Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2017;6:1s:102-108.

Therapeutic Host Response Approaches to Treat Periodontal Diseases

Anshuman Gautam[1*] Barsha Priyadarshini[2] Sneha Suresh[3] Artika Sharma[4] Vijay Prakash[5] Abhinav Jain[6]

[1]Senior Lecturer, Department of Periodontology and Oral Implantology, Dr. B.R. Ambedkar Institute of Dental Sciences and Hospital Patna, India.
[2]Medical Officer, Boudh District, Odisha, India.
[3]Senior Lecturer, Department of Periodontology and Oral Implantology, Hazaribagh College of Dental Sciences and Hospital, Hazaribagh, India.
[4]Private Consultant, Firozpur, Punjab, India.
[5]Senior Lecturer, Department of Periodontology and Oral Implantology, Dr. B.R. Ambedkar Institute of Dental Sciences and Hospital Patna, India.
[6]Senior Lecturer, Department of Oral and Maxillofacial Surgery, Uttranchal Dental and Medical Research Institute, Dehradun, India.

ABSTRACT

Background: Periodontitis is one of the most common oral diseases and is characterized by gingival inflammation and alveolar bone resorption. It is caused by host immune responses to periodontal micro-organisms. The field of "perioceutics", or the use of pharmacological agents specifically developed to better manage periodontitis, is emerging to aid in the management of susceptible patients who develop periodontal disease. Host modulatory therapy, which can be used to bring down excessive levels of enzymes, cytokines, and prostanoids as well as modulate osteoclast function, is the key to addressing many of these risk factors that have adverse effects on the host response. Although, innumerable therapies are beginning to surface, a handful of these have true potential in clinical practice.

Keywords: periodontitis, host modulation, cytokines, inhibition, HMT.

INTRODUCTION

Periodontal disease initiation and progression occurs as a consequence of the host immune inflammatory response to oral pathogens. Periodontal pathogens produce harmful by-products and enzymes that break down extracellular matrices, such as collagen, as well as host cell membranes, in order to produce nutrients for their growth and possibly subsequent tissue invasion. The inflammatory infiltrate from the gingival tissue can initiate tissue and alveolar bone destruction through the activation of several pro-inflammatory cytokines, including interleukin-1β, tumor necrosis factor-α and interleukin-6. Within the diseased periodontal tissues, activated osteoclasts comprise an integral component of bone destruction.[1] Approaches to block the progression of inflammatory bone loss observed in periodontitis include host modulation of matrix metalloproteinase or the blockage of inflammatory cytokines. More recently, inflammatory cell signaling pathways that generate these inflammatory and tissue destruction proteins have become promising therapeutic targets.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins, including prostaglandin E2, which is produced by a variety of resident and infiltrating cell types in the periodontium (including neutrophils, macrophages, fibroblasts and epithelial cells) in response to lipopolysaccharide. Prostaglandin E2 is a key inflammatory mediator in periodontal disease as it upregulates osteoclastic bone resorption, and prostaglandin E2 levels are significantly increased

Received: Jan. 11, 2017: **Accepted:** Mar. 7, 2017
*Correspondence Dr. Anshuman Gautam.
Department of Periodontology and Oral Implantology, Dr. B.R. Ambedkar Institute of Dental Sciences and Hospital Patna, India.
Email: a.gautam113@gmail.com

pISSN 2278-0076
eISSN 2321-9270

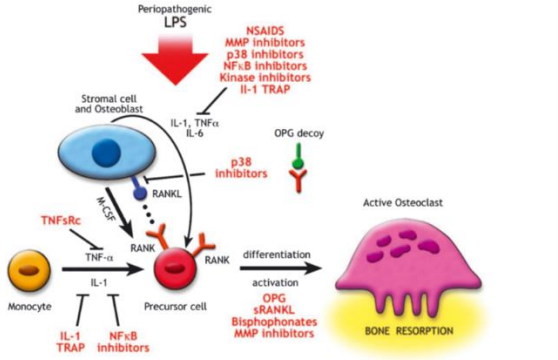

Fig 1: stimuli factors regulating osteoclast formation and function: cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and macrophage colony stimulating factor (M-CSF), produced by bone marrow stromal cells, osteoblasts, monocytes, and T cells are key regulators on this process.

in the tissue and gingival crevicular fluid of patients with periodontal disease compared to healthy controls.[3] Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonic acid metabolism. They are used to reduce tissue inflammation and pain, and are indicated in a variety of chronic inflammatory diseases. 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. Thus, 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. nonsteroidal anti-inflammatory drugs have been extensively reviewed as potential host response modulators for the treatment of periodontal disease , but unwanted effects (including the serious adverse effects of the selective cyclo-oxygenase-2 inhibitors) preclude their use as adjuncts to periodontal treatment.[4]

Bisphosphonates

Bisphosphonates represent a class of chemical compounds structurally related to pyrophosphate, which regulates mineralization by binding to hydroxyapatite crystals, but is not stable in vivo, undergoing hydrolysis of its P-O-P bond as a result of pyrophosphatase activity. The replacement of the oxygen atom with a carbon atom (creating a P-C-P bond) results in the formation of a bisphosphonate molecule that is chemically stable and resists hydrolysis via pyrophosphatase and alkaline phosphatase. Thus, bisphosphonates bind to hydroxyapatite crystals and prevent their dissolution. They also increase osteoblast differentiation and inhibit osteoclast activation, and are used extensively in the management of osteoporosis and other bone- resorptive conditions.[4]

A recent development has been the publication of several case reports of avascular necrosis of the jaws, particularly the mandible, following bisphosphonate therapy, with an increased risk of bone necrosis following dental extractions. This has been termed **bisphosphonate-associated osteonecrosis** and is a significant and clinically serious complication of bisphosphonate therapy.[5] Current guidance is to avoid extractions in patients who have received long- term bisphosphonate therapy and seek expert opinion. At the present time, there are no bisphosphonate drugs that are approved and indicated for use as adjuncts in the treatment of periodontal disease.

Subantimicrobial dose doxycycline

Subantimicrobial dose doxycycline remains, at present, the only systemic host response modulator specifically indicated as an adjunctive treatment for periodontitis. Subantimicrobial dose doxycycline 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 doxycycline at subantimicrobial doses as a host response modulator is that it inhibits the activity of MMPs by a variety of synergistic mechanisms independent of any antibiotic properties. Doxycycline was also confirmed as being a more effective inhibitor of

Table 1: Medications Currently Available For Controlling Inflammation/ Bone Resorption.

Anti-cytokine agents	
Anakinra	Recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist
Canakinumab	Recombinant, human anti-human- interleukin-1 monoclonal antibody that belongs to the IgG1/κ isotype subclass
Tocilizumab	Interleukin 6 receptor inhibiting monoclonal antibody
AMG714	Human monoclonal antibody against interleukin-15
Ustekinumab	Human monoclonal antibody. It is directed against interleukin-12 and interleukin-23
Rilonacept	Dimeric fusion protein blocks interleukin-1 beta and to lesser extent interleukin-1 alpha from interacting with cell-surface receptors
AIN457	Fully human IgG1κ monoclonal anti-interleukin 17 antibody that selectively neutralizes interleukin-17 A
Tumor necrosis factor-alpha antagonists **Adalimumab**	Human monoclonal antibody
Cetrolizumab pegol	Humanized tumor necrosis factor- alpha antibody
Entanercept	Tumor necrosis factor receptor
Golimumab	Fully human monoclonal tumor necrosis factor- alpha antibody
Infliximab	Chimeric monoclonal antibody
The Inhibitor of cytokines from the tumor necrosis factor superfamily	
Atacicept	Recombinant fusion protein that binds and neutralizes B-lymphocyte stimulator and a proliferation- inducing ligand

MMPs than either minocycline or tetracycline; doxycycline has a much lower inhibitory concentration (IC50 = 15lM) than minocycline (IC50 = 190 lM) or tetracycline (IC50 = 350 lM), indicating that a much lower dose of doxycycline is necessary to reduce a given collagenase level by 50% compared with minocycline or tetracycline. Furthermore, doxycycline has also been found to be more effective in blocking neutrophil collagenase activity (**MMP-8**) than fibroblast collagenase activity (**MMP-1**), suggesting that doxycycline can provide a safe method of reducing pathologically elevated collagenase levels without interfering with normal connective tissue turnover.[4]

MAPK inhibitors

Mitogen activated protein kinase (MAPK) pathway is one of the signal transduction pathways closely associated with inflammation.

MAPKs are divided into 3 families:-

- Extracellular signal-regulated kinases (ERK1/2)
- JNKs (c-jun N-terminal kinases)
- p38

Extracellular signal regulated kinases are activated by mitogens and growth factors. JNK and p38 are activated by the pro-inflammatory cytokines like interleukin-1 and tumor necrosis factor-α and cell stress-inducing factors, such as heat shock, osmotic shock, ultraviolet radiation and

oxygen radicals. All the MAPK families are expressed in periodontitis but the level of expression may differ depending upon the exact cell types activated and the amount of inflammation present.

Inhibitors of p38:-

These are also called as cytokine suppressive anti-inflammatory drugs (CSAIDs) and are responsible for inhibition of lipopolysaccharide induced tumor necrosis factor-α expression. They act through reversible, competitive binding to the ATP-binding pocket. The different drugs available are **SB203580, RWJ 67657, L-167307, VX-745, RPR200765A**, etc

Kirkwood et al. showed that p38a selective mitogen activated the protein kinase inhibitor, which prevents periodontal bone loss in rats.[6]

RWJ 67657 has been tested in human volunteers who were given endotoxin. After a single oral dose of RWJ 67657, serum levels of the pro-inflammatory cytokines tumor necrosis factor-α, interleukin-6 and interleukin-8 were decreased by 90% compared with their plasma peak. No major side effects were noted, even with the highest doses of p38 inhibitor. Phase II clinical trials of p38 inhibitors are underway in patients with rheumatoid arthritis.[6]

Inhibitors of JNKs:

They inhibit the production of pro-inflammatory compounds, diminish the production of tumor necrosis factor-α, interferon-γ, interleukin-6, COX-2, and matrix metalloproteinase and decreases joint destruction in the adjuvant arthritis model. Drugs available are **SP600125**.

Nitric Oxide Synthase Inhibitors

Nitric oxide (NO) is a short lived molecule implicated in a wide range of biological processes. It is a free radical with important physiological functions, which include cardiovascular, nervous system and immune homeostasis. It is synthesized from the substrate L-arginine by three isoenzymes called nitric oxide synthases (NOS).

While homeostasis requires low NO tissue levels, NO is produced at high and prolonged concentrations in response to pro-inflammatory stimuli such as lipopolysaccharide endotoxin via "inducible" NO synthases. High, local concentration of NO and **peroxynitrite** (a product of NO plus superoxide) are cytotoxic to bacteria, fungi, protozoa and tumor cells; however these reactive species may also cause deleterious host effects such as DNA damage, lipid peroxidation, protein damage and stimulation of inflammatory cytokine release.

NOS inhibitors help in inhibition of NOS by blocking inducible NO synthases, scavenging peroxynitrite and inhibiting cyclooxygenase. The pharmacological inhibition of NO synthases with **mercaptoalkylguanidine** (aminoguanidine 2.5 to 10mg/kg) or **L-arginine methyl ester** (L-NAME 5 to 20mg/kg) intraperitoneally is associated with decreased carrageenam-induced inflammation, depressed hemorrhagic shock and lower arthritis scores in animal models.[1] **Leitao et al** [7] found that nitric oxide synthase inhibition prevents alveolar bone resorption in experimental periodontitis in rats.

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids inhibit the production of not only prostanoid derived from the COX pathway but also of leukotrienes derived from the lipooxygenase pathway. **Varder et al** evaluated the use of omega-3 fatty acids with the purpose of blocking arachidonic acid cascade in induced periodontal disease in rats.[8]

The rationale behind the therapeutic approach is based on two facts:

- **Leukotriene B_4**, a mediator formed from arachidonic acid via lipooxygenase, plays a significant role in alveolar bone resorption
- Inhibition of COX with NSAIDs would result in the accumulation of arachidonic acid which could be metabolized by the lipooxygenase pathway and result in continuos bone loss.

The investigators combined omega-3 fatty acid with **celecoxib**, looking for synergism of the anti-inflammatory effects of these two agents. The associated therapy resulted in significant superior reductions on periodontal tissue levels of prostaglandins, leukotriene B_4 and platelet-activating factor, which is also a pro-inflammatory

mediator. No significant effect was observed on bone loss, which was related to the short period of evaluation.[8]

Chemically Modified Tetracyclines

Golub et al (1987) [9] produced first of their chemically modified tetracyclines now called CMTs by removing the dimethyl amino group from the carbon-4 position which is required for the antimicrobial activity of tetracyclines. They concluded that the resulting compound 4-dimethyl amino tetracycline, or CMT-1 had lost its antimicrobial property but have retained (actually showed enhanced) anti-collagenase activity both in vitro and in-vivo. CMTs are derivatives of tetracycline group of drugs which lack antimicrobial action but have potent host modulating effects. They inhibit pathologically elevated MMPs, pro-inflammatory cytokines and other destructive mediators. Bone resorption is also suppressed due to their combined anti-proteinase and apoptotic affects on osteoblasts and osteoclasts. Development of resistant bacteria and gastrointestinal toxicity seen with parent tetracyclines is not produced by CMTs. Hence CMTs are viewed as potential therapeutic agents in the management of chronic diseases like periodontitis.

A daily dose of 10 mg of **CMT-1** for 4 weeks reduced the host collagenases in the gingival tissues without development of resistant bacteria as opposed to parent tetracyclines. It also inhibited host collagenase to the same extent as doxycycline. **CMT-3** is specifically active against MMP-2, MMP-9 and MMP-14 isoenzymes due to its pleiotropic action towards MMPs. It exerts an inhibitory effect on MMPs in micro molar concentrations by decreasing trypsinogen-2 and inducible nitric oxide (iNOS) production.[10]

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. Thus, in 19 patients with chronic periodontitis who were scheduled for periodontal flap surgery, the patients were randomly allocated to receive subantimicrobial dose **doxycycline** (20 mg twice daily), **flurbiprofen** (50 mg four times per day), or a combination of the two drugs, for 3 weeks. Three weeks of subantimicrobial dose doxycycline alone produced a significant reduction in host-derived neutral proteinases, whereas flurbiprofen alone produced no reduction. However, the combination therapy produced a statistically significant synergistic reduction of collagenase, gelatinase and serpinolytic (a1-proteinase inhibitor-degrading) activities (of 69, 69 and 75%, respectively) and a lesser reduction of elastase activity (46%).[11]

A similar effect has also been described when **chemically modified tetracyclines** are administered together with **flurbiprofen** in arthritic rats.[12] Similarly, **CMT-8** has been combined with a **clodronate** in rats with experimental periodontitis. 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.[13] However, combination of these agents normalized the pathologically elevated levels of these MMPs, indicating a synergistic inhibition in this animal model. **Subantimicrobial dose doxycycline** has also been combined with the locally delivered **doxycycline gel** (10%; Atridox, CollaGenex Pharmaceuticals Inc., Newtown, PA), placed into pockets of >5 mm, in combination with root surface instrumentation in a placebo-controlled study of 171 subjects. This combination therapy resulted in significantly greater clinical improvements than instrumentation alone over 6 months, with mean probing depth reductions (in pockets that were >7 mm at baseline) of 2.4 mm in the combination group compared with 1.7 mm in the control group ($P < 0.01$).[14]

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. To date, only subantimicrobial dose doxycycline has been approved specifically as a host response modulator for the treatment of periodontitis and the majority of clinical trials of this drug have clearly demonstrated a benefit. Furthermore, the development of chemically modified tetracyclines is welcomed, as this will completely eliminate all concerns about any possible antimicrobial effects of

these agents. Given the safety of subantimicrobial dose doxycycline, it is likely that host response modulators with similar safety profiles will be welcomed by practising clinicians if proven to have a clinical benefit and minimal unwanted effects. Such drugs that target relatively specific aspects of pathogenic processes (and therefore tend to have more predictable outcomes) might be preferred in comparison to agents that have profound, and possibly unpredictable, effects on human inflammatory responses, such as evidenced in the recent, disastrous clinical trial of **TGN1412** (the activating superagonist anti-CD28 monoclonal antibody).[15]

CONCLUSION

To summarize, host response modulators must be viewed as comprising part of the overall management strategy for patients with periodontitis. Thus, they should form part of an integrated treatment approach, together with hygiene therapy, plaque control, root surface instrumentation, maintenance care and risk factor modification. Periodontal disease is an unfortunate and distressing condition, and many patients are relieved to realize that multifaceted treatment strategies are possible, including, for example, root surface instrumentation, enzyme suppression and modification of local and systemic risk factors. Thus, periodontal therapy in the 21st century should not only involve a high standard of clinical treatment and monitoring, but should also focus on patient involvement and improving the patient experience. The future will see a range of host response modulators developed as adjunctive treatments for periodontitis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV. Novel host response therapeutic approaches to treat periodontal diseases. Periodontolgy 2000: 43: 94-315

2. Carranza FA, editor: Clinical periodontology, ed-10, Philadelphia, 1996, Saunders

3. Offenbacher S, Heasman PA, Collins JG. Modulation of host PGE2 secretion as a determinant of periodontal disease expression. J Periodontol 1993: 64: 432-444

4. Preshaw PM. Host response modulation in periodontics. Periodontology 2000: 48: 92-110

5. Lam DK, Sandor GK, Holmes HI, Evans AW, Clokie CM. A review of bisphosphonate-associated osteonecrosis of the jaws and its management. J Can Dent Assoc 2007: 73: 417-422

6. Waykole YP, Doiphode SS, Rakhewar PS, Mhaske M. Anticytokine therapy for periodontal diseases: where are we now?. JISP:2009: 13(2): 64-68

7. Leitao RF et al: Nitric oxide synthase inhibition prevents alveolar bone resorption in experimental periodontitisin rats. J Periodontol. 2005; 76: 956-63

8. Serhan CN, Hamberg M, Samuelsson B: Lipoxins: novel series of biologically active compounds formed from arachinodic acid in human leukocytes. Proceedings of the national academy of sciences of united states of America: 81(19); 5335-39

9. Golub LM et al: A non-bacterial chemically modified tetracycline inhibits mammalian collagenase activity. J Dent Res: 66(8): 1310-14

10. Agnihotri R, Gaur S. Chemically modified tetracyclines: Novel therapeutic agents in the management of chronic periodontitis. Indian journal of pharmacology: 2012; 44(2) : 161-167

11. Lee HM, Ciancio SG, Tuter G, Ryan ME, Komaroff E, Golub LM. Subantimicrobial dose doxycycline efficacy as a matrix metalloproteinase inhibitor in chronic perio- dontitis patients is enhanced when combined with a non- steroidal anti-inflammatory drug. J Periodontol 2004: 75: 453–463.

12. Leung MK, Greenwald RA, Ramamurthy NS, Moak SA, Koszulinski R, Dieudonne D, Golub LM. Tenidap and flurbiprofen enhance uptake of matrix metalloproteinase inhibitor 4-dedimethylaminotetracycline in inflamed joints

of adjuvant arthritic rats. J Rheumatol 1995: 22: 1726–1731.

13. Llavaneras A, Ramamurthy NS, Heikkila P, Teronen O, Salo T, Rifkin BR, Ryan ME, Golub LM, Sorsa T. A combination of a chemically modified doxycycline and a bis- phosphonate synergistically inhibits endotoxin-induced periodontal breakdown in rats. J Periodontol 2001: 72: 1069–1077.

14. 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 mod- erate to severe periodontitis: a randomized, multi-center trial. J Periodontol 2008: 79: 33–41.

15. Strand V, Kimberly R, Issacs JD. Biologic therapies in rheumatology: lessons learned, future directions. Nar Rev Drug Discov 2007: 6: 75-92.