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Non-Surgical Chemotherapeutic Treatment Strategies for the Management of Periodontal Diseases

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Synopsis

Periodontal diseases are initiated by subgingival periodontal pathogens in susceptible periodontal sites. The host immune response towards periodontal pathogens helps to sustain periodontal disease and eventual alveolar bone loss. Numerous adjunctive therapeutic strategies have evolved to manage periodontal diseases. Systemic and local antibiotics, antiseptics, and past and future host immune modulatory agents are reviewed and discussed to facilitate the dental practitioner's appreciation of this ever-growing field in clinical periodontics.

Keywords

periodontics; antibiotics; antiseptics; host modulatory agent

Introduction

Periodontal disease is a chronic infection of the periodontium affecting soft and mineralized tissues surrounding the teeth. Periodontal disease progression is associated with subgingival bacterial colonization and biofilm formation that provokes chronic inflammation of soft tissues, degradation of collagen fibers supporting the tooth to the gingiva and alveolar bone, as well as resorption of the alveolar bone itself. Since the fundamental role of microorganisms in its etiology was systematically demonstrated some forty years ago, research efforts have long focused on identifying the pathogenic microorganisms and their virulence factors (1). The search for these putative microorganisms was driven, in part, by knowledge indicating that colonization of the oral cavity by commensal bacteria and presence of dental biofilm is normally associated with health, similarly to the colonization of the colon. In contrast, the microflora associated with periodontal disease was found to differ, with the biofilmdominated by anaerobic bacteria and spirochetes. To treat periodontal diseases as an infectious disease, numerous therapeutic strategies aimed at eradication of periodontal pathogens have been studied over the years, including local and systemic

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delivery of antimicrobial and antibiotic agents. This review will cover an update on chemotherapeutic agents used adjunctively to treat and manage periodontal diseases.

In the current paradigm of periodontal disease, specific periodontal pathogens are necessary for disease initiation; however, the extent and severity of tissue destruction are largely dependent on the nature of the host-microbial interactions. These interactions are dynamic, since both the microbial composition of the dental biofilm and the competency of host immune responses can vary, in the same individual, over time. This concept was developed in parallel to the advances on the understanding of the immune response, and research on periodontal disease has been emphasizing mechanisms of host-microbial interactions to understand the disease process, as well as for the development of novel therapeutic strategies. For the past two decades, the host response to the bacterial challenge originating from the dental biofilm has been considered to play a major role on both initiation of the disease and on the tissue destruction associated with its progress (2). The importance of host-microbial interactions is reinforced by epidemiological data indicating different susceptibilities to periodontal disease among individuals, in spite of the long-term presence of oral biofilm (3–5). Other studies demonstrating increased susceptibility and greater severity of periodontal disease in individuals with impaired immune response due to systemic conditions also indicate the significance of the host response to the bacterial challenge (6, 7). Both past and future directions of host-modulatory agents will be addressed here to provide the dental practitioner with a broader prospective of chemotherapeutic agents used to manage periodontal diseases.

Systemic Antibiotics

Traditional periodontal therapies have focused on the mechanical debridement of the root surfaces to maintain a healthy sulcus or produce an environment suitable for new attachment. The inability of mechanical treatment to produce a desirable root surface in all cases coupled with the nature and complexity of the subgingival biofilm has fueled the search for adjunctive treatment regimens that increase the likelihood to successfully manage periodontal diseases.

While more than 700 bacterial species may be present in the gingival sulcus, it is clear that only a subset of bacterial species are consistently found to be associated with diseased sites. These findings make the prospect of targeted antibiotic therapy an attractive goal. While a thorough review of the microbiology of periodontal diseases is beyond the scope of this chapter, the reader is referred to the many reviews including (8).

Systemic antibiotic therapy has the obvious advantage of generally conventional and acceptable delivery, especially if oral administration is utilized. Shortcomings to oral administration include issues of patient compliance with dosing recommendations and the variable absorption of the antibiotic from the gastrointestinal tract. Moreover, it is difficult to be certain that the antibiotic chosen will be effective against the periodontal pathogens present in the sulcus unless culture and sensitivity tests have been completed. Culture and sensitivity tests are particularly useful for those cases that do not respond well to conventional mechanical therapy and/or commonly chosen antibiotic regimens. Another often overlooked factor is that systemic antibiotics do not penetrate the subgingival biofilm to kill bacteria. Table 1 provides an overview of some orally active systemic antibiotics commonly used in clinical periodontics.

It is possible, based on the known spectrum of action of an antibiotic, and the cumulative research profiling the bacterial species in the sulcus, to choose an antibiotic that should be an effective pharmacological agent. Caution should be used, however, since none of these antibiotics is effective as a monotherapy to treat periodontal diseases. A systemically

administered antibiotic will not produce the same effective concentration in the sulcus as it might at another infected body site. Systemic antibiotics reach the periodontal tissues by transudation from the serum then cross the crevicular and junctional epithelia to enter the gingival sulcus. The concentration of the antibiotic in this site may be inadequate for the desired antimicrobial effect without mechanical disruption of the plaque biofilm. In addition to any effect produced in the sulcus, a systemically administered antibiotic will produce antimicrobial effects in other areas of the oral cavity. This additional effect will reduce bacterial counts on the tongue and other mucosal surfaces, thus potentially aiding to delay in re-colonization of subgingival sites by the offending bacteria. Research however, indicates that antibiotics are detectable in the gingival sulcus and the range of their concentrations in the gingival cervicular fluid is known to be in the therapeutic range for treatment efficacy. Table 2 provides information to facilitate the clinician's decision to the most reasonable choice of antibiotic, dose and duration of administration.

Many studies have described the effect of systemic antibiotic therapy on periodontal disease. Several different treatment regimens have been employed successfully to manage periodontal diseases. While it is not the intent of this discussion to review all the published studies in this area, the interested reader is referred to one of the many excellent, exhaustive reviews such as (9). Considering a number of studies, it can be stated generally that systemic antibiotic therapy has little effect on supragingival plaque accumulation with a possible exception in one study where doxycycline significantly decreased plaque accumulation at a twelve-week evaluation compared to placebo (10).

Except for the combination of metronidazole with amoxicillin, systemic antibiotic treatment produces no clinically significant effects on periodontal pocket depth reduction compared with controls. The combination of metronidazole and amoxicillin has been found to produce more pocket depth reduction than control medication (11). A seven-day regimen of systemic metronidazole significantly reduced the percentage of sites with bleeding compared to controls (12). Others have reported a 12-month reduction in bleeding after treatment with a metronidazole-amoxicillin combination compared to a placebo treatment (13). With respect to clinical attachment levels, systemic metronidazole and combinations of metronidazole with other antibiotics has shown improvement in several studies. Several investigators found significant improvement of attachment levels at sites initially 4–6 mm in depth with a seven-day treatment with metronidazole (14–16). Winkel et al. showed that the combination of metronidazole and amoxicillin for 7 to 14 days produced a significant increase in the percentage of sites showing improved attachment levels compared to control sites (11). A combination of metronidazole and clindamycin for three weeks also produced improved attachment levels. (17, 18).

Some data to date supports a clinical benefit from the use of azithromycin as a systemic approach in combination with mechanical routines. In one limited study, seventeen subjects receiving azithromycin (500 mg), three days before full-mouth scaling and root planing produced greater clinical improvement than in seventeen subjects treated with full-mouth scaling and root planing only (18). Dastoor et al. studied thirty patients who reported smoking more than one pack per day and presented with periodontitis. A comparison was made between the response to treatment with periodontal surgery and 500 mg azithromycin per day for three days and treatment with periodontal surgery only. The addition of azithromycin did not enhance improvement seen in both groups for attachment gain, depth reduction and reduction of bleeding on probing. However, the adjunctive use of azithromycin was associated with a lower gingival index at two weeks and what the authors saw as more rapid wound healing. The addition of azithromycin also produced reductions of red-complex bacteria that were maintained for up to three months (19).

The combination of amoxicillin (375 mg)/metronidazole (500 mg), each taken three times per day for seven days in conjunction with full-mouth periodontal debridement performed within a 48-hour period, produced more favorable clinical effects than the same full-mouth debridement routine alone. In the subjects treated with the antibiotics, probing depths showed a greater reduction with fewer bleeding sites upon probing and a smaller number of sites requiring additional therapy at six months following initial therapy (20).

A reasonable choice of a systemic antibiotic routine, particularly in the absence of culture and sensitivity testing, may be the combination metronidazole and amoxicillin, 250 to 500 mg of each, taken three times per day for eight days. Another reasonable choice may be the combination of metronidazole and ciprofloxacin, 500 mg of each, taken twice daily for eight days. This combination adds the benefit of treatment of infections with *Aggregatibacter actinomycetemcomitans*.

Concerns are frequently raised regarding bacterial resistance with systemic antibiotic therapy (21). This holds the potential for eliminating a possibly important or critical drug from the possible treatment options for diseases with more life threatening potential than the risk of ongoing periodontal disease. It is important to remember that systemic antibiotic therapy is not intended as a monotherapy but is always best as an adjunctive therapy combined with mechanical therapy and plaque control. Management of severe types of periodontitis should not rely only on systemic antibiotics used in conjunction with mechanical debridement but may require the subgingival administration of antiseptics and/or local antibiotics as well as periodontal surgery. (9).

Local Antibiotic Therapy

After considering the risk to benefit ratio of systemic antibiotic administration as a treatment for periodontal diseases, interest in local delivery of antibiotics developed. Historically, the first such local antibiotic therapy for periodontal disease was the Actisite™(not now commercially available) fiber system. Actisite™ was supplied as hollow, nonabsorbable fibers filled with tetracycline (12.7 mg/9 inch fiber). The fiber was inserted into the pocket, wrapped repeatedly circumferentially around the tooth keeping the fiber in the pocket. Often a periodontal dressing was placed to aid maintaining the fiber in the pocket. The fiber was retained for ten days until removed by the operator. During this ten-day period drug concentrations of more than 1300 μg/ml of tetracycline were achieved and maintained. When the fiber was removed the soft tissue was often distended allowing temporary improved access and visibility of the root surfaces for any additional root planing or calculus removal. Following removal of the fiber the soft tissues generally showed shrinkage, reduction of depths and a reduction of the clinical signs of inflammation. The Actisite™ system, while very effective, was tedious to use and required a second visit for removal of the fiber. These issues fueled the development of absorbable systems for antibiotic delivery.

The first resorbable local antibiotic system was Atridox™(Atrix Laboratories). In this system, longer half-lived doxycycline replaced tetracycline supplied at a concentration of 42.5 mg per unit dose of material. This system requires mixing powder and liquid components using two linked luer lock syringes. After adequate mixing, a blunt cannula is attached to one of the syringes and the material expressed from the syringe into the pocket. Atridox™ is absorbed after seven days and reports of antibiotic concentrations of 250 μg/ml in the pocket have been reported. No second visit for removal of the material is necessary. The application of Atridox™ can be somewhat tedious as the material tends to pull out of the pocket when the syringe is removed. Retaining the material with a periodontal dressing can be helpful but is often unnecessary. Atridox™ improved the local antibiotic delivery by allowing placement of the material to the depth of most pockets and in a manner that

allowed it to conform to the shape of the pocket unlike the solid fibers of Actisite™. Depending on the size of the pocket, more than one site could be treated with a single unit dose of Atridox™.

Further development of absorbable local antibiotic systems led to Arestin™ (OraPharma) that uses minocycline in a microsphere configuration, each sphere measuring 20–60 microns in diameter. Arestin™ is supplied in single dose units that are applied into the pocket with a reusable, sterilizable syringe. Each unit dose contains 1 mg of mincocycline. The sphere is a bioabsorable polymer of polyglycolide-co-dl lactide, which is hydrolyzed into CO_2 and H_2O. The antibiotic maintains therapeutic drug levels and remains in the pocket for 14 days. This configuration of material allows placement to the depths of most pockets and while the material cannot conform to the shape of the pocket as well as the Atridox™ gel, it is still easier to use than the solid Actisite™ fibers.

Another material, not now available in the United States, is Elyzol™(Colgate), a metronidazole gel system. This material is supplied as 25% metronidazole in a glyceryl mono-oleate and sesame oil base. The concentration of Metronidazole in this system is 250 mg/g of material that is applied as a gel using a syringe method.

Overall efficacy of local antibiotic therapies has been evaluated using meta-analysis of fifty articles, each reporting studies of at least six months follow-up (22). The meta-analysis considered studies of the addition of local adjuncts and found such additions provide generally favorable but minimal differences compared to scaling and root planing alone. Additional statistically significant depth reductions of 0.1–0.5 mm may be possible and smaller, less frequently statistically significant improvement in attachment levels were noted. The clinical effects of these various systems have been reported in several publications. Table 4 summarizes several studies of various local adjunctive materials. The overall treatment effect is somewhat variable and while found to be statistically significant has not resulted in widespread use of these systems by the clinical community.

Antiseptics

The use of chemical agents with anti-plaque or anti-gingivitis action as adjuncts to oral hygiene seems to be of limited value, since mouthrinses do not appreciably penetrate into the gingival crevice, but they show specific benefits when used as adjuncts to control gingival inflammation, especially in acute situations, post-surgically and during periods of interrupted hygiene (23). The American Dental Association (ADA) Seal of Acceptance is seen as a standard for oral health care products. The ADA Seal Program ensures that professional and consumer dental products meet rigorous ADA criteria for safety and effectiveness. Guidelines have been established for the control of gingivitis and supragingival plaque (http://www.ada.org/ada/seal/index.asp). These guidelines describe the clinical, biological, and laboratory studies necessary to evaluate safety and effectiveness and are subject to revision at any time (Table 5). Importantly, they do not describe criteria for evaluating the management of periodontitis or other periodontal diseases. All claims of efficacy, including health benefit claims, (e.g. gingivitis reduction), and claims which imply a health benefit (e.g. plaque reduction) must be documented. There will be two Seal statements to be used with an Accepted product, depending on whether or not the product's mechanism of action is related to plaque reduction.

The challenge for chemical plaque control is to develop an active antiplaque agent that does not disturb the commensal microflora of the oral cavity. Oral antiseptics have evolved from short-lived (effective soon after rinsing) first generation antimicrobials (Table 6), to second generation products, which have antimicrobial effects that last for a longer time period after the mouthrinse has been expectorated (Table 7).

On the downside, it is also recognized that oral hygiene products may have the potential for producing harm in the mouth, some of which are more serious and long-lasting than others. Harms range from production of a cosmetic nuisance, such as staining resulting from the use of cationic antiseptics like chlorhexidine and cetylpyridinium chloride, to more permanent damage to the dental hard tissues through possible erosive and abrasive effects of low-pH mouthrinses and toothpastes, respectively. Of serious concern is controversially the ability to produce carcinogenic changes to the oral mucosa through the use of alcoholic mouthrinses. Recently, the potential harm of oral hygiene products to oral and systemic health was fully reviewed with reference to present-day evidence (24).

Phenolic Compounds

Among the first generation antimicrobials, the phenolic compounds, such as Listerine™ and its generic version, are the only ones that have the ADA Seal of Acceptance to prevent and reduce supragingival plaque accumulation and gingivitis. Short-term studies have shown plaque and gingivitis reduction averaging 35% (25) and long-term studies have shown plaque reduction between 13.8 and 56.3% and gingivitis reduction between 14 and 35.9% (26, 27). Possible adverse effects reported in the literature include a burning sensation, bitter taste and possible staining of teeth

Chlorhexidine

Chlorhexidine gluconate (0.12%), such as Peridex® and Periogard®, is sold in the United States by prescription only. It was the first antimicrobial shown to inhibit plaque formation and the development of chronic gingivitis (28). Chlorhexidine is more effective against gram-positive than gram-negative bacteria. It does have anti-yeast properties. It has very low toxicity, since it is poorly absorbed from the GI tract and 90% is excreted in the feces. Chlorhexidine 0.12% is indicated for short-term (less than 2 months) use, intermittent short-term (alternating on and off every 1 to 2 months) and long-term (greater than 3 months to indefinitely) use (Table 8) depending on clinical indications. Of all the products included here, chlorhexidine appears to be the most effective agent for reduction of both plaque and gingivitis, with short-term reductions averaging 60% (29). Long-term reductions in plaque averaged between 45–61% and in gingivitis, 27–67% (23). Adverse effects reported include staining of teeth, mucositis and reversible epithelial desquamation, alteration of taste, and increased supragingival calculus (29, 30).

Other Antimicrobial mouthrinses

Several other agents have been evaluated for their effect on bacterial plaque and gingivitis, but results are inferior to those of chlorhexidine and phenolic compounds (see Table 9). Pires et al. (31) have concluded that a mouthwash containing a combination of Triclosan/Gantrez and sodium bicarbonate has an *in-vitro* antimicrobial activity superior to that of a placebo, but still inferior to that of chlorhexidine. Triclosan acts as a broad-spectrum biocide, targeting multiple nonspecific targets and causing disruption of bacterial cells. Although bacterial isolates with reduced susceptibility to triclosan were produced in laboratory experiments by repeated exposure to sublethal concentrations of the agent (32), the studies on oral-care formulations, like toothpastes and mouthrinses, report no significant changes in the microbial flora or the antimicrobial susceptibility of the microflora (33, 34).

Oxygenating agents have also been evaluated. While their anti-inflammatory properties result in less bleeding on probing, a major sign of periodontal inflammation, the bacteria causing the disease are not necessarily reduced (35). Safety questions such as tissue injury and co-carcinogenicity have been raised with the chronic use of hydrogen peroxide (36).

Table 10 shows studies comparing different mouthrinses used for plaque and gingivitis reduction. Chlorhexidine is reported as the gold standard with superior effectiveness when compared to other mouthrinses and when the possible adverse effects are taken into consideration, (Table 8). If chlorhexidine is effective 60% of the time, the phenolic compounds are next in effectiveness, reducing by about 35% the plaque formation and gingivitis. Sanguinarine and the quaternary ammonium compounds are next with 18% and 15%, respectively. The oxygenating agents are the least effective, showing 0% reduction in either plaque formation or gingivitis.

Anti-inflammatory agents for management of periodontal disease

It is well established that periodontal disease is an infectious disease and that the host immune and inflammatory response to the microbial challenge mediates tissue destruction (37). Considering that the primary etiology of the disease is the bacteria in plaque and their products, mechanical and chemical approaches to reduce the presence of periodontopathogens in the plaque have been largely used in the treatment of periodontal patients over the years (38). Most recently, a better understanding of the participation of host immune-inflammatory mediators in disease progression has increased the investigation of the use of modulating agents as an adjunctive therapy to the periodontal treatment. Inhibition or blockade of proteolytic enzymes, pro-inflammatory mediators and of osteoclast activity have been outcomes measured following use of these agents, which has lead to encouraging results in pre-clinical and clinical studies (39). More specifically, three types of host-modulatory agents have been investigated for the management of periodontitis including anti-proteinases, anti-inflammatory agents, and anti-resorptive agents.

One important group of proteolytic enzymes present in the periodontal tissues is the matrix metalloproteinases (MMPs), which include collagenases, gelatinases and metalloelastases. MMPs are produced by many periodontal tissues and are responsible for remodeling the extracellular matrix (40). In 1985, tetracyclines were found to have anticollagenolytic activity and proposed as potential host modulating agents for periodontal treatment (41). Initial studies demonstrated that doxycycline was the most potent tetracycline in inhibition of collagenolytic activities (42). This property of doxycycline provided the pharmacological rationale for the use of a low or subantimicrobial dose of doxycycline (SDD) that was shown to be efficient in inhibiting mammalian collagenase activity without developing antibiotic resistance (43).

Several clinical studies have been conducted assessing the benefits of the SDD as an adjunctive therapy to scaling and root planing (SRP) in the treatment of the periodontal disease. Reddy et al. recently presented a meta-analysis (39) of 6 selected clinical studies comparing (long-term) systemic SDD (20mg bid doxycycline) to placebo control in periodontal patients. A statistically significant adjunctive benefit on clinical attachment levels (CAL) and probing depth was found when SDD was used in combination with SRP, in both 4 to 6mm and ≥ 7mm pocket depth categories. Bleeding on probing (BOP) was not assessed in the meta-analysis but, in general, SDD did not improve this parameter when compared to placebo. No significant adverse effects were reported in any of the studies.

The non-steroidal anti-inflammatory drugs (NSAIDs) represent the next major pharmacological class of agents that has been well studied as inhibitors of the host response in periodontal disease. These agents are well known for the ability to prevent prostanoid formation. In this process, arachidonic acid liberated from membrane phospholipids of cells after tissue damage or stimulus is metabolically transformed via cyclooxygenase or lipoxygenase pathways in compounds with potent biological activities (37). The cyclooxygenase enzymes are recognized to have two isoforms: cyclooxygenase 1 (COX1)

which is a constitutive enzyme present in most of cells, and cyclooxygenase 2 (COX2), which is inducible and is present in cells involved in inflammation (44). The cyclooxygenase pathway produces prostaglandins, prostacyclin and thromboxane, called prostanoids. Some prostanoids have proinflammatory properties and have been associated with destructive process in inflammatory diseases. In periodontal diseases, Prostaglandin E_2 (PGE_2) has been extensively correlated to inflammation and bone resorption (37). Its levels in gingival tissues and in the gingival crevicular fluid (GCF) have been shown to be significantly elevated in periodontally diseased patients compared to healthy patients (45, 46).

Recently, selective NSAIDs capable of inhibiting COX-2 without affecting constitutive isoform COX-1, has indicated sharing the same bone sparing effects (47–50) without inducing adverse effects associated with COX-1 suppression, such as gastroduodenal problems and renal toxicity Several clinical trials have been conducted to test the effect of NSAIDs on periodontal status. In a systematic review (39), ten clinical studies in which therapeutic outcomes of NSAIDs were expressed in clinical attachment level (CAL) or alveolar crestal height as measured by subtraction radiography were selected. In these studies a variety of different NSAIDs were systemically or locally administered, including flurbiprofen, meclofenamate, ibuprofen, ketorolac, naproxen and aspirin. Although the heterogeneity of data did not permit a meta-analysis, limited quantitative analysis tended to show alveolar bone maintenance when NSAIDs were combined with mechanical therapy. Notably, none of these studies found significantly less attachment loss after NSAIDs adjunctive therapy when compared to SRP alone.

Alveolar bone loss/destruction is the hallmark feature of periodontal disease. The use of bone-sparing drugs that inhibit alveolar bone resorption is another facet of host-modulation therapy. Bisphosphonates are a class of agents that binds to the hydoxyapatite in the bone matrix to prevent matrix dissolution by interfering with osteoclast function through a variety of direct and indirect mechanisms (51). The principal therapeutic application for bisphosphonates is in the prevention and treatment of osteoporosis and also in the treatment of Paget's disease and metastatic bone disease (52). In periodontics, their use was proposed initially for diagnostic and therapeutic use. As therapeutic agents, bisphosphonates were shown to reduce alveolar bone loss and increase mineral density but not to improve other clinical conditions in animal periodontitis models (53, 54). Five studies that assessed the effect of bisphosphonates as an adjunctive agent to SRP in human periodontal treatment were found to date (55–59). Alendronate was the bisphosphonate used in four studies during a period of 6 months. One study used risedronate during 12 months (59). All the studies presented significant clinical improvement when compared to placebo, including: probing depth reduction, clinical attachment gain, bleeding on probing reduction, alveolar bone gain and increase in bone mineral density. These results encourage the use of bisphosphonates as an adjunctive agent to periodontal therapy. Additional more long term studies need to be implemented to confirm the benefits of these drugs.

Recently, high-dose and long-term use of bisphosphonates has been reported to be associated with osteonecrosis of the jaw (ONJ) (60, 61). Data from multiple sources indicates that patients with prior dental problems may have a higher risk of ONJ. However, as more data is being reported, it still remains controversial that bisphosphonates indeed are causative for ONJ. Since bisphosphonates are potent osteoclast inhibitors, their long-term use may suppress bone turnover and compromise healing of even physiologic micro-injuries within bone (62). Despite the encouraging therapeutic results to manage periodontal disease further long-term studies are warranted to determine the relative risk-benefit ratio of bisphosphonate therapy.

Future Non-Surgical Approaches

A variety of treatment strategies have been developed to target the host response for the management of periodontitis. MMP inhibitors such as low dose formulations of doxycycline have been used in combination with scaling and root planing (63) or surgical therapy (64). In addition, high-risk patient populations such as diabetics or patients with recurrent periodontal disease have benefited from systemic MMP administration (65–67). Encouraging results have been obtained following soluble antagonists of TNF and IL-1 delivered locally to periodontal tissues in nonhuman primates (68, 69). Other therapeutic strategies that are being explored are aimed at inhibiting signal transduction pathways involved in inflammation. Pharmacological inhibitors of NF-kB and p38 mitogen activating protein (MAP) kinase pathways are actively being developed to manage inflammatory bone diseases (70, 71). p38 inhibitors have already shown promise in preclinical models of periodontal diseases (2, 72). Using this novel strategy, inflammatory mediators including proinflammatory cytokines (IL-1, TNF, IL-6), MMPs and others would be inhibited at the level of cell signaling pathways required for transcription factor activation necessary for inflammatory gene expression or mRNA stability. These therapies may provide the next generation of adjuvant chemotherapeutics to manage chronic periodontitis.

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Table 1

Systemic antibiotics often used as adjuncts to mechanical periodontal therapy

Antibiotic Class	Agent	Effect	Target Organisms	Limitation
Penicillin	Amoxicillin	Bacteriocidal	Gram + and Gram −	Penicillinase sensitive Patient hypersensitivity
	Augmentin	Bacteriocidal	Narrower spectrum than Amoxicillin	More expensive than Amoxicillin
Tetracycline	Tetracycline	Bacteriostatic	Gram + > Gram −	Bacterial resistance
	Minocycline	Bacteriostatic	Gram + > Gram −	
	Doxycycline	Bacteriostatic	Gram + > Gram −	
Quinolone	Ciprofloxacin	Bacteriocidal	Gram − rods	Nausea, GI discomfort
Macrolide	Azithromycin	Bacteriostatic OR Bacteriocidal depending on concentration	Broad spectrum	
Lincomycin	Clindamycin	Bacteriocidal	Anaerobic bacteria	
Nitroimidazole	Metronidazole	Bacteriocidal to Gram −	Gram −; esp. *P. gingivalis* and *P. intermedia*	Not good choice for *A. Actinomycetemcomitans* infections

Table 2

Systemic Antibiotic Dosing Regimens

Single Agent	**Regimen**	**Dosage/Duration**
Amoxicillin	500 mg	Three times per day × 8 days
Azithromycin	500 mg	Once daily × 4–7 days
Ciprofloxacin	500 mg	Twice daily × 8 days
Clindamycin	300 mg	Three times daily × 10 days
Doxycycline or Minocycline	100–200 mg	Once daily × 21 days
Metronidazole	500 mg	Three times daily × 8 days
Combination Therapy		
Metronidazole + Amoxicillin	250 mg of each	Three times daily × 8 days
Metronidazole + Ciprofloxacin	500 mg of each	Twice daily × 8 days

Table 3

Local Antibiotic Delivery Systems

Antimicrobial Agent	Delivery Form	Drawback	GCF Concentration	Time to Absorption	Brand Name
Tetracycline 12.7 mg per nine inches of fiber	Hollow fibers	Must be removed	>1300 ug/ml for 10 days	Not absorbable	Actisite- not commercially available
10% Doxycycline	Fluid; multi-site depending on volume of site; in syringe	Often pulls out when removing syringe	250 ug/ml still noted at 7 days	21 days	Atridox
25% Metronidazole Gel	Fluid; multi-site depending on volume of site; in syringe	May require multiple applications for desirable results	More than 120 mg/ml of sulcus fluid in the first few hours	Concentration decreases rapidly after the first few hours (73)	Elyzol
2% Minocycline Spheres	Solid; in unit doses applied with syringe	Unit doses may not be sufficient for every site volume	Therapeutic drug levels for 14 days	14 days	Arestin
0.5% Azithromycin	Gel in syringe		Peak at 2 hrs at 2041 ug/ml decreased from 324 ug/ml on day 7 to 3 ug/ml on day 28	Still present at 28 days	Not commercially available

Table 4

Local Antibiotic System Studies

Agent	Subjects	Depth Change with S/RP Only	Depth Change with S/RP + Agent	Sites With At Least 2 mm Attachment Gain with S/RP + Agent
Tetracycline Fibers (74)	107	0.67	1.02 (fiber only)	Not reported
Doxycycline gel (75)	411	1.08	1.30 (drug only)	38% (drug only)
Doxycycline gel (76)	105	1.3	1.5	52%
Doxycycline gel (77)	48	1.5–2.19	1.63–2.29	34.4% vs. 18.1% S/RP only
Minocycline spheres (78)	728	1.08	1.32	42%
Minocycline spheres (79)	127	1.01	1.38	Not reported; reports attachment gain of 1.16 with agent, 0.8 S/RP only
Metronidazole gel (80)	206	1.3	1.5 (drug only)	Not reported
Azithromycin gel (81)	80	2.13	2.53	Not reported; reports greater gain at all time points with agent

Table 5

Guidelines for ADA acceptance of chemotherapeutic products for the control of gingivitis and supragingival dental plaque (http://www.ada.org/ada/seal/index.asp)

Product efficacy must be demonstrated by two independent, well-designed, 6-month clinical studies utilizing a placebo control and conducted by independent investigators.
All published studies assessing the effectiveness of the product must be referenced, including studies that do not show any effect.
All proprietary studies, including those that do not show any effect, must also be provided.
Studies should assess the ability of a chemotherapeutic agent to prevent or reduce gingivitis and to inhibit or reduce plaque formation or plaque pathogenicity.
Masked studies are required; uniquely labeled products must be used and group coding must be avoided.
At least one study shall be conducted on a US population.
Populations selected for the studies must be representative of individuals for whom the product is intended, which, in most cases, would be individuals with mild to moderate gingivitis.
Trials must report all treatment groups.
Statistically significant reductions in both the clinical manifestations of gingivitis and in the inhibition or reduction of plaque or plaque pathogenicity related to gingivitis must be demonstrated.
Reductions relative to plaque and gingivitis should be demonstrated after 6 months of use in two studies and be measured against a placebo control rather than baseline scores.
The product must show clinical significance in gingivitis reduction compared to placebo controls in at least two clinical studies.
Microbiological sampling should estimate plaque qualitatively to complement indices that measure plaque quantitatively.
Gingivitis measurements shall demonstrate: **1** that the estimated proportionate reductions [i.e. (control–active)/control] be no less than 15% in favor of the active treatment with a confidence interval of ± 10%, and statistically significant in each of at least two studies; **2** that, in addition, the (arithmetic) mean of the estimated proportionate reductions [i.e. (control–active)/control] across the above studies be no less than 20%.
Plaque measurements shall demonstrate that quantitative plaque reductions or reductions in plaque pathogenicity for those products whose antigingivitis action is through plaque reduction or modifications are statistically significant.
The most likely mechanism(s) of action of the product should be given, with supporting data.

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Table 6

First Generation Antimicrobials

Antimicrobial	Commercial Name	ADA Seal of Acceptance	Active ingredients	Alcohol content	Mechanism of Action	Efficacy published by the manufacturer
Phenolic Compounds	Listerine (Johnson & Johnson)	Yes	Essential oils: • Thymol (0.06%) • Eucalyptol (0.09%) • Methyl salicylate (0.06%) • Menthol (0.04%)	26.9%	Appears to be related to alteration of the bacterial cell wall	52% plaque reduction 36% gingivitis reduction (http://www.listerine.com/)
Sanguinarine	Viadent (Colgate)	No	0.03% Sanguinarine extract	5.5%	Alteration of bacterial cell surfaces so that aggregation and attachment is reduced	28% plaque reduction 24% gingivitis reduction (http://www.colgateprofessional.com/products/Viadent-Advanced-Care-Oral-Rinse/details)
Quaternary Ammonium Compounds	Cepacol and Scope (Procter & Gamble)	No	Cepacol: 0.05% CPC Scope: 0.045% CPC + 0.005% domiphen bromide	Cepacol: 14% Scope: 18.9%	Related to increased bacterial cell wall permeability which favors lysis, decreased cell metabolism and a decreased ability for bacteria to attach to tooth surfaces.	15.8% plaque reduction 15.4% gingivitis reduction (http://www.cepacol.com/products/mouthwash.asp) and (http://www.pg.com/product_card/prod_card_main_scope.shtml)

Table 7

Second Generation Antimicrobials

Antimicrobial	Cetylpyridinium chloride	Chlorhexidine
Commercial Name	Crest Pro-Health (Procter & Gamble)	Peridex (3M Espe) Periogard (Colgate)
ADA Seal of Acceptance	No	Yes
Active ingredients	0.07% CPC	0.12% Chlorhexidine gluconate (http://solutions.3m.com/wps/portal/3M/en_US/preventive-care/home/products/home-care-therapies/peridex/) and (http://www.colgateprofessional.com/products/Colgate-Periogard-Rinse-Rx-only/details)
Mechanism of Action	Bactericidal agent interacts with the bacterial membrane. The cellular pressure disrupts the cell membrane and effectively kills the bacteria.	Positively charged chlorhexidine molecule binds to negatively charged microbial cell wall, altering osmotic equlibrium, causing potassium and phosphorous leakage, precipitation of cytoplasmic contents and consequent cell death.
Efficacy published by the manufacturer	Similar to Listerine (http://www.dentalcare.com/soap/products/index.htm)	Certain aerobic and anaerobic bacteria reduction from 54 – 97% through six months use (http://solutions.3m.com/wps/portal/3M/en_US/preventive-care/home/products/home-care-therapies/peridex/) • 29% gingivitis reduction • 54% plaque reduction (http://www.colgateprofessional.com/products/Colgate-Periogard-Rinse-Rx-only/details)

Table 8

Chlorhexidine 0.12% Indications

Short-term indication (less than 2 months)	Intermitent short-term indications (alternating on and off every 1 to 2 months)	Long-term indications (greater then 3 months to indefinitely)
Gingivitis	Gingivitis	Patients with reduced resistance to bacterial plaque: AIDS, leukemia, kidney disease, bone marrow transplants, agranulocytosis, thrombocytopenia
Following periodontal and oral surgery	Periodontal maintenance	Physically handicapped patients: rheumatoid arthritis, scleroderma, disturbance of muscles and/or motor capacity and coordination
During initial periodontal therapy	Physically and/or mentally handicapped	Patients treated with: cytotoxic drugs, immunosuppressive drugs, radiation therapy.
Treatment of candidiasis	Extensive prosthetic reconstruction	

Table 9

Other antimicrobial mouthrinses

Antimicrobial	Commercial Name	ADA Seal of Acceptance	Active ingredients	Mechanism of Action	Efficacy
Oxygenating agents	Peroxyl (Colgate)	No	Hydrogen Peroxyde	Anti-inflammatory properties reduce bleeding on probing, a major sign of inflammation; bacterial load is not necessarily reduced; bubbling action cleans and alleviates discomfort to promote healing.	Long-term studies do not support effectiveness. Short-term studies offer contradictory findings.
Chlorine Dioxide	RetarDEX (Periproducts) Oxyfresh	No	1% chlorine dioxide	Stable, free radical and an oxidant with algicidal, bactericidal, cysticidal, fungicidal, sporicidal, and viricidal properties.	Minimal plaque reduction, but has shown decreases involatile sulfur compounds and halitosis.
Zinc Choride	Breath Rx	No	• Zinc chloride • Phenolic oils (Thymol and Eucalyptus oil)	Zinc has an affinity to sulfur and odorizes sulphydryl groups with zinc ions forming stable mercaptides with the substrate, the precursors, and/or the volatile sulfur compounds directly.	BreathRx is a scientific bad breath treatment specially designed to help treat both the causes of bad breath and the symptoms.
Triclosan	Not available in the US	N/A	Triclosan	A low toxicity, non-ionic phenolic derivative with a wide spectrum of antimicrobial and anti-inflammatory activities (82).	*In vitro* studies show antimicrobial activity superior to that of a placebo, but inferior to that of chlorhexidine (31)

Table 10

Comparison studies

Antiseptics compared	Methodology	Results	References
Listerine Viadent Peridex Placebo	31 volunteers with healthy gingiva ceased all oral hygiene procedures but rinsing with the designated mouthrinse for 21 days	Peridex was superior inits ability to maintain optimal gingival health during the entire time of mouthrinse use.	Siegrist et al. (83)
Listerine Peridex Placebo	Double-blind, controlled clinical trial. After a baseline complete dental prophylaxis, 124 healthy adults used the mouthrinse as a supplement to regular oral hygiene for 6 months.	Both Listerine and Peridex significantly inhibited development of plaque by 36.1% and 50.3%, respectively, and the development of gingivitis by 35.9% and 3.0.5% respectively, compared to placebo.	Overholser et. (30)
Chlorhexidine 0.12% Hydrogen Peroxide 1% Placebo	32 subjects ceased oral hygiene procedures, but rinsed, twice a day, with the designated mouthrinse for 21 days.	The chlorhexidine group showed 95% reduction in gingivitis incidence, 100% reduction in BOP, and 80% reduction in plaque scores compared to placebo.	Gusberti et al. (35)