

Chapter 7

The Taming of the Host - Host Modulation in Periodontitis

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Introduction

One of the significant periodontal findings in the last century was the discovery that plaque is the cause of periodontal disease. The realization that microbial plaque organized into biofilms clarified why antibiotics alone have limited long-term effect in the treatment of periodontitis. Biofilms are defined as “matrix enclosed bacterial populations, adherent to each other and/or to surfaces” (Costerton *et al* 1994). Biofilms are communities of bacteria that evolved to permit survival of the community as a whole. Because of its numerous characteristics such as differing pH, oxygen tension, primitive circulatory system and the presence of matrices, bacteria in the biofilm may have up to 1000 times decreased susceptibility to antibiotics compared to planktonic grown bacteria. Because of this unique nature of biofilms, mechanical plaque control remains the main mode of treatment of periodontal disease.

Lately the focus was changed when investigators began to document the host's contribution to disease pathogenesis. With the realization that plaque is necessary, but alone is not sufficient in the progression of periodontal disease, more emphasis was put on the role of host mediators in the

pathobiology of the disease. With this current realization of a link between host response and periodontal disease pathogenesis, it is intuitive that pharmaceutical inhibition of host response pathways may be an adjunctive strategy for treating periodontal disease (Paquette and Williams 2000).

In essence, high levels of interleukin-1 (IL-1), matrix metalloproteinase (MMPs), prostaglandins (PGE) and all other pro-inflammatory mediators are found in disease. (Figure 1) (Page 1998). In health, tissue inhibitor of MMPs, interleukin antagonists and interleukin-10 are the predominating mediators (Page 1998). The concept of mediating the host is focused on trying to decrease the high level of mediators that are found in periodontitis and also to increase or promote the levels of the mediators that are normally found in health.

Matrix Metalloproteinases (MMPs)

Because the clinical manifestation of periodontal disease involves attachment and bone loss, which histologically involves connective tissue destruction, the blocking of connective tissue mechanisms is a viable strategy for management of periodontal disease. Collagenases, elastase and acid proteases are the enzymes that digest and

Disease		Health
High	IL-1 β , TNG- α , INF- γ , PGE- ₂ , MMPs	Low
Low	IL-4, IL-10, TGF- β , IL-ra, TIMPs	High

Table 1. Essence of Pathogenesis of Periodontitis (Page RC 1998)

destroy the matrix of the gingival tissue and periodontal ligaments. There appear to be multiple opportunities to block MMPs, including blocking production of MMPs, blocking production of pro-enzyme and activating inhibitors. Some of the inhibitors involve action in removing Zn⁺⁺ and Ca⁺⁺, which are essential to the active sites of MMPs.

The initial demonstration that tetracycline antibiotics can inhibit host-derived matrix MMPs, by a mechanism independent of the antimicrobial properties of the drugs, was performed by Golub and co-workers (Golub *et al* 1983). In 1987, Golub *et al* described the new chemically modified tetracyclines (CMTs) which are devoid of antibacterial activity but retain their anticollagenase property. Because chemically modified tetracyclines are not yet approved for human use, the majority of the human clinical trials have involved the use of 20 mg or 50mg doxycycline (Periostat). In multiple clinical studies conducted using sub-antimicrobial dose doxycycline (SDD), there has not been a difference noted in the resistance level or composition of the oral flora (Walker *et al* 2000, Thomas *et al* 2000).

Several series of double-blind, placebo controlled clinical trials of three, six and nine months' duration on SDD have shown some degree of efficacy for these medications (statistically) based on prevention of attachment loss, pocket depth reduction as

well as inhibition of collagenase activity (Golub *et al* 1994, Crout *et al* 1996, Golub *et al* 1997, Caton *et al* 1999, Caton *et al* 2000).

With regards to MMP inhibition, Golub and colleagues (Golub *et al* 1990) demonstrated that a two-week regimen of SDD reduced collagenase level in the gingival crevicular fluid (GCF). However subsequent studies using SDD therapy adjunctive to routine scaling and root planing indicated that after cessation of SDD a rebound of collagenase activity was noted, suggesting that continuous drug therapy over a period of several months appears to be necessary for maintaining collagenase levels to near normal (Golub *et al* 2001, Ashley *et al* 1999).

One of the clinical studies of Periostat that was pivotal for the attainment of U.S. Food and Drug Seal of Approval was by Caton and co-workers in 2000. This study involved a total of 190 subjects with a treatment period of nine months. This study found statistically significant differences in the mean per-patient average attachment level with Periostat plus SRP compared with placebo plus SRP, with the treatment group having 0.38 mm better attachment gain. The clinical significance of 0.38 mm attachment gain after 9 months in the SDD group vs. placebo can be questioned (1.55 mm SDD vs. 1.17 mm placebo). The mean decrease in pocket depths (1.68 for SDD vs 1.20 mm for placebo) can be also be achieved by SRP alone in numerous studies. These studies, together with all other clinical

trials, should be interpreted with respect to their clinical relevance. Clinicians should evaluate the results cautiously with practicality and long-term benefit in mind. The suggestion that SDD should be routinely used as an adjunct to scaling and root planing in the treatment of chronic periodontitis should also be questioned with the knowledge that the majority of periodontal disease responds only to routine mechanical debridement.

Bisphosphonates

Bisphosphonates are non-biodegradable analogs of pyrophosphate that have a high affinity for calcium phosphate crystals. It has been observed that when osteoclasts phagocytize bone crystals containing bisphosphonates, osteoclastic activity is inhibited. Alendronate and tiludronate are some of its various forms. Bisphosphonates are powerful inhibitors of bone resorption. Although their mechanism of action has not yet been fully elucidated, it is thought that they inhibit osteoclasts from resorbing bone by interfering with their metabolic activity (ion transport) (Sato *et al* 1991). Various forms such as Alendronate and tiludronate are being used clinically to treat metabolic bone diseases in humans such as Paget's disease, hypercalcemia and osteoporosis (O'Doherty *et al* 1992, Thiebaud *et al* 1988, Thiebaud *et al* 1990).

Numerous studies have demonstrated some benefit in the management of periodontal disease exposure to bisphosphonates. Non-human primate models of periodontitis have been widely used to examine the effects of this potential therapeutic agent. Weinreb *et al* (1994) studied the histomorphometrical effects of Alendronate on bone loss caused by experimental ligature-induced periodontitis in an animal model. Bisphosphonates were administered via intravenous infusion of saline

solution (control) or alendronate (0.05 mg/kg and 0.25 mg/kg IV every 2 weeks for 16 weeks). Result showed that alendronate at 0.05 mg/kg significantly reduced bone loss associated with experimental periodontitis. In contrast, the higher dose of alendronate (0.25 mg/kg) was almost ineffective in blocking periodontal bone loss. The same biphasic response was observed in the 1992 Brunsvold *et al* study. The authors pointed out that the reason for this was unclear.

A combination study has been described by Llawaneras and co workers (2001) where a combined chemically modified doxycycline (CMT-8 given orally) and bisphosphonate (clodronate given subcutaneously) were used. The result showed no significant reduction in alveolar bone loss observed in CMT-8 and clodronate alone, but combination of sub-optimal CMT-8 and clodronate "normalised" elevated MMPs and reduced bone loss.

The unusual dose response pattern observed in numerous studies, where the lower dose produced better inhibition of bone loss than the higher dose, should point out that attempts to intervene in complex regulatory mechanisms should proceed with caution.

Although bisphosphonates are being used clinically to treat metabolic diseases such as Paget's disease, hypercalcemia and osteoporosis; the high dose used in the animal studies to control periodontitis is equivalent to 20-fold the dose proposed for the treatment of human osteoporosis. Therefore caution should be taken in translating the animal results to the clinical setting.

Prostaglandins

The synthesis and release of prostaglandins is one of the first host immunoinflammatory pathways implicated in periodontal disease. Prostaglandin is a potent mediator of bone resorption. The relationship of increased levels

of PGE₂ to periodontal disease is well-established. PGE levels are associated with disease severity at individual sites and at patient level and the highest level of prostaglandin tends to be in actively progressing sites (Williams *et al* 1990, Seymour *et al* 1988, Offenbacher *et al* 1986, Offenbacher *et al* 1992).

PGE₂ is produced primarily in the tissues via cyclooxygenase enzymes. Cyclooxygenase 1 (COX-1) is produced constitutively and is important for tissue homeostasis. In other words, COX-1 maintains “housekeeping” functions such as gastric cytoprotection and vascular and renal homeostasis. Cyclooxygenase 2 (COX-2) however, appears to be activated in inflammation and contributes to the increase in PGE₂ in periodontitis. In periodontal disease, monocytes and fibroblasts produce PGE₂ in response to activation by interleukin 1a (IL-1a), tumor necrosis factor a (TNF-a) and lipopolysaccharides (LPS).

In 1971, Vane and co-workers made a landmark discovery that NSAIDs blocked cyclooxygenase as their mechanism of action, thus inhibiting prostaglandin production. NSAIDs though, inhibit both COX-1 and COX-2 pathways, thereby also inhibiting the “housekeeping” functions of COX-1, causing renal and gastric side effects.

Numerous animal studies from the mid-70s to the present have shown some benefit in using NSAIDs in reducing bone resorption and inflammation. NSAIDs such as indomethacin, flubiprofen and naproxen were used, administered either orally or topically (Nyman *et al* 1979, Williams *et al* 1984, Williams *et al* 1988, Howell *et al* 1991). Human clinical studies also showed some degree of benefit from using NSAIDs in the prevention of bone loss in periodontitis (Feldman *et al* 1983, Williams *et al*, 1988, Jeffcoat *et al* 1991). Because of the numerous

side-effects associated with NSAIDs they cannot be used long-term, particularly for the specific control of periodontitis.

Although there is plenty of evidence from pre-clinical and clinical studies indicating inhibition of periodontal disease progression, the difference with placebo or antibiotic counterparts are rarely clinically dramatic (-/+ 1-2 mm in attachment gain). We do not know much about dosages of NSAIDs to be employed in human studies. It is not clear if we can rely on NSAIDs dosages used in the treatment of pain associated with rheumatoid arthritis to slow alveolar bone loss in periodontitis. Would increasing the dosage to attenuate the anti-inflammatory properties outweigh the potentially harmful side-effects (renal toxicity, gastric ulceration, internal bleeding etc)? Well-controlled longitudinal studies in humans on the effect of NSAIDs on periodontal disease progression, with tooth retention as the indication of success, are needed.

COX-2 Inhibitors

As mentioned above, NSAIDs block both COX-1 and COX-2, therefore inhibiting the beneficial “housekeeping” functions by COX-1. An exclusive COX-2 inhibitor was developed to prevent this from happening. Numerous studies published to date have focused on the efficacy of COX-2 inhibitors for treating acute pain, osteoarthritis and rheumatoid arthritis, with lower incidence of gastrointestinal adverse events than patients taking NSAIDs. COX-2 inhibitors (meloxicam, celecoxib, etc) have potencies for COX-2 that are 10-1000 fold higher than COX-1 in inhibiting enzymes associated with inflammation rather than those associated with homeostasis.

Bezerra *et al* (2000) studied Indomethacin (NSAID) and Meloxicam (COX-2 inhibitor)

Procedures	Pocket Depth Reduction (mm)	Attachment Gain (mm)
Scaling & Root Planing (SRP)	1.2 - 2.2 mm	0.55 - 1.33 mm
Open Flap Debridement	2 - 3 mm	1 - 1.5 mm
Tetracycline Fibre/SRP	1 - 2 mm	1.1 - 1.2 mm
Chlorhexidine Chip/SRP	0.95 mm	0.65 mm
Periostat/SRP	1 - 1.5 mm	0.9 - 1.22 mm
NSAID/SRP	1.5 - 2 mm	0.82 - 1.6 mm

Table 2. Comparison of different treatment modalities

in experimental periodontitis in rats. Their results showed that NSAIDs inhibited bone resorption and inflammation in a dose-dependent manner (0.5, 1 and 2 mg/kg), in a similar degree as COX-2 inhibitors, but with associated gastric and hemorrhagic lesions in rats. Hence, selective COX-2 inhibitors may exhibit a better clinical risk/benefit ratio than classical NSAIDs.

Interleukin-1 (IL-1)

IL-1 has been strongly associated with the pathogenesis of periodontitis (Williams 1990, Genco 1992, Gemmel *et al* 1997). Elevated levels in gingival crevicular fluid are associated with more severe periodontal disease. By binding specifically to their complimentary receptors, IL-1 with tumor necrosis factor trigger signaling events leading to tissue destruction. IL-1 also directly activates osteoclasts resulting in bone resorption. To maintain balance in health, IL-1 has endogenous inhibitors. The IL-1 inhibitor is structurally similar to IL-1 however it triggers no response when it binds to the IL-1 receptor (Dinarello 1996). IL-1 is potently induced by gram-negative bacteria through LPS production. It is mainly secreted by macrophages but can also be released from

blood platelets, fibroblasts and endothelial cells. IL-1 directly stimulates bone resorption, induces PGE2 and MMPs release from fibroblasts and monocytes thereby perpetuating further destruction (Dinarello 1996, Pfizenmaier *et al* 1996).

A few studies have looked at the potential for pharmacotherapeutics in inhibiting IL-1 by the use of its inhibitor (IL-1 receptor antagonist). Graves and co-workers (1998) demonstrated that the conversion from gingivitis to periodontitis in experimental periodontitis cases is characterized by the progressive movement of the inflammatory front toward alveolar bone and that application of IL-1 and TNF blockers inhibited this progression. Delima and co workers (2001) used experimental periodontitis in a monkey model treated with the IL-1 receptor antagonists. The experimental group showed reduction in connective tissue destruction by 51% and reduction in bone loss by 91%. The potential of this IL-1 receptor antagonist in treating human periodontitis should be investigated. Although early studies on risk/benefit of injecting IL-1 and TNF antagonist in animal model already showing some side-effects such as relative deficiency of macrophages in immune defense (Yang *et al* 1994).

What are the other fields of medicine doing?

The concept of host mediated destruction is also a topic of interest in other fields, particularly chronic inflammatory conditions such as rheumatoid arthritis (RA). RA and periodontitis have a very similar pathobiology (Mercado *et al* 1998, 2003). With the realization that an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines exists also in the pathogenesis of RA, emerging therapies are focusing on the inhibition of pro-inflammatory cytokines and destructive proteases. Littman *et al* 1994 demonstrated that Tenidap (Cox-2 inhibitor) reduces bone resorption and cartilage degradation in RA patients. Combination therapy of CMT (MMP-inhibitor) and Flubiprofen synergistically inhibited severe bone destruction in arthritic rats (Greenwald *et al* 1992). Synovial Injection of IL-1 ra versus placebo in a multi-center double-blind study in 175 RA patients; result showed significant improvement in test patients in terms of bone erosion, pain and clinical symptoms of RA (Campion *et al* 1996).

Conclusion

Looking at Table 2, where various treatment modalities are compared, it appears that the conventional mechanical debridement is still not far off, or even sometimes better, when compared to other treatment modalities such as chemotherapy or even host modulating agents. In general at this stage, clinicians should still try to eliminate the bacterial challenge using conventional therapy before administering systemic drugs whose objective is to alter the host response. It is important to keep in mind that drug administration is still

not a substitute for professional debridement and proper personal hygiene. It can still be considered that repeated debridement might achieve a larger improvement in clinical parameters than one episode of root planing plus SDD, which needs to be used for several months.

Significant advances in the study of host modulating agents in the treatment of periodontal and other chronic inflammatory diseases have been made in the last century. However, we still have gaps in our knowledge. Further studies on the genetic make-up and detailed studies on the pathophysiology of all the cells involved in the development of the disease are needed. As these drugs are developed, the safety of the people who are going to use them, their affordability and ease of use and of course the relative improvements that will happen after using these medications should be considered before administering them. These host modulating drugs, although not indicated for majority of the periodontitis patients, may someday make a difference in those patients who are highly susceptible to aggressive forms of the disease.

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