REVIEW ARTICLE

Anticytokine Therapy in Periodontal Diseases

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ABSTRACT

Periodontitis is a chronic inflammatory disease of bacterial origin and its progression depends on the host response where alterations in various cytokines levels help in the vicious cycle of bone loss and deeper bacterial ingress. Cytokines are known to play a key role in the pathogenesis of periodontitis by mediating the expressions of both innate and acquired immunities. The various pro-inflammatory cytokines and inflammatory mediators include interleukin (IL)-1β, IL-6, tumor necrosis factor α, IL-7, IL-17, matrix metalloproteinases, and prostaglandin E2 which cause periodontal disease progression by activating and accelerating osteoclastic activities and extracellular matrix degradation. Anticytokine therapy is one of the host modulation modalities which specifically target the regulation of immune and inflammatory response through suppressing pro-inflammatory cytokines. The present review highlights the work done by various researchers in studying the role of cytokines in periodontitis and assesses the currently available anticytokine therapies and its management. Preliminary results indicate that the therapeutic potential of these drugs is promising for the management of periodontitis. At present, these drugs are under clinical trials, hence, they still bear a restricted usage and further studies are anticipated toward the use of anticytokine therapy in the near future. Larger trials are needed for a further conclusive evidence of utility of anticytokine therapy in treating periodontal diseases.

Key words: Anticytokine therapy, anti-inflammatory cytokines, periodontal diseases, pro-inflammatory cytokines

INTRODUCTION

Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession, or both.[1] Although cause of periodontitis is specific pathogenic bacteria and their virulence factors, the host immune response to these bacteria is of fundamental importance.[2] Host reactions to these infecting agents result in the release of inflammatory mediators including pro-inflammatory cytokines. Cytokines are known to play a key role in the pathogenesis of various inflammatory disorders like periodontitis by mediating the expressions of both innate and acquired immunities. The various pro-inflammatory cytokines and inflammatory mediators include interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), IL-7, IL-17, matrix metalloproteinases (MMPs), and prostaglandin E2 (PGE2). By activating and accelerating osteoclastic activities and extracellular matrix degradation, these inflammatory cytokines are responsible for periodontal disease progression.[3] These cytokines also stimulate or inhibit activation, proliferation, and differentiation of various cells, regulate secretion of antibodies and other cytokines, hence, experts suggest that specific cytokine targeting should be considered as a complementary therapeutic scheme to the existing periodontal management protocols.[4]

Traditional periodontal treatment includes debridement of deep periodontal pockets and inflamed tissues. This may include the gold standard scaling and root planing and various periodontal surgical procedures. However in periodontal disease conditions where conventional treatments like SRP are not successful, the institution of host modulation therapy can be utilized as a predictable adjunct

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to therapeutic option. Host modulation therapy is one of the treatment methodologies to prevent and treat periodontal diseases by regulating the pro-inflammatory cytokines and inflammatory mediators.[5] Anticytokine therapy is one of these host modulation modalities which specifically target the regulation of immune and inflammatory response through suppressing pro-inflammatory cytokines. Therapeutically, anticytokine therapy has been used successfully in tissue destructive inflammatory diseases, such as rheumatoid arthritis (RA), Crohn's disease, and various other immune and inflammatory diseases.[6,7] Therefore, the use of anticytokine therapy has been employed in treatment of periodontitis by countering the actions of agents such as IL-1β, IL-6, and TNF-α which are specific to periodontal disease initiation and progression. Targeting these cytokines can have an edge effect in management of the inflammatory signs of periodontal disease. In addition, host modulating effect of anticytokine therapy is an added therapeutic merit in treating periodontal diseases.

CYTOKINES IN PERIODONTITIS

Cytokines are small, soluble signaling proteins produced by nucleated cells throughout the body, especially from lymphocytes (mainly T cells), monocytes, macrophages, granulocytes, epithelial cells, endothelial cells, and fibroblasts. Bennett and Beeson, 1953, begun the research in the field of cytokines with the identification of some of the factors like "endogenous pyrogen" which in later years well known as IL1.[8] Oppenheim, 2001, defined cytokines broadly based on their function as intercellular signals. Cytokines are secreted proteins that interact with specific cell-surface receptors and results in causing modulation and further mobilization of target cells. They are glycoproteins or soluble extracellular proteins whose role is crucial in intercellular regulation and mobilization of cells engaged in innate as well as adaptive inflammatory host defenses. Cytokines also have vital role in cell growth, differentiation, angiogenesis, and development and repair processes aimed at the restoration of homeostasis.[9] Arend had grouped cytokines under hematopoietic, growth and differentiation, immunoregulatory, pro-inflammatory, anti-inflammatory, and chemotactic factors and proposed the functional classification of cytokines[10] as given in Table 1.

Cytokines are extremely important in the progression of periodontitis where they act as key modulators for both homeostasis and inflammatory processes involved. Cytokines act in the first wave of responses against pathogens which further stimulate the barrier mechanism within connective tissues by activating lymphocytes and other accessory cell populations. Cytokines associated with innate immunity are IL-1, TNF-α, IL-12, IL-6, interferon (IFN)-α, and IFN-β and those associated with adaptive immunity are IL-2, IL-4, IL-5, IL-25, TGF-β, and IFN-γ.[11] The microbial challenge consisting of antigens, lipopolysaccharides, and other virulence factors, acts as an inducing stimulus to the cytokine producing cells. On stimulation, cytokine gene gets activated and releases cytokines such as IL-1α, IL-1β, TNF-α, and IL-6. These are pro-inflammatory in nature and remain persisted for prolonged periods at local inflammatory sites. Cytokines bind to specific receptors on target cells and initiate intracellular signaling cascade. This causes alteration in gene regulation and activation, thereby releasing secondary mediators such as MMPs and PGE2. These mediators cause connective tissue breakdown and bone resorption. This mechanism explains the initiation of periodontitis and its progression. Table 2 mentions role of certain cytokines in periodontal disease.[12-18]

Table 1: Functional classification of cytokines

Functional classification of cytokines*	
Family	**Members**
Hematopoietic	SCF, IL-3, TPO, EPO, GM-CSF, G-CSF, M-CSF
Growth and differentiation	PDGF, EGF, FGF, IGF, TGFb, VEGF
Immunoregulatory	TGFb, IFNg, IL-2, 4, 5, 7, 9–18
Pro-inflammatory	IL-1a, IL-1b, TNFa, LT, IL-6, LIF, IL-17
Anti-inflammatory	IL-1Ra, IL-4, IL-10, IL-13
Chemotactic	IL-8, MIP-1a, MIP-1b, MCP-1, RANTES

*EGF 5: Epidermal growth factor; EPO 5: Erythropoietin; FGF 5: Fibroblast growth factor; G-CSF 5: Granulocyte colony-stimulating factor; GM-CSF 5: Granulocyte-macrophage colony-stimulating factor; IFN 5: Interferon; IGF 5: Insulin-like growth factor; IL 5: Interleukin; IL-1Ra 5: Interleukin-1 receptor antagonist; LIF 5: Leukemia inhibitory factor; LT 5: Lymphotoxin; MCP 5: Monocyte chemotactic protein; M-CSF 5: Macrophage colony-stimulating factor; MIP 5: Macrophage inflammatory protein; PDGF 5: Platelet-derived growth factor; SCF 5: Stem cell factor; TGF 5: Transforming growth factor; TNF 5: Tumor necrosis factor; TPO 5: Thrombopoietin; VEGF 5: Vascular endothelial growth factor

NATURAL ANTI-INFLAMMATORY CYTOKINES

In contrast to the pro-inflammatory nature of cytokines, there are natural anti-inflammatory

Table 2: Major cytokines and their role in periodontitis progression

Cytokine	Researchers	Observation
IL-1	Charon *et al.*, 1982	Stimulates destruction of periodontium by causing release of MMPs and prostaglandin.[12]
	Matsuki *et al.*, 1993	Over expression of IL-1 , resulted loss of attachment and destruction of alveolar bone in transgenic mice.[13]
	Delima *et al.*, 2001	Inhibition of IL1 , significantly reduced inflammation, attachment loss, and bone resorption compared with controls.[14]
IL-6	Bozkurt *et al.*, 2000	Levels found increased in GCF of inflamed gingival tissues but not in healthy tissues and these increased IL-6 levels appear to have a role in bone resorption by stimulating formation of multinucleated cells similar to osteoclasts.[15]
IL-8	Dongari-Bagtzoglou and Ebersole, 1996	IL-8 has been detected in GCF of adult periodontitis patients and in both healthy and diseased tissues in the junctional and sulcular epithelium.[16]
TNF	Assuma *et al.*, 1998	TNF- is produced mainly in response to LPS and stimulates collagenase leading to tissue destruction. It has been shown to stimulate bone resorption by inducing proliferation and differentiation of osteoclast progenitors.[17]
IL-16	Souza *et al*	IL16 rs11556218 polymorphism was significantly associated to periodontitis. Structural modification of IL-16 would compromise its function in chemotaxis on CD4+ cells and also inflammatory cytokine production which would lead to a modulation of the immune response in the oral microenvironment.[18]

IL: Interleukin, TNF: Tumor necrosis factor

cytokines, such as major anti-inflammatory cytokines include IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. Specific cytokine receptors for IL-1, tumor necrosis factor-a, and IL-18 also function as pro-inflammatory cytokine inhibitors. IL-4 and IL-13 are potent anti-inflammatory cytokine which decreases osteoclastic activity by directly binding to osteoclast progenitor cells and hence decreasing bone resorption.[3,19] IL-6 has both pro-inflammatory and anti-inflammatory properties. It induces the synthesis of glucocorticoids and promotes the synthesis of IL1ra and soluble TNF receptor release in human volunteer.[20,21] IL-10 decreases RANKL and increases osteoprotegerin, thereby inhibits bone resorption.[22] IL-11 reduces tissue destruction by stimulation of a tissue inhibitor of MMP-1 (TIMP-1) and also inhibits TNF-α, IL-1β, IL-12, and nitric oxide.[23] This external neutralization of inflammatory cytokines can be useful as a therapeutic strategy in chronic inflammatory conditions.

ANTICYTOKINE THERAPY IN PERIODONTAL DISEASES

Cytokines bind to the receptors present on the target cells and cause its activation. Regulation of the effects of cytokines has been tried therapeutically in various tissue destructive inflammatory diseases, such as RA, Crohn's disease, and various other immune and inflammatory diseases. This cytokine inhibition is the basis for potential therapeutic modality, that is, anticytokine therapy in a variety of immune and inflammatory diseases, including periodontitis.[6,7]

Cytokine downregulation can be achieved by:

- Soluble cytokine receptors (derived from the proteolytic cleavage of the extracellular domain of cell bound cytokine receptors and are found in blood and extracellular fluid) which bind to the cytokine in solution and prevent signaling
- Receptor antagonists bind to the cytokine receptors on target cell and thus respective cytokine unable to bind, thereby blocking its action on target cells
- Transactivation – Soluble receptors bind the cytokine and docks on otherwise non-responsive cells to activate them
- Anticytokine antibodies which are antagonist in function and lower down the levels of cytokines directly.

Gokhale and Padhye noted that newer drugs such as bortezomib, infliximab, etanercept, vasoactive intestinal peptide, nitric oxide synthase inhibitors, and denosumab are developed as a result of better understanding of pathogenesis of inflammatory tissue destruction and may represent the future

of periodontal therapy.[24] Tocilizumab (TCZ) is a humanized monoclonal anti-human IL-6 receptor that inhibits IL-6-mediated pro-inflammatory activity. In experimental periodontitis induced by ligature; TCZ inhibited alveolar bone resorption and attachment loss. It was noted that inhibition of IL-6-mediated pro-inflammatory activity by IL-6R blocking reduced alveolar bone resorption and attachment loss supported by the modulation of the Th17 periodontal response.[25]

Martuscelli *et al.* in a study on dogs noted that subcutaneous injections of human recombinant IL-11 were able to slow the progression of attachment and radiographic alveolar bone loss in a ligature-induced beagle dog periodontal disease.[22] Lu *et al.* prepared IL 1 receptor antagonist loaded dextran/PLGA microspheres. In an *in vitro* experiment, they noted that microspheres can be easily prepared into a drug carrier with good biocompatibility and can effectively inhibit the gene expression of pro-inflammatory factors induced by IL-1β in human gingival fibroblasts. Hence, the microspheres are excellent candidate for periodontitis treatment.[26]

Bortezomib is a first in class proteasome inhibitor. Its utility in treatment of periodontal conditions has been elicited by various workers. Probable mechanisms include inhibition of inflammatory response of periodontal ligament cells, cytodifferentiation, and prevention of alveolar bone resorption.[27,28] Other drugs such as psoralen and angelicin also markedly decreased the mRNA expression and release of inflammatory cytokines (IL-1β and IL-8) by THP-1 cells in a dose-dependent manner in experimental models.[29]

Table 3: Commercially available anticytokine preparations

Targeted cytokine	Drug	Type of anticytokine activity	Significance
Anti-IL-1 therapy	Anakinra (Kineret®)	Cytokine antagonist	Slotwinska, 2013, reviewed the immunology associated with IL-1 receptor antagonist which blocks the biological activity of IL-1 by competitively inhibiting the binding of IL-1 to the cell membrane-bound IL-1R both *in vivo* and *in vitro*. It prevents cell signaling pathways, decreases inflammation and reduces tissue destruction in Periodontitis.[32]
	Gemfibrozil (Gem)	Disruption of cell signaling pathway	Corbett *et al.*, 2012, studied Gemfibrozil, a lipid-lowering drug in mouse which caused upregulation of IL-1RA thus suppressing activity of IL- by the inhibition of the PI3K-Akt pathway.[33]
Anti-TNF therapy	Infliximab™ (Remicade®)	Antibody to cytokine	Pers*et al.*, 2008, did periodontal evaluation after infusion of Infliximab, an IgG monoclonal antibody, which acts by neutralizing TNF- . RA patients with chronic periodontitis group and periodontally healthy group were compared after treatment with infliximab and concluded that infliximab can decrease clinical attachment loss in chronic periodontitis group.[34]
	Etanercept (Enbrel)®	Recombinant soluble receptor to TNF- α	Paola *et al.*, 2009, administered etanercept in rats with ligature induced periodontitis and found a significantly reduced degree of periodontal inflammation and tissue injury, infiltration of neutrophils, and the expression of cytokines (TNF-), and apoptosis genes (Bax and Bcl-2) expression.[35]
Anti-MAPK signaling pathway therapy	SD-282	Cytokine suppressive anti-inflammatory drugs	Kirkwood *et al.*, 2007, in a rat model evaluated the ability of orally active p38 MAPK inhibitor (SD-282) and observed reduced LPS-induced periodontal disease, inflammatory cytokine expression and alveolar bone loss due to inhibition of p38 mitogen-activated protein kinase (MAPK) signaling which is critical to inflammatory cytokine and LPS-induced cytokine expression.[36]

COMMERCIAL PREPARATIONS OF ANTICYTOKINE DRUGS

Periodontitis resembles RA closely as far as progression of disease, and role of cytokines in its pathogenesis is concerned and hence it is natural that anticytokine therapy has been employed in its treatment to counter actions of agents such as IL-1β, IL-6, and TNF-α which are specific to periodontal disease initiation and progression.[30] Studies have shown that utilization of soluble receptors, specific to inflammatory cytokines, can prevent stimulation of fibroblasts which play a key role in regulating biological events involved in the pathogenesis and progression of periodontal diseases.[31] Anticytokine treatment primarily targets production or actions of IL-1β, IL-6, and TNF-α, because they are necessary for the initiation and progression of periodontal diseases. At present, many of these anticytokine drugs are under clinical trial but few of them are approved for the clinical usage and are showing promising results in many inflammatory diseases like periodontitis. Few of these anticytokine drugs are enumerated in Table 3.[32-36]

NEWER THERAPEUTIC OPTIONS IN ANTICYTOKINE THERAPY

Gene Therapeutics

Human gingival fibroblasts have the potential to deport as anti-TNF-α system in periodontal tissue by secreting sTNF-RII antagonists for mTNFRs. Modified TNF-RII gene is introduced within these gingival fibroblasts to overexpress sTNF-RII and this soluble form blocks binding of TNF-α to mTNF-Rs by binding TNF-α around gingival fibroblasts. This has been found to be suitable in the treatment of chronic infections and inflammations and finds its place in treatment of periodontitis. There is evidence of infections without inflammatory symptoms, hence, the screening for latent infectious diseases should be performed when this type of anticytokine therapy is performed.[32]

LIMITATIONS OF ANTICYTOKINE THERAPY

1. Lack of large randomized trials in patients suffering from periodontal disease and use of anticytokine therapy
2. Trials of anticytokine drugs are largely restricted to their use in inflammatory and autoimmune disorders
3. Current research is largely restricted to *in vitro*, *in vivo,* and animal models of periodontal diseases
4. Drawback of anticytokine therapy is its systemic adverse reactions. Hence, use of such drug should have potential benefits outweighing potential risk of using such agents. However, novel drug delivery mechanisms to specific site may offer a system to bypass side effects of such drugs.

CONCLUSION

Anticytokine therapy has got merits of being an advanced therapeutic approach to chronic disorders like periodontitis. Targeting cytokines can have an edge effect in the management of the inflammatory signs of periodontal disease. In addition, host modulating effect of anticytokine therapy is an added therapeutic merit in treating periodontal diseases. However, certain demerits do occur with anticytokine therapy, like addressing only host-derived molecules cannot arrest the disease progression. Lack of large randomized trials still needed in patients suffering from periodontal disease and use of anticytokine therapy.

In this era of molecular biology where research has been focused on the genetic level of analysis, treatment should be focused on eliminating the root cause. For better understanding and targeting the cellular and molecular pathways of periodontal disease pathogenesis, periodontal advancement should be diverted toward the use of anticytokine therapy in the near future.

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