REVIEW ARTICLE

Role of Immunomodulators in Oral Diseases

Peeyush Shivhare[1],Lata Shankarnarayan[2], Ankur Singh[3], Shruti T Patil[4], Monu yadav[5]

1- Senior Lecture. Narsinhbhai Patel dental college and hospital. 2- Professor, head of the department, Rungta college of dental sciences and research, Bhilai, Chhattisgarh. 3- Senior Lecture. Narsinhbhai Patel dental college and hospital. 4- Senior Lecture, Narsinhbhai Patel dental college and hospital. 5- MDS, Lucknow.

Correspondence to:
Dr. Peeyush Shivhare, Senior Lecture. Narsinhbhai Patel dental college and hospital.
Contact Us: www.ijohmr.com

ABSTRACT

The oral cavity is a universe of various multiple diseases, which may be developmental, infective, inflammatory and immunological etc. Immunology plays a very important role in homeostasis but it possesses two edge sword actions. Either hypo or hyperimmunity both can cause systemic diseases which will manifest in the oral cavity. Immunomodulatory are the agents which modulate the body immunity according to the need. There are natural and synthetic immunomodulatory agents. This article is focused on the various immunomodulatory drugs which are used in various oral diseases.

KEYWORDS: Immunomodulation, Immunosuppression, Immunostimulation.

INTRODUCTION

The term "immunity" means the resistance exhibited by the host towards injury caused by microorganisms and their product. Immunity is of two types namely innate and acquired. Innate or native immunity is an individual immunity by virtue of his genetic and constitutional make up. It may be non-specific when it indicates a degree of resistance to infections in general or specific when resistance to a particular pathogen is concerned.Immunity which, an individual acquires during life is known as acquired immunity. Acquired immunity has two types, Active and passive. The active acquired immunity is the resistance developed by an individual as a result of an antigenic stimulus, which is also known as adaptive immunity. Passively acquired immunity is transmitted to a recipient in a "ready-made" form. Two basic types of acquired immunity are humoral immunity and cell-mediated immunity. The immunity in which the body develops circulating antibodies, which are globulin molecules in the plasma, and are capable of attacking the agent invaded is called Humoral immunity or B-cell immunity (because B lymphocytes produce the antibodies). The second type of acquired immunity is achieved by the formation of a large number of activated T lymphocytes that are specifically designed to destroy the foreign agent. This type of immunity is called Cell-mediated immunity or T-cell immunity (because the activated lymphocytes are T-lymphocytes). Cells those play important role in immunity are Lymphocytes (T lymphocytes, B lymphocytes), Macrophages, Dendritic cells & Langerhans cells, Natural killer cells, Plasma cells, Granulocytes, etc. (Figure – 1)

There are a number of immunological diseases affecting the oral cavity those have involute pathogenesis. In these cases, steroid is the mainstay, but steroid has their own deleterious side effect when utilized for longer time and even sometime steroid is not enough alone to remedy

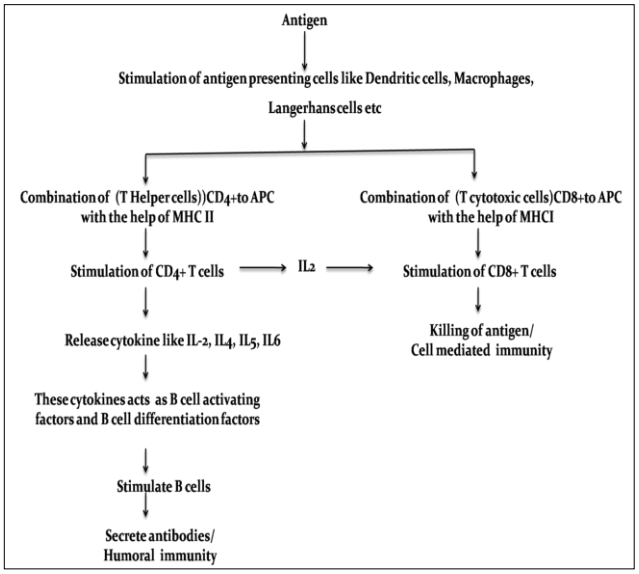

Figure – 1: Basic pathway of immunity.

disease due to involute pathogenic factors and some disease can be steroid resistant. In these cases, immunomodulatory drugs should be administered. Immuno Refers to immune response, immune system, and modulation is the act of modifying or adjusting according to due measure and proportion. Thus, immunomodulators are natural or synthetic substances that help to regulate or normalize the immune system.Immunomodulators modulate the immune reaction and decrement inflammatory replication. An immunomodulators should be given along with a steroid to spare side effect and speed the rejuvenating process. For these reasons these drugs come under the category of "steroid sparing drugs". Utilization of immunomodulators decreases the dose of steroid, decrement the chances of the deleterious effect of steroid and increment the

How to cite this article:
Shivhare P, Shankarnarayan L, Singh A, Patil ST, Yadav M. Role of Immunomodulators in Oral Diseases. Int J Oral Health Med Res 2015;2(3):73-80.

rejuvenating time. These drugs can be given alone too in certain circumstances like very astringent cases and cases non-respondent to steroids. Immunomodulatory drugs are divided into two main categories, are- Immunosuppressant and Immunostimulants.

Following are the conditions where immunomodulatory drugs should be advised:

- When no response to corticosteroids
- The cases where corticosteroids are contraindicated
- Cases resistant to steroids
- Recurrent cases
- Cases with the previous history of severe adverse effect with steroids.

There are many natural /herbal immunomodulators which strengthen weak immune systems and to moderate immune systems that are overactive.[5,6] (Table–1,2)

Herbal	Mechanism
Allium sativum (garlic)	Augments NK cells and macrophage activity
Aloe Vera (GhritaKumari)	Enhances antibody production and Th response, stimulates IL6, TNFα
Asparagus Racemosus (Satawar)	Inhibits toxins induced suppression of IL-1,TNFα and macrophage activity
AzadirachtaIndica(Neem)	Activates immune system, enhances macrophage phagocytosis, expression of MHC II molecules, IgM ,IgG
PhyllanthusEmblica (Amla)	Enhances NK cell activity
Curcuma Longa (Turmeric)	Increases mitogenic response of lymphocytes
NyctanthesArbor-Tristis (Harsinghar)	Stimulates humoral and Th response
OcimumSanctum (Tulsi)	Stimulates T cell proliferation, interferon production , auguments NK cells
PanaxGinseng (Ginseng)	Enhances circulating antibodies and antibody forming cells
WithaniaSomnifera (Ashwagandha)	Prevents myelosuppression caused by immunosuppressive drugs ,increases IL-1 ,TNF α

Table – 1: List of natural /herbal immunomodulators

CORTICOSTEROIDS

Corticosteroids are natural hormone released by adrenal cortex. These hormone have different role specially anti-inflammatory and immunosuppressive action, which are important to cure the oral disease. Its synthetic analogues are given in the form of the drug to cure multiple inflammatory and immunomodulatory drugs.

Mechanism of action: Inhibition of migration of leukocytes, Decrease the production of endothelial leukocyte adhesion molecule(ELAM) and ICAM in endothelial cell so the adhesion and localization is decreased, Decrease the chemotaxis, Inhibition of phagocytosis, Stabilization of membranes of the intracellular lysozyme, which contains hydrolytic enzymes so Inhibition of lysozyme release from

1. **Patil US et al 2012** [5]

a) Immunosuppressant

Mechanism	Drugs
1. Inhibitors of Lymphocyte Gene Expression	Glucocorticoids
2. Inhibitors of Lymphocyte Signaling	a) Calcineurin Inhibitors-Cyclosporine, Tacrolimus b) mTOR Inhibitors- Sirolimus, Everolimus
3. Cytotoxic Agents	a) Antimetabolites-Azathi-prine,Mthotrexate, leflunomid. b) Alkylating agents- Cyclophosphamide
4. Cytokine Inhibitors	a) TNF-α Inhibitors-Etanercept, Infliximab, Adalimumab b) IL-1 Inhibitors-Anakinra c) IL-2 Inhibtors- Daclizumab, Basiliximab
5. Antibodies against Specific Immune Cell Molecules	a) Polyclonal Antibodies-Antithymocyte Globulin (ATG) b) Monoclonal Antibodies-Alemutuzmab, Muromunab
6. Inhibitors of Immune Cell Adhesion	Efalizumab (LFA-1 Inhibitor)
7. Miscellaneous	Rho (D) Immune Globulin

b) Immunostimulant

Bacillus Calmette-Guerin (BCG):

Levamisole

Thalidomide

Recombinant Cytokines-Interferons, Interleukins, Colony stimulating factors

2) Pagare SS et al [6]

A) Immunosuppressants

Mechanism	Drugs
Those which act by general suppression of all immune responses	i) Antimetabolites—azathioprine, methotrexate, cyclophosphamide, chlorambucil ii) Nucleotide synthesis inhibitors— mycophenolate mofetil, leflunomide
Those which are specific suppressants of certain immune responses	Antilymphocytic serum (ALS), cyclosporine,tacrolimus, sirolimus
Highly selective monoclonal antibodies	a) Depleting antibodies (against T cells, B cells or both)—muromonab, rituximab, antithymocyte globulin. b) Non-depleting antibodies and fusion proteins—daclizumab, basiliximab
Those which reduce the unwanted reactions due to immune responses, by their anti-inflammatory actions	Glucocorticoids—prednisolone, thalidomide
B) Immunostimulants	
Increasing the humoral antibody responses	Amantadine, tilorone BCG vaccine
Enhancing the phagocytic activity of macrophages	Recombinant cytokines— interferons, interleukin-2
Modifying the cell mediated immune responses	Thalidomide, levamisole

Table – 2: Classification of immunomodulator drugs

granulocyte, Release of anti-inflammatory molecules such as lipocortin-1, interleukins IL-10, IL-1ra, and nuclear factor-B, by macrophages, eosinophils, lymphocytes, dendritic cells, neutrophils, and endothelial and epithelial cells, Induction of lipocortins in macrophage, endothelium, fibroblast which inhibit phospholipase A2 and decrease PG, Decrease production of IL1, 2, 3, 6, TNF-α, GM-CSF, Interferon, induce the transcription of the gene encoding the inhibitor of Nuclear Factor Kappa B subtype a (IkBa), which reduces the amount of NF-B that translocates to the nucleus and the secretion of pro-inflammatory cytokines and Suppress T cells by decreasing the number of circulating T lymphocytes.

Indication: Oral indication these are mainly based on immunomodulatory action are: Oral Lichen Planus, Oral submucous fibrosis, Aphthous stomatitis, Pemphigus, Pemphigoid, Erythema multiforme, Epidermolysis bullosa, Behcet's Disease, Orofacial Granulomatosis, Sjogren syndrome. [8 – 20] (Table – 3)

Diseases	Administration
Lichen planus	Topical Corticosteroids Drug of choice 0.05% clobetasol propionate, 0.1 %Triamcinolone acetonide, 0.05%fluocinonide0.1%, fluocinolone acetonide Apply 2-3 times/day for 3 weeks, followed by tapering during the following 9 weeks Intralesional Corticosteroids Used tomanage persistent localized lesion and lesions unresponsive to topical therapy. 10-20mg of insoluble Triamcinolone acetonide is diluted with 0.5ml saline or 2%lidocaine injected to lesion which solubilize gradually 3-4 times/week or 2 times/week Systemic Corticosteroids Should be administered only in recalcitrant lesions 1mg/kg body weight for 7 days, followed by a reduction of 10 mg each subsequent day.
Oral submucous fibrosis	Although it is a chronic inflammatory disease , immunological features had been discovered. Intralesional submucosal injections of a combination of dexamethasone (4 mg/ml) and two parts of hyaluronidase (1500IU) diluted in 1.0 ml of 2% xylocaine twice a week.
Recurrent Aphthous stomatitis	Topical corticosteroids Topical corticosteroids should be advised in moderate cases where primary methods have been failed. Topical agents are Dexamethasone 0.05 mg/ml rinsing three times a day, Dexamethasone 0.05 mg/ml with 0.2% chlorhexidine mouthwash for rinsing thrice a day, Clobetasol ointment 0.05% in orabase (1:1), Fluocinonide ointment 0.05% in orabase (1:1) three times a day, Triamcinolone acetonide 0.1% oral paste. Systemic corticosteroid therapy Recommended for patients with recalcitrant cases Hydrocortisone 20 mg or triamcinolone 4 mg, Prednisolone (10-30mg/day) for 10-15 days.
Pemphigus	Prednisolone doses of 40–60 mg /day for mild case and 60–100 mg/ day in severe case for about 6–8 weeks.If there is no response within 5–7 days, the dose should be increased in 50–100% increments until there is disease control. If doses above 100 mg/ day are required, pulsed intravenous CS could be considered.
Mucous Membrane Pemphigoid	Topical drugs Fluocinonide 0.05% or clobetasol propionate 0.05% in an adhesive thrice daily for 9–24 weeks).Triamcinolone acetonide can be used intralesionally (in a dilution of 5.0–10 mg/ml) to treat isolated erosions. Systemic corticosteroid Prednisolone 40 mg daily for 5 days followed by 10–20 mg daily for 2 weeks.
Erythema Multiforme	Doses of prednisolone 0.5–1.0 mg/kg/day tapered over 7–10 days can be given
Stevens-Johnson syndrome, Toxic epidermal necrolysis	Intermittent administration of high doses of intravenous corticosteroid and cyclophosphamide, (Pulsed therapy)usually three daily doses of dexamethasone (100 mg) or methylprednisolone (500–1000 mg) and a single dose of cyclophosphamide (500 mg) given monthly

Table – 3: Main indications of corticosteroids in the diseases of the oral cavity.

Adverse effect

a) Side effects of systemic steroids:

Cushing's habitus, Osteoporosis, Growth retardation: in children, Hyperglycemia, may be glycosuria, precipitation of diabetes, Glaucoma, Posterior Subcapsular cataract may also develop after long term use for several years, especially in children, Suppression of HPA axis- acute adrenal insufficiency, Psychiatric disturbances, Peptic ulceration, Delayed healing: of wounds and surgical incisions, Susceptibility to infection, Fragile skin, purple striae, Muscular weakness. [21]

b) Side effects of topical steroids

i) Local adverse effects of topical steroids Thinning of epidermis, Dermal changes- Atrophy, Telangiectasia, striae, Easy bruising, Hypopigmentation, Delayed wound healing, Fungal & bacterial infections, Candidal infection (25-55%), Burning mouth, Hypogeusia.

ii)Systemic side effects of topical steroids-Adrenal pituitary suppression– large amounts applied repeatedly. [8, 9, 21]

Contraindications: Peptic ulcer, Diabetes mellitus, Hypertension, Pregnancy (risk of fetal defects), Tuberculosis and other infections, Osteoporosis, Herpes simplex keratitis, Psychosis, Epilepsy, CHF, Renal failure. [21]

AZATHIOPRINE

Azathioprine a purine antimetabolite is an immunosuppressive drug. It is an imidazolyl derivative of 6-mercaptopurine. It is used along with a steroid to spare the side effect of long term uses of steroids.Azathioprine is metabolized by thiopurine methyltransferase(TPMT). Ideally the doses should be titrated according to the individual activity of TPMT.[21, 5, 6]The mechanism of action of the drug is given in figure – 2. [5, 21]

Following exposure to nucleophiles
↓
azathioprine is cleaved to 6-mercaptopurine,
↓
6-Thio-IMP(inosine monophosphate)
↓
6-thio-GMP (guanosine monophosphate)
↓
6-thio-GTP, (guanosine triphosphate)
↓
which is incorporated into DNA.
↓
Disrupts the formation of DNA and RNA as well as the process of cell division
↓
Suppress cell mediated immunity

Figure – 2: Mechanism of action of Azathioprine

Therapeutic Uses:

- Recurrent aphthous stomatitis /Behcet's syndrome
  - ✓ Used for chronic cases, are non-respondent to primary drugs.
  - ✓ 1 to 2 mg/kg/day (100–150 mg/day),[23]
  - ✓ Starting with 50 mg/day and escalated up to 150 mg/day. [24]
- Lichen planus
  - ✓ 50 mg twice daily orally (about 2mg/kg-day) for a period of 3 to 7 months. [25]
- Pemphigus vulgaris
  - ✓ 0.5–4 mg /kg depending on thiopurine methyltransferase (TPMT) level. [16]
- Mucous membrane pemphigoid (MMP)
  - ✓ 1–2 mg/kg daily depending on thiopurine methyltransferase levels.[18]

Adverse effects: Bone marrow suppression, including lycopene, thrombocytopenia, anemia, increased susceptibility to infections, hepatotoxicity, alopecia, GI toxicity, pancreatitis.

Hence, complete blood count examination before and during azathioprine treatment is mandatory.[5, 6, 21]

CYCLOSPORINE

Cyclosporine, a cyclic polypeptide consisting of 11 amino acids is produced by the fungus species Beauveria Nivea. It is a Calcineurin Inhibitors.It preferentially inhibits antigen-triggered signal transduction in T lymphocytes, the blunting expression of many lymphokines, including IL-2 and the expression of antiapoptotic proteins. [5, 21](Figure – 3)

Indications:

- Recurrent apthous stomatitis /Behcet's syndrome
  - ✓ Topical cyclosporine100mg/ml for moderate cases
  - ✓ Systemic cyclosporine 3 to 6 mg/kg/day for chronic case.[26]
- Lichen planus
  - ✓ Recalcitrant cases of OLP
  - ✓ Mouth rinse-5 ml of medication (containing 100 mg of cyclosporine per milliliter) three times daily (i.e., 500-1500mg/day).[27]
  - ✓ In a bioadhesive 100 mg/ml, added to the alcohol phase of Zilactin to a final concentration of 0.5 mg/dl. [10,28]
- Mucous membrane pemphigoid -100 mg/ ml can be given.[29]

Adverse effect[5,6, 21]

Gingival hyperplasia, Headache, Hyperkalemia, GI disturbances, Tremors, Hypertrichosis.

Normally activated Calcineurin phosphorylates NFAT-1(nuclear factor of T cell) which is a transcription factor that initiates IL-2 production and promote proliferation of helper and cytotoxic T cells
↓
When cytoplasmic NFAT is dephosphorylated
↓
It translocates to the nucleus and complexes with nuclear components required for complete T-cell activation including trans-activation of IL-2 and other lymphokine genes.
↓
Cyclosporine forms a complex with cyclophilin, a cytoplasmic receptor protein present in target cells.
↓
This complex binds to calcineurin, inhibiting Ca2+-stimulated dephosphorylation of the cytosolic component of nuclear factor for activated T-cells (NFAT).
↓
Cyclosporine also increases expression of transforming growth factor-b (TGF-b), a potent inhibitor of IL-2-stimulated T-cell proliferation and generation of cytotoxic T lymphocytes (CTL).

Figure – 3: Mechanism of action of cyclosporine

TACROLIMUS

Tacrolimus (FK506) is a macrolide antibiotic produced by Streptomyces tsukubaensis. Topical tacrolimus seems to penetrate the skin better than topical cyclosporine. [5, 21] (Figure – 4)

Like cyclosporine, tacrolimus inhibits T-cell activation by inhibiting calcineurin.
↓
Tacrolimus binds to an intracellular protein FK506-binding protein-12 (FKBP-12) an immunophilin structurally related to cyclophilin.
↓
A complex of tacrolimus-FKBP-12, Ca2+, calmodulin, and calcineurin then forms,
↓
calcineurin phosphatase activity is inhibited,
↓
prevents dephosphorylation and nuclear translocation of NFAT
↓
inhibits T-cell activation

Figure – 4: Mechanism of action of tacrolimus

Indications:

- Lichen planus
  - ✓ 0.1% Tacrolimus application2-4 times a day for 4-8 weeks.
  - ✓ This drug used topically can control symptoms and significantly improve refractory erosive oral LP. [30]
- Pemphigus Vulgaris/Mucous membrane pemphigoid -0.1% tacrolimus ointment twice daily for 3 to 4 weeks[31]

Adverse effect: Nephrotoxicity, neurotoxicity, GI complaints, hypertension, hyperkalemia, hyperglycemia.[5, 6, 21]

PIMECROLIMUS [32]

Pimecrolimus is an ascomycin macro lactam derivative. mechanism of action is similar to tacrolimus i.e. pimecrolimus attaches to macrophilin-12 (also referred to as FKBP-12) thus inhibiting calcineurin. Pimecrolimus inhibit T-cell activation by stopping the synthesis and release of cytokines from the T-cells. Pimecrolimus also prevent the release of inflammatory cytokines and mediators from mast cells.1% Pimecrolimus application2-4 times a day for 4-8 weeks has been advised for the treatment of oral lichen planus.

MYCOPHENOLATE MOFETIL:

It is a 2-morpholinoethyl ester of mycophenolic acid. [21] The mechanism of action of this drug is given in figure – 5.[5, 6, 21]

It is a prodrug
↓
Rapidly hydrolyzed to the active drug, mycophenolic acid (MPA),
↓
Inhibit inosine monophosphate dehydrogenase (an important enzyme in the de novo pathway of guanine nucleotide synthesis).
↓
B and T lymphocytes are highly dependent on this pathway for cell proliferation
↓
MPA therefore selectively inhibits lymphocyte proliferation and functions including antibody formation, cellular adhesion, and migration

Figure – 5: Mechanism of action of mycophenolate mofetil

Indication:

- Lichen planus- 2–4 g day[33]
- Mucous membrane pemphigoid /- 35-45 mg/kg/day[34]
- Pemphigus Vulgaris-2-2.5 g/day

Adverse effects: [5, 6, 21]
Leukopenia, diarrhea, and vomiting, sepsis associated with cytomegalovirus.

CYCLOPHOSPHOMIDE

These drugs are most lethal to rapidly proliferating tissues and appear to cause cell death when they tend to divide. The cytotoxic activity of these drugs correlates with the degree of DNA alkylation.[5, 21](Figure – 6)

It is an Alkylating agent
↓
introduce alkyl groups by forming covalent bonds with nucleophilic moieties such as phosphate, hydroxyl, carboxyl, amino and imidazole groups present in DNA or RNA.
↓
By cross linking in between the strands of DNA they prevent the cell division and protein synthesis.

Figure – 6: Mechanism of action of cyclophosphamide.

Adverse effect[5, 6, 21]
Neutropenia, Thrombocytopenia, Pancytopenia, GI disturbances, Alopecia, Raised transaminases.

Indications
Pemphigus and mucous membrane pemphigoid- can be used alone i.e.0.5–2 mg/kg daily or with steroid in the form of pulse therapy for severe cases.[35, 36]

METHOTREXATE

It is an antimetabolite. It suppresses DNA and RNA synthesis during S phase of the cell cycle.[21] The mechanism of action of the drug is given in figure – 7.[5,6,21]

Drugs competitively inhibit dihydrofolate reductase
↓
Prevent conversion of dihydrofolate(DHF) to trihydrofolate (THF)
↓
Normally THF is required in purine and pyramidine synthesis
↓
So suppress DNA and RNA synthesis

Figure – 7: Mechanism of action of methotrexate

Indication:

- Recurrent aphthous stomatitis /Behcet's syndrome
  - ✓ 7.5 to 20 mg of Methotrexate weekly has been proved to be effective in severe oro-genital lesions. [26]
- Lichen planus
  - ✓ 7.5-10 mg weekly for 8 weeks. [37]
- Mucous membrane pemphigoid
  - ✓ The dose ranges from 5 to 25 mg given weekly.
  - ✓ Mean duration of the therapy is 15 months, ranging from 8–22 months. [36]

Adverse effect: Mylosuppression, Hepatotoxicity, Alopecia, Oral ulceration, GI disturbances. [5, 6, 21]

LEVAMISOLE

Levamisole a heterocyclic compound was synthesized originally as an anthelmintic, but appears to restore

depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages.[21] The mechanism of action of this drug is given in figure – 8.[5,6,21]

Physiologically, thymopoietin affects many components of the immune system including both neutrophils, macrophages, and lymphocytes and its therapeutically important actions are probably targeted at stimulation of phagocytosis and stimulation of regulatory T cells to restore homeostasis in a disturbed immune system.

↓

Levamisole mimic the thymic hormone thymopoietin.

↓

So forms thymopoietin-mimetic tertiary structure,

↓

stimulate lymphocytes by its imidazole component,

↓

It also potentiates the activity of human interferon, Inhibit aerobic tumor glycolysis

Figure – 8: Mechanism of action of levamisole.

Doses:

- Aphthous
  - ✓ 150mg/day with or without combination with steroids (15 mg Prednisolone). [38]
- Lichen planus
  - ✓ 150- 300 mg/day for 3 months (Monotherapy) [39]
  - ✓ 150 mg/day levamisole and 15 mg/day Prednisolone for 3 consecutive days each week. [40]
- Mucous membrane pemphigoid
  - ✓ Dose ranging from 5 to 25 mg given weekly.
  - ✓ Mean duration of the therapy is15 months, ranging from 8–22 months.[36]

Adverse effects: Flu-like symptoms, GI disturbances, headache, dizziness, insomnia, thrombocytopenia, Granulocytopenia, allergic manifestation, muscle pain. [5,6,21]

THALIDOMIDE

Thalidomide was first marketed in West Germany in the year 1957 with the trade-name Contergan. A German drug company named Chemie Grunenthal developed and prescribed as a sedative or hypnotic and antiemetic for the treatment of morning sickness. But now due to its immunomodulatory action it is used for a number of conditions including: ,multiple myeloma, erythema nodosum leprosum and a number of other cancers, Crohn's disease, sarcoidosis, graft-versus-host disease , rheumatoid arthritis, & for some symptoms of HIV/AIDS. [5, 21]

Mechanism of action: It inhibits TNF-α, IL-6, IL-10 and IL-12 production, modulates the production of IFN-γ and increases the production of IL-2, IL-4 and IL-5 by the cells of immune system. It increases lymphocyte count, costimulates T cells and modulates natural killer cell cytotoxicity. It also inhibits NF-κBand COX-2 activity. [5, 21]

Indications:

- Recurrent Aphthous stomatitis
  - ✓ 100 to 200 mg/day to start with and to be continued till remission, followed by a maintenance dose of 50 to 100 mg daily or 50 mg every other day.[41]
- Lichen planus
  - ✓ It is an effective treatment of severe corticosteroid resistant erosive oral lichen planus cases.
  - ✓ Topical- Thalidomide 1% paste (150 mg Thalidomide powder dissolved in pure glycerol into a paste)Apply 3 times/day for 1 week
  - ✓ Systemic-Initial dose of 50 to 100 mg/day. [42]

Contraindications: Known hypersensitivity to thalidomide, Pregnancy or breastfeeding, Patient age < 12 years, Patients who are unable or unwilling to comply with required contraceptive measures. [5, 21]

Adverse effect: Teratogenicity causes phycomelia (due to antiangigenesis and inactivation of the protein cereblon), Somnolence, Edema, Hypotension, Headache, Haematuria, Arthralgia, Myalgia, Increased bilirubin, Neutropenia, Leucopenia, Lymphopenia, Constipation, Peripheral neuropathy, Dizziness, Paraesthesia. Patient should undergo STEPS (System for Thalidomide Education and Prescribing Safety) before prescribing this drug. [5, 21]

DIAMINO DIPHENYL SULPHONE (DAPSONE)

Dapsone is a widely used drug in the long-term treatment of leprosy.

Indications:

- Recurrent Aphthous stomatitis
  - ✓ Dapsone is given as 100mg orally in divided doses and can be increased at the rate of 50mg/day per week to a maximum dose of 300mg/ day. [43]
- Mucous membrane pemphigoid
  - ✓ Dapsone 25 mg daily for 3 days, then 50 mg daily for 3 days, then 75 mg per day for 3 days, then 100 mg per day for another 3 days, then rising to 150 mg daily on the seventeenth day.[44]

Adverse effect- Hemolytic anemia, methemoglobinemia, anemia and agranulocytosis.

EFALIZUMAB

Efalizumab is an antibody (recombinant humanized monoclonal antibody) used as an immunosuppressant in the treatment of psoriasis. It is a monoclonal antibody, binds to the CD11a subunit of lymphocyte function-associated antigen 1and acts as an immunosuppressant by suppressing lymphocyte activation and the migration of cell out of blood vessels into tissues.[5,21] Efalizumab binds to LFA-1 (lymphocyte function associated antigen) and

prevents the LFA-1-ICAM (intercellular adhesion molecule) interaction to block T-cell adhesion, trafficking, and activation. Adverse includes bacterial sepsis, viral meningitis, and invasive fungal disease[21].An nitial dose of 0.7 mg/kg, followed by a dosage of 1.0 mg/kg per week, approximately 3 weeks had been administered successfully in erosive lichen planus.[45]

BACILLUS CALMETTE-GUERIN (BCG)

Live bacillus Calmette-Guerin (BCG) is an attenuated, live culture of the bacillus of Calmette and Guerin strain of Mycobacterium bovis. The cytotoxic effect of BCG could result from the direct action of the CD4 cells or from the cytotoxic effect of the released cytokines and the activation of other cytotoxic cells [cytolytic T-lymphocytes, macrophages, natural killer or lymphokine-activated killer cells].[5, 21] Intralesional injection of 0.5 ml BCG-PSN every other day for 2 weeks can be administered in cases of erosive lichen planus.[46]

BASILIXIMAB

It is a chimeric mouse-human monoclonal antibody to α chain (CD25) of the IL-2receptor of T cells. Basiliximab is an immunosuppressant agent used to prevent immediate transplant rejection in people who are receiving kidney transplants, in combination with other agents. Basiliximab competes with the IL-2 to bind to the alpha chain subunit of the IL2 receptor (CD 25) on the surface of the activated T lymphocytes, hence preventing the receptor from signaling. This prevents T cells from dividing, and also from activating the B cells, that are responsible for the production of antibodies and prevent the expansion of the CD4 and CD8.It is indicated for refractory cases of oral lichen planus[5, 21,47]

ETANERCEPT

Etanercept is a complete human Tumor Necrosis Factor-a receptor fusion protein that binds TNF-alpha with greater affinity than the natural receptors. It is approved for the treatment of inflammatory conditions like ankylosing spondylitis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis arthritis & psoriasis in the USA, Canada, and Europe. It is indicated for refractory cases of oral lichen planus. Etanercept (2×25 mg/week subcutaneously) was successful in a regressed oral ulcer in Behçet's disease. [21,48]

INFLIXIMAB

It is a Chimeric monoclonal antibody obtained by exposing the mice to human TNF- α, used to treat autoimmune diseases. The drug cross-links with membrane-bound TNF—α receptors on the cell surface to inhibit T-cell and macrophage function and to prevent the release of other proinflammatory cytokines (IL-1, IL-6 and 8 along with collagenase and metalloproteinases. These are advised in cases of refractory and recurrent oral and genital aphthous ulcer in a dose of 5 mg/kg body weight intravenously.[21, 49]

INTERFERON

Interferons are compounds produced by the body that perform functions related to the immune system, which is the body's defense against invading pathogens. Recombinant interferon refers to interferon compounds produced by the recombinant techniques. Interferon causes induction of certain enzymes by binding to cell surface receptors, inhibition of cell proliferation, and enhancement of immune activities, including increased phagocytosis by macrophages and augmentation of specific cytotoxicity by T lymphocytes[5, 21]. For Behcet's syndrome, Intermediate (e.g. 6 × 106 IU thrice a week) or high doses (e.g. 9×106 IU thrice a week) of Interferon alpha 2 a (Roferon A) and b (Intron A) are principally more effective than low doses (3 ×106 IU thrice a week). Lower doses are recommended as a maintenance therapy when treatment is successful in the first 1 to 4 months. [50]Intralesional injection of interferon gamma (0.01– 10.0 U/mL) 3 times a day for 6 months can be given in oral submucous fibrosis.[51]

COLCHICINE

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. [52]

REFERENCES

1. Abbas AK, Litchman AK, Pober JS. Cellular and molecular immunology.3rd ed. Harcourt Brace & Company Asia Pvt ltd, Singapore.1997.
2. Ketchum PA. Microbiology-Concepts and Applications. John Wiley & sons. Inc, Newyork.1988.
3. Kumar V, Cotran RS, Robbins SL. Robbins Basic Pathology 7th ed. Elsevier, India Pvt ltd, New Delhi; 2003.
4.Slots J, Taubman MA. Contemporary Oral Microbiology and Immunology. Mosby-Year Book Inc, St. Louis, Missouri. 1992.
5.Patil US, Jaydeokar AV, Bandawane DD. Immunomodulators: A Pharmacological Review. Int J Pharm Pharm Sci, 2012 Vol 4, Suppl 1, 30-36
6.Pagare SS, SinghiR, VahanwalaS, Nayak CD. Rationale in usage of immunomodulators for management of head, face and neck cancers. International Journal of Head and Neck Surgery, September-December 2012; 3(3):154-157
8. Kallali B et al. Corticosteroids in dentistry. Indian acad ora med 2011;23(2):128-131.
9. Vijayavel T et al. Corticosteroids in oral diseases. Indian Journal of Drugs and Diseases. 2012;1(7):168-170
10. Lodi G, Scully C,Carrozzo M, Griffiths M,. Sugerman PB, Thongprasom K.Current controversies in oral lichen planus: Report of an international consensus meeting. Part 2. Clinical management and malignant transformation.Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:164-78)

11. Randell S, Cohen L. Erosive lichen planus. Management of oral lesions with intralesional corticosteroid injections. J Oral Med 1974;29:88-91
12.Carbone M, Goss E, Carrozzo M, Castellano S, Conrotto D, Broccoletti R, et al. Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up. J Oral Pathol Med 2003;32:323-9.
13.Rajendran R et al. Cell-mediated and humoral immune responses in oral submucous fibrosis (OSMF). Cancer, 1986, 58: 2628-263
14.Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC. clinical evaluation of different treatment methods for oral submucous fibrosis. A 10 year experieince with 150 cases. J Oral Pathol Med 1995 ;24:402
15.Scully C, Gorsky M, Lozada-Nur FL.The diagnosis and management of recurrent aphthous stomatitis A consensus approach J Am Dent Assoc 2003;134(2):200-207
16.Harman KE, Alberts Black MM, et al. Guidelines for the management of pemphigus vulgaris. British Journal of Dermatology 2003; 149: 926–937.
17.Ratnam KV, Phay KL, Tan CK. Pemphigus therapy with oral prednisolone regimens. Int J Dermatol 1990; 29: 363–7.
18.ScullyC, Muzio LL. Oral mucosal diseases: Mucous membrane pemphigoid. British Journal of Oral and Maxillofacial Surgery 46 (2008) 358–366
19.Crispian Scully, Jose Baganb. Oral mucosal diseases: Erythema multiforme. British Journal of Oral and Maxillofacial Surgery2008;46: 90–5.
20. Kardaun SH, Jonkman MF.Dexamethasone Pulse Therapy for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Acta Derm Venereol 2007; 87: 144–148
21. Brunton LL, Parker KL, Blumenthal DK, Buxton ILO.Goodman & Gilman's Manual of
Pharmacology and Therapeutics.McGraw-Hill.2008
22.M.A. González-Moles and C. Scully Management with Topical Corticosteroids: (2) Protocols. Monitoring of Effects and Adverse Reactions, and the Future.J Dent Res 2005 84: 294
23.Hamuryudan V, Ozyazgan Y, Hizli N et al. Azathioprine in Behcet's syndrome: effects on long-term prognosis. Arthritis Rheum 1997; 40: 769–774.
24. Vivek V, Bindu J Nair. Recurrent Aphthous Stomatitis: Current Concepts in Diagnosis and Management. Journal of Indian Academy of Oral Medicine and Radiology, 2011;23(3):232-236
25.Kaushal K et al. Azathioprine for the Treatment of Severe Erosive Oral and Generalized Lichen Planus.Acta Derm Venereol 2001. 378-38
26.Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC.Practical aspects of management of recurrent aphthous stomatitis. J Eur Acad Dermatol Venereol. 2007;21(8):1019-26.
27.Eisen D, Griffiths CE, Ellis CN, Nickoloff BJ, Voorhees JJ. Cyclosporin wash for oral lichen planus. Lancet 1990;335: 535-6.
28.Epstein JB. Topical cyclosporine in a bioadhesive for treatment of oral
lichenoid mucosal reactions An open label clinical trial. Oral Surg Oral Med Oral Pathol Oral 1996;82:532-6
29. Azana JM, de Misa RF, Boixeda JP, Ledo A. Topical cyclosporine for cicatricial pemphigoid. J Am Acad Dermatol 1993;28:134–5.
30.Morrison L, Kratochvil FJ III, Gorman A. An open trial of topical tacrolimus for erosive oral lichen planus. J Am Acad Dermatol 2002; 47:617-20.
31.Gunther C, Wozel G, Meurer M, Pfeiffer C. Topical tacrolimus treatment for cicatricial pemphigoid. J Am Acad Dermatol 2004;50:325–6.
32.Gorouhi F et al. Randomized trial of Pimecrolimus cream versus Triamcinolone acetonide paste in the treatment of oral lichen planus. J Am Acad Dermatol 2007 Nov; 57(5) :806-13
33.Wee JS . Efficacy of Mycophenolate mofetil in severe mucocutaneous lichen planus: a retrospective review of 10 patients.Br J Dermatol 2012; 167(1):36-43
34. Ali FA , Ali JA. Pemphigus vulgaris and mucous membrane pemphigoid: Update on etiopathogenesis, oral manifestations and management. J Clin Exp Dent. 2011;3(3):e246-50.
35,Brody HJ, Pirozzi DJ. Benign mucous membrane pemphigoid. Response to therapy with cyclophosphamide. *Arch Dermatol* 1977;113:1598–9.
36. Neff AG, Turner M, Mutasim DF. Treatment strategies in mucous membrane pemphigoid. Therapeutics and Clinical Risk Management 2008:4(3) 617–626
37.Malekzad F. Low dose Methotrexate for the treatment of generalized lichen planus.Iran J Dermatol 2011; 14: 131-135
38. Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. *Am J Helath Syst Pharm* 2001; 58: 41–50.
39. Tai Hyok et al.Levamisole Monotherapy for Oral Lichen Planus. Ann Dermatol Vol. 21, No. 3, 2009
40. Lu Sy et al.Dramatic response to Levamisole and low-dose prednisolone in 23 patients with oral lichen planus: a 6-year prospective follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:705-709.
41.Grinspan D, Blanco GF, Aguero S. Treatment of aphthae with thalidomide. *J Am Acad Dermatol* 1989; 20: 1060–1063
42. Wu Yet al.A randomized double-blind, positive-control trial of topical Thalidomide in erosive oral lichen planus Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Aug;110(2):188-95.
43.Mimura MAM,Hirota SK, Sugaya NN, Sanches Jr. JA, Migliari DA. Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. Clinics. 2009;64(3):193-8.
44.Rogers III RS, Seehafer JR, Perry HO. Treatment of cicatricial (benign mucous membrane) pemphigoid with dapsone. *J Am Acad Dermatol* 1982;6:215–23.
45.Cheng A. Oral Erosive Lichen Planus Treated With Efalizumab. Arch Dermatol/142, 2006 680-82
46.Xiong C et al. The efficacy of topical intralesional BCG-PSN injection in the treatment of erosive oral lichen planus: a randomized controlled trial. J Oral Pathol Med 2009 Aug; 38(7) :551-8
47. Rebora A, Parodi A, Murialdo G. Basiliximab Is Effective for Erosive Lichen Planus. Arch Dermatol. 2002;138(8):1100-1101
48.Melikoglu M, Fresko I, Mat C *et al*. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. *J Rheumatol* 2005; 32: 98–105
49.Haugeberg G, Velken M, Johnson V. Successful treatment of genital ulcers with infliximab in Behçet's disease. *Ann Rheum Dis* 2004; 63: 744–745.
50.Zouboulis Ch C, Orfanos CE. Treatment of Adamantiades-Behçet's disease with systemic interferon alfa. *Arch Dermatol* 1998; 134: 1010–1016
51.Haque MF, Meghji S, Nazir R, Harris M. Interferongamma (IFN-gamma) may reverse oral submucous fibrosis. J Oral Pathol Med.2001;30: 12–21.
52.Fontes V, Machet L, Huttenberger B, Lorette G, Vaillant L.Recurrent aphthous stomatitis: treatment with colchicine.An open trial of 54 cases.*Ann Dermatol Venereol* 2002; 129:1365–1369.

Source of Support: Nil
Conflict of Interest: Nil