Role of Immunomodulators in Oral Diseases

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INTRODUCTION

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.

How to cite this article:

Figure – 1: Basic pathway of immunity.

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 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
rejuvenating time. These drugs can be given alone too in certain circumstances like very astringent cases and cases non-responsive 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)

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

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

   a) Immunosuppressant

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inhibitors of Lymphocyte</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Gene Expression</td>
<td></td>
</tr>
<tr>
<td>2. Inhibitors of Lymphocyte</td>
<td>a) Calcineurin Inhibitors-Cyclosporin, Tacrolimus</td>
</tr>
<tr>
<td>Signaling</td>
<td>b) mTOR Inhibitors- Sirolimus, Everolimus</td>
</tr>
<tr>
<td>3. Cytotoxic Agents</td>
<td>a) Antimetabolites-Azathioprine, Methotrexate, leflunomide</td>
</tr>
<tr>
<td></td>
<td>b) Alkylating agents- Cyclophosphamide</td>
</tr>
<tr>
<td>4. Cytokine Inhibitors</td>
<td>a) TNF-α Inhibitors-Enanect, Infliximab, Adalimumab b) IL-1 Inhibitors-Anakintra</td>
</tr>
<tr>
<td></td>
<td>c) IL-2 Inhibitors- Daclizumab, Basiliximab</td>
</tr>
<tr>
<td>5. Antibodies against Specific</td>
<td>a) Polyclonal Antibodies-Antihymocyte Globulin (ATG)</td>
</tr>
<tr>
<td>Immune Cell Molecules</td>
<td>b) Monoclonal Antibodies-Alemturazumab, Muromunab</td>
</tr>
<tr>
<td>6. Inhibitors of Immune Cell</td>
<td>Efalizumab (LFA-1 Inhibitor)</td>
</tr>
<tr>
<td>Adhesion</td>
<td></td>
</tr>
<tr>
<td>7. Miscellaneous</td>
<td>Rho (D) Immune Globulin</td>
</tr>
</tbody>
</table>

b) Immunostimulant

Bacillus Calmette-Guerin (BCG):
Levamisole
Thalidomide
Recombinant Cytokines-Interfons, Interleukins, Colony stimulating factors

2) Pagare SS et al 3

A) Immunosuppressants

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those which act by general suppression of all immune responses</td>
<td>Antilymphocytic serum (ALS), cyclosporine, tacrolimus, sirolimus</td>
</tr>
<tr>
<td>Those which are specific suppressants of certain immune responses</td>
<td>Highly selective monoclonal antibodies</td>
</tr>
<tr>
<td>a) Depleting antibodies (against T cells, B cells or both)—muromonab, rituximab, antithymocyte globulin. b) Non-depleting antibodies and fusion proteins—daclizumab, basiliximab</td>
<td></td>
</tr>
<tr>
<td>Those which reduce the unwanted reactions due to immune responses, by their anti-inflammatory actions</td>
<td>Glucocorticoids—prednisolone, thalidomide</td>
</tr>
</tbody>
</table>

8) Immunostimulants

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing the humoral antibody responses</td>
<td>Amantadine, tikocrine BCG vaccine</td>
</tr>
<tr>
<td>Enhancing the phagocytic activity of macrophages</td>
<td>Recombinant cytokines— interferons, interleukin-2</td>
</tr>
<tr>
<td>Modifying the cell mediated immune responses</td>
<td>Thalidomide, levamisole</td>
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</tbody>
</table>

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 α (IκBα), 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)

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Administration</th>
</tr>
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</table>
| 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 to manage 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 (1500U/I) 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. |

**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, Telangectasia, striae, Easy bruising, Hypopigmentation, Delayed wound healing, Fungal & bacterial infections, Candidal infection (25-55%), Burning mouth, Hypoguesia.

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), and 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.

**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),
  - Starting with 50 mg/day and escalated up to 150 mg/day.

- **Lichen planus**
  - 50 mg twice daily orally (about 2mg/kg-day) for a period of 3 to 7 months.

- **Pemphigus vulgaris**
  - 0.5–4 mg /kg depending on thiopurine methyltransferase (TPMT) level.

- **Mucous membrane pemphigoid (MMP)**
  - 1–2 mg/kg daily depending on thiopurine methyltransferase levels.

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

Hence, complete blood count examination before and during azathioprine treatment is mandatory.

**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.

**Indications:**

- **Recurrent apthous stomatitis /Behcet’s syndrome**
  - Topical cyclosporine100mg/ml for moderate cases
  - Systemic cyclosporine 3 to 6 mg/kg/day for chronic case.

- **Lichen planus**
  - Recalcitrant cases of OLP

**CYCLOSPORINE**

Mouth rinse-5 ml of medication (containing 100 mg of cyclosporine per milliliter) three times daily (i.e., 500-1500mg/day).

In a bioadhesive 100 mg/ml, added to the alcohol phase of Zilactin to a final concentration of 0.5 mg/ml.

- Mucous membrane pemphigoid -100 mg/ ml can be given.

**Adverse effect**

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

Normally activated Calcineurin phosphorylates NFAT-(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).

**TACROLIMUS**

Tacrolimus (FK506) is a macrolide antibiotic produced by Streptomyces tsukubaensis. Topical tacrolimus seems to penetrate the skin better than topical cyclosporine.

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 application 2-4 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 application 2-4 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

![Figure 5: Mechanism of action of mycophenolate mofetil](image5.png)

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 6: Mechanism of action of cyclophosphamide](image6.png)

**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, carbonyl, 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](image6.png)

**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, 5, 21

![Figure 7: Mechanism of action of methotrexate](image7.png)

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

**LEVAMISOLE**

Levamisole a heterocyclic compound was synthesized originally as an anthelmintic, but appears to restore...
The depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages. The mechanism of action of this drug is given in figure – 8.

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-nimetic 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**
  - 150 mg/day with or without combination with steroids (15 mg Prednisolone).
- **Lichen planus**
  - 150–300 mg/day for 3 months (Mono therapy)
  - 150 mg/day levamisole and 15 mg/day Prednisolone for 3 consecutive days each week.
- **Mucous membrane pemphigoid**
  - Dose ranging from 5 to 25 mg given weekly.
  - Mean duration of the therapy is 15 months, ranging from 8–22 months.

**Adverse effects:** Flu-like symptoms, GI disturbances, headache, dizziness, insomnia, thrombocytopenia, Granulocytopenia, allergic manifestation, muscle pain.

**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.

**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-κB and COX-2 activity.

**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.
- **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.

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

**Adverse effect:** Teratogenicity causes phycemelia (due to antiangiogenesis 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 100 mg orally in divided doses and can be increased at the rate of 50 mg/day per week to a maximum dose of 300 mg/day.
- **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.

**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 1 and acts as an immunosuppressant by suppressing lymphocyte activation and the migration of cell out of blood vessels into tissues. 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. An initial 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.  

**BACILLUS CALMETTE-GUERIN (BCG)**

Live bacillus Calmette-Guerin (BCG) is an attenuated, live culture of the bacillus 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].  

Intralvesional injection of 0.5 ml BCG-PSN every other day for 2 weeks can be administered in cases of erosive lichen planus.  

**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 (2x25 mg/week subcutaneously) was successful in a regressed oral ulcer in Behcet’s disease.  

**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. 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. Intralvesional injection of interferon gamma (0.01- 10.0 U/mL) 3 times a day for 6 months can be given in oral submucous fibrosis.  

**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.  

**REFERENCES**


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