Literature Review

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Modulation of host response - use in periodontal diseases

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Abstract

The basis of the macroorganism's reaction is the inflammatory response to the presence of plaque biofilm, modified by genetic factors (which explains why the rapidly progressive forms of periodontitis have a tendency for family aggregation), as well as systemic environmental factors (smoking, diabetes, stress).

Periodontal diseases are multifactorial, complex diseases driven by the immune-inflammatory response to bacterial plaque in susceptible patients. The importance of the body's response as a determinant in susceptible patients has led researchers to identify the genetic frequency that characterizes individuals as resistant or susceptible to the disease. Researchers are also investigating host response modulating therapies (HMTs) aimed at modifying or reducing the destructive aspects of the immune response so that the immune-inflammatory response to bacterial plaque is less damaging to the periodontal tissues. As the pharmaceutical industry develops, HMTs as an adjunctive therapy in periodontal disease will target different aspects of the body's response.

Keywords: *periodontal diseases, host response modulation therapy, immune-inflammatory response*

Introduction

Host response modulation therapy (HMT) is a concept which goal is to reduce tissue destruction, stabilise or regenerate the periodontium by modifying or suppressing the body's destructive response processes, by enhancing the protective or regenerative response. Host response modulation therapy includes systemic or local medication that are part of the periodontal treatment and are applied as an adjunct to conventional scaling and root planning (SRP) therapy, or as part of the surgical treatment. The interest in HMTs use in the treatment of periodontitis is crucial for a better understanding of the pathogenesis of periodontitis and

the importance of the host response in susceptibility to the disease and its progression. The application of HMTs offers a new, more modern level of periodontal treatment strategies. (1,2)

Historically, the treatment of periodontitis has focused on reducing the bacterial load through scaling and root planning (SRP), improving and maintaining the patient's oral hygiene, and applying surgical techniques to treat periodontitis. But the outcome after conventional therapy for chronic diseases such as periodontitis is not always predictable and stable. Periodontal disease and health can be considered as a balance between the persistent bacterial load and the available pro-inflammatory factors, acting in the direction of its resolution and suppressing the destructive processes.(3) Plaque biofilm removal by SRP and reduction of the bacterial load affects only one of the factors of the developing pathogenic process and the available antigenic load that triggers an inflammatory response in the adjacent tissues. It is known that the bacterial load cannot be completely eliminated after SRP because the bacterial species quickly recolonize. Host response modulation therapy has the potential to suppress destructive processes, direct protective processes in the host response, and in combination with conventional therapy leading to reduction in bacterial load, the observed balance between health (resolution of inflammation and healing) or disease progression (ongoing action of proinflammatory factors) to be determined in the direction of the body's response to healing.(4) Host response modulation therapy is important in the treatment of the side effects in the body caused by the interaction between microorganisms and the macroorganism. It is the host response that determines much of the tissue destruction leading to the clinical signs of periodontitis. Host response modulation therapy cannot interrupt the body's normal defense mechanisms or inflammation, but it can enhance the inflammatory process in order to increase the opportunistic response in order to heal and achieve periodontal stability.(5) Various medications have been studied as modulating the host response, which can be divided into agents for systemic administration: NSAIDs, Sirtuins (SIR-2), Resveratrol, Bisphosphonates, non-antibiotic modifications of tetracyclines, chemical modifications of curcumin, etc. and topical agents: the enamel matrix proteins, platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF), and bone morphogenic proteins.(6,7,8,9,10)

Currently, most therapeutic approaches are focused on how the host response can be aimed in the direction of controlling the excessively expressed local inflammatory process. Many of the host responses can be influenced, for example modifying the action of proteolytic enzymes such as matrix-metalloproteinases, stimulating cellular activity, as well as changing the extracellular matrix. It is likely that in the future, most effective therapeutic approaches will involve complex and synergistic response-modulating therapies in combination with conventional treatment targeting the microbial etiology. (11)

Results

The following potential response-modulating therapies are being considered:

Systemic:

- blocking the production of pro-inflammatory cytokines and prostaglandins with anti-inflammatory drugs
- inhibiting the matrix metalloproteinases (MMPs) with antiproteinases
- turning off the cellular and molecular cycle of the inflammatory process endogenously with the application of lipoxins or resolvins and natural phenols.

Systemically administrated drugs

Anti-inflammatory agents used to block the production of pro-inflammatory cytokines and prostaglandins

NSAIDs are known to suppress prostaglandins including PGE2, which is produced by neutrophils, macrophages, fibroblasts and gingival epithelial cells in response to the presence of lipopolysaccharides (LPS), as components of the cell wall of Gr negative microorganisms. Prostaglandin E2 (PGE2) has long been studied in periodontal disease because of evidence that it affects bone resorption by increasing the number of osteoclasts, as well as the fact that PGE2 levels are elevated in patients with periodontal disease compared to healthy individuals (12,13,14). Prostaglandin E2 also inhibits fibroblast function and has a suppressive and modifying effect on the body's immune response (15). NSAIDs have the property of suppressing prostaglandins, thereby reducing tissue inflammation. NSAIDs are also used in the treatment of pain in acute and various chronic inflammatory conditions. Clinical studies have shown that systemic administration of NSAIDs, such as Indomethacin, Flurbiprophen, and Naproxen over a three-year period, significantly slows alveolar bone loss compared to placebo. (12) In addition, selective COX-2 inhibitors are considered more promising as an adjunctive therapy in the treatment of periodontitis. The COX enzyme, which converts arachidonic acid to prostaglandins, requires the presence of two functionally distinct isoforms, COX-1 and COX-2. Cyclooxygenase-1 has established antiplatelet and cellular protective effects, while cyclooxygenase-2 is induced after stimulation by various cytokines, growth factors and lipopolysaccharides, resulting in the production of increased amounts of prostaglandins. Therefore, inhibition of COX-2, by selective COX-2 NSAIDs, results in a greater reduction of inflammation. In recent years, two approaches of host response modulation therapies with anti-inflammatory drugs have mainly been studied:
The first approach is related to the use of non-steroidal anti-inflammatory drugs that suppress the body's inflammatory response by affecting the well-known inflammatory mediators: prostanoids, cytokines, tumor necrosis factor-α, etc., and have a suppressive effect on osteoclasts and bone loss (7,12,16). In addition to NSAIDs, there is increasing interest in a new category of agents that also suppress the host inflammatory response, but do not act on the acute phase of inflammation, but prevent its persistence. These are the so-called resolvins. These compounds include derivatives of omega-3 fatty acids such as: docosahexaenoic acid, eicosapentaenoic acid, as well as lipoxins, which are derivatives of arachidonic acid. Other agents modulating the host response, such as sirtuins (SIR-2) - a type of protein. These proteins have the ability to influence aging processes, DNA transcription, cell apoptosis, inflammation, stress resistance, as well as mitochondrial biogenesis. Resveratrols (natural phenols and phytoalexins) are another type of agent that has also been discussed as a possibility for influencing the body's inflammatory response. There is evidence that they protect against diabetes, osteoporosis, stimulate the heart condition in patients with cardiovascular diseases and have a beneficial effect in the presence of inflammation. (5,17,18)

Antiproteinase agents to inhibit matrix metalloproteinases (MMPs).

The currently known antiproteinases used in periodontitis therapy are the tetracyclines. In addition to antimicrobial activity, they have the ability to inhibit neutrophils, osteoclasts and matrix metalloproteinases (MMPs), especially MMP-8 and MMP-9 (neutrophil collagenases) known to be involved in periodontal destruction. Tetracyclines have an anti-inflammatory effect and act as osteoprotectors, inhibiting

osteoclasts. Doxycycline is the most studied and the most potent collagenase inhibitor of the group of tetracyclines in use (19,20,21,22).
It is logical that in recent years, regarding the use of agents modulating the host response, the focus should be more on the second treatment approach - the one that suppresses the breakdown of connective tissue in periodontitis and other chronic inflammatory diseases. The use of these agents is based on the newly developed non-antibiotic modifications of tetracyclines (especially chemical modification of doxycycline). (23) It relies on the following mechanisms of action:

✓direct suppression of activated matrix metalloproteinases in connective tissue
✓suppressing the action of pro-inflammatory cytokines;
✓increase in collagen synthesis, osteoblastic activity and bone formation.

Most studies on the administration of subantimicrobial doses of Doxycycline in patients with periodontitis have shown statistically significantly better results in CAL gain and PD reduction when 20 mg of Doxycycline (Periostat® - doxycycline hyclate) 2 per day for 3-9 months is used as adjunct to conventional therapy (SRP). (24)
The drug Periostat® is approved for additional therapy to conventional therapy for periodontitis. The prescribed dose of 20 mg has a pronounced therapeutic effect on enzymes, cytokines and osteoclast inhibition, more than other antibiotic agents used. The research studies performed did not establish an antimicrobial effect of SDD on the normal oral flora or the bacterial flora in other parts of the human body. (25)
The other category of new medicinal agents with anti-collagenase action are chemical modifications of curcumin. Curcumin is a compound with a proven anti-inflammatory effect, but it is insoluble and poorly absorbed, which significantly limits its clinical application. To avoid these inconveniences, 16 chemically modified types of Curcumin have been developed to date. Two of them, modified curcumin-2.24 and curcumin-2.5, have proven efficacy as inhibitors of matrix metalloproteinases. Both chemically modified drugs are also effective in suppressing the known inflammatory mediators: interleukin-1β, interleukin-6, prostaglandin E2, monocyte chemoattractant protein-1, as well as against MMP-9 secreted by human monocytes and neutrophils. The effects of chemically modified curcumin-2.24 have recently been associated with reduced activation of nuclear-factor kappa-light-chain - a stimulator of activated B-cells that regulate the transcription of a number of gene products associated with inflammatory diseases. (18)

Agents used to inhibit bone resorption - Bisphosphonates

In the last 10 years, the use of bisphosphonates as osteoprotective agents has been included in the control of osteoporosis and various osteoresorptive diseases. Bisphosphonates are medications that are often used to treat malignant hypercalcemia, bone metastases, in the treatment of breast cancer, prostate carcinoma, lung carcinoma, renal carcinoma, nasopharyngeal malignancies and thyroid carcinoma. Main drugs from the group of bisphosphonates are: Zoledronate, Alendronate, Ibandronate, Etidronate, Risedronate and Clodronate (26,27). They are absorbed by the bone and delivered locally during the acidification (increased acidity) associated with osteoclast activity. Bisphosphonates inhibit bone resorption by reducing osteoclast activity. Therefore, they may have a potential role in inhibiting alveolar bone loss in patients with periodontitis and peri-implantitis. Their exact mechanism of action has not been clarified, but studies show that bisphosphonates interfere with osteoblastic metabolism and the secretion of lysosomal enzymes. More recent research has highlighted that bisphosphonate also have anti-collagenase properties. The duration of

taking bisphosphonates is long - on average for 24 months, which is why their systemic effects are manifested and persist for a long period. Bisphosphonate necrosis of the jaws is their important side effect, first mentioned in 2003 in the specialised literature. (8,26,27) In 2014, the American Association of Oral and Maxillofacial Surgeons proposed a change in nomenclature and the disease is now designated as medication-related osteonecrosis of the jaw. In order to prevent bisphosphonate necrosis, during surgical interventions performed on patients taking bisphosphonates: it is necessary to observe some rules:

✓Tooth extractions should be as atraumatic as possible.
✓Surgical wounds should be closed primarily by suturing.
✓Sharp bone edges need to be smoothed.
✓Three days preoperatively and 7 days postoperatively, it is necessary to prescribe antibiotic prophylaxis - with Amoxiclav or Clindamycin
✓After any surgical procedure performed, these patients need to observe strict oral hygiene and use rinses with chlorhexidine or other antibacterial agents.

Conclusion

The control of the microorganisms that cause periodontal infection continues to be leading for effective periodontal treatment. Understanding the importance of the host response and the influence of risk factors, to date, allows clinicians to provide a variety of additional treatment strategies for their patients.
If a decision is made to administer a host modulation therapy, this should be discussed with the patient and the rationale for such treatment should be explained in detail. This takes time at the chair and a lot of information so that the patient takes an interest in their disease so that they can be motivated to follow strict plaque control and be familiar with the procedures included in the treatment plan.
Patient consent to host modulation therapy is greatly facilitated by emphasising that HMT does not replace good plaque control, precise non-surgical periodontal therapy by clinicians to reduce bacterial load, especially when treating patients with condition-modifying risk factors.
It is responsibility of the clinicians to be able to select and provide the appropriate treatment to the patient after discussion and informed consent. Good communication and showing interest in the patient's condition are necessary for maximum patient compliance and modification of identified risk factors. It is important to emphasise that the most favorable outcome of the treatment is obtained from the application of the targeted therapeutic approach selected individually for each patient.

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