International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 05 Issue: 03 | Mar-2018 www.irjet.net p-ISSN: 2395-0072

Chemically Modified Tetracycline: A Review

Dr. Gowri Pendyala[1], Dr. Amit Mani[2], Dr. Asawari Lawande[3], Dr. Amola Patil[3]

[1]Reader, Dept. of Periodontology, Rural Dental College, Maharashtra, India.
[2]Professor & Head, Dept. of Periodontology, Rural Dental College, Maharashtra, India.
[3]Post-graduate student, Dept. of Periodontology, Rural Dental College, Maharashtra, India.

Abstract: *Periodontal pathogens and destructive host responses are involved in the initiation and progression of periodontitis. The emergence of host response modulation as a treatment concept has resulted from our improved understanding of the pathogenesis of periodontal disease. A variety of drugs have been evaluated as host modulation agents (HMA), including Non Steroidal Anti Inflammatory Drugs (NSAIDS), bisphosphonates, tetracyclines, enamel matrix proteins and bone morphogenetic proteins. Chemically modified tetracyclines (CMTs) are one such group of drugs which have been viewed as potential host modulating agents by their anticollagenolytic property. The CMTs are designed to be more potent inhibitors of pro inflammatory mediators and can increase the levels of anti inflammatory mediators.*

Key words: Anti-collagenolytic property1, chemically modified tetracyclines2, host modulation3, matrix metalloproteinases4, tetracycline5

Introduction

Periodontal disease is a complex microbiologic disease caused by various gram positive and gram negative microorganisms leading to the destruction of periodontal supporting tissues i.e. gingiva, periodontal ligament, cementum and alveolar bone. This microorganism and their products such as endotoxins alters immune-inflammatory response of host. Current concepts are based on mechanical scaling and root planning to remove bacterial deposits, calculus and cementum contaminated by bacteria and endotoxins and some therapeutic alternatives such as systemic and local antibiotics have been used to modulate host's response.

Among the antibiotics class tetracycline is widely used because of it's broad spectrum action against gram positive and gram negative microorganism. Tetracycline was first introduced into clinical practice by Duggar in 1948. Tetracycline has a antimicrobial action, anticollagenase property, anti inflammatory property , inhibits bone resorption and it's prolonged substantivity.[1] Now it is known that destruction of supporting periodontal tissues is primarily related to host derived enzymes, cytokines and inflammatory mediators, it has been lead to increased use of agents capable of modulating the host response.[2] The tetracyclines has found widespread local and systemic applications and in recent times has emerged as an efficient host-modulating agents (HMAs). Sub-antimicrobial dose doxycycline (SDD) , only FDA approved host modulating agent commercially available as Periostat is indicated as an adjunctive treatment for chronic periodontitis patients. It is prescribed 20 mg (Periostat), twice daily for 3 months and maximum to 9 months. SDD and the other tetracyclines has got the ability to down regulate MMPs by a variety of mechanisms, by decreasing proinflammatory cytokines and increasing anti-inflammatory cytokines . At the same time tetracyclines has adverse effects like gastrointestinal disturbances , developmental deformities of bone and teeth and development of antibiotic-resistant microorganisms which led to development of CMTs.[1]

Host-modulation therapy along with conventional mechanical therapy is an ideal approach for the treatment of periodontal disease. Chemically modified tetracycline is the potent host modulating agent. CMTs are derivatives of tetracycline in which antibiotic property has been remmoved , but retain the host modulatory, anticollagenolytic property.[3]

Golub et al.[4] in 1987 put forward that the antimicrobial and anti-collagenase properties of tetracyclines are situated in different parts of four ringed structures. Alterations in the structure of tetracyclines were made which invented the CMTs. Presently, CMT 1-8 have been evolved.Among them CMT-1, CMT-3 and CMT-8 have been used for periodontal applications.

Host Response in Periodontitis

dental plaque biofilm is the primary etiology for periodontitis.[5] Microorganisms present in biofilm destroy the periodontal tissues by both direct and indirect mechanisms. Once the bacterial virulence factors (lipopolysaccharide cell wall and endotoxins) have surpass the local defense mechanisms, they stimulate a myriad of reactions in the host [Figure 1], resulting in loss of soft connective tissue elements and bone resorption.

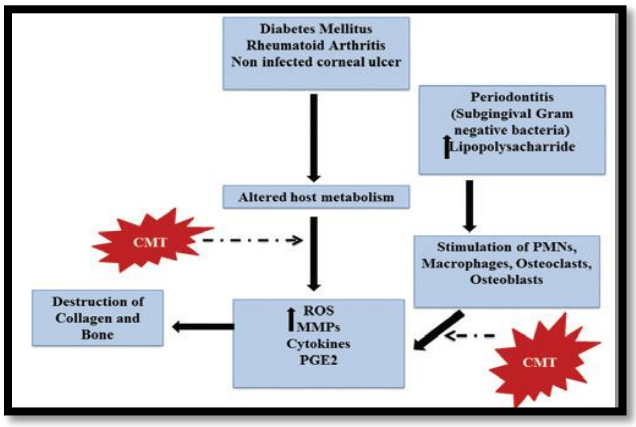
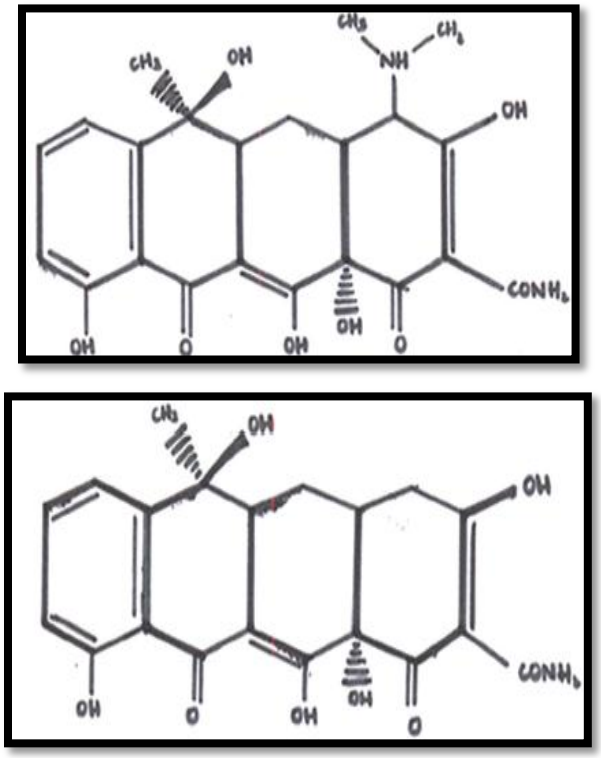


Figure 1: Host response in various chronic inflammatory conditions

Structure of CMT

According to Golub et al. antimicrobial activity of tetracyclines is because of carbon-4 position side-chain. The chemically modified tetracyclines (CMTs) were discovered by eliminating the dimethylamino group from the carbon-4 position of the A ring of the four ringed (A, B, C, D) structure. The resulting compound, 4-de-dimethyl amino tetracycline (CMT-1) did not have antimicrobial property but the anti collagenase activity was retained.



Tetracycline

CMT 1
Currently about ten CMTs including
CMT-1 (4 dedimethylaminotetracycline), CMT - 2 (tetracyclinonitrile),
CMT-3 (6-deoxy-6-demethyl-4-de dimethylaminotetracycline) and
CMT-4(7-chloro-4-de dimethylaminotetracycline),
CMT-5 (tetracycline pyrazole),
CMT-6 (4-dedimethyl amino. 4-hydroxytetracycline),
CMT-7 (12_-deoxy-4-dedimethyl amino tetracycline
CMT-8 (4-dedimethylamino doxycycline) have been developed.

Anti-collagenase activity of the CMTs are because of Ca2+ and Zn2+ binding sites present at the carbonyl oxygen and the hydroxyl groups present on carbon no -11, 12. The CMT-5 is a pyrazole analog of tetracycline, formed by the replacement of carbonyl oxygen at C-11 and the hydroxyl group at C-12 by nitrogen atoms. It does not have metal binding site and therefore it is inactive against the MMPs.[6] Tetracyclines has so many adverse effect which was overcome by the CMTs. Therefore CMTs are amneable to use for longer duration.

Mechanism of action

The action of CMTs as HMT agents in the treatment of periodontitis by inhibiting MMPs, inhibiting proinflammatory cytokines, inducible nitric oxide synthase (iNOS) and inhibiting bone resorption and by increasing the attachment of fibroblasts and connective tissues to the tooth surface[Figure2].[7]

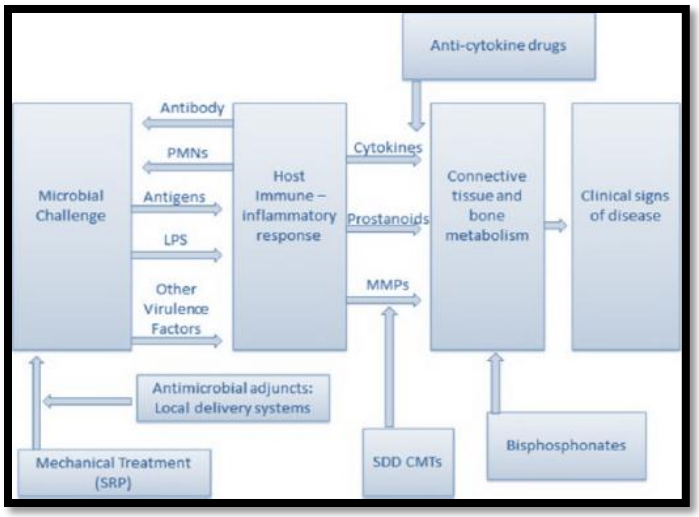


Figure 2 - Schematic illustration of the pathogenesis of periodontitis, targets for host modulation.

Inhibition of MMPs

Effect of CMTs on MMP has been widely discussed in the management of periodontitis.[8] It consists inhibition of the active MMPs with the help of Ca2+ and Zn2+-binding sites, inhibition of reactive oxygen species-mediated activation of pro-MMPs, proteolysis of pro-MMPs into enzymatically inactive fragments, protection of α-1 proteinase inhibitor from MMPs, reduction in the activity of serine proteinases. The major source of collagenases is Polymorphonuclear leucocytes (PMNs) that mediate the connective tissue breakdown during inflammatory periodontal disease, while the fibroblasts contribute the collagenase required for connective tissue remodeling in normal gingiva. The anti-collagenase activity present on carbon no. 11 & 12 of the four ringed structure of CMTs is specific against the collagenase produced from neutrophils but not the fibroblasts. This action of CMTs is important as this helps in the reduction of pathologic concentrations of collagenases enzyme without affecting the normal collagen turnover required to maintain the tissue integrity. The CMT-3 is specifically active due to CMT – 3's pleiotropic action toward MMPs it is stimulated against MMP-2, MMP -9 and MMP-14 isozymes. In addition to this,it also exerts an inhibitory effect on MMPs in micromolar concentrations by reduction in trypsinogen-2 and inducible nitric oxide (iNOS) production.[9] A study comparing six different CMTs in inhibition of MMPs showed that the CMT-8 was most effective inhibitor of periodontal breakdown. Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-.6 (IL-6) and MMPs CMT -8,-1, -3, -4, -7 and doxycycline were inhibited in descending order.[7]

Anti-inflammatory actions

Inhibition of inducible nitric oxide synthase

CMT-3 also exihibited the inhibitory action on inducible nitricoxide synthase activity, thus decreasing nitric oxide which is one of the activators of MMPs. The end product of NO, peroxynitrite radical is highly cytotoxic, inhibits collagen and proteoglycan synthesis and upregulates the MMP expression. Inhibition of iNOS production causes reduction in the peroxynitrite levels, thus preventing denatuartion of proteins. CMT-3 and CMT-8 are most effective and have maximum inhibitory effect on the iNOS and CMT-1 and-2 had an intermediary effect while CMT-5 was not effective.[10]

Biologic role of CMT in inflammation and wound healing

LPS-stimulated products of host immune cells, IL-1β, IL-6, IL-8, TNF-α and prostaglandin-E2 (PGE2) are inhibited by CMT by suppressing phosphorylation of the nuclear factor κ-B cell signaling pathway. The CMT-3 imparts an inhibitory action on cyclooxygenase-2 (COX-2)-mediated PGE-2 production. They are considered to be strong inhibitors of proinflammatory mediators and can increase levels of anti-inflammatory mediators such as IL-10. CMTs increase integrin expression on endothelial cells in inflammation, counteract the effects of transforming growth factor-β (TGF-β)-induced expression of MMPs, enhance phagocytosis by increased expression of FcγRIII, and stimulate fibroblasts to produce protease inhibitors like tissue inhibitors of matrix metalloproteases (TIMPs).[11]

Inhibition of bone resorption

CMTs (CMT-3 and CMT-8) retards osteoclastic bone resorption (Figure 3)and enhances bone formation and wound healing and inhibit proteinases produced by the action of microbes. CMT-1,-3, -6, -7 and -8 were potent inhibitors of osteoblastic collagenase in culture specifically CMT-8. CMTs impairs bone resorption by different mechanisms which consist of reduction in number of osteoclasts by inhibiting their development and inducing apoptosis, by disrupting the ruffled border thereby increasing the size of clear zone, by decreasing the production of osteoclastic enzymes like TRAP and Cathepsin-L which degrade organic components of bone, inhibits osteoclastogenesis, increased intracellular calcium levels which makes the osteoclasts to detach from bone resorbing site, inhibits osteoclasts collagenase production and also decreases acid production, thereby retarding bone resorption, thus preventing the destructive progression of periodontal disease.[12] CMTs encourage matrix and collagen deposition and inhibit bone resorption through anti-MMP and pro-TIMP actions and decreased action of inflammatory cytokines (e.g. IL-1, IL-6, TNF-α) and PGE2. These pleiotropic action of CMT provide significant therapeutic potential for the treatment of periodontitis.

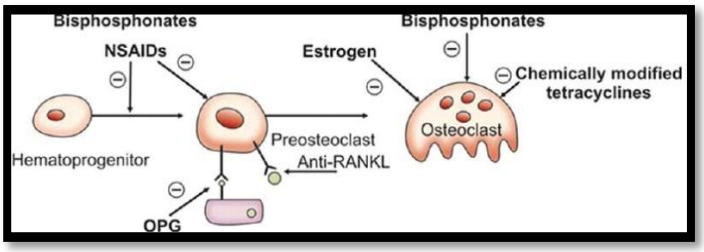


Figure 3 : showing effect of various host modulating agent on bone resorption.

Applications of CMT

1) Noninfected corneal ulcers
2) Rheumatoid arthritis
3) Diabetes mellitus
4) Tumor metastasis
5) antifungal properties[13]
6) epidermolysis bullosa and acute respiratory distress syndrome[14,15]

Conclusions

The CMTs are still under research in humans as they lack approval due to concerns like excessive suppression of MMPs which may alter the normal turnover rate of collagen. Further research is needed on CMTs which may be useful in suppressing the extracellular MMPs and the intracellular targets are warranted.

REFERENCES

1. Golub LM, Suomalainen K, Sorsa T. Host modulation with tetracyclines and their chemically modified analogues. Curr Opin Dent 1992;2:80-90.

2. Oringer RJ. Research, Science, and Therapy Committee of the American Academy of Periodontology. Modulation of the host response in periodontal therapy. J Periodontol 2002;73:460-70.

3. Sapadin AN, Fleischmajer R. Tetracyclines: Nonantibiotic properties and their clinical implications. J Am Acad Dermatol 2006;54:258-65.

4. Golub LM, McNamara TF, D'Angelo G, Greenwald RA, Ramamurthy NS. A non-antibacterial chemically-modified tetracycline inhibits mammalian collagenase activity. J Dent Res 1987;66:1310-4

5. Page C, Kornman S. The pathogenesis of human periodontitis: An introduction. Periodontol 2000. 1997;14:9-11.

6. Golub LM, Lee HM, Lehrer G, Nemiroff A, McNamara TF, Kaplan R, et al. Minocycline reduces gingival collagenolytic activity during diabetes: Preliminary observations and a proposed new mechanism of action. J Periodontal Res 1983;18:516-26.

7. Ramamurthy NS, Rifkin BR, Greenwald RA, Xu JW, Liu Y, Turner G, et al. Inhibition of matrix metalloproteinase-mediated periodontal bone loss in rats: A comparison of 6 chemically modified tetracyclines. J Periodontol 2002;73:726-34.

8. Patel RN, Attur MG, Dave MN, Patel IV, Stuchin SA, Abramson SB, et al. A novel mechanism of action of chemically modified tetracyclines: Inhibition of Cox-2-mediated prostaglandin E2 production. J Immunol 1999;163:3459-67.

9. Roy SK, Kendrick D, Sadowitz BD, Gatto L, Snyder K, Satalin JM, et al. Jack of all trades: Pleiotropy and the application of chemically modified tetracycline-3 in sepsis and the acute respiratory distress syndrome (ARDS). Pharmacol Res 2011;64:580-9.

10. Trachtman H, Futterweit S, Greenwald R, Moak S, Singhal P, Franki N, et al. Chemically modified tetracyclines inhibit inducible nitric oxide synthase expression and nitric oxide production in cultured rat mesangial cells. Biochem Biophys Res Commun 1996;229:243-8.

11. Steinsvoll S. Periodontal disease, matrix metalloproteinases and chemically modified tetracyclines. Microb Ecol Health Dis 2004;16:1-7.

12. Holmes SG, Still K, Buttle DJ, Bishop NJ, Grabowski PS. Chemically modified tetracyclines act through multiple mechanisms directly on osteoclast precursors. Bone 2004;35:471-8.

13. Liu Y, Ryan ME, Lee HM, Simon S, Tortora G, Lauzon C, et al. A chemically modified tetracycline (CMT-3) is a new antifungal agent. Antimicrob Agents Chemother 2002;46:1447-54.

14. Steinberg J, Halter J, Schiller H, Gatto L, Carney D, Lee HM, et al. Chemically modified tetracycline prevents the development of septic shock and acute respiratory distress syndrome in a clinically applicable porcine model. Shock2005;24:348-56. 44.

15. White JE. Minocycline for dystrophic epidermolysis bullosa. Lancet 1989;1:966.