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# Review Article

## A Comprehensive Review on Immunomodulators and Their Applications in Dentistry

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***ABSTRACT:***
Immunomodulators are agents that modify the immune response and have emerged as significant tools in various fields, including dentistry. Their applications range from managing autoimmune disorders such as oral lichen planus to enhancing healing processes post-surgery and in the treatment of periodontitis. These agents can improve the host's defense mechanisms against infections and assist in the management of inflammatory conditions affecting the oral cavity. Clinical studies indicate that the use of immunomodulators can lead to reduced symptoms, improved healing times, and better overall outcomes for patients undergoing dental treatments. This review examines the types of immunomodulators commonly used in dental practice, their mechanisms of action, therapeutic applications, and potential side effects, emphasizing their growing importance in enhancing patient care and treatment outcomes in dentistry.
**Keywords:** Immunomodulators, Immunity, Dentistry

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### INTRODUCTION

The concept of "immunity" refers to the host's ability to resist damage caused by microorganisms and their products. Immunity is categorized into two forms: innate and acquired. Innate or native immunity is based on an individual's genetic and constitutional characteristics. This form of immunity may be non-specific, providing general resistance to infections, or specific, conferring resistance against a particular pathogen. In contrast, acquired immunity is developed over an individual's lifetime. This type of immunity includes active and passive forms. Active acquired immunity, also known as adaptive immunity, arises when an individual builds resistance in response to an antigenic stimulus. In passive acquired immunity, resistance is conferred to an individual in a preformed state. Acquired immunity can further be divided into humoral and cell-mediated immunity. Humoral immunity, or B-cell immunity, involves the production of circulating antibodies—globulin molecules produced by B lymphocytes—that attack invading agents. The second type, cell-mediated immunity or T-cell immunity, is characterized by the proliferation of activated T lymphocytes specifically designed to eliminate foreign agents. Key cellular components involved in immunity include lymphocytes (T and B lymphocytes), macrophages, dendritic cells, Langerhans cells, natural killer cells, plasma cells, and granulocytes.[1,2]

A variety of immunological disorders affecting the oral cavity exhibit complex pathogenesis. In such instances, corticosteroids are commonly used as the primary treatment; however, prolonged use of corticosteroids can result in significant adverse effects. Furthermore, corticosteroids might not always suffice due to the intricate pathogenic factors, and some conditions may even exhibit resistance to steroids. In these situations, the administration of immunomodulatory drugs becomes essential. Immunomodulatory agents, which can be either natural or synthetic substances, function by adjusting or normalizing the immune response. By modulating immune activity and reducing inflammatory processes, immunomodulators can enhance the therapeutic outcome. When combined with steroids, these agents help mitigate adverse effects, expedite recovery, and are thus classified as "steroid-sparing drugs." The incorporation of immunomodulators allows for a reduction in steroid dosage, thereby minimizing harmful side effects and promoting quicker recovery. In specific scenarios, such as highly severe cases or those unresponsive to corticosteroids, immunomodulators may be utilized independently. These agents are categorized into two primary types: immunosuppressants and immunostimulants. Immunomodulatory drugs are recommended in the following situations: lack of response to corticosteroids, contraindications to corticosteroid use, steroid-resistant cases, recurrent conditions, and instances where severe adverse reactions to steroids have previously occurred.[3,4]

**Immunomodulators:** Immunomodulators play a vital role in fine-tuning the immune system, helping to orchestrate the immune response to either amplify the defense against pathogens or suppress overactive responses that may cause tissue damage. Their ability to influence factors such as the strength, nature, duration, and efficiency of immune reactions makes them critical in managing various diseases.

In the broader context of dentistry, immunomodulators offer significant potential in managing oral health conditions. Many dental diseases, including gingivitis and periodontitis, are characterized by inflammation where the immune system's response can sometimes lead to the destruction of supporting tissues. These diseases affect the immunological microenvironment by increasing the activity of leukocytes and inflammatory molecules. While such changes aim to control infections, they often result in excessive inflammation, damaging tissues like gums and bone around teeth.

Employing immunomodulatory strategies in dentistry involves tailoring the immune environment to treat and prevent inflammatory dental diseases effectively. This includes therapies designed to restore immune balance, facilitating the healing of oral tissues. Anti-inflammatory treatments can help reduce inflammation, while innovative dental therapies focus on enhancing the immune milieu to support tissue repair and regeneration. By encouraging cell homing and stimulating tissue repair, these approaches aim to restore oral health and maintain the function and integrity of dental structures.

Overall, immunomodulators represent a powerful tool in dentistry, not only in enhancing defense mechanisms against diseases but also in managing conditions by rebalancing and optimizing the immune response to maintain dental health and prevent disease progression.[5,6]

**Immunosuppressants:** Immunosuppressants, a special type of immunomodulators, work to tone down the immune system's activity. They're mainly used when the immune system is too hyperactive and starts causing damage, inflammation, or autoimmune issues. These drugs are particularly handy in preventing organ rejection after transplantation and in managing autoimmune diseases and allergies. By calming down immune cell activation, reducing cytokine production, or blocking immune signaling pathways, immunosuppressants help bring harmony and prevent damage caused by an overzealous immune response. Some common immunosuppressants include cyclosporine A, tacrolimus, azathioprine, mycophenolate mofetil, prednisone, and muromonab.[7]

**Immunostimulants:** Immunostimulants are potent agents that boost or enhance the immune system's activity. They're pivotal when it's crucial to fortify the body’s defenses, particularly during infections or cancer treatment. By enhancing the function of immune cells and increasing the production of cytokines, immunostimulants can support the body in its fight against harmful pathogens and even help in the recognition and destruction of cancer cells. Additionally, these agents can improve antigen presentation, thereby augmenting the efficacy of vaccines and other immunizations.

In the field of cancer treatment, immunostimulants play a significant role in immunotherapy, prompting the immune system to identify and eradicate cancer cells. Their ability to potentially recruit the immune system for tumor destruction is contributing to remarkable advances in cancer therapies.[8]

**Examples of immunostimulants include:**[9,10]

**Interferon-Gamma:**Enhances the activity of macrophages and natural killer cells.

**Interleukin-2 (IL-2):** Increases the proliferation and activation of T cells.

**Bacillus Calmette-Guérin (BCG):** Used in vaccines and as a treatment for bladder cancer.

**Lipopolysaccharides (LPS):** Stimulate immune responses through toll-like receptor pathways.

**Glucan:** Stimulates immune responses, enhancing the activity of macrophages and neutrophils.

**Isoprinosine:** Enhances lymphocyte proliferation.

The use of immunostimulants marks a promising avenue in therapeutic interventions, offering hope for more effective treatments by leveraging the body's natural defensive systems.

| Table 1: Various Immunosuppressant and Their Mechanism | |
|---|---|
| **Mechanism** | **Drugs** |
| Inhibitors of Lymphocyte Gene Expression | Glucocorticoids |
| Inhibitors of Lymphocyte Signaling | Calcineurin Inhibitors-Cyclosporine, Tacrolimus<br>mTOR Inhibitors- Sirolimus, Everolimus |
| Cytotoxic Agents | Antimetabolites- Azathi-prine, Mthotrexate, Leflunomid.<br>Alkylating agents- Cyclophosphamide |
| Cytokine Inhibitors | TNF-α Inhibitors-Etanercept, Infliximab, Adalimumab<br>IL-1 Inhibitors - Anakinra<br>IL-2 Inhibtors- Daclizumab, Basiliximab |
| Antibodies against Specific Immune Cell Molecules | Polyclonal Antibodies-Antithymocyte Globulin (ATG)<br>Monoclonal Antibodies- Alemutuzmab, Muromunab |
| Inhibitors of Immune Cell Adhesion | Efalizumab (LFA-1 Inhibitor) |
| Miscellaneous | Rho (D) Immune Globulin |

| Table 2: Various Immunostimulants and Their Mechanism | |
|---|---|
| **Mechanism** | **Drugs** |
| Increasing the humoral antibody responses | Amantadine, tilorone BCG vaccine |
| Enhancing the phagocytic activity of macrophages | Recombinant cytokines—interferons, interleukin-2 |
| Modifying the cellmediated immuneresponses | Thalidomide, levamisole |

**Clinical Applications of Immunomodulators:** In certain situations, the immune response within the oral cavity may become excessively active, leading to inflammatory conditions such as periodontitis, where the immune response to bacterial infection causes tissue damage. To address this heightened immune activity and avert further damage, immunosuppressants are employed. Specific immunosuppressants used in this context include glucocorticoids (corticosteroids), tacrolimus and cyclosporine, azathioprine, and methotrexate. Corticosteroids, either topical or systemic, are administered to alleviate painful oral ulcerations, such as aphthous ulcers or oral lichen planus, by attenuating inflammation and facilitating healing. These corticosteroids are also prescribed for acute or chronic oral inflammatory conditions, including allergic reactions and autoimmune disorders affecting the oral mucosa. Topical preparations of tacrolimus and cyclosporine are employed in the treatment of oral lichen planus, an autoimmune disorder impacting the oral mucosa, to suppress immune response and reduce inflammation. These agents may also be utilized in the management of mucous membrane pemphigoid, an autoimmune blistering disorder affecting the oral mucosa. In severe oral mucosal diseases such as pemphigus vulgaris or pemphigoid, these immunosuppressants help control immune-mediated tissue damage. Methotrexate is considered for patients with recurrent aphthous ulcers that are unresponsive to other treatments, as it modulates immune responses to decrease the frequency and severity of ulcers.

Enhancing the immune response in dentistry and oral health is vital for combating infections, promoting healing, and preventing complications post-procedures. Immune response enhancement through various agents offers a targeted approach to manage different oral health conditions:

**Immunostimulants in Oral Surgery and Implantology**[9,10]

1. **Levamisole:** Historically used as an anti-parasitic agent, Levamisole has shown significant potential in enhancing immune reactions. In dentistry, it is particularly beneficial for individuals suffering from conditions like oral lichen planus—a chronic inflammatory condition. Levamisole works by improving the immune system's ability to heal tissue damage, reducing inflammation and preventing disease progression.
2. **Thalidomide:** Known for its strong immune-modulating properties, Thalidomide is deployed in reducing episodes of recurrent aphthous ulcers, which are painful and recurrent oral lesions. Thalidomide's mechanism involves suppression of tumor necrosis factor-alpha (TNF-α), a cytokine involved in systemic inflammation, thus alleviating the frequency and severity of ulcers.
3. **Dapsone:** Used primarily as an antibiotic, Dapsone’s impact on the immune system is crucial, especially in managing mucous membrane pemphigoid. This condition involves

blistering of the mucous membranes, and Dapsone assists by modulating immune responses to prevent and manage blister formation, thereby promoting healing and comfort for patients.

**Periodontics and Gum Infection Management:** Immunostimulants serve a pivotal role in periodontics, particularly in managing gum infections. By enhancing the local immune response, these agents help control bacterial infections that afflict gum tissues, promoting tissue regeneration and preventing disease progression. This approach is crucial not only for treating existing periodontal disease but also for maintaining long-term oral health and preventing future recurrences.[11]

**Efalizumab and Severe Psoriasis Treatment:**Efalizumab, a monoclonal antibody, mainly employed for severe psoriasis, has shown therapeutic benefits in managing oral lichen planus by targeting specific immune pathways. It mitigates inflammation and accelerates healing, offering a dual approach by controlling both external skin manifestations and oral lesions, hence providing a comprehensive therapeutic strategy.[12]

**BCG in Oral Cancer Therapy:**BCG is originally a vaccine for tuberculosis, but its utility in oral cancer treatment is being explored due to its ability to stimulate a targeted immune response against cancer cells. Through this focused immune activation, BCG therapy aims to enhance the body's natural defense mechanisms to suppress tumor growth and progression, potentially improving patient outcomes in oral oncology.

The application of these immunostimulants represents a tailored approach in oral health management. By selecting the appropriate agent based on specific oral conditions and understanding its mechanism of action, dental professionals are equipped to deliver personalized and effective care, promoting optimal oral health and patient satisfaction.[13-15]

**Colchicine in Aphthous Ulcer:** Colchicine suppresses the cell-mediated immune responses. In a more recent open study of 20 patients, colchicine (1.5 mg/day for 2 months) produced a significant decrease in the pain scores and frequency of the self-reported aphthous ulcers. Unfortunately, not all the patients get benefit from the colchicine therapy, and at least 20% have the painful gastrointestinal symptoms or diarrhea, and can affect the reproductive system (causing infertility) in young males. Combined colchicine and thalidomide therapy may provide an occasional benefit in the recalcitrant RAS.[16-19]

## CONCLUSION

The incorporation of immunomodulators in dental practices demonstrates a promising avenue for enhancing treatment efficacy and patient outcomes. Their ability to modulate immune responses can significantly aid in managing various oral diseases and improving healing post-treatment. However, careful consideration of their use is essential due to potential side effects and patient variability. As research evolves, the understanding and application of immunomodulators in dentistry are likely to expand, providing dental professionals with innovative strategies to address complex oral health issues. Ongoing studies and clinical trials will further elucidate the therapeutic potential of these agents, paving the way for their optimal integration into standard dental care protocols.

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