Pharmacological agents for periodontal regeneration: A review

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Abstract

The diseases of the periodontium are common, affecting up to 90% of the global inhabitants. The mildest form of periodontal disease presents itself as gingivitis, which is reversible and mainly caused by the bacterial biofilm on teeth and adjacent gingiva.

Whereas, periodontitis is the moderate to severe form of periodontal disease and results in loss of connective tissue and bone support and is one of the major causes of adult tooth loss. The ultimate goal of periodontal treatment is to prevent further attachment loss and regenerate periodontal supporting tissues. To achieve successful periodontal regeneration, various therapeutic strategies are available. Over the past two decades, a variety of pharmacological agents have been studied for regeneration of lost periodontal structures. This informational review paper describes the various pharmacological agents which are considered important for promoting periodontal regeneration.

Keywords: Bisphosphonates, host modulation therapy, periodontal regeneration, pharmacological agents

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Introduction

The structures comprising the periodontium include the gingiva, periodontal ligament, cementum and alveolar bone. Several diseases affect the composition and integrity of periodontal structures causing the destruction of the connective tissue (CT) matrix and cells, the loss of fibrous attachment and the resorption of alveolar bone. These changes often lead to tooth loss.[1]

Therapeutic modalities should aim not only in arresting and preventing the progress of periodontal tissue destruction but also at reestablishing and regenerating the periodontal tissues previously lost to disease. Agents that modulate the host response for periodontal repair and regeneration include, exogenous growth and differentiation factors, attachment factors which enhance the normal wound healing response that may be of insufficient magnitude to promote complete regeneration of all attachment structures.[2] Over the past two decades, a variety of pharmacological agents have been studied for their possible roles in the management of periodontal disease and regeneration of its structures.[3]

Host modulation therapy is a treatment approach aiming to stabilize or even regenerate the periodontium and reduce the destruction of tissues by down-regulating or modifying the destructive components of host response and up-regulating the protective or regenerative aspects. Restoring a balance between the pro-inflammatory mediators and destructive enzymes with that of the anti-inflammatory mediators and enzyme inhibitors is the ultimate purpose of host modulatory therapy [Figure 1]. Host modulating agents can be used as adjuncts to scaling and root planning (SRP) and can be either systemically administered or delivered locally at the intended site. Host modulation with chemotherapeutics or drugs is an exciting new adjunctive therapeutic option for the management of periodontal diseases.[4]

Non-steroidal Anti-inflammatory Drugs (NSAID’s)

NSAID’s are a class of drugs that provide analgesic, antipyretic and anti-inflammatory effects.

The basis of anti-inflammatory drugs in periodontal disease treatment is related to the control of prostaglandin E2 (PGE2) through the inhibition of cyclooxygenase-2 (COX-2) enzyme. Higher levels of PGE2 are associated with increased gingival inflammation and alveolar bone loss (Noguchi and Ishikava, 2007, Reynolds et al., 2007, Tripton et al., 2003).[5]

Arachidonic acid metabolites are pro-inflammatory mediators that have been involved in a wide variety of resorptive processes involving bone, including diseases such as chronic periodontitis. These mediators can be potentially inhibited by NSAIDs, such as aspirin, ibuprofen, flurbiprofen, and naproxen.
NSAIDs inhibit the enzyme COX, thereby preventing the production of arachidonic acid metabolites. Use of NSAIDs results in decreased levels of pro-inflammatory mediators that may limit the host-mediated alveolar bone destruction observed in periodontitis and peri-implant disease [Figure 2].[6]

Offenbacher et al. (1984) found increasing levels of PGs in crevicular fluid in patients with periodontitis and PGE2 levels were 3-fold higher in patients with juvenile periodontitis as compared to patients to patients with adult periodontitis.[2]

A double-masked randomized controlled clinical trial was conducted in a total of 29 patients with mandibular dental implants. Evaluation of healing after dental implant placement was done for a period of 3 months following administration of 100 mg flurbiprofen, 50 mg flurbiprofen, or placebo. All the patients were evaluated using digital subtraction radiography, and they found that, in the high-dose flurbiprofen group a decrease in bone loss was noted after 6 months in implants (P < 0.001).[6]

Bisphosphonates (BP’s)

BPs were introduced in 1990 for treatment of osteoporosis and osteolytic tumors. They are second group of drugs under investigation for their ability to modulate the bone loss and prevent bone resorption. They are primarily used to treat hypercalcemia, Paget’s disease and osteoporosis. They are non-biodegradable analogs of pyrophosphate that have a high affinity for calcium phosphate crystals and that inhibit osteoclast activity.[4]

BPs are drugs that suppress bone turnover, primarily through effects on osteoclasts, and are commonly prescribed to prevent skeletal-related events in malignancy and for benign bone diseases such as osteoporosis.[5]

Figure 1: The potential application of host modulation as a therapeutic intervention in the pathogenesis of periodontitis. PMNs: Polymorphonuclear leukocytes, CT: Connective tissue; LPS: Lipopolysaccharide[6]

Figure 2: Mechanism of action of non-steroidal anti-inflammatory drugs – they inhibit the synthesis and release the synthesis of prostaglandins

Figure 3: Molecular structure of natural pyrophosphate and bisphosphonates (BP). The central carbon of BP confers stability to the molecule and prevents enzymatic acid hydrolysis from occurring[6]

Structure of BPs

BPs are synthetic molecules with a structure similar to inorganic pyrophosphates (Rogers et al., 2000) [Figure 3]. Pyrophosphates are endogenous regulators of bone mineralization, which can be found naturally in the blood serum, and they have the capacity to chelate calcium and to regulate the bone mineralization process (Lin, 1996; Rodan, 1998). The biological inhibitory effects of
BP on osteoclast-mediated bone resorption were discovered in 1968 (Fleisch, 2002). BPs are resistant to enzymatic and chemical breakdown, and they present an affinity to the mineral phase of the bone due to their chelating properties for calcium (Rogers et al., 1999). They present a P–C–P molecular structure.  

**Generations of BP’s**

There are three generations of BPs known to exist. The first generation has alkyl side chains (etidronate), the second generation includes amino-BPs with an amino-terminal side chain (alendronate) and the third generation (zoledronate) has a cyclic side chain.

**Mechanism of action**

Several modes of action have been investigated including BP mediated inhibition of the development of osteoclasts, induction of osteoclastic apoptosis, reduction of activity, prevention of the development of osteoclasts from hematopoietic precursors, and stimulation of production of an osteoclast inhibitory factor. It has also been shown that the BP alendronate caused a rise in intracellular calcium levels in an osteoclast-like cell line. This finding is of great interest since it could suggest the presence of a receptor for BPs on osteoclasts.  

The proven efficacy of BPs to inhibit the osteoclastic bone resorption has led to their use in the management of periodontal diseases as a host modulating factor in the perspective of preventing the alveolar bone loss (Parfitt, 1994). BPs could be used in conjunction with regenerative therapies, and even for stimulation of bone growth into and around endosseous implants.

Existing literature demonstrate a further benefit of the systemic administration of BPs in addition to mechanical debridement compared with mechanical debridement alone. This benefit is mainly the reduction of alveolar bone loss and the preservation of the alveolar bone height. On the subject of the clinical parameters, some trials failed to show a significant improvement (El-Shinnawi and El-Tantawy, 2003), whereas other studies reported that BPs supported (in addition to inhibiting alveolar bone loss) the periodontal healing, in particular, the reduction of probing pocket depth and tooth mobility (Rocha et al., 2001; Takaishi et al., 2001, 2003; Lane et al., 2005).  

Various studies using topically administered BPs have been carried out in the recent past due to the serious side-effects of systemically administered BPs leading to osteonecrosis of the jaws and these studies have reported a significant improvement in the post-operative percentage of bone defect fill, prevention of bone resorption as well as the elevated effects of locally delivered BPs on the osteoconductive and regenerative potential of various bone grafts used in the treatment of periodontal diseases.

**Statins**

Statins are also called as HMG-CoA reductase inhibitors. They are a class of drugs which is used to lower the cholesterol levels. They mainly act by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver, and contributes to produce about 70% of total body cholesterol.

**Molecular structure of statins**

Statins have potential anti-inflammatory effect. Statins in systemic and local application enhance osteoblastic differentiation and bone formation by upregulating bone morphogenic proteins and by blocking the intermediate metabolites of the mevalonate pathway. Because of these effects, statins can be used in treating periodontal disease and promoting periodontal regeneration.

Additionally, it has been observed that statins like simvastatin, atorvastatin, and cerivastatin markedly enhance gene expression for vascular endothelial growth factor, which is involved in the process of endochondral bone formation and stimulates osteoblastic differentiation leading to new bone formation. It has also been suggested that statin use was associated with decreased tooth loss in chronic periodontitis patients.

An *in vitro* study was conducted by Yazawa et al., using periodontal ligament cells obtained from human teeth and it was seen that simvastatin significantly enhanced cell proliferation and metabolism dose-dependently after 24 h. Simvastatin concentrations of 10-8 and 10-7 M showed the maximum effect and after 7 days, alkaline phosphatase activity was boosted dose-dependently and at a concentration of 10-8 M showed the maximum effect.

Pradeep et al., recently in a clinical study reported a greater reduction in the gingival index and probing depth (PD) at

**Figure 4: Molecular structure of statins**
sites treated with SRP and locally delivered simvastatin as compared to SRP plus placebo in human subjects with chronic periodontitis. In addition, more clinical attachment level gain as well as significant intrabony defect fill was seen in the simvastatin-treated individuals.[14]

Antimicrobial Agents

Antiproteinases used in the treatment of periodontitis are tetracyclines. Along with antimicrobial activity, tetracycline agents have the ability to inhibit neutrophils, osteoclasts, and matrix metalloproteinases (MMPs) that appear to be involved in the destruction of the periodontium. Tetracyclines have an anti-inflammatory action and may be bone-sparing through inhibition of osteoclasts. Doxycycline is the most studied and strongest collagenase inhibitor of the used tetracyclines.[6]

MMP is considered to be the key initiators of collagen degradation thus contributing to bone resorption in inflammatory diseases. Subantimicrobial doses of doxycycline are a known MMP inhibitors and hence inhibits bone resorption.[15]

Recently, a formulation containing a sub antimicrobial dose of doxycycline (Doxycycline hyclate 20 mg; Periostat, CollaGenex, Pharmaceuticals Newton PA) is FDA approved and ADA accepted. It is indicated as an adjunct to SRP in the treatment of chronic periodontitis. It has been evaluated as 20 mg taken twice daily for up to 9 months of continuous dosing in clinical trials. The 20 mg twice per day dose exerts its therapeutic effect by enzyme, cytokine, and osteoclast inhibition, rather than by any antibiotic effect.[4]

Golub et al. (1990) studied the effects of low dose doxycycline therapy on the gingival crevicular fluid in human subjects. A 2 weeks regimen of these capsules (each containing 20 or 30 mg of the drug) significantly reduced the excess host collagenase activity in extracts of inflamed gingival tissues. This effect was not reduced in placebo, treated patients who had adult periodontitis.[2]

Chemically modified tetracyclines tackle periodontitis by prevention of breakdown of CT. They mainly act by inhibition of metal-dependent MMPs, scavenging the reactive oxygen species, enhancing the attachment of fibroblasts and CTs to the tooth surface, suppression of neutrophils, inhibition of generation of metabolites of arachidonic acid by blocking the PGE2 synthesis and phospholipase A2, and hence regenerating lost periodontium.[16]

Azithromycin is an azalide, a subclass of macrolide antibiotic used extensively in medicine for the treatment of a wide range of bacterial infections. It inhibits some Gram-positive bacteria, some Gram-negative bacteria, and many atypical including few common periodontopathogens. Apart from their antibiotic properties they also have well-documented immune-modulating/anti-inflammatory effects. Azithromycin is significantly concentrated in macrophages, neutrophils and particularly in the fibroblasts; all of these cells play a major role in the pathogenesis of most periodontal diseases. Use of azithromycin in the treatment of advanced periodontal diseases has shown significant results. Azithromycin could also have a triple role in the resolution and treatment of periodontal diseases such as anti-inflammatory activity, suppressing periodontopathogens and healing through persistence at low levels fibroblasts and macrophages in periodontal tissues, even after a single course of three tablets.[17]

Hormonal Therapy

Parathyroid hormone (PTH)

The mechanism of the PTHs action is complex and involves pathways linked to common signaling peptides that affect osteoblast gene transcription. In vitro studies, in vivo experiments, and clinical trials demonstrated that intermittent PTH 1-34 administration induced anabolic effects on cancellous and cortical bone, enhanced bone mass, and increased mechanical bone strength.[18]

Estrogen

The relationship between estrogens and periodontal tissues was studied mainly for its possible implication in the inflammatory process, with a clear demonstration that estrogens do not increase inflammation. Most cells in the periodontium (fibroblasts, endothelial cells, epithelial gingival cells, osteoclasts, and osteoblasts) express estrogen receptors α and β. It is well known that estrogens decrease bone resorption and have a positive effect on bone formation.[19] Treatment with estrogens clearly inhibits bone loss as well as bone turnover and increases bone mineral density. There is substantial evidence that estrogen inhibits both osteoclast activity and differentiation by regulating the production of stimulatory and inhibitory cytokines by osteoblasts and monocytes. Various reports also have linked estrogen deficiency and osteoporosis to increased oral bone resorption, attachment loss, and tooth loss.[20]

Selective estrogen receptor modulators (SERMs)

The discovery of the agents able to exert full or partial estrogen effects on various tissues led to the development of a new class of drugs known as SERMs. The mechanism by which SERMs inhibit bone resorption is likely to be the same as estrogen’s mechanism, by blocking production of cytokines that promote osteoclast differentiation and by promoting osteoclast apoptosis.[20]

Teriparatide

It is a recombinant form of PTH consisting of the first 34 amino acids of PTH. Since it is identical to a portion of human PTH, it is known as biosynthetic human PTH. It is a highly potent anabolic (i.e. bone growing) agent and most commonly used in the treatment of osteoporosis.

The biological actions of teriparatide and PTH are mainly activated through specific, G-protein-dependent, high-affinity membrane cell-surface receptors. These receptors are mainly demonstrated in osteoblasts and renal tubular cells. It has been
demonstrated that ligand binding promotes a cascade that energize protein kinase-1, protein kinase C, cyclic adenosine monophosphate (cAMP) and phospholipase C. The activation of these pathways results in an up-regulation of the number of active osteoblasts, a down-regulation in osteoblast apoptosis and probably, increase of bone lining cells as newly formed osteoblasts, thereby enhancing bone strength, structural integrity, mass and diameter, as well as increasing serum and urinary levels of markers of bone resorption and formation. Individuals treated with teriparatide have shown up-regulation of basic fibroblast growth factor 2 (bFGF-2). Since bFGF-2 enhances the proliferation and differentiation of osteoblast progenitor cells, this cytokine could play a major role in the bone formative response to teriparatide therapy.\(^5\)

**Miscellaneous Drugs**

**Anti-arthritic medications**

Anti-arthritic medications have also been suggested to be of potential benefit, but their mechanism of action is unclear at this time. However, gold salts like aurofin, aurothioglucose, aurothiomalate, sometimes used to treat arthritis have been shown to accumulate in gingiva and gingival crevicular fluid, and may produce an antibacterial and anti-inflammatory at the site of periodontal infections (Freeman et al. 1984, Polson et al. 1984).\(^{21}\)

**Cimetidine**

Cimetidine is a powerful H2 (Histamine) receptor antagonist, and hence eliminates histamine’s inhibitory effects on immune response, thereby acting as a modulator of inflammation and immunity by inhibiting neutrophil chemotaxis and superoxide production, increasing cAMP levels and down-regulating cytokines. Topically active cimetidine is a potent inhibitor of periodontal inflammation caused mainly by P. gingivalis, this morphologic and histologic evidence was provided by Hasturk et al. (2006) and they also showed that it can arrest and/or prevent tissue destruction and influence cell populations present in the inflammatory cell infiltrate.\(^{10}\)

**Hyaluronic acid (HA)**

HA is a polysaccharide (glycosaminoglycan), also known as hyaluronan or hyaluronate, it has a high molecular weight and has a major role in the activity of extracellular matrices, including those of non-mineralized and mineralized periodontal tissues. It contributes significantly to cell migration, proliferation and tissue hydrodynamics and is a vital component of the extracellular matrix. Hyaluronan is also produced in the presence of endotoxins by fibroblasts, and it plays a crucial anti-inflammatory role by facilitating healing and inhibition of tissue destruction.\(^{22}\)

Ballini et al. in a study found that there were good capabilities in accelerating new bone formation in the infra-bony defects when autologous bone was combined with an esterified low-molecular HA preparation.\(^{23}\)

HA shares bone induction characteristics with bone morphogenetic protein-2 and osteopontin which are majorly osteogenic in nature.\(^{24}\) It accelerates the bone regeneration via proliferation, successive differentiation and chemotaxis of mesenchymal cells.

Another study was conducted by Engström et al. to investigate the anti-inflammatory effect and the effect on bone regeneration of Hyaluronan in surgical and non-surgical groups. On radiographic examination, in the non surgical group there was no statistical difference, whereas the reduction in the bone height was seen for both groups after scaling. PD significantly reduced after the surgical treatment as well as after SRP.\(^{25}\)

**Conclusion**

Periodontopathic microorganisms and destructive host response are involved in the initiation and progression of periodontal disease, and there are situations in which conventional therapy does not always achieve the desired clinical outcome.

The improved understanding of the host bacterial interactions and the host immune-inflammatory response leading to periodontal tissue destruction has led to the development of Host modulation therapy. The risk/benefit ratio concerned to the use of host modulating agents are yet to be established even though the usefulness and efficacy of these agents have been demonstrated by many clinical trials and have been approved by FDA for the management of periodontitis. Furthermore, continuous research in this field and Multicenter clinical trials are necessary to completely evaluate the benefits, usefulness and the risks associated with the long-term administration of these agents and also to enable planning of customized treatment approach for periodontal diseases by targeting inflammatory host response.

**References**