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Review

Therapeutic strategies in the treatment of periodontitis

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Abstract

Periodontitis is a chronic inflammatory process which affects the tooth - supporting structures of the teeth. The disease is initiated by subgingival periopathogenic bacteria in susceptible periodontal sites. The host immune response towards periodontal pathogens helps to sustain periodontal disease and eventual alveolar bone loss**.** Although scaling and root planing is the standard treatment modality for periodontitis, it suffers from several drawbacks such as the inability to reach the base of deep pockets and doesn't arrest migration of periodontal pathogens from other sites in the oral cavity. In order to overcome the limitations of scaling and root planning, adjunctive chemotherapeutics and host modulatory agents to the treatment are used. These therapeutic agents show substantial beneficial effects when compared to scaling and root planning alone. This review will cover an update on chemotherapeutic and past and future host immune modulatory agents used adjunctively to treat and manage periodontal diseases.

Keywords: periodontitis, periodontal therapy, antibiotics, antiseptics, host modulatory agents

Introduction

Periodontal disease is a chronic infection of the periodontium that affects the soft and mineralized tissues surrounding the teeth (Hajishengallis and Lambris, 2012). Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis (Schwach-Abdellaoui et al., 2000). Together with dental caries, periodontal disease is the most common chronic disease in the dental fields being severe enough to lead to tooth loss in 10 - 15% of adults (Kantarci and Van Dyke, 2005). Recent studies have shown that several systemic illnesses such as rheumatoid arthritis and cardiovascular disease might be also linked to the presence of periodontitis (Kinane and Lowe, 2000).

The clinical signs of periodontitis include inflammatory changes in gingival tissues, bleeding upon probing, attachment loss and periodontal pocket formation. Periodontal pockets provide nutritious and anaerobic environment for the so called periopathogenic bacteria colonization and multiplication (Schwach-Abdellaoui et al., 2000). Among the 700 bacterial taxa that have been identified to inhabit periodontal pockets, only a small group of 10 to 15 species has been identified as being significantly associated with periodontitis (Slots, 2002). The bacterial microflora found in periodontits is complex; moreover studies have shown that the various clinical forms of periodontitis are associated with different periopathogenic bacteria (Haffajee and Socransky, 1994). The most important periodontal pathogens are Gram negative, facultative anaerobic species such as *Actinobacillus actinomycetemcomitans, Porphyromo-*

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nas gingivalis, Dialister pneumosintes, Bacterioides forsythus and *Treponema denticola* (Slots, 2002; Jain et al., 2008).

Scientific research aimed at elucidation of etiopathogenesis of periodontal disease implies that periodontal disease is an inflammatory condition caused by the accumulation of periopathogenic bacteria on tooth surfaces in the form of oral biofilms (Bostanci et al., 2011). The subgingival bacterial colonization and biofilm formation provokes chronic inflammation of soft tissues, degradation of collagen fibres supporting the tooth to the gingival and alveolar bone as well as resorbtion of the alveolar bone itself (Krayer et al., 2010).

Although bacteria are the primary etiological cause of periodontal disease, the expression of bacterial pathogenic factors alone is probably not sufficient to cause periodontitis. Immunopathogenesis of periodontitis, similar to inflammatory bowel disease is hypothetised to involve immune-inflammatory pathways in both diseases. It has been found that individual response is affected by genetic signaling pathways that influence the expression of inflammatory mediators in response to bacterial lypopolysaccharides (Goracinova et al., 2012).

As discussed by Brandztaeg P., progressive immunopathology of chronic inflammatory mucosal diseases in general appears to be a result of perturbation of a tightly controlled cytokine network with abnormal crosstalk between several cell types (Brandztaeg, 2001).

Tissue destruction is a result of the mobilization of host tissues via activation of monocytes, fibroblasts and other host cells. The activation of these host cellular elements by bacterial factors, in particular bacterial lipopolysacharide (LPS), is thought to stimulate both catabolic cytokines (TNF- α, IL-1, IL-6) and inflammatory mediators including arachidonic acid metabolites such as prostaglandin E_2 (PGE_2). These cytokines and inflammatory mediators in turn promote the release of tissue-derived enzymes, matrix-matalloproteinases, which are destructive to the extracellular matrix and bone. Also, evidence indicates that periodontal disease is an autoimmune disorder triggered by infectious organisms and an abnormal response to collagen in the periodontium. Current research in periodontal pathobiology has identified a novel cytokine, IL-17 which is thought to play an important role in triggering autoimmune responses (Suresh, 2011).

The treatment of periodontal disease as an infection has been well studied through the years. This so called antimicrobial approach includes local or systemic delivery of antimicrobial agents (local/ systemic antibiotics) or topical antiseptics. These treatment strategies however may be insuficient to block or inhibit the host mediated tissue destruction of the periodontium.

The current concept in periodontal treatment emphasizes on host - microbial interactions to understand the disease process, as well as to develop novel therapeutic strategies known as host modulatory therapies (Krayer et al., 2010). The development of effective host-modulatory pharmacotherapies that specifically target the host response mechanisms and the introduction of such therapies as an adjunct to traditional antimicrobial interventions might represent a new, integrated approach in the management of periodontal disease. This rewiev will cover current antimicrobial therapy as well as the possibilities for future developments in the treatment of periodontal disease.

Antimicrobial approach in the treatment of periodontitis

Systemic antibiotics

The traditional antimicrobial treatment of periodontitis consists mainly of mechanical debridement (scaling and root planning, SRP) of root surfaces in order to disrupt the bacterial biofilm (Herrera et al., 2012). This antimicrobial procedure usually stops the progression of attachment loss but in patients who are infected by invasive periopathogenic bacteria (*Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis* or *Prevotella intermedia*) it is impossible to gain therapeutic benefit using mechanical debridgement only.

Systemic antibiotics are of particular benefit in combating severe forms of periodontal disease such as aggressive periodontitis and necrotizing periodontitis (Slots, 2002). Prime candidates for systemic antibiotic therapy are patients who exhibit continuous periodontal breakdown and alveolar bone loss despite mechanical debridement.

Systemic antibiotics enter periodontal tissues and the periodontal pockets via serum and can affect organisms outside the reach of cleaning instruments or topical anti-infective chemotherapeutics. They have the advantages of conventional and acceptable delivery for the patients (Krayer et al., 2010). Systemic antibiotic therapy has also the potential to suppress periodontal pathogens residing on the tongue or other oral surfaces, thereby delaying subgingival recolonisation of pathogens (Slots, 2002).

The administration of systemic antibiotics in the periodontal treatment has been well studied and documented. Early approaches to systemic antibiotics in periodontal treatment included mainly single drug therapies. Systemic antibiotic monotherapies include administration of amoxicillin, metronidazole, tetracyclines (doxycycline), clindamycin, azitromycin, claritromycin and ciprofloxacin as an adjunct to mechanical debridement. Since periodontal lesions often harbor a mixture of pathogenic bacteria, today's approach recommends, where necessary, usage of combinations consisting of two antibiotics (Slots, 2002; Slots & Ting, 2002).

Current literature supports the clinical benefit from the use of azithromycin as a systemic antibiotic in combination with mechanical mechanical debridgement (Hirsch et al., 2011). The addition of azithromycin in periodontal therapy reduces the red complex bacteria and gives rapid wound

healing (Krayer et al, 2010; Dastoor et al., 2007). Some evidence exists to support the use of azithromycin in the treatment of periodontitis because of its anti-inflammatory effects on the gingiva. The fact that systemic administration of azitromycin produces relatively high and sustained levels in gingival crevicular fluid (GCF) could provide a rationale for future clinical evaluation of its benefit in the treatment of periodontitis (Lai et al., 2011).

Claritromycin, a closely related macrolide to azythromycin, is actively transported and concentrated inside oral epithelial cells and gingival fibroblasts reaching higher concentrations in gingival tissue when compared with those obtained in serum (Lai et al., 2011; Chou and Walters, 2008; Burell and Walters, 2008). Current findings suggest that this antibiotic could be of particular value in periodontitis assotiated with infections caused by *A. actinomycetemcomitans*.

Clindamycin (lincosamide) inhibits the bacterial protein synthesis by binding to the 50S ribosomal unit. Depending on the local drug concentration and the susceptibility of bacteria, clindamycin has either bacteriostatic or bactericidal effect. Due to its potential to cause serious adverse effects, such as pseudomembraneous colitis, this therapy should be considered only in patients suffering from aggressive and/or refractory periodontitis (Horz and Conrads, 2007).

Other systemic monotherapies consist of administration of fluoroquinolones which are bactericidal and interfere with bacteria DNA packaging, transcription and replication. Older quinolones such as ciprofloxacin are only recommended as part of the combined therapies. Newer quinolones such as moxifloxacin and levofloxacin have an extended spectrum of activity and serve as "reserve antibiotics" in intensive care patients. Their regular prescription even in the cases of aggressive periodontits cannot be recommended (Horz and Conrads, 2007).

Valuable combination therapies include metronidazole-amoxicillin (250-375 mg of each 3 x daily for 8 days) for *A. actinomycetemcomitans* or metronidazole-ciprofloxacin (500 mg of each 2 x daily for 8 days) for mixed anaerobic infections (Slots and Ting, 2002).

The combination of metronidazole-amoxicillin is known as the "van Winkelhoff combination". In conjunction with scaling and root planning (SRP), it provides a substantial benefit than SRP alone. In addition, the data from Slots and Ting suggest that this combination is suitable choice for approximately 70% of severe periodontitis patients (Slots and Ting, 2002).

The combination of metronidazole-ciprofloxacin has been suggested as an adjunctive therapy for periodontal infections when enteric rods, pseudomonas or *A. actinomycetemcomitans* are present or in the cases of penicillin allergy. Another combination that can be of use is amoxicillin + clavulanic acid/metronidazole, however, no real advantage over metronidazole-amoxicillin is observed in the majority of periodontal cases (Horz and Conrads, 2007). Commonly used antibiotics and their dosage in adult periodontitis are shown in Table 1.

Research data have shown that antibiotics are detectable in GCF in the therapeutic range for treatment efficacy. However, disadvantages include inadequate drug concentration in the periodontal pocket, rapid decline of the plasma antibiotic concentration to subtherapeutic levels, high peak plasma concentration that might be associated with side effects. Another frequently overlooked factor is that systemic antibiotics do not penetrate the subgingival biofilm to kill bacteria.

Concerns are raised regarding periopathogenic bacterial resistance with systemic antibiotic therapy. Therefore, systemic antibiotic therapy should be administered only after proper patient evaluation. Systemic antibiotic therapy that is properly selected to patients with aggressive periodontitis can give rise to a striking clinical outcome. In patients with chronic periodontitis, the utility of systemic antibiotics is not as clear. Patients with gingivitis or chronic periodontitis who respond well to conventional scaling and root planning may not benefit significantly from additional antibiotic therapy.

Table 1. Antibiotics used frequently in the treatment of periodontal diseases

Antibiotic	Dosage in adult periodontitis
Metronidazole	500 mg three times daily
Clindamycin	150 mg three times daily for eight days
Penicillins (amoxicillin)	250-500 mg three times daily
Tetracyclines (doxycycline)	200 mg initially, 100 mg for seven days
Azithromycin	250-500 mg for three days
Claritromycin	500 mg 2 x daily for three days
Fluoroquinolones (ciprofloxacin)	500 mg twice a day for eight days
Amoxicillin/Metronidazole	250-375 mg of each 3 x daily for 8 days
Metronidazole/Ciprofloxacin	250 mg of each 2 x daily for 8 days
Amoxicillin + clavulanic acid/metronidazole	250 mg 3 x daily for 8 days

Local antimicrobials

Advances in understanding the etiology and pathogenesis of periodontits have led to the development of effective pharmacological interventions. In this regard, safe and efficacious medications can be delivered into periodontal pockets to suppress or eradicate the periopatogenic bacteria or modulate the immune response, thereby limiting periodontal tissue destruction.

Local delivery formulations are of particular use in cases where systemic drug application seems inappropriate, such as localised periodontitis (Horz and Conrads, 2007). They are highly desirable due to lower incidence of undesirable side effects, improved efficacy and enhanced patient compliance.

Drug delivery devices intended for the periodontal pockets can be made as fibers, strips, films, injectable gels, micro/nanoparticulate systems or vesicular systems (Schwach-Abdellaoui et al., 2000; Jain et al., 2008). Tetracycline-HCl, doxycycline, minocycline, metronidazole, chlohexidine and ofloxacin are among the antimicrobials that have been used in the formulation of local delivery devices for direct pocket placement in the treatment of periodontitis. Some of the commercially available local delivery systems for periodontal treatment and their characteristics are given in Table 2.

Although many publications on the local delivery concept have appeared in periodontal literature since 1970s, there are surprisingly few studies that demonstrate clinical efficacy using controlled release local delivery systems in periodontitis patients. Despite the reported clinical success, currently available controlled release formulations suffer from several disadvantages: the requirement for mechanical binding of the drug delivery system to a tooth surface to prevent removal of the system from the periodontal pocket as a result of the positive flow of GCF from the pocket into the oral cavity; the requirement for removal of tooth-bound, non-biodegradable drug delivery systems at the termination of the treatment, poor retention of oil-based delivery systems within the aqueous environment of the periodontal pocket and potential deleterious effects of plasticizers leached from solid polymeric drug delivery systems on the periodontal tissues. In conclusion, the publications dealing with efficacy studies suggest that the controlled delivery devices are useful adjunct to conventional surgical and non-surgical treatment but are no substitute for these measures. Even though scientific evidence would support the adjunctive use of local antimicrobials in these clinical indications, there are some important issues that might limit their effectiveness: clinical management properties, as some products are difficult to handle and require extensive dental office time; pharmacokinetic profiles, as some products have short-term duration in the pocket and are cleansed by the GCF, which requires a high number of chair visits to sustain their antibacterial activity (Herrera et al., 2012).

Topical antiseptics

Topical antiseptics represent a group of agents which applied to living tissues are able to prevent or arrest the growth or action of microorganisms. Antiseptics possess broader activity spectrum than antibiotics and in contrast to antibiotics, often have multiple intracellular targets which reduce likelihood of resistance development (Slots, 2002).

Table 2. Commercially available local delivery systems for periodontal treatment

Commercial product	Local delivery system	Therapeutic compound	Application	Advantages
Actisite™	Nonabsorbable Fiber	25% tetracycline HCl	1 application 7 day treatment Chairside	Bactericidal High levels of tetracycline in GCF
Atridox™	Gel	10% doxycycline hyclate	1 application 7 day treatment Chairside	Forms solid implant Biodegradable bactericidal
Arestin™	Microspheres	1mg minocycline HCl	1 application 14 day treatment Chairside	Bioadhesive Biodegradable Bactericidal
Periocline® Dentomycin®	Gel	2% minocycline HCl	1 application 14 day treatment Chairside	Bioadhesive Biodegradable bactericidal
Periochip®	Thin, solid, chip	2.5 mg chlorhexidine digluconate	1 application 7 day treatment Chairside	Biodegradable bactericidal
Elyzol®	Gel	25% metronidazole benzoate	2 applications 7 day treatment Chairside	Biodegradable bactericidal

Povidone-iodine

The broad spectrum antibacterial properties of povidone-iodine are well known in medicine. This compound is effective against various periodonthopatic bacteria and against cytomegalovirus activity, a herpes virus implicated in the pathogenesis of periodontitis. Povidone-iodine does not exhibit adverse side effects such as discoloration of teeth and tongue or change in taste as seen with chlorhexidine. It has low potential for developing resistance and adverse effects, broad availability; it is easy to use and has low financial cost. For subgingival irrigation in the treatment of periodontitis, an effective concentration is 10% povidone-iodine is applied repeatedly by an endodontic syringe to obtain a contact time of at least 5 min. Investigators have also reported a favorable clinical outcome after treating advanced periodontitis with subgingival povidone-iodine and systemic antibiotics (Gossi et al., 1997; Slots, 2002).

Sodium hypochlorite

Sodium hypochlorite has been used as an endodontic irrigant for more than 75 years. Sodium hypochlorite has many of the properties that an ideal antimicrobial agent should possess: broad antimicrobial activity, rapid bactericidal action, relative non-toxicity at use concentrations, no color or staining, ease of access and very low cost. No contraindications have been observed. That sodium hypochlorite application might improve periodontal histological healing was suggested by Perova et al. (Perova et al., 1990). Considering sodium hypochlorite significant antimicrobial properties and good safety profile and the promising reaserch data, it seems logical to recommend hypochlorite subgingival irrigation as part of patient's oral self-care regimen.

Chlohexidine

The use of chlohexidine as an auxiliary antibacterial and antifungal agent in dentistry has a long tradition and has been well documented. As a highly cationic compound, it remains on oral surfaces for a prolonged period after a single usage.

Chlohexidine is a diphenyl compound that is effective against bacteria and exhibits limited activity against viruses. Chlorhexidine gluconate (0,12%), such as Peridex® and Periogard®, is sold in the United States by prescription only. It is more effective against Gram positive than Gram negative bacteria. Chlorhexidine 0,12% is indicated in short-term (less than 2 monts) use, intermittent short-term (alternating on and off every 1 to 2 monts) and long term use (longer than 3 months), depending on clinical conditions. Unfortunatelly, even low concentrations may be toxic to gingival fibroblasts and reduce the production of collagen and non-collagen proteins, potentially impeding periodontal healing (Marrioti and Rumpf, 1999).

Corticosteroids for local application on the periodontium

Corticosteroids are a group of drugs that has been used in every aspect of clinical medicine due to their potent anti-inflammatory and immunosuppressant properties (Savage and McCullogh, 2005).

The anti-inflammatory action of administered corticosteroids are as a result of several different mechanisms. Topically, their predominant anti-inflammatory action appears to be on eicosanoid formation. Corticosteroids stimulate the production of various polypeptides, collectively called lipocortin that inhibits phospholipase A2 activity. Another corticosteroid induced-complex, vasocortin has been found to inhibit oedema formation. Corticosteroids are thought to in some ways stabilize lysosomal membranes, thus suppressing the release of lytic enzymes (Fachin et al., 2009).

Several animal studies have confirmed that systemic administered steroids have adverse effects on the periodontium and its response to bacterial plaque (Seymour, 2006). Experimental studies have demonstrated that the use of systemic corticosteroids can provoke many conditions, from gingival ulceration to the downmigration of the epithelium, attachment loss and disruption of transseptal fibers (Garsia et al., 2010).

There are few studies that address the effect of locally applied corticosteroids on periodontal healing. When steroids are injected directly into the gingival tissue, they cause a histological reduction in capillary permeability, a reduction in plasma cells and granulation tissue, an inhibition of collagen synthesis and a clinical improvement in hemmoragic and hypoplastic gingivitis (Safkan and Knuuttila, 1984). Although studies about local application of corticosteroids are scarse in literature, current research data suggest that corticosteroids show favorable effect on periodontal healing and posses antiresorbtive effects. Dexamathasone directly affects osteoclast formation and activity, stimulating the proliferation and differentiation of human osteoclast precursors, and inhibiting the bone resorbtion activity in mature osteoclasts (Hirayama et al., 2002). Teeth treated with 0.05% clobetasol and 0.05% fluocinonide show favorable periodontal healing; the higher potency corticosteroid clobetasol exerts more favorable healing than the lower potency fluocinonide. It remains unclear whether the antiresorbtive effect of these compounds can be further enhanced by using corticosteroid with increased potency and its anti-inflammatory properties. Although concern exists that the use of corticosteroids locally in the periodontium may induce hypothalamus-pituitary-adrenal axis, it has been reported that the highest possible amounts used are unlikely to result in any systemic side effect (Kirakozova et al., 2009).

Budesonide is a new generation corticosteroid with potent local anti-inflammatory effect which could be used in the treatment of periodontal disease. Animal studies have

shown that inhaled budesonide could not modulate periodontal breakdown. This might be due to inappropriate formulation and dosage. Additional studies are needed to estimate the effects of budesonide on the oral mucosa and the periodontium (Daudt et al., 2011).

While topical application of corticosteroids for skin disorders is well documented, there is considerably less critical information available for lesions of the oral mucosa, including periodontal disease. Therefore, there is a need for further research into therapeutic systems that improve local delivery of corticosteroids to oral mucosa and periodontium as well as controlled clinical studies in order to evaluate the clinical effectiveness of these formulations attended for treatment of periodontal lesions.

Host modulatory therapies

In periodontal disease, typical antimicrobial intervention procedures, such as scaling and root planning (SRP), boast some success in removing etiologic agents associated with inflammation, thereby helping to arrest periodontitis. However, such procedures do not inhibit the host mediated tissue destruction and do not offer necessary resolution of inflammation to restore tissue homeostasis (Van Dyke, 2008).

Ever since 1985, research in periodontics has been focused closely on bacterial-host interaction, leading to "host-bacterial interrelationship era". During this era it was recognized that although there is evidence that specific bacterial pathogens initiate pathogenesis of disease, the host response to these pathogens is equally important in mediating connective tissue breakdown and bone loss. It has become evident that host-derived inflammatory mediators such as matrix metalloproteinases (MMPs), cytokines and other inflammatory molecules such as PGE_2 are responsible for the majority of tissue destruction in the periodontium.

This shift has led to the development of the so called Host Modulatory Therapies (HMT) which can improve therapeutic outcomes, slow the progression of the disease, allow for more predictable management of patients and possibly even work as preventive agents against the development of periodontits (Thompson, 2001; Reddy et al, 2011).

In the last two decades scientists have investigated various host modulating strategies in both animal and human experimental models. Up to date, specific aspects considered for modulation of periodontitis pathogenesis include:

- regulation of production of arachidonic acid metabolites
- regulation of bone remodeling
- regulation of matrix metalloproteinase (MMPs) activity
- regulation of nitric oxide synthase activity

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Arachidonic acid (AA) is a 20-carbon polyunsaturated fatty acid (eicosanoid) liberated from membrane phospholipids by the action of phospholipase A_2. Free AA is metabolized via cyclooxygenase (COX) or lypooxygenaze (LO) pathways. AA is enzymatically oxidized by COX leading to synthesis of prostanoids (prostaglandins, prostacyclin and tromboxan) or by the action of LO to form leukotrienes. Over decades, AA metabolites have been established as mediators of tissue destruction in various inflammatory conditions such as rheumatoid arthritis and periodontal disease.

The non-steroidal anti-inflammatory drugs are a group of pharmacological agents that has been well studied as an inhibitor of the host response in periodontal disease. These agents have been shown to prevent formation of arachidonic acid metabolites, especially prostaglandins which have an important role in the pathogenesis of periodontitis (Salvi and Lang, 2005; Kirkwood et al., 2007).

In vitro and *in vivo* preclinical studies using NSAIDs have shown the extensive ability of these drugs to reduce prostanoid formation by inhibiting COX enzymes. Suppression of osteoclast differentiation, as measured by decreased osteoclast numbers and concomitant decreased alveolar bone resorbtion, is the most frequent sequela following systemic or local delivery of NSAIDs (Kirkwood et al., 2007).

Several adjunctive clinical trials have been conducted with NSAIDs. In a systematic review (Reddy et al., 2003), ten clinical studies, in which the therapeutic outcome of NSAIDs were expressed as clinical attachment level or alveolar crestal hight were selected. In these trials, a variety of different NSAIDs, including flubiprofen, meclofenamate, ibuprofen, ketorolac, naproxen and aspirin, were systemically or locally administered. The limited quantitative analysis tended to show significant benefit related to alveolar bone preservation when NSAIDs were associated with conventional therapy.

More recently, a selective COX-2 inhibitor (nimesulide)/scaling and root planning therapy was compared with a non-selective COX inhibitor (naproxen)/scaling and root planning on periodontal clinical parametars and on gingival tissue levels of prostaglandin E_2. No additional increase was observed in clinical attachment levels and probing depth reduction after both adjunctive therapies when compared with a placebo/ scaling and root planning group.

Based on clinical results to date, additional long-term studies are necessary to provide support for the adjunctive use of NSAIDs in the treatment of periodontal disease (Kirkwood et al., 2007).

Biphosphonates

Alveolar bone resorbtion is the principal sequel and the cause of tooth loss in patients afflicted by periodontal disease. The use of bone-sparing agents such as biphospho-

nates that inhibit alveolar bone resorbtion is another field in host-modulation therapy.

Biphosphonates are a class of drugs structurally similar to pyrophosphate, a component of human bone metabolism. It binds to hydrohyapatite crystals of bone and prevents their dissolution by interfering with osteoclasts function through a variety of direct and indirect mechanisms (Rogers et al., 2000). As therapeutic agents, biphosphonates were shown to reduce alveolar bone loss and increase mineral bone density, but there was no improvement in clinical conditions in animal periodontitis models (Reddy et al., 1995). Five studies that assessed the effect of biphosphonates as an adjunctive agent to scaling and root planning in human periodontal treatment have been found to date. Aledronate was used in four studies and risendronate was used in a 12-month study. All the studies presented significant clinical improvement when compared with placebo. These results encourage the use of biphosphonates as adjunctive agents to periodontal therapy. However, additional studies are further needed in order to evaluate the relative risk-benefit ratio of biphosphonate therapy.

Regulation of matrix metalloproteinase activity

Matrix metalloproteinases (MMPs) represent a family of zinc-dependent membrane-bound and secreted proteolytic enzymes. Their main function is to catalyze the breakdown of proteins in the cell plasma membrane or within the extracellular matrix (Salvi and Lang, 2005). Deregulation of MMPs activity is involved in a variety of pathological conditions such as rheumatoid arthritis, tumor cell metastasis and periodontal disease (Yoon et al., 2003).

The ability of tetracycline and doxycycline to inhibit MMP activity was first identified in the early 1980s. Tetracyclines block the active enzyme and inhibit reactive oxygen species that might be involved in the activation of these enzymes (Kornman, 1999).

Initial studies have demonstrated that doxycycline was the most potent tetracycline in the inhibition of collagenolytic activities. A subantimicrobial dose (20 mg twice daily) of doxycycline (SDD) with the purpose of long term administration in patients suffering from periodontitis was introduced and shown to down regulate collagenase activity without the emergence of doxycycline-resistant microorganisms or typical adverse events (Salvi and Lang, 2005). Thus far, one approved host modulation therapy (HMT) prescribed as systemic SDD (Periostat®, CollaGenex Pharmaceuticals Inc., Newtown, PA, USA) in conjunction with mechanical periodontal therapy is available in some countries (Bostanci et al., 2011).

Nitric oxide synthase (NOS) inhibitors

NO is a short-lived molecule implicated in a variety of biological processes ranging from immune homeostasis to cancer (Brennan et al., 2003). It is synthetised in vivo from the substrate L-arginine by three isoenzymes called niric oxide synthases (NOSs).

Oral bacteria have been postulated to trigger iNOS upregulation in periodontal tissues (Lohinai et al., 2001). Being highly reactive, NO attacks thiol residues inducing lipid peroxidation, protein and DNA damage and stimulating cytokine release (Brennan et al., 2003). Although NO has an antimicrobial protective activity, its elevated concentration in periodontium has a cytotoxic effect towards host cells.

Nitric oxide synthase (NOS) inhibitors such as marcaptoethylguanidine have demonstrated protective effects against bone resorbtion and inflammatory process in ligature-induced periodontitis in rats (Lohinai et al., 1998; Leitao et al., 2005). Since several studies have confirmed that NO has a deleterious role in the pathophysiology of periodontitis, the modulation of its activity may prevent tissue destruction.

Disruption of cell signaling pathways as an approach in the treatment of periodontits

Strategies for preventing cell activation seek to inhibit the intracellular transduction of signals produced when ligands bind to their membrane receptors. Signal transduction pathways are activated not only by cytokines, but also by other factors, such as bacterial proteins, lipopolysaccaharide, or environmental stress. These stimuli act on receptors that are coupled to the signal transduction pathways, causing activation of transcription factors and other proteins that control of cytokines, proteases and many other compounds involved in the inflammatory process. Inhibition of signal transduction pathways would be expected to abolish cell activation by cytokines or other stimuli and the production of pro-inflammatory cytokines. Cytokines and bacterial components activate many signal transduction pathways. The most important signal transduction pathways in periodontal disease include the mitogen activated protein kinase (MAPK), nuclear factor kappa B (NF-κB) and janus tyrosine kinase-signal transducer and activator of transcription (JAK/STAT).

The NF-κB pathway

The transcription factors NF-κB are homo- or heterodimers found in the cytoplasm of most human cells. The NF-κB family of transcription factors has been shown to be involved in many different pathways and has a central role in regulating the expression of a wide variety of genes that control both innate and adaptive immune responces. *In vitro* studies have established that both *P. gingivalis* and other periopathogenic bacteria can activate NF-κB pathway in periodontal tissues (Sugita et al., 1998). Bacterial LPS, IL-1 and TNF-α, present in large quantities in periodontal tissues, can also activate NF-κB.

NF-κB activation is regulated primarily though inhibi-

tors of NF-κB (IκB). Many strategies to prevent activation of NF-κB are based on the modulation of IκB, as proteasome inhibitors that block degradation of IκB, and overexpression of IκB by recombinant protein or gene therapy (Souza et al., 2010). The IKK inhibitor, BMS-345541, was evaluated in collagen-induced arthritis model in mice and decreased both synovial inflammation and joint destruction (McIntyre et al., 2003). Other strategies to block the NF-κB activity that are being developed by pharmaceutical industry are being based on targeting the DNA binding activity of NF-κB or blocking the nuclear translocation of NF-κB dimers.

Despite the potential use of this pathway in development of therapeutic interventions for immune/inflammatory diseases, NF-κB also play key role in normal physiological processes. Therefore, general blockade of NF-κB results in unwanted side effects as liver failure related to hepatocyte apoptosis (Maeda et al., 2003).

The MAPK pathway

MAPKs represent a family of protein kinases that mediate fundamental biological processes and cellular responses to different extracellular stimuli through multiple receptors (Kyriakis et al., 2001).

MAPKs are divided into three subfamilies: the extracellular signal regulated kinases (ERK1/2); JNKs; and p38 which are all assumed to be expressed in periodontal lesions.

The p38 MAPK is activated mainly within cells involved in the inflammatory process. Activation of p38 induces synthesis of IL-1, IL-6, IL-8 and TNF-α, either via direct activation of gene transcription or via mRNA stabilization (Kirkwood et al., 2003)

The role of p38 MAPK in the various stages of inflammation has prompted the production of several imidazole compounds capable of inhibiting p38 (SB203580, RWJJ 67657, L- 167307, VX-745, RPR200765A and others). These pharmacological inhibitors are cytokine suppressive anti-inflammatory drugs (CSAIDSs) responsible for in vitro and in vivo inhibition of lipopolysaccharide-induced TNF-α expression (Adams et al., 2001). They have been evaluated in several murine models of periodontal disease and/or rheumatoid arthritis and have prevented the pregression of the disease and bone resorbtion.

The efficacy of anticytokine biotherapies in patients with inflammatory diseases is a proof that blocking the effects of a cytokine can slow down the disease process. However, MAPKs play significant role of many physiological processes and suppression of their function may lead to a number of problems. One of the reasons for the unacceptable side effects might be the cross reactivity against other kinases or other cellular signaling molecules (Cohen et al., 2002).

JAK/STAT pathway

Many cytokines and growth factors (interferons, interleukins, epidermal growth factor, growth hormone, erythropoietin and others) exert their biological functions through JAK/STAT signal transduction pathway. The JAK/STAT pathway is the signaling target of many cytokines which are thought to have biologically significant roles in periodontal disease (INF-γ, INF-α, IL-1, IL-4, IL-6, and IL-10). Several studies have shown that STAT pathways are activated in a ligature-induced experimental periodontitis in rats (Garsia de Aquino et al., 2009). To date no studies with STAT inhibitors are available in periodontal disease despite the potential role of these proteins in expression of important genes related with inflammatory diseases.

It is now clear that JAK/STAT pathway have a fundamental role in inflammatory diseases onset and progression. This pathway can affect the expression of various genes with pro-inflammatory and anti-inflammatory activity. Furthermore, the modulation of this pathway on cytokine signaling increases the possibility that these proteins may prove to be excellent targets for the discovery of drugs that can manipulate cytokine outcomes to resolve disease.

Tumor necrosis factor antagonists to block inflammatory diseases

TNF-α and IL-1, inflammatory cytokines, are released by activated monocytes, macrophages and T lymphocytes. They promote inflammatory responses that are of great importance in rheumatoid arthritis and periodontal disease.

Patients with rheumatoid arthritis and periodontal disease have high concentration of TNF-α in the synovial fluid and gingival crevice fluid, respectively. Both, TNF-α and IL-1, have been found in high concentrations in periodontal lesions and at sites of active bone resorbtion (Ejeil et al., 2003; Gamonal et al., 2000; Gorska et al., 2003). Reduction of the bacteria and their metabolic by-products by periodontal treatment also results in a decrease in both IL-1 and TNF-α, also paralleled by improvement in clinical parameters (Gamonal et al., 2000).

The use of cytokine receptor antagonists to inhibit periodontal disease progression investigated in a ligature-induced periodontitis non human primate model partially inhibited disease progression (Delima et al., 2001). Etanercept is a dimeric, soluble form of 75-kDa TNF-α receptor. The anti-inflammatory effects of etanercept are a result of its ability to bind to TNF-α, preventing it from interacting with cell surface receptors and rendering it biologically inactive. Etanercept can also modulate biological responces that are induced or regulated by TNF-α. In an animal study, etanercept demonstrated significant effect on plasma extravasation periodontitis. Further results indicated that etanercept treatment reduced the expression of iNOS and prevented the loss of antiapoptotic pathway in, as yet, unidentified mechanism (Di Paola et al., 2007).

At present, non-glycosilated sIl-1Ra, known as Anakinra (Kineret, Amgden Inc., Thousand Oaks, CA, USA) has been used to treat rheumatoid arthritis (RA) and other rheumatic disorders (Burger et al., 2006). Recent clinical studies indicate that Anakinra is safe and well tolerated treatment suitable for long term use in RA, although its anti-inflammatory effects are inferior to those of anti-TNF-α treatments, due possibly to its short half-life (Cohen et al., 2002; Fleischmman et al., 2006).

Infliximab and adalimumab are novel anti-TNF-α therapy used in the treatment of rheumatoid arthritis. Several studies have evaluated the influence of this treatment on periodontal parametars. The results from the studies suggest that patients on anti-TNF-α therapy exert lower GCF levels of TNF-α and milder periodontal disease compared with patients who do not receive this medication (Ortiz et al., 2009; Persson, 2012).

Blocking the activity of pro-inflammatory cytokines may be a benefitial therapeutic modality for periodontitis. The blockage of TNF-α pathway offers significant potential in blocking disease progression and would probably positively influence host defense functions.

Nutrients as modulators of inflammation in periodontits

Omega-3 fatty acids have been demonstrated to protect mice against numerous bacteria. These compounds inhibit the synthesis of lipid mediators of inflammation (prostaglandins and arachidonic acid), alter the cellular functions of polymorphonuclear leukocytes and modulate lymphocyte proliferation and cytokine production. In addition, these compounds have been shown to increase endogenous host anti-oxidant capacity. A recent study investigated the synergistic anti-inflammatory effects of omega-3 fatty acids and celecoxib. The combined therapy resulted in superior reductions on periodontal tissue levels of prostaglandins, leukotriene B4 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 (Vardar et al., 2005). These therapeutic modalities require further epidemiological studies for evaluation of the relations between nutritients with antioxidant properties and periodontal disease.

Summary

On the basis of current clinical data, it seems reasonable to conclude that the immunoinflammatory response is sufficiently protective in most patients such that minimal periodontal destruction will occur with routine oral hygiene. Regular bacterial control, such as scaling and root planning, seems to be the most practical approach in periodontal therapy.

For individuals who exhibit severe aggressive periodontitis or other highly susceptible populations (smokers, diabetes patients, patients positive for the IL-1 phenotype) host modulation seems to be an appropriate therapeutic strategy.

A variety of treatment strategies have been developed to target the host response to periodontal infection. MMP inhibitors such as low dose formulations of doxycycline have been used in combination with SRP or surgical therapy. In addition, high-risk patient groups such as diabetics or patients with recurrent periodontitis have benefited from the systemic MMP administration. Encouraging results have been obtained following soluble antagonists of TNF-α and IL-1 delivered locally in non-human primates. Other therapeutic strategies that are being explored involve inhibition of signal transduction pathways involved in inflammation. Pharmacological inhibitors of NF-κB and p38 mitogen activating protein (MAP) kinase pathways are actively being developed to manage inflammatory bone diseases. P38 inhibitors have shown promise in preclinical models of periodontal disease.

Using these novel strategies may provide the next generation of adjuvant chemotherapeutics to manage chronic periodontitis. It seems likely that host modulators together with control of the bacterial challenge will become a practical approach to the management of patients with increased risk for periodontal disease.

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Резиме

Терапевтски пристапи во третманот на пародонталната болест

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Клучни зборови: пародонтопатија, терапија на пародонтална болест, антибиотици, антисептици, имуномодулаторен агенс

Пародонтопатијата претставува хроничен инфламаторен процес кој ги зафаќа потпорните структури на забите. Оваа болест започнува како резултат на инфекција со периопатогени бактерии на места кои се предиспонирани за развој на болеста. Бактериската инвазија води кон развој и прогресија на болеста која резултира во зафатеност на сите структури на пародонтот меѓу кои и ресорбција на алвеоларна коска. Иако механичкиот, нехируршки третман на пародонталната болест е основен третман, тој поседува одредени недостатоци како што се ограничена можност за третман на длабоките пародонтални џебови, како и олеснета миграција на периопатогени бактерии од други места во усната шуплина. Со цел да се надминат овие ограничувања, како дополнување на основниот третман се користат хемотерапевтици и имуномодулаторни агенси. Примената на овие агенси во комбинација со механички третман покажува значително поголем терапевтски ефект во споредба со ефектот добиен со механички третман. Во овој труд ќе биде направен преглед на хемотерапевтиците, како и имуномодулаторните агенси кои се користат во третманот на пародонталната болест.