivity to phosphates
2. Gastro intestinal upset

Metformin

The use of metformin, an Antidiabetic agent, is associated with a reduced risk of fractures in patients with diabetes, suggesting that metformin exerts a beneficial effect on bone tissues. Bak EJ et al (2010) conducted a study to assess the effect of metformin on alveolar bone loss in ligature-induced periodontitis. The metformin treatment induced a significant reduction in alveolar bone loss. With regards to osteoblast differentiation, metformin augmented the mineralization of MC3T3-E1 cells approximately two-fold over the non-treated cells.[37]

Modulation of Nitric Oxide Synthase

Nitric oxide (NO) is a free radical which is produced at high and prolonged concentrations in response to pro-inflammatory stimuli.

Inhibition of NO

The pharmacological inhibition of NO synthases with mercaptoalkylguanidine is associated with decreased inflammation, depressed hemorrhagic shock and lower arthritis scores in animal models.**Error! Bookmark not defined.**A study utilizing a ligature induced periodontitis rat model demonstrated that administration of an NO inhibitor (mercaptoethylguanidine) resulted in decreased bone loss. **Lohinai et al (2001)**[38] and **Lohinai et al (2003)** found a reduction of alveolar bone loss and gingival inflammation after the use of a selective iNOS inhibitor mercaptoethylguanidine confirming that NO has a deleterious role in the pathophysiology of periodontitis and that its modulation may prevent tissue destruction.

Locally Administerd Host Modulating Agents

A number of local host modulation agents are being investigated as adjuncts to surgical procedures, to improve 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

Enamel matrix proteins mainly amelogenin, are secreted by Hertwig's epithelial root sheath during tooth development and induce acellular cementum formation.

One enamel matrix protein derivative obtained from developing porcine teeth has been approved by U.S Food and Drug Administration (FDA) and marketed under trade name Emdogain. The basic rationale behind using Emdogain is that it will act as a tissue healing modulator that would mimic the events that occur during root development and help stimulate periodontal regeneration.[39,40,41]

1. Platelet derived growth factors

Platelet derived growth factor (PDGF), as a host modulating agent can increase chemotaxis of neutrophils and monocytes, stimulate fibroblasts proliferation and extracellular matrix synthesis, increase proliferation and differentiation of endothelial cells, stimulate proliferation of mesenchymal progenitor cells and differentiation of fibroblasts.[42]There are three known types (isoforms) of PDGF: AA, BB, and AB; each has a different structure.

FDA has approved Growth factor Enhanced Matrix, GEM 21S® (Osteohealth, Shirley, NY) which is a combination of a bioactive highly purified recombinant human PDGF-BB with an osteoconductive bone matrix.[43] **Nevins et al. (2005)** demonstrated that the purified rhPDGF-BB mixed with bone allograft results in robust periodontal regeneration in both Class II furcations and interproximal intrabony defects.[44]

2. Bone morphogenetic proteins (BMPs)

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. Other various applications for rhBMP-2 includes ridge augmentation or sinus elevation procedures to provide adequate bone stock for implant placement.

Absorbable collagen sponge (ACS) containing recombinant human BMP-2 has been approved for clinical use in certain oral surgery procedures, including localized alveolar ridge augmentation, under the name INFUSE® Bone Graft (Medtronic, Minneapolis, MN, USA) and InductOS™ (Wyeth, Maidenhead, UK). These ACS release the protein over time in the location where it is implanted and provides a scaffold on which new bone can grow. As the graft site heals, the ACS is absorbed and replaced by bone.[45]

3. Bisphosphonate

The bisphosphonates are bone seeking agents that inhibit bone resorption by disrupting

osteoclast activity, interfere with osteoblast metabolism and secretion of lysosomal enzymes.[46] More recent evidence has suggested that bisphosphonates also possess anticollagenase properties.[47]Some bisphosphonates have

the unwanted effects of inhibiting bone calcification and inducing changes in white blood cell counts. Also, there have been recent reports of avascular necrosis of the jaws following bisphosphonate therapy, with the resultant risk of bone necrosis following dental extractions. The recent reports of bisphosphonate related osteonecrosis of the jaw (BRONJ), although primarily associated with intravenous administration of bisphosphonates rather than oral administration, has impeded the development of bisphosphonates as an HMT to manage periodontitis.

At present there are no bisphosphonate drugs that are approved and indicated for treatment of periodontal diseases.

1. NSAIDs

Since NSAIDs are lipophilic and are well absorbed into gingival tissues, its topical application is possible. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine rinse and S-ketoprofen dentifrice[48], piroxicam**Error! Bookmark not defined.**and meclofenamic acid in inhibiting gingivitis and progression of periodontitis.

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 gastrointestinal adverse events than does treatment with non-selective NSAIDs. No NSAIDs yet approved for periodontal disease.

2. Hypochlorous Acid and Taurine-N-Monochloramine

These are the end-products of the neutrophilic respiratory burst, modulate the host inflammatory response by inhibiting the production of interleukin-6, prostaglandins, and other proinflammatory substances.

Recently, Lorenz et al. (2009) assessed the influence of 2 and 3% N-chlorotaurine mouth rinse on dental plaque and demonstrated that rinsing with 10 mL of the test solution two times daily for 4 days reduced the plaque vitality.

3. Cimetidine

Cimetidine is a powerful H2-(Histamine) receptor antagonist, and hence eliminates histamine's inhibitory effects on immune response, thereby acting as a modulator of inflammation and immunity by inhibiting neutrophil chemotaxis and superoxide production, increasing cyclic adenosine monophosphate (cAMP) levels and down-regulating cytokines. Hasturk et al. (2006) provided morphological and histological evidence to prove that topically active cimetidine is a potent inhibitor of P. gingivalis elicited periodontal inflammation and can arrest and/or prevent tissue destruction and influence cell populations present in the inflammatory cell infiltrate. [49]

Other Host Modulating Agents

Periodontal vaccines, probiotics and nutrients are discussed here as other host modulatory therapies.

Periodontal Vaccines

The concept that vaccination against periodontal pathogens can confer protection against periodontitis was first demonstrated in rodent studies where whole bacterial cells (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.[50]

Currently, besides the enterotoxin-based approaches, toll-like receptor agonists and synthetic analogues are key targets of the pharmaceutical industry for developing vaccine adjuvants to prevent infectious diseases or destroy tumors. As yet, there are no periodontal vaccine trials that have been successful in satisfying all requirements.

Probiotics

According to the WHO probiotics are defined as viable micro-organisms that confer health benefit when administered in sufficient doses.[51]Recently,**Teughels et al (2011)** explored the use of probiotics in influencing the periodontal microbiota and periodontal health by either direct microbiological interactions or by immunomodulatory interactions.[52]

Nutrients

The damage mediated by reactive oxygen species can be mitigated by antioxidants through three separate mechanisms namely:

- Scavengers of free radicals as they are formed.
- Sequestering transition metal ions.
- Catalyzing formation of other molecules

Major extracellular antioxidants include vitamin C, vitamin E, carotenoids, reduced glutathione and omega 3 fatty acids.

Conclusion

The concept of modulating host destructive pathways as a strategy for treating periodontal diseases has come a long way since the 1970s. Studies by a number of researchers and clinicians worldwide clearly demonstrate that blocking specific inflammatory mediators and/or enzymes can be efficacious in slowing periodontal disease progression. 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.

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