Regeneration, Reconstruction & Restoration **Hypothesis**

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Effect of Anti-Cytokine Treatment on the Success Rate of Vital Pulp Therapy

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Abstract

Human dental pulp is a unique connective tissue able to respond to the invasion of pathogens and their by-products in the root canal system via inflammatory reactions in order to remove etiological factors and encourage healing; resulting in "Pulpitis", which is namely defined by the accumulation of inflammatory mediators, specifically pro-inflammatory cytokines and chemokines. However, if the inflammation progresses and pathogens are not appropriately reduced or eliminated, pulp necrosis will ultimately occur; causing the need for radical pulpectomy and consequently, loss of tooth vitality. Vital pulp therapy (VPT), as a concrete example of regenerative endodontics, is based upon minimally invasive concept; in which the conservation of compromised or inflamed dental pulpal tissue is of critical importance for dentine-pulp regeneration. Pro-inflammatory cytokines, as host modulators, play a significant role in the amendment of intensity and duration of immune response to pathogenic factors. Since the modulation of inflammation is crucial in reaching successful outcomes in VPT, anti-cytokine therapy may assist in achieving the aforementioned results. In addition, when the amount of pro-inflammatory cytokines increases, the pulpal inflammation seems to escalate and negatively affect the tissue healing. Therefore, if cytokines are modulated, the inflammatory process can be favourably controlled, and the healing of dental pulp tissue may be promoted.

Keywords: Cytokines; Endodontics; Inflammation; Regenerative endodontic procedures; Vital pulp therapy.

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1. Introduction

Host modulation therapy (HMT) is deliberated as an approach shown to reduce tissue destruction, and regenerate or stabilise inflamed tissues through the modification of host response factors (1). Additionally, HMT seems to enhance the possible prospects of wound healing via the regulation of destructive inflammatory processes, in which the balance of mediators involved in pro- and anti-inflammatory reactions is restored (2, 3). For the last few decades, HMT has been considered as an approach for the treatment of chronic diseases; e.g. osteoporosis and rheumatoid arthritis (RA) (4). In addition, psoriasis vulgaris has been reported to be successfully treated with the simultaneous application of low-doses of interleukin IL-4, IL-10 and IL-11 (5). Furthermore, infliximab, i.e. a chimeric monoclonal antibody-based drug, has been prescribed to target tumor necrosis factor (TNF)-α for the treatment of RA as well as several other inflammatory conditions; e.g. Crohn's disease and ankylosing spondylitis (6, 7). Moreover, various studies have introduced and investigated different modulation agents; including tetracycline, chemically modified tetracycline, non-steroidal anti-inflammatory drugs, bisphosphonates, synthetic matrix metalloproteinase inhibitors, recombinant tissue inhibitors of matrix metalloproteinase, and anti-cytokines agents; e.g. IL-1 and TNF blockers (8).

Cytokines, as well as chemokines, are elaborated as the main mediators in the process of inflammation. They are molecules for cell signaling; helping cells to communicate in immune responses, while encouraging them to move towards sites of inflammation, infection or trauma. Cytokines can be categorized into two pro-inflammatory and anti-inflammatory subsets. Pro-inflammatory mediators provoke immune responses resulting in the destruction of target tissue whereas anti-inflammatory cytokines are responsible for preventing inflammatory responses, inhibiting the destruction of corresponding tissues (9, 10).

Recently, and owing to the successful outcomes of HMT in medicine, host modulation has been investigated in dentistry (3). Initially, William and Golub introduced HMT to modulate the host response in the development of periodontal diseases in 1990 (11). Periodontal pathosis stems from the inflammation of periodontal tissues induced by bacterial plaque which produces toxins that cause localized host response, employ inflammatory cells, initiate production of prostaglandins or cytokines, secrete lytic enzymes, and cause osteoclastogenesis. HMT is currently used as an adjunct to conventional periodontal treatments with degrees of success (12). Moreover, it has been revealed that when IL-1 is inhibited, significant reduction in inflammation and loss of connective tissue attachment would be expected. Furthermore, a substantial decrease in bone resorption induced by related periodontal pathogens has been reported (13). Seemingly, use of anti-inflammatory and anti-oxidant agents in the treatment of periodontitis as an HMT strategy could be an acceptable therapeutic method for clinical success (14).

2. Hypothesis

The local use of anti-cytokines seems to hypothetically manage the inflammation of dental pulp and assist endodontic regeneration in VPT.

3. Evaluation of the hypothesis

Pulpitis, as one of the most common dental diseases, is characterized by the inflammation of dental pulpal tissue and its immunological reactions; which could result in undesirable changes in the state of inflamed pulp (15). Several factors play important parts in the host response; including inflammatory mediators (e.g. cytokines and proteases), growth factors and antimicrobial peptides which assist the connective pulpal tissue in its defense mechanisms (16). However, due to the critical and crucial functions of the dental pulp in nutrition, immunocompetence and innervation of the tooth, pulp vitality should be preserved to enhance the mechanical resistance of tooth structure and reassure its long-term survival (17).

In regenerative endodontics, vital pulp therapy (VPT) is referred to as a state-of-the-art concept in which preservation of pulp and prevention of inflammation progression are addressed, resulting in pulp-dentine regeneration (18, 19). To succeed in VPT, the management of pulp inflammation is needed; since inflammation appears to contribute to the removal of micro-organisms and their by-products as well as stimulation for repair and healing (20). In other words, modulation of inflammation or host modulation in dentine-pulp complex can be considered an adjunct for more successful VPTs through the facilitation of pulp healing and regeneration.

4. Discussion and implications

Vital pulp therapy modalities, which are based on anti-inflammatory approaches to therapeutically manage the state of pulp, have been reported in different studies. In a recent study, it has been shown that the localized use of meloxicam could significantly decrease pulpal inflammation (21). In a comparable investigation, it has been demonstrated that Resolven E1 (RVE1) is able to reduce the necrosis of inflamed pulp and conserve pulp vitality in an in vivo environment. Moreover, the amount of pro-inflammatory cytokines, i.e. TNF-α, IL-1β, and IL-6 released from lipopolysaccharide-stimulated human dental pulp stem cells, were experimentally declined using RVE1 (22). Therefore, the modulation of pulpal inflammation may act as an adjunctive treatment to facilitate the regeneration, repair and healing of connective pulpal tissue. Thus, regenerative endodontic procedures, specifically VPTs, using local anti-cytokine therapy may encourage the modulation of dental pulp inflammation and betterment of outcomes (i.e. pulp-dentine regeneration) of the treatment modality.

Pulpitis is commonly accompanied by dental caries, leading to the invasion of micro-organisms and their by-products through dentinal tubules. Pulpitis is conventionally classified into reversible and irreversible subcategories; however, in both conditions, bacterial penetration causes defence reactions in the dental pulp, including inflammatory and immune responses. These responses trigger a significant process comprising different factors and various elements; e.g. cytokines (23, 24). Inflammatory cytokines, specifically TNF-α, IL-1α, IL-1β,

IL-2, IL-6 and IL-8, play major roles in the introduction of immunological responses in the dental pulp after bacterial invasion (25). Tumor necrosis factor-α is elaborated as one of the most important cytokines responsible for the management of early response of the host to the inflicted damages or injuries affecting the dental pulp. In addition, TNF-α plays a significant role in the early and subsequent stages in the inflammatory process of pulp (26). Interleukin-1 has shown to possess numerous biological functions and appeared to be able to modulate genes present in the dental pulp inflammatory process. Its two subclasses, i.e. IL-1α and IL-1β, have displayed agonistic functions and can land on the same receptor (27). IL-2 has shown to stimulate clonal expansion, encourage T-cell proliferation, amplify B-cell antibody secretion and trigger the transcription of cytokines in the inflamed pulp (28). It has been revealed that IL-6 has various biological activities in the dental pulp; including, but not limited to, production of antibodies, activation of T-cells, differentiation of B-cells, angiogenesis and other inflammatory phenomena (29). Nonetheless, cytokines can demonstrate simultaneous pleasures and problems; e.g. they can contribute to the attraction and infiltration of immune cells as well as the elimination of micro-organisms while destroying the dental pulp (14). Therefore, the reduction of inflammation using anti-cytokine therapy could be considered in the regeneration and/or healing of dental pulpal tissues. Anti-cytokine therapy has been also studied for the improvement of osteogenesis in dental implantology (30).

If pulpal inflammation persists or pulpitis becomes chronic, degeneration, destruction and ultimately necrosis of the dental pulp could occur; specifically due to its confinement in the surrounding hard tissue (dentine) and lack of sufficient room for further swelling (31). Consequently, promotion of a relatively inflammation-free environment after the removal of affected or inflamed pulp could encourage the regeneration of remaining connective tissue at the dentine-pulp complex. To accomplish the aforementioned setting, cytokines, mediators and molecules, capable of controlling early pro-inflammatory responses and attracting necessary cell population to the site, should be modulated; where anti-cytokine therapy could be deliberated as a solution (32). Thus, cytokines could be a promising target for the state-of-the-art strategies in the modern era of therapeutic treatments; in which anti-cytokine therapy comprises the up-regulation of anti-inflammatory mediators and down-regulation of pro-inflammatory agents (9). Shima et al. has recently shown that Tocilizumab, as a monoclonal antibody and anti-cytokine, can be used against human IL-6R for the treatment of Castleman disease, Takayasu arteritis, giant cell arteritis, juvenile idiopathic arthritis and RA (33). Furthermore, Infliximab is given consideration for the treatment of RA and ankylosis spondylitis as a chimeric monoclonal antibody triggering TNF-α (34). However, there are disadvantages to the systemic anti-cytokine therapy; i.e. the high toxicity and low efficacy of immunotherapeutic methods (35). Moreover, the evaluation of anti-cytokine treatment and its effect(s) on the target site is difficult and has remained a great challenge (33).

The local use of anti-cytokines seems to hypothetically manage the inflammation of dental pulp and assist endodontic regeneration in VPT. Recent local use of an anti-cytokine, i.e. anti-IL-17, in VPT has been successfully investigated on an animal subject (36). Several studies have reported that there are different anti-inflammatory methods for the proper management of inflamed dental pulp; e.g. changes to pulp-capping biomaterials, application of stem cells, natural derivation of compounds as well as chemicals and phototherapy. Since there appear to be comparable physio-pathological mechanisms between chronic inflammatory diseases and pulpitis, it could be assumed that the anti-cytokine molecules could be applied as adjuncts in the protocols implemented for VPT as immunomodulatory therapy (6). Additionally, to overcome unknown inflammatory conditions, effective bio-materials or agents should be sought to assist the treatment of carious exposed pulp (37, 38). The local delivery of anti-cytokines could ease the targeted agent delivery and control the release of the agents, i.e. anti-cytokines, into the inflamed tissues. Micro- or nanoparticles, hydrogels, and dendrimers may be the vehicle priorities to locally carry and transfer anti-cytokines to the desired tissues. It has been recently shown that microparticles are able to carry drugs, i.e. antibiotics, for use in endodontic applications (39); and if properly designed, they as well as other local delivery systems should be able to transfer anti-cytokines to the root canal system.

5. Conclusions

For years, numerous investigations have claimed that the treatment of mature permanent teeth with irreversible pulpitis using non-surgical root canal therapy has shown a higher success rate compared to VPT (40). Nonetheless, it has been demonstrated that the original dental pulp connective tissue as well as its characteristics and functions are biologically superior to the root canal obturation

materials; which lack biological immune defense systems and innervation of sensory nerves. Therefore, it could be inferred that the survival of endodontically treated teeth is lower than that of teeth treated with VPT modalities. As a result, the treatments which can protect, dress, heal and respect the dental pulp should be taken into account.

Although Evidence indicates the importance of inflammation present in the repair process of the compromised pulp, the management of excess inflammation is of high significance in VPT; since different degrees of inflammation can affect the process of pulpal healing. Cytokines, as inflammatory biomarkers, are the responsible factors for the advancement of inflammation towards tissue necrosis, and thus, their levels seem to correspond with the degree or extent of inflammation progression as well as bacterial invasion. Consequently, it could be expected that using anti-cytokines, i.e. anti-cytokine therapy, may be deliberated as an effective adjunct to VPT concept.

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Ethics

Not applicable.

Author contributions

Seyedeh Sareh Hendi, Mohammad Jafar Eghbal, Saeed Asgary: Conceptualization, Methodology, Validation, Writing - Original draft, Writing - Review & Editing, Supervision

Conflict of interest

The authors declare no conflict of interest.

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References

1. Joseph A, Nalini H, Kumar A, Devi R. Pharmacotherapy for host modulation in periodontal disease: A review. J Indian Acad Dent Spec Res. 2015;2:35.

2. Ipshita S, Kurian IG, Dileep P, Guruprasad C, Singh P, Pradeep A. Host modulation therapy: An updated review. J adv clin res insights. 2017;4(2):55-8.

3. Kamil MA. Host modulatory agents in periodontics the valuable innovation. J Dent Med Sci. 2016;15(6):105-11.

4. Shinwari MS, Tanwir F, Hyder PR, Bin Saeed MH. Host modulation therapeutics in periodontics: role as an adjunctive periodontal therapy. J Coll Physicians Surg Pak. 2014;24(9):676-84.

5. Lotti T, Hercogova J. Successful treatment of psoriasis with low-dose per os interleukins 4, 10, and 11. Dermatol Ther. 2015;28(1):1-2.

6. Arora S, Cooper P, Friedlander L, Rizwan S, Seo B, Rich A, et al. Potential application of immunotherapy for modulation of pulp inflammation: Opportunities for vital pulp treatment. Int Endod J. 2021;54(8):1263-74.

7. Eng GP, Bouchelouche P, Bartels EM, Bliddal H, Bendtzen K, Stoltenberg M. Anti-drug antibodies, drug levels, interleukin-6 and soluble TNF receptors in rheumatoid arthritis patients during the first 6 months of treatment with adalimumab or infliximab: a descriptive cohort study. PloS one. 2016;11(9):e0162316.

8. Preshaw PM. Host modulation therapy with anti-inflammatory agents. Periodontol 2000. 2018;76(1):131-49.

9. Jangid K, Ramamurthy J, Mathew V, Jayakumar N. Anti-cytokine therapy in periodontitis. Res J Pharm Biol Chem Sci. 2015;6(1):372-6.

10. Patil A, Mahale S. Cytokines and anti-cytokine therapy in periodontal disease. J Med Dent Sci. 2017;16(3):63-70.

11. Assuma R, Oates T, Cochran D, Amar S, Graves D. IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. J Immunol Res. 1998;160(1):403-9.

12. Delima AJ, Karatzas S, Amar S, Graves DT. Inflammation and tissue loss caused by periodontal pathogens is reduced by interleukin-1 antagonists. J Infect Dis. 2002;186(4):511-6.

13. Sulijaya B, Takahashi N, Yamazaki K. Host modulation therapy using anti-inflammatory and antioxidant agents in periodontitis: a review to a clinical translation. Arch Oral Biol. 2019;105:72-80.

14. Khorasani MM, Hassanshahi G, Brodzikowska A, Khorramdelazad H. Role(s) of cytokines in pulpitis: latest evidence and therapeutic approaches. Cytokine. 2020;126(2):154896.

15. Rechenberg D-K, Galicia JC, Peters OA. Biological markers for pulpal inflammation: a systematic review. PloS one. 2016;11(11):e0167289.

16. Zanini M, Meyer E, Simon S. Pulp inflammation diagnosis from clinical to inflammatory mediators: a systematic review. J Endod. 2017;43(7):1033-51.

17. Komabayashi T, Zhu Q. Innovative endodontic therapy for anti-inflammatory direct pulp capping of permanent

teeth with a mature apex. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(5):e75-e81.
18. Santos JM, Pereira JF, Marques A, Sequeira DB, Friedman S. Vital pulp therapy in permanent mature posterior teeth with symptomatic irreversible pulpitis: a systematic review of treatment outcomes. Medicina. 2021;57(6):573.
19. Parhizkar A, Asgary S. Local Drug Delivery Systems for Vital Pulp Therapy: A New Hope. International Journal of Biomaterials. 2021;2021:5584268.
20. Taha NA, About I, Sedgley CM, Messer HH. Conservative management of mature permanent teeth with carious pulp exposure. J Endod. 2020;46(9):S33-S41.
21. Li J-Y, Wang S-N, Dong Y-M. The effect of topical application of meloxicam on inflamed dental pulp. J Dent Sci. 2021;16(3):915-21.
22. Chen J, Xu H, Xia K, Cheng S, Zhang Q. Resolvin E1 accelerates pulp repair by regulating inflammation and stimulating dentin regeneration in dental pulp stem cells. Stem Cell Res Ther. 2021;12(1):1-14.
23. Koli B, Chawla A, Logani A, Kumar V, Sharma S. Combination of nonsurgical endodontic and vital pulp therapy for management of mature permanent mandibular molar teeth with symptomatic irreversible pulpitis and apical periodontitis. J Endod. 2021;47(3):374-81.
24. Kermeoğlu F, Aksoy U, Sebai A, Savtekin G, Özkayalar H, Sayıner S, et al. Anti-inflammatory effects of melatonin and 5-methoxytryptophol on lipopolysaccharide-induced acute pulpitis in rats. Biomed Res Int. 2021;6:1-8.
25. Dincer GA, Erdemir A, Kisa U. Comparison of neurokinin A, substance P, interleukin 8, and matrix metalloproteinase-8 changes in pulp tissue and gingival crevicular fluid samples of healthy and symptomatic irreversible pulpitis teeth. J Endod. 2020;46(10):1428-37.
26. Nguyen V, Chen Y-W, Johnson JD, Paranjpe A. In vivo evaluation of effect of preoperative ibuprofen on proinflammatory mediators in irreversible pulpitis cases. J Endod. 2020;46(9):1210-6.
27. Šubarić L, Mitić A, Matvijenko V, Jovanović R, Živković D, Perić D, et al. Interleukin 1-beta analysis in chronically inflamed and healthy human dental pulp. Vojnosanit Pregl. 2017;74(3):256-60.
28. Kritikou K, Imre M, Tanase M, Vinereanu A, Totan AR, Spinu T-C, et al. Biochemical mapping of the inflamed human dental pulp. Appl Sci. 2021;11(21):10395.
29. Giuroiu CL, Vataman M, Melian G, Bularda D, Lozneanu L, Salceanu M, et al. Detection and assessment of interleukin 6 in irreversible pulp inflammation. Rev Chim. 2017;68(2):323-7.
30. Yang F, Zhang X, Huang H, Wu G, Lippuner K, Hunziker EB. Anticytokine activity enhances osteogenesis of bioactive implants. Tissue Eng Part A. 2021;27(3-4):177-86.
31. Giraud T, Jeanneau C, Rombouts C, Bakhtiar H, Laurent P, About I. Pulp capping materials modulate the balance between inflammation and regeneration. Dent Mater. 2019;35(1):24-35.
32. Zaky S, Shehabeldin M, Ray H, Sfeir C. The role of inflammation modulation in dental pulp regeneration. Eur Cell Mater. 2021;41:184-93.
33. Shima Y. Cytokines involved in the pathogenesis of SSc and problems in the development of anti-cytokine therapy. Cells. 2021;10(5):1104.
34. Fabri GMC, Pereira RMR, Savioli C, Saad CG, de Moraes JCB, Siqueira JTT, et al. Periodontitis response to anti-TNF therapy in ankylosing spondylitis. J Clin Rheumatol. 2015;21(7):341-5.
35. Rallis KS, Corrigan AE, Dadah H, George AM, Keshwara SM, Sideris M, et al. Cytokine-based cancer immunotherapy: Challenges and opportunities for IL-10. Anticancer Res. 2021;41(7):3247-52.
36. Liu M, Zhao Y, Wang C, Luo H, Peng A, Ye L. Interleukin-17 plays a role in pulp inflammation partly by WNT5A protein induction. Arch Oral Biol. 2019;103:33-9.
37. Elsalhy M, Azizieh F, Raghupathy R. Cytokines as diagnostic markers of pulpal inflammation. Int Endod J. 2013;46(6):573-80.
38. Louwakul P, Lertchirakarn V. Response of inflamed pulps of rat molars after capping with pulp-capping material containing fluocinolone acetonide. J Endod. 2015;41(4):508-12.
39. Parhizkar A, Nojehdehian H, Tabatabaei F, Asgary S. An Innovative Drug Delivery System Loaded with a Modified Combination of Triple Antibiotics for Use in Endodontic Applications. International Journal of Dentistry. 2020;2020:8859566.
40. Lin LM, Ricucci D, Saoud TM, Sigurdsson A, Kahler B. Vital pulp therapy of mature permanent teeth with irreversible pulpitis from the perspective of pulp biology. Aust Endod J. 2020;46(1):154-66.