Anuj Singh Parihar

Host Modulation in Periodontology

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INTRODUCTION

Periodontitis was believed to be an inevitable consequence of aging & uniformly distributed in population. This age old belief was again supported by another belief that disease severity was directly proportional to plaque levels. But in mid 1990's early insight about complex diseases like periodontitis, led to new conceptual models of pathogenesis.[1] In recent years the role of microorganisms as the principle etiologic factor in periodontal diseases has gained new perspectives. Periodontal disease is a multifactorial & complex disease which is characterized by an up regulated or maladapted immune inflammatory response to bacterial plaque which predisposes to periodontal breakdown. Although periodontal disease is initiated by bacteria colonizing the tooth surface & gingival sulcus, the host response is believed to play an important role in breakdown of connective tissue & bone.[2]

Thus it can be summarized that periodontopathogens are necessary to cause periodontal disease but they are not sufficient to cause the disease. In response to infectious or inflammatory, two distinct yet intricately linked immune response occurs – innate & adaptive. The immune system is essential& the body must be marshal the innate & adaptive responses in order to stave off infection. However, in inflammatory disease the response becomes chronic & tissues do not return to homeostasis.[3] The development of an immune inflammatory response during periodontitis in susceptible individuals results in local production of variety of inflammatory mediators. The development of an immune inflammatory response during periodontitis in susceptible individuals results in local production of variety of inflammatory response during periodontitis in susceptible individuals results in local production of variety of inflammatory mediators. Pro-inflammatory cytokines molecules & cytokine network plays an essential role in pathogenesis of periodontal disease.

Microbial antigens & virulence factors elicit an immediate inflammatory & immune response from the host. The host reacts to microbial insults by producing cytokines, kinins, complement activation & matrix metalloproteinases. Some of these inflammatory mediators participate in periodontal ligament & bone destruction. Constituents of biofilm stimulate host cells to produce a proinflammatory cytokines including IL-1, IL-6 & TNF- which may include connective tissue & alveolar bone resorption.[4] Prostaglandin E2 (PGE2) which may arachidonic acid metabolite play a critical role in regulation of periodontal disease.[5] Moreover, it is consensus that matrix metalloproteinases (MMP's) produced by both infiltrating & resident cells of periodontium plays a role in periodontal disease.[4] Again, it has also been reported that reactive oxygen species (ROS) such as nitric oxide which has been shown to be toxic when present at high levels .[5]

Periodontal treatment, through the ages has focused on the reduction of bacterial infection by mechanical removal of infectious agents i.e (SRP). However, this conventional approach of elimination of infectious agents may not always provide the assurance of a definitive treatment of periodontitis. Thus, this short come has led to use of other sophisticated biological modalities.

Today our knowledge about pathogenesis of periodontal disease has gained new perspectives. This understanding has thus opened new horizon for researchers to explore a novel approach of treatment by means of host response modulation. This treatment concept is aimed at reducing tissue destruction & stabilizing or even regenerate the periodontium by modifying or downregulating the destructive aspects of host response & upregulating protective or regenerative responses. Host modulation therapy offers a potential to move the periodontal treatment to next level.

The various natural inherent defense mechanism have demonstrated to moderate the host response & co-ordinate the resolution of inflammation.

Lipoxins, one such endogenous molecule are liberated during host defense & inflammation have demonstrated as having inflammation resolving properties by stopping signals for polymorphonuclear neutrophils mediated tissue injury. [6] Similarly, it has been shown that imbalance between activated matrix metalloproteinases & their endogenous inhibitors leads to pathological breakdown of extracellular matrix during periodontitis.[4] Moreover, activities of IL-1,TNF-α & interferon-γ are counterimbalanced by production of IL-4, IL-10 & TGF-β.[7] A soluble factor, osteoprotegrin (OPG) binds to RANKL & inhibits the differentiation of osteolcalasts .[8]

Therefore, it appears logical that drug preparations that mimic these endogenous anti-inflammatory mechanisms may prove to be an effective strategy of periodontal treatment. Thus, host modulation therapy (HMT) is designed to block various pathways which are responsible for periodontal disease. These pathways include arachidonic acid metabolites,matrix metalloproteinases, proinflammatory cytokines, production of nitric oxide & regulation bone remodeling. Compared to other treatment approaches host modulation therapy presents as a treatment modality with relatively fewer side effects. Thus host modulation therapy (HMT) may prove to be an effective mode of treating periodontal disease.

Therefore, the aim of this review is to provide comprehensive information & to update about various therapeutic methods to modify the host response as an adjunctive treatment for periodontitis.

REVIEW OF LITERATURE

A) REVIEW OF LITERATURE ON MODULATION OF ARACHIDONIC ACID METABOLITES

1. **Feildman et al (1983)**[74] investigated the effect of non-steroidal anti-inflammatory drugs on the alveolar bone levels in 75 patients with a long term history of aspirin and/or indomethacin therapy.This study concluded that the inhibition of bone loss found in their study could be due to the chronic ingestion of aspirin or aspirin and indomethacin.

2. **Heasman et.al (1989)**[75] investigated the effects of a topical NSAID solution flurbiprofen on the development of experimentally-induced gingivitis in human. The authors concluded that systemic absorption of flurbiprofen reduces the severity of developing inflammatory lesion.

3. **Williams et.al (1989)**[76] examined the effect of the NSAID, flurbiprofen in 56 individuals with radiographic evidence of alveolar bone loss.Subjects were followed a period of 2 years. This study concluded that the NSAID flurbiprofen, as an inhibitor, of cyclooxygenase, can inhibit human alveolar bone loss as measured radiographically.

4. **Reddy et.al (1993)**[77] studied the effect of the non-steroidal anti-inflammatory drug, meclofenamate sodium (Meclomen), as an adjunct to scaling and root planing on the progression of alveolar bone loss associated with rapidly progressive periodontitis (RPP). Based on the observations obtained from this study, the authors concluded that meclofenamate sodium

may have a potential role in treatment regimens for patients with rapidly progressive periodontitis.

5. **Heasman et.al (1993)**[78] examined the effects of a potent cyclooxygenase inhibitor, flurbiprofen, on both clinical parameters and on release of PGE_2, TxB_2 and LTB_4 during the development of inflammation using the experimental gingivitis model in 21 humans. The authors reported that flurbiprofen controls gingival inflammation at both preventive and therapeutic levels in the experimental gingivitis model and suggested that this effect could be associated with an inhibition in the production of cyclooxygenase metabolites that indirectly affects GCF- LTB_4 levels.

6. **Heasman et.al (1994)**[79] conducted a study which was aimed at investigating the effect of a systemic flurbiprofen preparation (100 mg daily) on the resolution of experimental gingivitis in 47 human volunteers. The authors concluded that the flurbiprofen has a beneficial effect by increasing the rate of resolution of inflammation.

7. **Jeffcoat et al (1995)**[80] assessed the efficacy of a topical NSAID rinse, containing ketorolac tromethamine as the active agent. 55 adult periodontitis patients were studied in this 6-month study. Systemic flurbiprofen was used as a positive control. Standardized radiographs were taken at baseline, at 3 and at 6 months by digital subtraction radiography. It was concluded that ketorolac rinse preserved more alveolar bone than systemic flurbiprofen and that ketorolac rinse may be beneficial in the treatment of adult periodontitis.

8. **Preshaw et.al (1998)**[81] investigated the effects of topical ketorolac tromethamine mouthrinse (0.1%) on gingival crevicular fluid (GCF)

prostaglandin E_2 (PGE_2) concentrations. This study concluded that ketorolac mouth rinse controlled the elevation of GCF PGE2 compared to placebo, but did not actually reduced GCF PGE2 concentrations.

9. **Bichara et.al (1999)**[82] studied the effect of a one week course of postsurgical naproxen (500mg, twice daily for one week) on the osseous healing in intrabony defects treated with polylactide bioabsorbable membranes. The observations obtained form the study stated that, an administration of postsurgical naproxen did not produce superior defect fill compared to that obtained with polylactide bioabsorbable membranes alone.

10. **Pouliot et.al (1999)**[83] investigated the impact of metabolically stable LX and ATL analogues on TNF-α induced neutrophil response. The authors concluded that both LXA4 and ATL are regulators of TNF α -directed neutrophil actions and stimulate IL-4 to play an important role in preventing periodontal disease.

11. **Bezerra M. (2000)**[84] compared the effect of selective COX-2 inhibitors – meloxicam and indomethacin on alveolar bone loss (ABL) in an experimental periodontitis model in rats. The authors suggested that both indomethacin and meloxicam prevented ABL and reduced inflammatory changes through COX inhibition. They also observed that meloxicam displays similar efficacy and less gastric damage than indomethacin.

12. **Paquette et.al (2000)**[85] evaluated the pharmacodynamic effects of the NSAID, ketoprofen on gingival crevicular fluid (GCF) prostanoids. The authors concluded that both topical and systemic ketoprofen therapies pharmacodynamically reduce GCF PGE_2 levels in adult periodontitis subjects resulting in inhibition of disease progression.

13. **Holzhausen et.al (2002)**[86] studied the effect of a selective cyclooxygenase-2 inhibitor (celecoxib) on alveolar bone resorption in experimentally induced periodontal disease in rats. It was concluded that the systemic therapy with the celecoxib could modify the progression of experimentally induced periodontitis in rats.

14. **Vardar et.al (2003)**[87] compared the effects of selective cyclooxygenase (COX)-2 inhibitor (nimesulide) and non-selective COX-1/COX-2 inhibitor (naproxen) as an adjunct to non-surgical (SRP) periodontal therapy in chronic periodontitis patients on the gingival tissue levels of prostaglandin PGE_2 and $PGF_{2ά.}$ The authors concluded that nimesulide may have additional inhibitory effects on gingival tissue $_{PGF2ά}$ levels in the first week following non-surgical periodontal treatment. However, it has an insignificant effect on reducing PGE_2 levels in gingival tissue.

15. ***Serhan et.al (2003)***[88] concluded LXs can be targets for novel approaches to diseases, e.g., periodontitis and arthritis, where inflammation and bone destruction are features.

16. **Gurgel et.al (2004)**[89] conducted a study which stated that selective cyclooxygenase-2 inhibitors may reduce bone loss associated with experimental periodontitis and that there is no remaining effect after its withdrawal.
17. **Sekino et.al (2005)**[90] conducted a study on eleven subjects to evaluate the effect of systemic administration of ibuprofen on gingivitis and de novo plaque formation. The authors concluded that ibuprofen administered via the systemic route has an effect on gingivitis but not on de novo plaque formation.

18. **Kurtis et.al (2007)**[91] investigated the effect of systemic flurbiprofen administration as an adjunct to SRP in smoker and non-smoker patients with chronic periodontitis. therapy, a more statistically significant reduction was observed in group 3. The authors concluded that better results were found in smokers as compared to non smokers.

19. **C. Alec Yen et al (2008)**[92] **tested the** efficacy of celecoxib (COX-2 inhibitor) in conjunction with scaling and root planing (SRP) in subjects with chronic periodontitis (CP). This study concluded that celecoxib can be an effective adjunctive treatment to SRP to reduce progressive attachment loss in subjects with CP.

20. **Thais M. Oliveira et al (2008)**[93] evaluated the effect of a preferential cyclooxygenase (COX)-2 inhibitor meloxicam on VEGF expression and alveolar bone loss in experimentally induced periodontitis. The data of this study suggested that systemic therapy with meloxicam can modify the progression of experimentally induced periodontitis in rats by reducing VEGF expression and alveolar bone loss.

B) REVIEW OF LITERATURE ON MODULATION OF HOST MATRIX METALLOPROTEINASES

1. **Golub et.al. (1995)**[94] evaluated the effect of low-dose doxycycline on host-derived collagenase activity in gingival tissues of adult periodontitis patient. They concluded that the pathologically-elevated tissue-degrading activities can be directly inhibited by pharmacologic levels of doxycyline.

2. **Crout et.al (1996)**[95] investigated the clinical results of a "cyclical" 6-month regimen of low dose doxycyline and its effect on GCF collagenase activity in adult periodontitis patients. The authors concluded that low dose doxycycline inhibits tissue destruction in the absence of either antimicrobial or significant anti-inflammatory efficacy; and that long-term low dose doxycycline could be a useful adjunct to instrumentation therapy in the management of the adult periodontitis patient.

3. **Veronica and Bisada (1998)**[96] compared the efficacy of the combined systemic use of doxycycline and a non-steroidal anti-inflammatory drug (ibuprofen),as an adjunctive treatment to scaling and root planing for adult periodontitis. . The authors concluded that systemic doxycycline alone or in combination with ibuprofen results in a statistically significant yet modest clinical improvement in patients with moderate adult periodontitis.

4. **Caton et.al (2000)**[97] conducted a study which assessed the efficacy of subantimicrobial dose doxycycline in conjunction with scaling and root planing (SRP) over a 9 month period in patients with adult periodontitis. They concluded that the use of SDD 20 mg twice daily augment the attachment gains achieved with SRP, with statistically significant

improvements in CAL and PD relative to placebo after only 3 months of use and further improvements were evident after 6 months of SDD treatment.

5. **H. Nakaya et al (2000)**[98] investigated the regulatory effects of a bisphosphonate, tiludronate, on MMP levels and activity in human periodontal cells. This study demonstrated an inhibitory effect of tiludronate on the activity of both MMP-1 and MMP-3.

6. **Golub et.al (2001)**[99] carried out a study to determine appropriate dosage of administration regimens using subantimicrobial dose doxycycline (SDD) as an adjunctive therapy in patients with adult periodontitis. This study concluded that the administration of 20 mg of twice daily over an extended period can reduce pathologic elevations in GCF collagenase activity and improve attachment level measurements in patients with periodontitis and that the improvement in parameters occurred without any apparent side effects.

7. **Ramamurthy et.al (2002)**[100] tested the efficacy of doxycycline and 5 different chemically modified tetracyclines (CMTs) to prevent matrix metalloproteinase (MMP)-dependent periodontal tissue breakdown in an animal model of periodontitis. The authors concluded that MMP-mediated bone loss in this model can be prevented by inhibition of MMPs using CMTs.

8. **Novak et.al (2002)**[101] studied the use of adjunctive host modulation therapy in form of subantimicrobial doxycycline (SDD) for treating severe, generalized periodontitis**.** The authors concluded that SDD as an adjunctive treatment provides clinically and statistically significant benefits in the reduction of deep pockets in patients with severe, generalized periodontitis.