



**ORIGINAL RESEARCH PAPER**

**Oral Medicine & Radiology**

**IMMUNOMODULATORS IN DENTISTRY, AN UPDATED REVIEW**

**KEY WORDS:** Immunity, immunosuppressant, immunostimulants.

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**ABSTRACT**

Immunity plays a vital role in maintaining the health of an individual. Immunomodulators are a class of drugs that maintain the homeostasis of the immune system when it is altered by any disease. The immunity can be either improved or suppressed with immunostimulants and immunosuppressant respectively. These drugs are inevitably used in the treatment of various oral diseases. This review article focuses on the various immunomodulators used in dentistry.

**INTRODUCTION:**

Immunity is the phrase used to describe the host's defences against harm from microbes and their by-products.<sup>(1)</sup> There are two types of immunity: innate and acquired. An individual's innate or native immunity results from his or her genetic and constitutional makeup. Acquired immunity refers to immunity that a person develops over the course of their lifetime. The two categories of acquired immunity are active and passive.<sup>(1)</sup> Immunomodulators limit or regulate the immune system's activity, which reduces the immune system's ability to cause inflammation.<sup>(2)</sup>

**IMMUNOMODULATORS CLASSIFICATION:**

Immunostimulants and immunosuppressant are the two basic classifications of immunomodulators. Immunosuppressive drugs are further divided into Steroids, steroid sparing drugs and biologics.<sup>(3)</sup> Immunostimulants are classified into bacterial products, complex carbohydrates, vaccinations (antigens and adjuvants), cytokines, immunoenhancing medications, plant extracts, and animal extracts.<sup>(4)</sup>

**APPLICATIONS IN DENTISTRY**

**1. Glucocorticoids:** White blood cell function is inhibited by glucocorticoids, which also stabilise lysosome membrane, prevent plasminogen activation, reduce the production of inflammatory mediators.<sup>(5)</sup>

**Oral submucous fibrosis:** Dexamethasone 4 mg/ml intralesional injections with hyaluronidase- once every 2 weeks for 20 weeks. Triamcinolone (10 mg/ml) acts as an alternative. Burning feeling may be alleviated by systemic prednisone (30-40 mg/day for 14-28 days,) or hydrocortisone (100 mg/day).<sup>(6)(6)</sup>

**Oral lichen planus:** 0.05% clobetasolpropionate gel, 0.1-0.05% betamethasone valerate gel, 0.05% fluocinonide gel, 0.05% clobetasol ointment or cream, and 0.1% triamcinolone acetone ointment. Triamcinolone acetone is used as a lozenge or as an orabase.<sup>(7)</sup> In cases with erosive lichen planus that are resistant to treatment, **systemic corticosteroids** are utilised (40 to 80 mg every 6-7 days). To prevent adrenal crisis, withdrawal must be managed by lowering the dose by 5 mg/week.<sup>(8)</sup> Steroid injections intravenously and subcutaneously have been said to relieve pain more quickly than topical treatment.<sup>(6)</sup>

**Erythema multiforme:** A brief course of systemic glucocorticoids could be used to treat moderate to severe cases of EM.<sup>(7)</sup> Systemic prednisone 0.5-1.0 mg/kg/day or pulse methylprednisolone 1 mg/kg/day for 3 days are the two

main forms of initial treatment, 3 consecutive daily infusions of 20-30 mg/kg to a maximum of 500 mg.<sup>(9)</sup> Topical steroids - triamcinolone, fluocinonide, and clobetasol propionate.<sup>(9)</sup>

**Mucous membrane pemphigoid:** Prednisone- 1-2 mg/kg/day for multiple oral lesions, tapering off gradually. Steroids with cyclophosphamide 0.5-2 mg/kg/day, azathioprine 1-2 mg/kg/day or mycophenolatemofetil 2.2-2.5 g/day have shown promising outcomes.<sup>(6)</sup>

**Bullous pemphigoid:** For mild disease, prednisolone 20 mg/day or 40 mg/day and 50-70 mg for severe disease. Clobetasol propionate cream is used for mild cases; moderate cases 1.0-1.5 mg/kg/day, oral prednisolone 0.5 mg/kg/day for severe cases. Intralesional triamcinolone acetone 3-10 mg/ml for resistant lesions.<sup>(10)</sup>

**TMJ Arthritis:** Methylprednisolone diluted with lidocaine injection significantly reduce joint pain.<sup>(6)(11)</sup>

**2. STEROID SPARING DRUGS:** To avoid negative effects and hasten the healing process, immunomodulators should be used with steroids hence these medications fall within the category of "steroid sparing medicines"<sup>(11)</sup> Steroid-sparing medications are categorised as: alkylating agents, Antimetabolite and antibiotic/calcineurin Inhibitors<sup>(12)</sup>

**Cyclophosphamide:** Alkylating agent, Cyclophosphamide binds to DNA, more effective against B cell. Advised dose- 1 gm IV /4 weeks .Used to treat Pemphigus, Wegener's granulomatosis, Granulomatosis with polyangitis, SLE, and Scleroderma. Adverse effects - acute bone marrow suppression, carcinogenesis, teratogenicity, interstitial lung fibrosis, and susceptibility to infections, sterility, amenorrhea, nephrotoxicity, cystitis, and cardiovascular problems<sup>(12)</sup>

**Cyclosporine:** The fungus species Beauveria Nivea produces cyclosporine, a calcineurin inhibitor. It suppresses T cells' antigen-triggered signal transduction, reducing the production of numerous lymphokines.<sup>(3)(18)</sup>

**Indications:** Behcet's syndrome/recurrent aphthous stomatitis -For mild cases, topical cyclosporine 100 mg/ml; 3 to 6 mg/kg/day of systemic cyclosporine for chronic cases.<sup>(14)</sup>

**Lichen planus:** Mouth rinse consisting of 5 ml of cyclosporine 100 mg/ml.<sup>(1)</sup> 100 mg/ml of cyclosporine for mucous membrane pemphigoid.<sup>(1)</sup> Adverse effects are Gingival hyperplasia, Headache, Hyperkalemia, GI

disturbances, Tremors, Hypertrichosis.<sup>(13)</sup>

**TRACOLIMUS:** A macrolide antibiotic. The skin seems to absorb topical tacrolimus more effectively than topical cyclosporine.<sup>(9)(13)</sup> 0.1% Tacrolimus ,2-4 times a day for 4–8 weeks is used in the treatment of lichen planus. When used topically it lessens refractory erosive oral Lichen planus and control symptoms .0.1% tacrolimus ointment twice daily for 3 to 4 weeks is beneficial treating Pemphigus vulgaris/Mucous Membrane Pemphigoid<sup>(1)(9)</sup>

Nephrotoxicity, neurotoxicity, gastrointestinal issues, hypertension, hyperkalemia, and hyperglycemia are some side effects. According to certain research, tacrolimus can stop epithelial cells from developing cancer.<sup>(13)(19)</sup>

**DAPSONE:** Dapsone (sulfone antibiotic) inhibits neutrophil chemotaxis by inhibiting myeloperoxidase and acts as an anti-inflammatory against PMN. Indicated for the treatment of epidermolysis bullosa, Behcet's illness, recurrent aphthous stomatitis, erythema multiforme. Dose- 25 to 50 mg/ day.<sup>(12)(16)</sup>

**AZATHIOPRINE:** A purine antimetabolite. It is a 6-mercaptopurine imidazolyl derivative. Thiopurinemethyltransferase (TPMT), breaks down azathioprine ,thus doses should ideally be adjusted based on the individual TPMT activity.<sup>(13)</sup> Therapeutic indication: Behcet's syndrome/recurrent aphthous stomatitis: The dosage ranges from 1 to 2 mg/kg/day (100-150 mg/day), lichen planus: 50 mg twice daily orally (or 2 mg/kg per day) ,for 3-7 months, Pemphigus vulgaris: 0.5 to 4 mg/kg ,mucous membrane pemphigoid 1-2 mg/kg every day depending on TPMT level. Side effects include thrombocytopenia, anaemia, increased susceptibility to infections, alopecia, gastrointestinal toxicity, pancreatitis, and bone marrow suppression. Thus, a thorough blood count examination is required both before and during azathioprine treatment.<sup>(13)</sup>

**METHOTREXATE:** Inhibits DNA and low quantities of RNA production during the S phase which interferes with transmethylation processes. Recommended dosage: 15 mg/week, with 1 mg/day of folate. Hepatotoxicity, marrow suppression, mouth ulcers, and alopecia are undesirable consequences.<sup>(12)(16)</sup> MTX is used as an adjuvant to treat breast cancer, bladder cancer, osteosarcoma and lymphomas and resistant autoimmune diseases including rheumatoid arthritis, psoriasis, myasthenia gravis, oral lichen planus.<sup>(17)</sup>

**3. BIOLOGICS:** Any medicine made from a biological is considered a biopharmaceutical. Immunocytes or their by-products are frequently the focus of biologics, which target particular proinflammatory cascade steps. It obstructs pathways implicated in the pathophysiology of immune-mediated and malignant illnesses.<sup>(18)</sup> In comparison to traditional immunosuppressant, these act as a pathogenesis-based treatment rather than just palliative care.<sup>(19)</sup>

**A. TNF alpha-inhibitors:**

Etanercept, a fusion protein that resembles type II TNF receptors, inhibits the circulation of lymphotoxin A and TNF. Sjogren's syndrome and Behcet's disease are the two main indications. Dosage: 25–50 mg, twice weekly.<sup>(12)(18)</sup>

Infliximab , a human monoclonal antibody against TNF, indicated in Behcet's disease, Sjogren's syndrome, rheumatoid arthritis, Psoriatic arthritis, Ankylosing Spondylitis, plaque psoriasis, ulcerative colitis and Crohn's disease. It is given intravenously (3–5 mg/kg) every 2–6 weeks. Adverse effects- Injection and infusion site reactions, risk of respiratory and opportunistic infections and reactivation of tuberculosis.<sup>(12)(18)</sup>

Abatacept, a lymphocyte activity inhibitor is used in Rheumatoid arthritis therapy. Negative effects- infections and increased risk of developing cancer.<sup>(12)(18)</sup>

**B. Agents that prevent lymphocyte activity (B cell modulators):**

A monoclonal antibody **rituximab** acts on CD20 protein, which is found on the surface of B cell. 375 milligram/m<sup>2</sup> of height/ week. Serious infusion reactions, cardiac arrest, infections, and progressive multifocal encephalopathy - negative consequences. Treatment recommendations for NHL (B cell variation), SLE, Pemphigus, Pemphigoid, Epidermolysis Bullosa, Ig G4 associated salivary illness, Sjogren's syndrome<sup>(12)(18)</sup>. An observational study in patients with Pemphigus vulgaris treated with rituximab, a biosimulant of rituximab exhibited excellent results with significant decrease in anti-Desmoglein3 values<sup>(19)</sup>

**C. Interleukin inhibitors:**

Monoclonal antibody muromonab-CD3: It attaches to the monomorphic CD3 chain, which is a part of the T-cell receptor complex and is involved in cell signalling, proliferation, and antigen recognition. The T-cell receptor is quickly internalised as a result of antibody therapy, which prevents the antigen from being recognised later. Cytokine release syndrome, high temperature, chills, headache, nausea/vomiting, diarrhoea, and abdominal discomfort are side effects. It is not frequently used since it can cause severe pulmonary oedema, acute respiratory distress syndrome, and cardiovascular collapse.<sup>(12)</sup>

Biologics that prevent angiogenesis like Bevacizumab and anti-EGFRs like cetuximab have considerably increased the survival of patients with oral cancer.<sup>(12)</sup>

**IMMUNOSTIMULANTS:**

Specialized immunostimulants stimulate the immune system to respond to a particular antigen, toxin or foreign substance. Immunodeficiency and persistent infections are treated with **nonspecific** immunostimulants which function without antigenic specificity.<sup>(4)(21)</sup> The various reasons for its use includes bacterial antibiotic resistance, allergic antibiotic responses, immunosuppressive state.<sup>(4)</sup>

**SYNTHETIC IMMUNOSTIMULANTS**

(a) Levamisole, a synthetic medication works by producing monocytes, macrophage, B and T cells. Levamisole has been used with prednisolone to treat aphthous ulcers and cimetidine to treat resistant warts. Drawbacks- allergies, motion sickness, muscle discomfort.<sup>(3)(22)</sup>

(b) Thalidomide, helps patients with erythema nodosum by lowering their levels of circulating TNF. Recurrent Aphthous Stomatitis: Start with 100 to 200 mg/day, continue until remission; 50-100mg daily or 50mg everyday as a maintenance dose .It is a successful treatment for steroid resistant cases of erosive OLP.<sup>(9)</sup>

(c) Isoprinosine, increases cytokine levels such as IL-1, IL-2, and IFN; lymphocyte proliferation is boosted, increasing the number of active T cells. Epstein-Barr, Measles, and Herpes infections are treated with it. Drawbacks- CNS depression, nausea, increased uric acid levels in blood and urine.<sup>(9)(4)</sup>

**COMPLEX CARBOHYDRATES**

**Glucans:** The main roles of glucans were detected in cancer treatment, infection, stress reduction and restoration of damaged bone marrow. Zymosan was found to be a key ingredient for non-specific immunomodulation and could cure the myelosuppression brought by chemotherapy. The recent studies have shown that daily therapy with soluble or insoluble -glucan led to a 70%-95% reduction tumour size.<sup>(4)(23)</sup>

**Prebiotics:** Immunosaccharides are a class of prebiotics that enhance innate immunological responses such as phagocytic activation, neutrophil activation, activation of the alternative complement system, and increased lysozyme activity.<sup>(4)</sup>

**PLANT DERIVED IMMUNOSTIMULANTS:**

The active substances in medicinal plants have been known as immunostimulants, growth promoters, appetite stimulant. Tulsi, neem, amla, purple Fruited Pea Eggplant, bhingraj, ginger, green tea, saffron, night flowering Jasmine are few plant derived immunostimulants which augment immunity and act as antioxidant which is essential in cancer prevention and therapy.<sup>(4)</sup>

**RECENT ADVANCES OF IMMUNOMODULATORS:**

Vitamin C typically functions as a reducing agent and aid in treating periodontitis by lowering the extracellular oxidants of neutrophils which reduce inflammation in periodontitis.<sup>(24)</sup> A broad-spectrum immunomodulatory substance called CC-122-thalidomide derivative, exhibits pluripotent abilities, anticancer and immune cell regulation. A thalidomide analogue, CC-220-iberdomide used to treat systemic lupus erythematosus and relapsed/refractory multiple myeloma.<sup>(25)</sup> Drugs like Abrocitinib, 200mg daily, upadacitinib, 30 mg daily has been proved to be effective against atrophic dermatitis.<sup>(26)</sup>

**Stem cells derived from human exfoliated deciduous teeth (SHEDs)** are considered for cell-based or cell-free therapy and tissue engineering because of their proliferative, multipotency and immunomodulation.<sup>(27)</sup>

Tea tree oil and its derivatives is found to have antifungal, cytotoxic and immunomodulatory properties which can be used against *Candida albicans* and in patients under cancer therapy.<sup>(28)</sup>

Antigens and medications for anticancer immunotherapy can be delivered by RBCs. To strengthen the immune response, it can bind antigens and deliver them to immune cells.<sup>(29)</sup>

Immunotherapy serves as the foundation for the prevention of diabetes. At low doses, researchers discovered that combining anti-CD3 antibody with a drug anakinra resulted in the permanent reversal of type 1 diabetes in mice.<sup>(30)</sup>

**CONCLUSION:**

Immunomodulators are an important part of the dental armamentarium and can be used to treat a wide range of oral diseases. Dentists should be aware about the available drugs and its recent advances. Immunomodulators being a double edged sword should be used in appropriate doses and duration and requires proper monitoring to prevent adverse reactions.

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**REFERENCES**

1. Shivhare P, Shankarnarayan L, Singh A, Patil ST, Yadav M. Role of immunomodulators in oral diseases. *Int J Oral Health Med Res.* 2015;2:73-80.
2. Vahanwala S, Pagare SS, Singhi R, Nayak CD. Rationale in Usage of Immunomodulators for Management of Head, Face and Neck Cancers. *International Journal of Head and Neck Surgery.* 2014 Apr 1;3(3):154-7.
3. Patil US, Jaydeokar AV, Bandawane DD. Immunomodulators: A pharmacological review. *Int J Pharm Pharm Sci.* 2012;4(Suppl 1):30-6.
4. Jain P, Darji P, Thakur BS, Jain A, Jain PK, Khare B. Immunostimulants: Concepts, Types and Functions. *Asian Journal of Dental and Health Sciences.* 2022 Dec 15;2(4):26-34.
5. Kiran MS, Vidya S, Aswal GS, Kumar V, Rai V. Systemic and topical steroids in the management of oral mucosal lesions. *Journal of pharmacy & bioallied sciences.* 2017 Nov;9(Suppl 1):S1.
6. Basirat M, Kia SJ, Motevasseli S, Dadvar Z. Corticosteroids Indications in Oral and Maxillofacial Diseases: Side Effects, Dosage, and Administration. *Journal of Dentomaxillofacial.* 2018 Jun 10;7(2):51-6.
7. Sanghavi J, Aditya A. Applications of corticosteroids in dentistry. *Journal of Dental and Allied Sciences.* 2015 Jan 1;4(1):19.
8. Lohokare AU, Nisa SU, Mhapuskar A, Lakhani KS. Applications of corticosteroids in oral diseases—A narrative review. *SRM Journal of Research*

- in Dental Sciences. 2023 Jan 1;14(1):41.
9. Bhanot R, Mago J. Corticosteroids in dentistry. *Indian Journal of Dental Sciences.* 2016 Oct 1;8(4):252.
10. Kasperkiewicz M, Schmidt E. Current treatment of autoimmune blistering diseases Current drug discovery technologies. 2009 Dec 1;6(4):270-80.
11. Panat SR, Upadhyay N, Khan M, Iqbal MA. Corticosteroids used in dentistry: An update. *Journal of Dental sciences and oral rehabilitation.* 2014 Apr;5(2):89-92.
12. Konidena A, Sharma S, Patil DJ, Dixit A, Gupta R, Kaur M. Immunosuppressants in Oral Medicine: A Review. *Journal of Indian Academy of Oral Medicine and Radiology.* 2017 Oct 1;29(4):306-13.
13. Brunton LL, Parker KL, Blumenthal D, Buxton I. Manual of pharmacology and therapeutics. The MacGraw Hill Company, USA. 2008;13:229.
14. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. *Journal of the European Academy of Dermatology and Venereology.* 2007 Sep;21(8):1019-26.
15. Vahanwala S, Pagare SS, Singhi R, Nayak CD. Rationale in Usage of Immunomodulators for Management of Head, Face and Neck Cancers. *International Journal of Head and Neck Surgery.* 2014 Apr 1;3(3):154-7.
16. Kavanaugh A, Broide DH. Chapter 94: Immunomodulators. In Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske R, Simons FE, editors. *Middleton's Allergy: Principles and Practice.* 7th ed. USA: Mosby Elsevier. p.1643-8.
17. Ko mi ski P, Halik PK, Chesori R, Gniazdowska E. Overview of dual-acting drug methotrexate in different neurological diseases, autoimmune pathologies and cancers. *International journal of molecular sciences.* 2020 May 14;21(10):3483.
18. Georgakopoulou E, Scully C. Biological agents: what they are, how they affect oral health and how they can modulate oral healthcare. *British Dental Journal.* 2015 Jun 26;128(12):671-7.
19. Georgakopoulou EA, Andreadis D, Arvanitidis E, Loumou P. Biologic agents and oral diseases—an update on clinical applications. *Acta Dermatovenerol Croat.* 2013 Jan 1;21(1):24-34.
20. Bardazzi F, Loi C, Vara G, Patrizi A, Di Altobrando A. Efficacy and safety of biosimilar rituximab in the treatment of pemphigus vulgaris: a single center experience of 12 cases. *Journal of Dermatological Treatment.* 2022 Jan 2;33(1):580-2.
21. Labh SN, Shakya SR. Application of immunostimulants as an alternative to vaccines in health management in aquaculture. *International Journal of Fisheries and Aquatic Studies.* 2014;2(1):153-6.
22. Biswajit D, Suvakanta D, Chandra CR, Jashabir C. An overview of levamisole hydrochloride with immunostimulant activity. *Am J Pharm Health Res.* 2014;2(4):1-9.
23. Jat D, Thakur N, Jain DK, Prasad S, Yadav R. Iris ensata Thunb: Review on Its Chemistry, Morphology, Ethno Medical Uses, Phytochemistry and Pharmacological Activities. *Asian Journal of Dental and Health Sciences.* 2022 Mar 15;2(1):1-6.
24. Yang B, Pang X, Li Z, Chen Z, Wang Y. Immunomodulation in the treatment of periodontitis: Progress and perspectives. *Frontiers in immunology.* 2021 Nov 19;12:781378.
25. Gao S, Wang S, Song Y. Novel immunomodulatory drugs and neo-substrates. *Biomarker Research.* 2020 Dec;8:1-8.
26. herucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZ, Rochweg B, Di Giorgio S, Arents BW, Burton T, Spuls PI, Küster D. Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. *JAMA dermatology.* 2020 Jun 1;156(6):659-67.
27. Guo R, Yu J. Multipotency and Immunomodulatory Benefits of Stem Cells From Human Exfoliated Deciduous Teeth. *Frontiers in Dental Medicine.* 2022 Feb 15;3:805875.
28. Ramage G, Milligan S, Lappin DF, Sherry L, Sweeney P, Williams C, Bagg J, Culshaw S. Antifungal, cytotoxic, and immunomodulatory properties of tea tree oil and its derivative components: potential role in management of oral candidosis in cancer patients. *Frontiers in microbiology.* 2012 Jun 18;3:220.
29. Zhang X, Luo M, Dastagir SR, Nixon M, Khamhoung A, Schmidt A, Lee A, Subbiah N, McLaughlin DC, Moore CL, Gribble M. Engineered red blood cells as an off-the-shelf allogeneic anti-tumor therapeutic. *Nature Communications.* 2021 May 11;12By(1):2637.
30. Deweerd S. Cell savers: in type 1 diabetes, the immune system goes haywire and depletes insulin-producing cells. Drugs that interfere with this process could one day reverse the disease's course. *Nature.* 2012 May 17;485(7398):S4-.