

Topical Non-Steroidal Immunomodulators in Dermatology

Abstract

Immunological abnormality is the pathological basis of many dermatological disorders. Although steroids are the backbone of topical therapy in dermatology, the side effects are encountered quite frequently. Thorough knowledge of non-steroidal immunomodulators will broaden our treatment options. A summary of important non-steroidal immunomodulators has been given to help the residents understand the mechanism of action, indications, application, and adverse effects of these drugs.

Keywords: Immunomodulators, topical, zinc

Introduction

Immunomodulators are the agents that modify the response of the immune system by stimulating or suppressing the immune system.^[1] They act by two mechanisms: 1) immunosuppression—reduction in the immune response in autoimmune diseases and allergies and 2) immunostimulation—enhancement of the immune surveillance against various infections or malignancies.

The topical agents have been classified into steroidal and non-steroidal immunomodulatory agents.^[2] Topical steroids are widely used immunomodulators in dermatology. However, the pharmacological resistance and side effect profile of potent steroids preclude their long-term usage. This review outlines the major non-steroidal drugs which are useful alternatives in chronic dermatological disorders.

The topical non-steroidal immunomodulators of dermatological importance are:

1. Macrolactams:

These compounds bind to calcineurin blocking its ability to dephosphorylate the transcription factor NFAT-1 (nuclear factor of activated T cells 1). This prevents its translocation into the nucleus, and transcription of gene-encoding IL-2 (interleukin 2) is blocked, causing reduced proliferation of T cells.^[3] Pimecrolimus acts by reducing NFAT-2 activity in follicular keratinocytes when applied

topically.^[3] It suppresses thymic stromal lymphopoietin (TSLP) which is an IL-7-like cytokine having a role in allergic inflammation.

Sirolimus acts by binding to its target protein serine-kinase, the mTOR (mammalian target of rapamycin) that regulates cell growth. It also inhibits vascular endothelial growth factor (VEGF).^[4] Various calcineurin inhibitors are summarized in Table 1.

2. Contact allergens:

These compounds act by inducing an allergic reaction in a naïve host. According to the theory of “antigenic competition,” an immunological response to one antigen inhibits the development of the immune response to other unrelated antigens.^[6] Used widely as contact allergens in the past, these are now accepted as immunomodulators due to the following actions:

- a. Immunoregulatory activity: They cause increased expression of VEGF in follicular keratinocytes and endothelial cells in the skin of the affected alopecia areata cases which stimulates angiogenesis. They also increase the expression of skin-associated chemokine CCL27 on keratinocytes, which stimulates the accumulation of cutaneous lymphocyte-associated antigen (CLA+) T-cell subsets to replace autoreactive (allergen-specific)

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Table 1: Macrolactams with their formulations, indications, applications, and safety profiles

Drug	Indication	Formulation	Application	Safety profile	Special remarks
Tacrolimus	Atopic dermatitis*, psoriasis, pyoderma gangrenosum, lichen planus, GVHD, allergic contact dermatitis, rosacea, discoid lupus erythematosus, SLE and dermatomyositis, CAD, allergic asthma, allergic rhinitis and conjunctivitis, vitiligo, and venous ulcerations in rheumatoid arthritis	0.1% ointment, 0.03% ointment	Twice daily	Burning sensation, erythema, headache. Safe above 2 years of age.	Isolated from <i>Streptomyces tsukubaensis</i>
Pimecrolimus	Atopic dermatitis*, Genital lichen sclerosus, seborrheic dermatitis, Fox-Fordyce disease, GVHD, vitiligo, and discoid lupus erythematosus	1% ointment	Twice daily	Burning sensation, erythema, headache. Safe above 2 years of age	Isolated from <i>Streptomyces hygroscopicus var. ascomycetes</i>
Sirolimus	Tuberous sclerosis, facial angiofibroma	0.5% (<12 years), 1% (>12 years) ointment/cream ^[4]	Once daily thrice week for 9 months	Erythema, irritation	Isolated from <i>Streptomyces hygroscopicus</i>
Cyclosporine	Oral pemphigus, oral lichen planus, Pyoderma gangrenosum ^[2]	100 mg/ml solution	5ml mouth wash thrice daily Used as a dressing	No side effects ^[5]	Isolated from <i>Tolypocladium inflatum gams.</i> Also reduces pain in pyoderma gangrenosum. ^[5]

*FDA - Approved indications; GVHD - Graft versus host disease, SLE - Systemic lupus erythematosus; CAD - Chronic actinic dermatitis

CD4+ T-cell subsets. They inhibit the T cells which release interferon- γ (IFN- γ) and transforming growth factor- β (TGF- β) and stimulate the T cells which release cytokines responsible for the release of IL-2, IL-8, IL-10, and tumor necrosis factor-alpha (TNF- α) which plays a role in proliferation of epithelium.

- b. Anti-tumor activity: Dinitrochlorobenzene (DNCB) acts by haptization, i.e., combines with weak tumor antigens and develops an immune response against the tumor cells. However, none of the dermatological indications is FDA-approved.

Various contact allergens are summarized in Table 2.

3. Immunostimulators: Imiquimod is a non-nucleoside heterocyclic amine.^[7] It activates toll-like receptor 7 (TLR-7) and induces secretion of TNF- α , IFN- γ , IFN- α , IL-6, IL-1 α , IL-1 β , IL-8, IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF).^[7] FDA-approved indications include genital warts, actinic keratosis (AK), and basal cell carcinoma (BCC). Other off-label indications are cutaneous warts, molluscum contagiosum, melanoma in situ, herpes simplex,^[7] keloids,^[2] and extramammary Paget's disease.^[2] Resiquimod is an imidazoquinoline amine^[8] and a potent, soluble analog of imiquimod. Above agents with their formulations, indications, applications, and side effects are given in Table 3.

4. Miscellaneous:

- a. Zinc:

Zinc is an essential micronutrient which plays an important role in immune regulation, reproduction,

and wound healing. Important properties are as follows:

- Anti-inflammatory: It inhibits IFN- γ -induced activation of keratinocytes as well as the production of TNF- α ^[10] and IL-6.^[10]
- Antiviral properties: Its TLR-mediated action is responsible for dendritic cell regulation. It is required for normal T-cell production^[10] and Langerhans cell (LC) survival. It has been found that lower zinc levels induce apoptosis of LC. Hence, immune function is impaired in zinc-deficient states.
- Activity on melanocytes: Zinc upregulates the proliferation of melanocytes.
- Anti-pruritic activity: It inhibits mast cell degranulation and reduces the secretion of histamine.^[10]

The various formulations of zinc with their details are given in Table 4:

- b. Vitamin D analogs:

They act by binding to the vitamin D receptors on the keratinocytes, reducing the proliferation of keratinocytes and inducing differentiation. They act on activated mononuclear cells to inhibit the release of IL-6 and IFN- γ . The only FDA-approved indication is psoriasis.^[18] Off-label it has shown efficacy in morphea, vitiligo, epidermolytic hyperkeratosis, ichthyosis, porokeratosis, pityriasis rubra pilaris, prurigo nodularis, and cutaneous T-cell lymphoma.

Table 5 shows a summary of various vitamin D analogs:

Table 2: Contact allergens with their formulations, indications, applications, and safety profiles

Drug	Indication	Formulation	Application	Safety profile	Special remarks
Diphenyl cyclopropanone (DPCP)	Warts, alopecia areata	2% acetone solution for alopecia areata 1-3% acetone solution for warts	Sensitization is performed on one half of the scalp with the drug. Patients wear a wig or protective hat for 2 days to avoid contact eczema and elicitation of photoallergy in areas other than the scalp. Two weeks later, the previously sensitized scalp area is challenged weekly with increasing concentrations of the same agent (0.000001-2%), until an eczematous reaction occurs.	Side effects include localized contact eczema (erythema, blistering), spread of contact eczema to distant sites, and regional lymphadenopathy.	-
Squaric acid dibutyl ester (SADBE)	Alopecia areata, warts	2% solution in acetone	Same as above	Side effects are localized contact eczema (erythema, blistering), spread of contact eczema to distant sites, and regional lymphadenopathy	-
Dinitrochlorobenzene (DNCB)	Bowen disease, actinic keratosis, basal cell carcinoma, HIV infection, and severe atopic dermatitis. ^[3]	2% solution in acetone	Same as above	Side effects are localized contact eczema (erythema, blistering), spread of contact eczema to distant sites, regional lymphadenopathy, and mutagenicity	Positive Ames test, not used now. DNCB modulates LC function, which plays an important role in HIV infection

HIV - Human immunodeficiency virus; DPCP - Diphenylcyclopropanone; SADBE - Squaric acid dibutyl ester; DNCB - Dinitrochlorobenzene; LC - Langerhans cell

Table 3: Immunostimulators with their formulations, indications, applications, and safety profiles

Drug	Indications	Formulation	Application	Safety profile	Special remarks
Imiquimod	Genital warts* Basal cell carcinoma (<2cm)* Actinic keratosis*	3.75% cream, 5% cream, 5% cream, 2.5% cream, 3.75% cream 5% cream	Imiquimod thrice a week for 16 weeks. Once daily for 5 days a week for 6-12 weeks ^[8] Once daily at bed time for 2 weeks. Treatment free period of 2 weeks, followed by a 2 nd cycle. Application to a treatment area of approximately 25 cm ² on the face or scalp (not both simultaneously) twice weekly for 16 weeks	Generally well tolerated. Few side effects include erythema, irritation, flu-like symptoms, and pruritus	Applied to the affected area at bed time and left in place for 8 h then washed with soap and water ^[7]
Resiquimod	Herpes simplex Actinic keratosis	0.01% gel 0.01% cream 0.03% cream	Thrice a week Thrice a week for 4 weeks ^[9]	Well tolerated. Erythema, scabbing, arthralgia, myalgia, and flu-like symptoms ^[9] are some of the reported side effects.	

*FDA - Approved indications

c. Anthralin:

It causes the formation of reactive oxygen species. It causes inhibition of deoxyribonucleic acid (DNA) synthesis, repair, and replication within keratinocytes, lymphocytes, and fibroblasts and inhibits mitochondrial metabolism.^[2] Anthralin has an inhibitory effect on LC.^[19]

The only FDA-approved indication is chronic plaque psoriasis. Off-label it has shown efficacy in alopecia areata. It is available as an ointment, cream, or gel (0.1–5%). A novel lecithinized microemulsion

system composed of isopropyl myristate acetate and polyoxyethylene sorbitan oleate which contains dithranol has shown enhanced skin penetration, which enhances topical delivery of dithranol.^[19]

Application is initiated with a lower concentration such as 0.1% for 10–20 mins. The duration of treatment is increased gradually weekly until the total contact is up to 1 hour and then washed off to prevent cutaneous irritation. Side effects include irritant contact dermatitis and staining of clothes, hair, and nails.

Table 4: Various zinc formulations with their formulations, indications, applications, and safety profiles

Drug	Indications	Formulation	Application	Safety profile	Special remarks
Zinc sulfate	Herpes genitalis ^[11]	1-4% solution	Once daily	No major side effects	Prevents recurrences ^[11]
Zinc sulfate	Acne vulgaris	5% solution	Twice daily	No major side effects	By reducing <i>Propionibacterium acnes</i> -induced lipases and free fatty acid levels ^[12]
Zinc sulfate	Verruca plana ^[12]	10% solution	Thrice a week for 4 weeks	No major side effects	
Zinc sulfate	Melasma ^[11]	10% solution	Twice daily	No major side effects	Peeling and sunscreen properties ^[11]
Zinc sulfate	Bromhidrosis ^[13]	15% solution	Once daily for 2 weeks, followed by weekly for 2 months	Slight irritation reported in a few cases. No major side effects	
Zinc pyrithione	Localized plaque psoriasis ^[14]	0.25% cream	Twice daily		
Zinc pyrithione	Pityriasis versicolor	1% solution	Once daily	No major side effects	It has direct cytotoxic action on the fungus, anti-inflammatory ^[11]
Zinc oxide	Diaper dermatitis ^[11]	Paste	Once daily	No major side effects	
Zinc oxide	As a component of sunscreen and calamine ^[15]	5% gel	As needed	No major side effects	UV A1 blocker
Zinc undecylenate	Dermatophytosis ^[16]	20% powder	Twice daily	No major side effects	Reduces itching and burning sensation in addition to improvement in the lesion
Zinc + Clobetasol	Chronic eczema ^[17]	2.5% zinc + 0.05% clobetasol cream	Once daily	No major side effects	

UVA - Ultraviolet A

Table 5: Vitamin D analogs with their formulations, indications, applications, and safety profiles

Drug	Indications	Formulation	Application	Safety profile	Special remarks
Calcipotriol (synthetic analogue)	Plaque psoriasis*, ichthyosis, morphea, vitiligo, cutaneous T-cell lymphoma	50µg/g cream, ointment, solution	Twice daily	Safe in children and non-teratogenic. Adverse effects include hypercalcemia, irritation, photosensitivity, and allergic contact dermatitis	Maximum recommended dose 100g/week in adults Maximum recommended dose 50g/week in children
Calcitriol (natural bioactive form)	Psoriasis*, prurigo nodularis, morphea, vitiligo, ichthyosis, and epidermolytic hyperkeratosis	3µg/g ointment	Twice daily	Well tolerated. Hypercalcemia, irritation, photosensitivity, and allergic contact dermatitis may be observed. Not recommended in children <15 years and pregnant women	Maximum recommended dose 200g/week in adults Maximum recommended dose 100g/week in children
Tacalcitol	Psoriasis	4µg/g ointment	Once daily	Mild irritation	-
Maxacalcitol	Psoriasis	25µg/g ointment	Once daily	Slight irritation	No hypercalcemia reported

*FDA - Approved indication

d. Interferon:

Immunoregulatory action is by induction of class I & II MHC (major histocompatibility complex) antigens, increase in the number of natural killer (NK) cells, and inhibition of production of T-helper-2 (TH2) cytokines such as IL-4, IL-5, and IL-6.^[2] Topical IFN- α has been used for the treatment of herpes simplex in various studies which have shown efficacy in reducing the viral shedding and recurrences.^[20] IFN- α -2b eyedrops have been proposed for the management of BCC as an adjuvant at a dose of 1 drop of IFN- α -2b at 1 million IU/mL 4 times per day for 3 to 4 months

and 1 drop every 12 hours as maintenance therapy.^[21] No side effects have been reported with topical therapy.

Conclusion

When used judiciously and cautiously, non-steroidal immunomodulators are safe and effective alternatives in the management of dermatological diseases with a wide range of applications.

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Conflicts of interest

There are no conflicts of interest.

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