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Original Research Paper

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# STEROID SPARING DRUGS IN IMMUNE MEDIATED MUCOCUTANEOUS DISEASES-A REVIEW ON THERAPEUTIC REGIMEN

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| **Dr. Paramasivam Preethi*** | 1st Year Postgraduate Student. *Corresponding Author |
| **Dr.R.R. Mahendra Raj** | M.D.S, Professor And Head Of The Department. |
| **Dr Thalaimalai Saravanan** | M.D.S, Professor |
| **Dr K.R.Shakila** | M.D.S,Professor, Department of oral medicine and radiology, Karpaga vinayaga institute of dental sciences, Kanchipuram. |

**ABSTRACT** Corticosteroid remains mainstay of treatment for immune mediated mucocutaneous disorders. The very usefulness of the drug, which has become a double-edged sword, when used for long time. The administration of immunomodulators decrease the dose of steroids, reduces the steroid side effects and improves rejuvenation time. In addition to immunomodulatory drugs there are some drugs that are used to spare corticosteroids in the treatment of immune mediated mucocutaneous diseases. This review attempts to elicit the use of steroid sparing drugs in immune mediated diseases.

**KEYWORDS :** steroid sparing drugs, immunomodulators, immunosuppressants

## INTRODUCTION:

Discovery of corticosteroids made a massive breakthrough in medicine, which simulate the body's stress hormones, could help reduce the symptoms of inflammatory diseases and suppress the immune system. While corticosteroid, is useful in treating many kinds of diseases, they also carry list of potential side effects. Many immunological diseases affect the oral cavity, making pathogenesis more difficult. In these cases, the steroid stays the backbone,sometimes steroid isn't sufficient alone to cure illness because of complex pathogenic components and some sickness can be steroid-resistant. In such instances, immunomodulating drugs should be administered. Immunomodulators should be given along with a steroid to spare side effects and speed the rejuvenating process. The administration of immunomodulators decrease the dose of steroids, reduces the steroid side effects and improves rejuvenation time. For these reasons, these immunomodulatory drugs come under the category of steroid-sparing drugs.This review ascertain the use of steroid sparing durgs in immune mediated mucocutaneous and its therapeutic regimen.

## Immunologically Mediated Mucocutaneous Disease:

Immunologically mediated illnesses that have an effect on the oral mucosa present with inflammation and lack of epithelial integrity, via a cell and/or humoral immunity mediated attack at the epithelial-connective tissue targets.

They may be grouped under the following categories
(I) AUTOIMMUNE DISORDERS
(II) HYPERSENSITIVITY DISORDERS/ALLERGIES
(III) PRIMARY OR SECONDARY IMMUNODEFICIENCIES
(IV) IMMUNOPROLIFERATIVE DISORDERS [1]

## Following are the conditions where immunomodulatory drugs should be advised:

*When no reaction to corticosteroids*
*The instances in which corticosteroids are contraindicated*
*Cases resistant to steroids*
*Recurrent cases*
*Cases with a preceding records of excessive side effects with steroids.*[2]

## Immunomodulators

Immunomodulators can be further classified into
I. IMMUNOSTIMULANTS
II. IMMUNOSUPPRESSANTS.

Based on the origin and mode of action, immunosuppressants can be widely categorized as
(i)Traditional immunosuppressants
(ii)Steroid sparing drugs
(iii)Biologics[3]

## Steroid Sparing Drugs:

Sometimes immunosuppressive medicines are given similarly to or in place of steroid therapy to decrease the dose of steroids needed, and that, spare a number of the unwanted side effects of steroid therapy. Hence they are called as steroid sparing drugs .

## The achievement of corticosteroid-sparing therapy can be described as –

(1) the capacity to reduce systemic corticosteroid to a day-by-day dose of 10 mg of oral prednisone or less
(2) clinically decreased inflammation
(3) stabilization or improvement in signs and symptoms along with pain
(4) patient tolerance of any drug-associated side effects

## BASED ON MECHANISM OF ACTION

### Alkylating Agents

1. Cyclophosphamide
2. Chlorambucil

### Antimetabolites

1. Azathioprine
2. Methothrexate
3. Mycophenolate Mofetil

### Antibiotics

1. Dapsone

### Calcineurin Inhibitor

1. Cyclosporine
2. Tacrolimus
3. Sirolimus

**Alkylating Agents:**

**Cyclophosphamide:**

Cyclophosphamide is an *alkylating agent* that forms covalent bonds with DNA, thereby leading to DNA fragmentation, mutations, and cell death. suppresses the B-cell function more than the T-cell function. It suppresses cellular immunity[4]

**Indication:**

***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

**Dexamethasone Cyclophosphamide Pulse (DCP) Therapy**

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| Day 1 | 100mg Dexamethasone IV in 500ml of 5% Dextrose, in 2 hours |
| Day 2 | 100mg Dexamethasone IV + 500mg of Cyclophosphamide in 500ml of 5% Dextrose, in 2 hours |
| Day 3 | 100mg Dexamethasone IV in 500ml of 5% Dextrose in 2 hours + Cyclophosphamide 50mg oral daily except on day of IV Cyclophosphamide |

In case of diabetic patients, 10 units of soluble insulin is added for every 500ml bottle of 5% dextrose and the patient's regular treatment for diabetes is continued.

**cyclophosphamide Pulse**

Cyclophosphamide 500 mg was dissolved in 25 ml of distilled water which was added to 500 ml of 5% dextrose and given slowly intravenously over 60 minutes. It was followed by 500 ml of normal saline. Similar pulses were performed again monthly for 12 months and twice a month for further 6 pulses. Patients were then followed for one year[6]

***Lichen Planus***

oral cyclophosphamide was administered at a dosage of 50 mg/day for six weeks[7]This helps in the reduction of the steroid dosage or induce remission, but their use is limited by toxic effects and cost. Cyclophosphamide has been the traditional steroid-sparing agent of choice for patients with severe disease or rapid progression. [8]

**Adverse Effect:**

Leukopenia, Thrombocytopenia, Diffuse loss of hair, Gonadal damage, Carcinogenesis.[9]

**Chlorambucil:**

Chlorambucil is an alkylating agent it preferentially affects B cells over T cells

**Indication:**

***Pemphigus vulgaris and pemphigus foliaceus***

chlorambucil as a potential adjuvant therapeutic approach for pemphigus patients who have failed treatment with other immunosuppressive regimens. [10]

***Bullous pemphigoid***

When bullous pemphigoid were treated with a combination of chlorambucil and a systemic corticosteroid, corticosteroid requirement during therapy was reduced by 50% compared with that reported for corticosteroid and azathioprine.[11]

**Side Effect:**

Bone marrow suppression, gonadal dysfunction, gastrointestinal upset, cystitis, pulmonary fibrosis, hepatitis, rash, and CNS stimulation

**Antimetabolites:**

**Azathioprine:**

azathioprine impairs T-cell lymphocyte function and essential components of T-cell activation (e.g., interleukin-2), and is more selective for T lymphocytes than for B lymphocytes immunosuppressive effects on T cells.

**Indication:**

***Pemphigus vulgaris***

Used as first-line steroid sparing agent. [12]AZA started at the dose of 50 mg/day, which could be increased to 2.5 and 1.5 mg/kg/day for those with high or intermediate/low TPMT activity, respectively[13]

***Mucous membrane pemphigoid (MMP)***

1–2 mg/kg daily depending on thiopurine methyltransferase levels. [14]

***Lichen planus***

50 mg twice daily orally (about 2mg/kg-day) for a period of 3 to 6months. [15]

**Adverse Effect:**

Myelosuppression, gastrointestinal upset, nausea, vomiting, and diarrhoea

**Methotrexate:**

Methotrexate is a synthetic folic acid analogue highly valued for both its anti-inflammatory and anti-proliferative properties. Considered one of the original immune-modifying agents, it is used widely for the treatment of steroid-recalcitrant inflammatory diseases. [16]

**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. [17]

***Lichen planus***

7.5-10 mg weekly for 8 weeks. [18]

***Pemphigus***

MTX therapy with a recommended dose of 10 to 20 mg/week to experience clinical improvement and also to taper, and even discontinue steroids [13] Methotrexate is a steroid sparing agent and is recommended as a 2nd line adjuvant in the third-line treatment of moderate to severe pemphigus vulgaris and pemphigus foliaceus.

***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 [19]

**Side Effect:**

Myelosuppression, Hepatotoxicity, Alopecia, Oral ulceration, GI disturbances

**Mycophenolate Mofetil:**

Mycophenolate mofetil (MMF) is a new systemic immunosuppressive agent whose use is rapidly increasing. MMF, an inhibitor of inosine monophosphate dehydrogenase, attenuates lymphocyte proliferation[20]

**Indication:**

Lichen planus- 2–4 g day [21]
Mucous membrane pemphigoid - 35-45 mg/kg/day
Pemphigus Vulgaris-2 g/day [22]

**Adverse Effects:**

Leukopenia, diarrhoea, and vomiting, sepsis associated with cytomegalovirus

**Antibiotics:**

**Dapsone:**

Dapsone and other sulphonamides have been used successfully in the treatment of patients with a variety of blistering skin diseases. [23]

**Indication:**

***Recurrent Aphthous stomatitis***

(Dapsone, 100–150 mg/day) [24]

***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.

***Pemphigus vulgaris***

Dapsone is recommended in a dose of 100 mg/d or up to 1.5 mg/kg/d as a steroid-sparing agent. [25]

***Bechet's disease.***

Dapsone (100–150 mg/d p.o.) [17]

**Adverse Effect:**

Haemolytic anaemia, methemoglobinemia, anaemia and agranulocytosis.

**Calcineurin Inhibitor:**

**Tacrolimus:**

Tacrolimus (FK 506) is a macrolide immunosuppressant which possesses similar but more potent immunosuppressant properties compared with cyclosporin, inhibiting cell-mediated and humoral immune responses. [26]

**Indication:**

***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. [27]

**Pemphigus Vulgaris/Mucous membrane pemphigoid** -0.1% tacrolimus ointment twice daily for 3 to 4 weeks [28]

**Adverse effect:**

Nephrotoxicity, neurotoxicity, GI complaints, hypertension, hyperkalaemia, hyper-glycemia.

**Cyclosporin:**

It unique immunosuppressive properties specifically and reversibly acts on lymphocytes (in particular T helper cells), producing selective suppression of cell-mediated immunity. This suppression is contingent on the mode of activation and is calcium-dependent. [29]

**Indication:**

***Recurrent aphthous stomatitis /Bechet's syndrome***

Topical cyclosporine100mg/ml for moderate cases

Systemic cyclosporine 3 to 6 mg/kg/day for chronic case. [30]

***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). [31]

***Mucous membrane pemphigoid***

100 mg/ml can be given [32]

**Adverse Effect:**

Gingival hyperplasia, Headache, Hyperkalaemia, GI disturbances, Tremors, Hypertrichosis

**CONCLUSION:**

The prevalence of the precept immune-mediated diseases affecting the oral cavity is 0.8%. Oral corticosteroids are the primary line of treatment in the control of immune-mediated diseases. Steroid sparing drugs are indicated in sufferers in whom systemic steroids are useless or are contraindicated or need to be discontinued due to side effects. Steroid sparing drugs may be used as an adjuvant to corticosteroids or as a monotherapy, and choice of the drug and outcome of its use in immune-mediated disorder is particular for an individual. Therefore, the risk-advantage ratio has to be considered while prescribing a steroid-sparing therapy. As the variety of randomized control trials, the usage of steroid-sparing drugs for control of immune-mediated diseases is scarce, we need to apply those drugs with caution.

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