ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)
IJDSIR : Dental Publication Service
Available Online at:www.ijdsir.com
Volume – 7, Issue – 5, September – 2024, Page No. : 289 - 297

Host Modulation Therapy

[1]Dr Athul Kanmani, Post Graduate, Resident, Department of Periodontics, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

[2]Dr Subair Kayakool, Professor, Department of Periodontics, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

[3]Dr Anil Melath, Professor and HOD, Department of Periodontics, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

[4]Dr Arjun MR, Reader, Department of Periodontics, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

[5]Hannah Thomas, Final Year Undergraduate, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

[6]Goutham, Final Year Undergraduate, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

Corresponding Author: Dr Athul Kanmani, Post Graduate, Resident, Department of Periodontics, Mahe Institute of Dental Sciences and Hospital, Mahe, Puducherry

Citation of this Article: Dr Athul Kanmani, Dr Subair Kayakool, Dr Anil Melath, Dr Arjun MR, Hannah Thomas, Goutham, "Host Modulation Therapy", IJDSIR- September – 2024, Volume –7, Issue - 5, P. No. 289 – 297.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Host modulation therapy (HMT) represents a significant advancement in the management of periodontal diseases, focusing on altering the host response to reduce tissue destruction and enhance repair mechanisms. Traditional periodontal treatments primarily target bacterial pathogens, but the recognition that host factors play a critical role in disease progression has shifted attention towards modulating the inflammatory response and bone metabolism. HMT involves the use of pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs), sub-antimicrobial dose doxycycline (SDD), and bisphosphonates to manage the host's immune response and inflammatory mediators. Emerging therapies also include biologics and synthetic matrix metalloproteinase inhibitors. These agents aim to reduce the production of pro-inflammatory cytokines, inhibit collagenase activity, and promote bone formation. Clinical studies have demonstrated that HMT, when used adjunctively with conventional mechanical therapies, can improve clinical outcomes, reduce periodontal pocket depths, and support alveolar bone preservation. Despite its potential, HMT poses challenges such as patient compliance, long-term safety, and cost considerations. Continued research and development are essential to optimize these therapies, ensure their efficacy, and integrate them into comprehensive periodontal treatment protocols. Host

modulation therapy offers a promising approach to managing periodontal diseases by addressing the underlying inflammatory processes and supporting periodontal regeneration.

Keywords: Lipoxins, Doxycycline, Prostaglandin, Bisphosphonates, Nutrients.

Introduction

A relatively recent addition to the dental community is the term "host modulation." It simply implies adjusting or regulating the harmful or destructive elements of the inflammatory host response that arises in the periodontal tissues due to the ongoing challenge posed by the subgingival bacterial plaque in the periodontal environment [(1)].

The periodontal disease Is caused by periodontal pathogens found in microbial biofilms. These pathogens break down extracellular matrices like collagen and host cell membranes to produce nutrients for their growth and potentially tissue invasion. Dangerous by products and enzymes such as hyaluronidases, collagenases, and proteases are produced during this process [(2)]. As a result, the periodontal tissues experience a host immune-inflammatory response that is characterized by the production of inflammatory cytokines, such as interleukins (IL), tumor necrosis factor-α (TNF-α), prostanoids, such as prostaglandin E2, and enzymes, such as matrix metalloproteinases (MMPs)[(3)]. Since the host immune system's primary purpose is to eradicate microbial infections and safeguard the host, its anti-inflammatory cytokines and enzymes often regulate the amount of these inflammatory mediators in periodontal tissues[(2)]. An individual's exposure to periodontal disease is mostly determined by the immune-inflammatory response that takes place in the periodontal tissues after prolonged exposure to bacterial plaque[(4)].

In the past twenty years, numerous pharmaceutical compounds have been investigated for their potential use as host modulators in the treatment of periodontal disease. These consist of the tetracycline class of compounds, bisphosphonates, and nonsteroidal anti-inflammatory medications[(5)].Lipoxins, soluble cytokine blockers, and anti-cytokine medications are some of the more recent medications that may be helpful in the treatment of periodontal disease. To date, only one systemic medication Has been licensed specifically as a host response modulator for the treatment of periodontal disease, and that is sub antimicrobial dose doxycycline [(6)].

Systemically administered drugs

Host modulating agents acting against MMPs

Various host cells secrete MMPs endopeptidases, which are essential for the breakdown of the extracellular matrix and basement membrane, as well as for modifying the effects of cytokines and osteoclast activation[7]. When periodontal disorders are actively active, microbial attack causes an increase in the production and activity of these MMPs. If the endogenous metalloproteinases inhibitors are unable to control this excessive production and activity, the result is significant tissue loss. Synthetic inhibitors of MMP called host modifying agents have been created to obstruct this degradation of host tissues. These inhibitors often contain a chelating group, which binds to the catalytic zinc atom at the active site of MMPs to stop them. [8]The Food and Drug Administration (FDA) has authorized the use of a tetracycline-based host modifying agent, also known as SDD – sub-antimicrobial dose of doxycycline (Doxycycline hyclate 20 mg; Periostat, CollaGenex, Pharmaceuticals Newton PA), as an adjuvant to periodontal therapy. For extended periods of therapy, refills may be given. A typical prescription for

Periostat (20 mg doxycycline tablets) is for at least 3 months (180 tablets, 1 tablet twice day until complete) [9].

Tetracycline analogues as host modulating agents

The dimethylamine group at carbon 4 (C4) in ring "A" of the tetracyclic naphthacene carboxamide ring system, which gives tetracycline its antibacterial activity, is what gives it its structure.

Golub, McNamara, and colleagues created 4-de dimethylaminotetracycline, or CMT, by removing the dimethylamino group from the carbon-4 position of the "A" ring. This process eliminated the drug's antimicrobial efficacy but did not lessen its capacity to block collagenase activity. [10]

Host-modifying substances that target metabolites of arachidonic acid

Prostaglandins are a key modulator of bone loss in periodontitis, as Dybvig recently confirmed. [11]

Several authors have shown how NSAIDs, such as flurbiprofen[12], indomethacin[13], and naproxen[14], can prevent gingivitis and the advancement of periodontitis. NSAIDs limit the action of both cyclooxygenase isozymes (COX-1 and -2).

According to Serhan et al., lipoxins (LX) are produced endogenously late in inflammation through cell-cell interaction when a second lipoxygenase (e.g., 5-LOX) interacts with a lipoxygenase product (e.g., hydroxyeicosatetraenoic acid), which is generated earlier from archidonic acid. These lipoxins have the potential to be both pro-resolving and anti-inflammatory. As a result, LXs may be targeted by HMT to treat periodontitis. [15]

Agents that modify the host and inhibit cytokines

As a result, HMT against cytokines, or cytokine therapy, may prove to be a successful treatment for periodontal diseases. Pro-inflammatory (e.g., IL-1α, IL-1β, IL-6, TNF-α, IFN-γ, etc.) and anti-inflammatory (IL-4, IL-10, etc.) cytokines can be very effective at controlling the negative effects of the host immune response[16].

Lipid-inflammatory mediators as potential HMT targets

Other endogenous chemical mediators that have been demonstrated to facilitate resolution and counter-regulate excessive acute inflammation include protectins, resolvins, and the recently discovered maresins. These are produced by lipoxygenases (LOX) and cyclooxygenases (COX) in a series of steps starting with precursors such as omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Similar to lipoxins, these endogenous chemical mediators also limit neutrophil recruitment, among other functions. [17].

Host modulating agents acting against bone resorption

Bisphosphonates

Bisphosphonates, which are analogues of pyrophosphate, have the ability to inhibit osteoclastic bone resorption. In addition to promoting osteoblast differentiation and preventing osteoclast activation, bisphosphonates are known to bind to hydroxyapatite crystals and stop them from dissolving. The effects of bisphosphonates on bone at the cellular and tissue levels have been compiled and characterized by Giannobile WV. These medications may be taken orally or intravenously by patients with Paget's disease, osteoporosis, and bone metastases, according to FDA approval.

Given its ability to preserve bone, bisphosphonates may also be useful in the treatment of periodontal disorders. In rats with experimental periodontitis, Shoji et al.'s 1995 study showed that systemic bisphosphonate therapy might stop alveolar bone loss. [18,19].

Nitric oxide synthase

Mercaptoethyl guanidine (MEG), a specific inhibitor of iNOS, has been shown by Lohinai et al. (1998) to protect against bone deterioration in rat periodontitis caused by ligature. It was recently demonstrated by Leitao et al. (2005) that NOS inhibitors stop alveolar bone resorption in cases of experimental periodontitis.[20]

Further host modulatory treatments

Probiotics:

According to Teughels et al. (2011), who investigated the potential of probiotics to modify the oral microbiota and periodontal health through immunomodulatory or direct microbiological interactions, probiotics may present beneficial opportunities to influence these parameters.

Periodontal vaccine:

I Yokoyama et al. (2007) showed that IgY-GP, an egg yolk antibody that fights Porphyromonas gingivalis, is a successful immunotherapeutic treatment for periodontitis. In a similar vein, Choi et al. documented that earlier immunization of mice against Fusobacterium nucleatum affected the humoral, cellular, and molecular responses of the host immune system to Porphyromonas gingivalis.[22,23]

Nutrients:

The main extracellular antioxidants found in nutrients, such as carotenoids, reduced glutathione, vitamin C, and omega-3 fatty acids, can also scavenge free radicals as they arise, sequester transition metal ions, and catalyze the formation of other molecules, all of which can act as modulators of inflammation. According to studies, cranberry juice also contains molecules that prevent lipopolysaccharide-activated gingival fibroblasts from producing MMPs, interleukin-6, interleukin-8, and prostaglandin E. As a result, it has the potential to be used as a novel host-modulating agent to prevent tissue destruction during periodontitis[24].

Locally administered HMT

Enamel matrix protein

Periodontal fiber and alveolar bone regeneration are secondary outcomes of the recruitment of cementoblasts to the root surface by enamel matrix proteins (EMD), which also drives these cells to generate root-cementum. With FDA approval, a derivative of enamel matrix is now commercially accessible as Emdogain® (Biora AB, Malmö, Sweden) for the treatment of periodontal problems. Using Emdogain is primarily justified by the fact that it functions as a tissue-healing modulator, simulating the processes involved in root growth and promoting periodontal regeneration.[25]

Bone morphogenetic protein

Under the brand names Induct OSTM (Wyeth, Maidenhead, UK) and INFUSE® Bone Graft (Medtronic, Minneapolis, MN, USA), absorbable collagen sponge (ACS) containing recombinant human BMP-2 has been approved for clinical usage in specific oral surgical procedures, including localized alveolar ridge augmentation. These ACS act as a scaffold for the growth of new bone, releasing the protein over time at the implanted site. The graft site heals, allowing bone to grow in its place and absorb the ACS.[26]

Platelet derived growth factors

Nevins et al. (2005) showed that robust periodontal regeneration in both interproximal intrabony defects and Class II furcations is produced by combining pure rhPDGF-BB with bone allograft.[27]

The FDA has approved Osteohealth's Growth-factor Enhanced Matrix, GEM 21S® (Shirley, NY), which combines an osteoconductive bone matrix with a highly pure, bioactive recombinant human PDGF-BB.

NSAID'S

Topical administration of NSAIDs is feasible due to their lipophilic nature and high absorption rate into gingival tissues. Meclofenamic acid, piroxicam, ketorolac tromethamine rinse, and S-ketoprofen dentifrice are among the NSAIDs that have been studied for topical application in terms of their ability to prevent gingivitis and the advancement of periodontitis.[28]

Cimetidine

Topically active cimetidine is a potent inhibitor of P. gingivalis-elicited periodontal inflammation, effectively stopping and/or preventing tissue destruction and influencing cell populations present in the inflammatory cell infiltrate, as demonstrated by morphological and histological evidence presented by Hasturk et al. (2006).[29]

Host modulation and comprehensive Periodontal management

For periodontitis, mechanical removal of calculus and plaque is thought to be the best course of action. This therapeutic strategy hasn't really changed over time, despite much discussion regarding matters like the advantages of manual versus ultrasonic cleaning, or the degree of root surface smoothness ⁄ hardness to be achieved.. Conventionally, this procedure is sometimes known as -root planning, while the phrase root surface instrumentation is now favored because it's thought that 'Planing' places too much of an emphasis on the removal of cementum and dentine from the root to create a smooth, hard surface, which has now been demonstrated as unnecessary for periodontal healing(30).The outcomes that can be expected following nonsurgical periodontal therapy are remarkably consistent. for example, for those pockets initially 4–6 mm deep, mean probing depth reductions of approximately 1.0–1.5 mm and mean attachment gains of 0.5–1.0 mm can be expected(30) . For deeper pockets (7 mm or greater), mean probing depth reductions of 2.0–2.5 mm and mean attachment gains of 1.0–1.5 mm can be expected (15). in many patients, nonsurgical management alone (comprising oral hygiene instruction, root surface instrumentation and periodontal maintenance care) may be sufficient to result in clinical improvements and control of periodontal disease. However, there are many patients in whom treatment responses following conventional treatment are more limited and both patient and clinician may ask if anything further can be done. This led to the development of host modulation as a treatment strategy that can be used in addition to conventional treatment approaches. This includes(31):

- Reduction in the bacterial burden (by root surface instrumentation and hygiene therapy).
- Risk factor modification (by smoking cessation and improved diabetes control).
- Host response modulation.

Host modulatory therapy is a treatment concept that aims to decrease the bacterial load thus giving tissue destruction and stabilize the periodontium by down regulating or modifying destructive aspects and ⁄ or up regulating protective or regenerative components of the host response. Host modulatory therapies could systemically or locally delivered pharmaceuticals that are prescribed as adjuncts to other forms of periodontal treatment. Host modulatory therapies offer the opportunity to move periodontal treatment strategies to a new level. Historically, periodontal treatment has focused on reducing the bacterial challenge by root surface instrumentation. However, the outcomes after conventional treatment of this chronic disease are not always optimal, predictable or stable. Periodontal disease can be viewed as a balance between

(a) a persisting bacterial burden and pro-inflammatory destructive events in the tissues, and

(b) resolution of inflammation and down regulation of destructive processes. Reducing the bacterial bio-burden by root surface instrumentation targets one aspect of the pathogenic process by reducing the antigenic challenge that drives the inflammatory response in the tissues.

However, total elimination of all subgingival bacteria is not achievable (or even desirable), and recolonization by putative pathogens occurs. Host response modulation therefore offers the potential for down regulating destructive aspects of the host response so that, in combination with conventional treatments to reduce the bacterial burden, the balance between health (characterized by resolution of inflammation and wound healing) and disease progression (characterized by continued pro-inflammatory, destructive events) is tipped in the direction of a healing response. In periodontitis, the host is responsible for total tissue breakdown that occurs, leading to the clinical signs of disease. Host response modulators offer the potential for modulating or reducing this destruction by ameliorating excessive or pathologically elevated inflammatory processes to enhance opportunities for would healing and periodontal stability [32].

Emerging Host Modulatory Therapies

Host response modulation has emerged as a valid treatment concept for the management of periodontal disease and represents a significant step forward for clinicians and patients. To date, only sub antimicrobial dose doxycycline has been approved specifically as a host response modulator for the treatment of periodontitis. Further research is necessary to evaluate the efficacy of sub antimicrobial dose doxycycline in primary care, and also to focus on very long-term outcomes, such as prevention of tooth loss. The health economics of therapy should also be investigated: thus, if subantimicrobial dose doxycycline confers significant clinical improvements, the cost of medication may be offset by the reduced need for additional treatment such as periodontal surgery. Future developments in relation to subantimicrobial dose doxycycline will include modified-release formulations that achieve sustained plasma concentrations of doxycycline over 24 h, but only require once per day dosing, thereby improving patient compliance. Furthermore, the development of chemically modified tetracyclines is welcomed, as this will completely eliminate all concerns about any possible antimicrobial effects of these agents. Given the safety of subantimicrobial dose doxycycline, it is likely that host response modulators with similar safety profiles will be welcomed by practising clinicians if proven to have a clinical benefit and minimal unwanted effects [33].

Cytokine antagonists, such as interleukin-1 receptor antagonist or soluble tumor necrosis factor-a receptors, which competitively inhibit receptor-mediated signal transduction, may offer potential in the treatment of periodontal disease [34,35]. However, a degree of caution is required, as, for example, the monoclonal antibody to tumour necrosis factor (infliximab), which has been successfully used over recent years in the treatment of rheumatoid arthritis, has also been associated with the re-emergence of latent tuberculosis infection in a small percentage of patients[36]. Thus, we must carefully evaluate newer agents that, while modifying inflammatory responses, may also have unexpected effects on host defences.

Interleukin-11 has anti-inflammatory effects including inhibition of tumor necrosis factor alpha [37] and recombinant human interleukin-11 has been shown to result in significant reductions in the rate of attachment

and bone loss over an 8-week period in experimental periodontitis in dogs [38]. Inhibition of cytokine receptors, soluble cytokine blockers and anti-inflammatory cytokines therefore hold promise for the future.

The future will see a range of host response modulators developed as adjunctive treatments for periodontitis. At present, subantimicrobial dose doxycycline provides improvements in probing depth reductions and attachment gains compared with root surface instrumentation alone [39], and is the only licensed and approved host response modulator available to dentists to date. Although the use of nonsteroidal anti-inflammatory drugs has been associated with reduced alveolar bone loss, the unwanted effects of these drugs precludes their use. Similarly, although data supporting the use of bisphosphonates to improve clinical periodontal status have been published, given the association with osteonecrosis, further studies are warranted to determine the risks and benefits of these drugs. Lipoxins and compounds that block cytokine receptors have been shown to reduce gingival inflammation and bone loss in animal models and may represent the future of host response modulation for treating periodontal disease, although this remains to be demonstrated in clinical trials in humans.

Conclusion

The improved understanding of the host-bacterial interactions and the host immuno-inflammatory response leading to periodontal tissue destruction has led to the development of HMT. Though the efficacy and usefulness of host modulating agents have been demonstrated by many clinical trials and have been approved by FDA for the management of periodontitis, yet the risk/benefit ratio relating to the use of these drugs has yet to be established. Multicenter clinical trials are necessary to fully evaluate the benefits of these agents and to weigh their usefulness against the risks associated with their long-term administration. Furthermore, continuous research in this field would also enable fabrication of individualized treatment for periodontal disease targeting inflammatory host response. The current article emphasizes the promising potential of various host-modulating agents (the most crucial component of perioceutics) in the management of periodontal diseases [40].

References

1. Al-Shammari KF, Giannobile WV, Aldredge WA, Iacono VJ,Eber RM, Wang HL, Oringer RJ. Effect of non-surgical Periodontal therapy on C-telopeptide pyridinoline crosslinks (ICTP) and interleukin-1 levels. J Periodontol 2001:72: 1045–1051.
2. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV. Novel host response therapeutic approaches to treat periodontal diseases. Periodontol 2000. 2007;47:294–315.
3. Preshaw PM. Host response modulation in periodontics. Periodontol 2000. 2008;48:92–110.
4. Giannobile WV. Host-Response Therapeutics for Periodontal Diseases. J Periodontol. 2008;79:1592–600.
5. Barksby HE, Lea SR, Preshaw PM, Taylor JJ. The Expanding family of interleukin-1 cytokines and their role in destructive inflammatory disorders. Clin Exp Immunol 2007: 149:217–225.
6. Bezerra MM, de Lima V, Alencar VB, Vieira IB, Brito GA,Ribeiro RA, Rocha FA. Selective cyclooxygenase-2 inhibition prevents alveolar bone loss in experimental periodontitis in rats. J Periodontol 2000: 71: 1009–1014.
7. Ryan ME, Golub LM. Modulation of matrix metalloproteinase activities in periodontitis as a

treatment strategy. Periodontol 2000. 2000;24:226–38.

8. Caton J, Ciancio S, Crout R, Hefti A, Polson A. Adjunctive use of subantimicrobial doxycycline therapy for periodontitis. J Dent Res. 1998;77:1001.
9. Ryan ME. Nonsurgical approaches for the treatment of periodontal diseases. Dent Clin N Am. 2005;49:611–36.
10. 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.
11. Weaks-Dybvig M, Sanavi F, Zander H, Rifkin BR. The effect of indomethacin on alveolar bone loss in experimental periodontitis. J Periodontal Res. 1982;17:90–100.
12. Heasman PA, Offenbacher S, Collins JG, Edwards G, Seymour RA. Flurbiprofen in the prevention and treatment of experimental gingivitis. J Clin Periodontol. 1993;20:732–8.
13. Nyman S, Schroeder HE, Lindhe J. Suppression of inflammation and bone resorption by indomethacin during experimental periodontitis in dogs. J Periodontol. 1979;50:450–61.
14. Howell TH, Jeffcoat MK, Goldhaber P, Reddy MS, Kaplan ML, Johnson HG, et al. Inhibition of alveolar bone loss in beagles with the NSAID naproxen. J Periodontal Res. 1991;26:498–501.
15. Van Dyke TE. Control of inflammation and periodontitis. Periodontology 2000. 2007;45:158–66.
16. Rodríguez-Rabassa M, López P, Sánchez R, Hernández C, Rodríguez C, Rodríguez-Santiago RE, Orengo JC, Green V, Yamamura Y, Rivera-Amill V Int J Environ Res Public Health, 17(3):E689, 21 Jan 2020.
17. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008;8:349–61.
18. Tenenbaum HC, Shelemay A, Girard B, Zohar R, Fritz PC. Bisphosphonates and periodontics: Potential applications for regulation of bone mass in the periodontium and other therapeutic/diagnostic uses. J Periodontol. 2002;73:813–22
19. Shoji K, Horiuchi H, Shinoda H. Inhibitory effects of acbisphosphonate (risedronate) on experimental periodontitis in rats. J Periodontal Res. 1995;30:277–84.
20. Lohinai Z, Benedek P, Feher E, Gyorfi A, Rosivall L, Fazekas A, et al. Protective effects of mercaptoethylguanidine, a selective inhibitor of inducible nitric oxide synthase, in ligature-induced periodontitis in the rat. Br J Pharmacol. 1998;123:353–6.
21. Teughels W, Loozen G, Quirynen M. Do probiotics offer opportunities to manipulate the periodontal oral microbiota? J Clin Periodontol. 2011;38:159–77.
22. Rose ME, Orlans E, Buttress N (1974)Immunoglobulin classes in the hen's egg: their Segregation in yolk and white. Eur J Immunol 4, 521-523
23. Yokoyama K, Sugano N, Shimada T, Shofiqur RA, Ibrahim el-SM, Isoda R, et al. Effects of egg yolk antibody against Porphyromonas gingivalis gingipains in periodontitis patients. J Oral Sci. 2007;49:201–6.
24. La VD, Howell AB, Grenier D. Cranberry proanthocyanidins inhibit MMP production and activity. J Dent Res. 2009;88:627–32.

25. Heijl L, Heden G, Svardström G, Ostgren A. Enamel matrix derivative (Emdogain) in the treatment of intrabony periodontal defects. J Clin Periodontol. 1997;24:705–14.
26. URIST, M.R.: The substratum for Bone Morphogenesis, Develop Biol (suppl), pp 125-163, 1970.
27. Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, et al. Platelet derived growth factor (rhPDGF-BB) stimulates bone fill and rate of attachment level gain, results of a large, multicenter randomized controlled trial. J Periodontol. 2005;76:2205–15.
28. Howell TH, Fiorellini J, Weber HP, Williams RC. Effect of the NSAID piroxicam, topically administered, on the development of gingivitis in beagle dogs. J Periodont Res. 1991;26:180–3.
29. Brockmeyer, N. H., E. Kreuzfelder, W. Guttmann, L. Mertins, M. Goos, and E. E. Ohnhaus. 1989. Cimetidine and the immuno-response in healthy volunteers. J. Investig. Dermatol. 93:757-761
30. Cobb CM. Clinical significance of non-surgical periodontal therapy: an evidence-based perspective of scaling and root planing. J Clin Periodontol 2002: 29(Suppl. 2): 6–16.
31. Preshaw PM, Hefti AF, Jepsen S, Etienne D, Walker C, Bradshaw MH. Subantimicrobial dose doxycycline as Adjunctive treatment for periodontitis. A review. J ClinPeriodontol 2004: 31: 697–707.
32. Perio2000
33. Strand V, Kimberly R, Isaacs JD. Biologic therapies in rheumatology: lessons learned, future directions. Nat Rev Drug Discov 2007: 6: 75–92.
34. Dinarello CA. The many worlds of reducing interleukin-1. Arthritis Rheum 2005: 52: 1960–1967.
35. Levine SJ. Mechanisms of soluble cytokine receptor generation. J Immunol 2004: 173: 5343–5348.
36. O'Neill LA. Targeting signal transduction as a strategy to treat inflammatory diseases. Nat Rev Drug Discov 2006: 5:549–563.
37. Trepicchio WL, Bozza M, Pedneault G, Dorner AJ. Recombinant human IL-11 attenuates the inflammatory response through down-regulation of proinflammatory cytokine release and nitric oxide production. J Immunol 1996: 157: 3627–3634.
38. Martuscelli G, Fiorellini JP, Crohin CC, Howell TH. The effect of interleukin-11 on the progression of ligature-induced periodontal disease in the beagle dog. J Periodontol 2000: 71: 573–578.
39. Kinane DF, Attstrom R. Advances in the pathogenesis of periodontitis. Group B consensus report of the fifth European Workshop in periodontology. J Clin Periodontol 2005: 32: 130–131.
40. Gulati M, Anand V, Govila V, Jain N. Host modulation therapy: An indispensable part of perioceutics. J Indian Soc Periodontol. 2014 May;18(3):282-8. doi: 10.4103/0972-124X.134559. PMID: 25024538; PMCID: PMC4095617.