Topical immunomodulators in dermatology

Khandpur S, Sharma VK, Sumanth K

Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi - 110029, India.

Correspondence:
Sujay Khandpur, MD, DNB, MNAMS
E-mail: shaifalikhandpur@eth.net

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ABSTRACT

Topical immunomodulators are agents that regulate the local immune response of the skin. They are now emerging as the therapy of choice for several immune-mediated dermatoses such as atopic dermatitis, contact allergic dermatitis, alopecia areata, psoriasis, vitiligo, connective tissue disorders such as morphea and lupus erythematosus, disorders of keratinization and several benign and malignant skin tumours, because of their comparable efficacy, ease of application and greater safety than their systemic counterparts. They can be used on a domiciliary basis for longer periods without aggressive monitoring. In this article, we have discussed the mechanism of action, common indications and side-effects of the commonly used topical immunomodulators, excluding topical steroids. Moreover, newer agents, which are still in the experimental stages, have also been described. A MEDLINE search was undertaken using the key words "topical immunomodulators, dermatology" and related articles were also searched. In addition, a manual search for many Indian articles, which are not indexed, was also carried out. Wherever possible, the full article was reviewed. If the full article could not be traced, the abstract was used.

KEY WORDS: Topical immunomodulator, dermatological diseases

The skin is a large immune organ. It consists of keratinocytes that play a key role in immune recognition by producing a variety of cytokines. It also contains antigen-presenting cells (Langerhans cells) that communicate with immunocompetent T lymphocytes in the dermis and provide an optimum environment for the induction of immune reactivity. Several cutaneous disorders occur as a result of an imbalance in the immunological pathway.

Topical immunomodulators are molecules that modify the immune response locally when applied to the skin. They either upregulate (immunostimulation) or down regulate (immunosuppression) the immune response. They have been tried in a variety of dermatoses in which alteration in cutaneous immunology is central to their pathogenesis. They are classified into steroidal and non-steroidal immunomodulatory agents. Topical corticosteroid is the classical immuno-modulator, which by itself is a large topic. In this article however, we will focus on non-steroidal immunomodulatory agents.

Classification

Macrolactums
- Tacrolimus
- Pimecrolimus
- Sirolimus
- ABT-281
- Cyclosporin

Contact allergens
- Diphencyprone or Diphenylcyclopropenone (DPC)
- Squaric acid dibutyl ester (SADBE)
- Dinitrochlorobenzene (DNCB)

Immunostimulators
- Imiquimod
- Resiquimod

Miscellaneous agents
- Calcipotriol
- Anthralin
- Topical Zinc
- Topical interferon
- Intralesional interferon
- Intralesional BCG

Macrolactum Immunomodulators

Topical tacrolimus (FK 506)

It is a macrolide, produced by *Streptomyces tsukabaensis*, a fungus found in the soil of Mount Tsukuba, the science city of Japan, where initial isolation and characterization of this drug was performed. The name of the drug is a neologism, composed of **t**sukuba, m**acrol**ide and **immu**nosuppression.

Tacrolimus (TAC) has been used both intravenously and orally for the prevention of organ rejection after allogenic kidney, liver or bone marrow transplantation. It exerts efficacy topically in many immune-mediated dermatoses as well. It penetrates the cutaneous barrier to a much greater extent

than cyclosporine, but is not metabolized locally in the skin. It is only minimally absorbed, with 0.5% of the locally applied drug detected in blood, which is undetectable or subtherapeutic.

Mechanism of Action

TAC inhibits the maturation and activation of T-cells and blocks transcriptional activation of several lymphokine genes by binding to cytosolic proteins known as macrophilins.[1] This complex blocks calcineurin, inhibits transcription of the nuclear factor of activated T cells (NF-AT)-dependent genes thus preventing interleukin- (IL) 2, 4 and 5 production, downregulates IL-8 receptors on the keratinocytes and alters the expression of functionally relevant surface molecules on Langerhans cells.

Topical uses

Atopic dermatitis (AD): Topical TAC ointment (0.3%, 0.1%, 0.03%), applied twice daily, is safe and effective in both childhood and adult cases of AD over a period of 1 year. Nakagawa et al[2] in an open-label trial, reported successful use of all the three concentrations with twice daily application for up to three weeks. Another double-blind randomised placebo-controlled trial undertaken on 215 patients of moderate to severe AD using 0.03%, 0.1% and 0.3% strengths or vehicle applied to a defined area of 200 and 1000 cm^2 for three weeks, with the study endpoint being change in summary score for erythema, oedema and pruritus, showed a median percentage decrease in summary score of 75% for patients receiving 0.3% TAC, 83.3% with 0.1% ointment and 66.7% with 0.03% TAC as compared to 22.5% for patients receiving vehicle alone.[3] Significant improvement in Dermatology Life Quality Index (DLQI) has been observed in the adults, children, and toddlers using either 0.03% or 0.1% ointment.[4] Controlled studies have also shown better to equal results on comparing with mid-potency topical steroid (0.12% betamethasone valerate ointment).[5]

Psoriasis: Topical TAC has shown encouraging results in inverse psoriasis because of the enhanced local penetration in occluded intertriginous areas and in psoriasis involving the face.[6] It has been found ineffective in chronic plaque psoriasis involving the trunk and extremities, due to its inability to penetrate the thick hyperkeratotic lesions. However, the lesions improved after descaling and application under occlusion, suggesting that optimisation of application is crucial in psoriasis.

Alopecia areata: The application of topical TAC in the Dundee experimental bald rat model and in C3H/HeJ mice was able to induce hair regrowth.[7] However, it failed to produce hair growth in a human patient when used alone or in combination with a high potency steroid.[8]

Pyoderma gangrenosum: TAC inhibits neutrophil chemotaxis by suppressing granulocyte-macrophage colony stimulating factor and IL-8. Topical TAC, 0.3%, in carmellose sodium paste, led to complete healing within 8 weeks in 5 patients.[9]

Lichen planus: 0.1% ointment led to rapid resolution of erosive mucosal LP in 3 of 6 patients after 4 weeks of twice daily application and beneficial effect was seen in all the cases.[10]

Graft versus host disease: In a series of 18 patients, 70% cases had rapid alleviation of erythema and pruritus on applying 0.1% ointment, although they additionally required systemic photochemotherapy to achieve complete remission.[11]

Allergic contact dermatitis: Dinitrobenzene-induced allergic contact dermatitis can be prevented by pretreatment with TAC. In 5 patients pretreated with 0.3%, 0.1% and 1.0% ointment, and a fourth area left untreated prior to contact sensitization with DNCB, there was no histological evidence of inflammation in the TAC-treated skin while the control area developed significant inflammation.[12]

Rosacea: Goldman demonstrated complete resolution of erythema in 3 cases of steroid-induced rosacea after 7 to 10 days of 0.075% ointment application.[13]

Cutaneous lupus erythematosus and dermatomyositis: Topical TAC has been used effectively to treat erythematous facial lesions of SLE and dermatomyositis.[14] Of the 11 patients, 6 cases (3 SLE, one DLE and 2 dermatomyositis) showed marked regression of skin lesions with significant improvement in oedema and telangiectasia.

There are reports of its successful use in ichthyosis linearis circumflexa and recalcitrant leg ulcers associated with rheumatoid arthritis and in seborrheic dermatitis, dyshidrotic eczema, hand eczema and vitiligo.[15,16]

Adverse effects: Transient burning or heat sensation at the site of application is frequently observed. It tends to decrease after repeated applications. Other side-effects include skin erythema, flu-like symptoms, headache and skin infection.[17] It does not cause skin atrophy despite prolonged application.
Available in India as Tacroz (0.03%), Rs.160/- and Tacroz forte (0.1%) ointment, Rs. 405/-, 5gm, Gracewell, Tacrovate (0.03%), Rs.160/- and Tacrovate forte (0.1%), Rs. 405/-, 5 gm, Ochoa Laboratories.

Liposomal tacrolimus (LTAC)

Liposomal drug delivery may increase penetration of skin and allow slow release of active compound locally with diminished toxicity. The effect of LTAC on Balb/C skin graft survival and on ovalbumin-induced delayed type hypersensitivity reaction in C57 BL/6 mice has been tested.[18] Topical application of LTAC achieved nine times more concentration of the drug at the target site than systemic TAC. The combination of systemic and topical LTAC significantly increased mean skin graft survival compared with systemic TAC. The authors opined that topical LTAC may also be a more effective delivery system than systemic TAC for the treatment of psoriasis.

Pimecrolimus (ASM-981)

It is a semi-synthetic product of ascomycin, which is a fermentation product of *Streptomyces hygroscopicus* var *ascomycetes*.

Similar to TAC, pimecrolimus interacts with macrophilin-12 and inhibits T-cell stimulation by antigen presenting cells, blocking both T helper cell 1 (Th1) cytokines such as IL-2 and interferon (IFN)-γ and T helper cell 2 (Th2) cytokines including IL-4 and IL-10.[1] It also inhibits mast cell release of hexosaminidase, tryptase and histamine.

Topical uses

Atopic dermatitis: Pimecrolmus 1% ointment, applied twice daily, was found superior to placebo with no adverse effects in 34 cases of mild to moderate AD.[19] In another double-blind randomised trial involving 260 cases, 0.2%, 0.6% and 1% cream was found more effective than the vehicle or betamethasone-17-valerate 0.1% cream.[20]

Psoriasis: In a randomised, double-blind, within-subject comparison in 10 patients for 2 weeks using microplaque assay, 0.3% and 1% ointments under occlusion, were shown to have comparable efficacy to clobetasol-17-propionate ointment (0.05%).[21]

Allergic contact dermatitis: In a multicentric study on 66 nickel-induced allergic contact dermatitis patients, ASM 981 cream was found to be significantly superior to placebo.[22]

Adverse effect includes mild burning sensation. It does not produce skin atrophy or dermal thinning.

Sirolimus

Sirolimus, formerly called rapamycin, is another macrolactum immunomodulator, with molecular weight of 914 Da. Like tacrolimus, it binds to macrophilin-12. The target structures of the sirolimus-macrophilin-12 complex are a group of proteins named mammalian targets of rapamycin or sirolimus effector proteins. Sirolimus also inactivates the cell cycle at the G1 to S phase.[23]

Topical uses

So far, no clinical data on humans is available. In animal skin allergic contact dermatitis models, both 1.2% and 2% concentrations in ointment base have not been found effective.[23]

ABT- 281

It is a potent inhibitor of production of both Th1 and Th2 cytokines. It has shown potent topical activity in swine model of allergic contact hypersensitivity.[24]

Topical cyclosporine

Cyclosporine A (CyA), isolated from the fungus *Tolypocladium inflatum gams*, is a lipophilic cyclic polypeptide and a calcineurin inhibitor. Although it has poor skin penetration due to high molecular weight (1202.635 Da), it has been tried in many dermatoses.

Psoriasis: It has not yielded satisfactory results in psoriasis, despite its use in various concentrations (1%, 5%, 10%), as gel or ointment, under occlusion or in combination with penetration enhancers like 18% propylene glycol and 2% laurocapram.[25-27]

Alopecia areata: Topical CyA has been used with little efficacy in alopecia areata. In an open trial in 10 patients of alopecia areata and universalis, 10% CyA as oily preparation, produced no beneficial response after 12 months of therapy.[28] In another placebo-controlled study, a 10% oily solution also did not produce cosmetically acceptable results after 6 months of therapy although small tufts of terminal hair grew in 33% cases.[29] Liposomal preparation is being developed for use in alopecia areata.

Oral lichen planus: Its beneficial effect in erosive LP was first reported in 1988 and confirmed by a double-blind study 2 years later.[30,31] Subsequently, inconsistent response with success rates of 37-80% has been reported for both oral and vulvar LP in both open- and placebo-controlled trials, probably due to differences in the dosage and modes of application of the drug (oral rinse better than oily solution).[31,32]

Oral pemphigus: A 63-year-old woman with debilitating oral pemphigus not responding to systemic immunosuppressives and topical steroids, improved considerably in 6 months by using CyA as a 5-minute mouthwash three times a day (5ml of 100mg/ml).[33] Prolonged once a day treatment was effective in maintaining remission. In another study, of 3 patients, 2 cases improved with thrice daily mouthwashes prescribed for 8 weeks, although they required both prednisolone and a third agent to control the disease.[34]

Behcet's disease: In a randomised placebo-controlled trial, CyA, 70 mg/g orabase, was not found effective in treating recurrent oral aphthous ulcers in Behcet's syndrome.[35]

Pyoderma gangrenosum: In a case report, complete healing of large recalcitrant PG ulcers over the shins could be achieved in 7 months by adding topical CyA to oral azathioprine and triamcinolone acetonide injections.[36]

Benign Familial Pemphigus of Hailey-Hailey: Topical CyA (Sandimune oral solution, Sandoz Pharmaceuticals) was found significantly more effective than potent topical steroid in two cases, with complete reepithelization of erosions after 2 months.[37]

Contact Allergens

Diphencyprone or Diphenylcyclopropenone (DPC)

It has been widely used topically for the treatment of alopecia areata and common warts since 1980.

Mechanism of action

In alopecia areata: It is based on 'antigenic competition' theory, which proposes that immune reaction to one antigen may inhibit the development of immune response to other antigens. In untreated disease, the peribulbar infiltrate consists of predominantly CD4+ T cells, with a CD4:CD8 ratio of approximately 4:1. On treatment with DPC, this ratio changes to 1:1, reflecting a relative increase in peribulbar CD8+ T cells. It is possible that suppressor T cells may non-specifically in-

hibit immune reaction to an unidentified hair-associated antigen, which is assumed to be the main target in the pathogenesis of alopecia areata. DPC also reduces the abnormal expression of human leucocyte antigens (HLA)-A, B, C and -DR in the epithelium of hair follicles.

In Warts: The mechanism of action is not clear. It triggers a non-specific cell-mediated immune response, triggering virus-infected cell lysis and death.

Topical uses

Alopecia areata: The treatment protocol has been published in several studies.[38-40] Most patients studied have been those with alopecia totalis, universalis, or severe alopecia areata.

Mode of application: Patients are sensitised by applying 2% solution in acetone to a 5 x 5 cm area of the scalp with a cotton swab. Often, an eczematous response is seen 5 to 7 days after initial sensitisation. Elicitation of allergic contact dermatitis can begin as early as 2 weeks after sensitisation. It is important to perform elicitation on one side of the scalp, or on one half of a hairless patch, to rule out a possible spontaneous remission. DPC is applied weekly, using the lowest concentration (eg.0.0000001%, 0.000001%, 0.00001%, 0.0001%, 0.001%, 0.01%, 0.05% 0.1%, 0.5% 1%, or 2%) that maintains erythema, itching and scaling for 2 to 3 days. In a few patients, even a 2% concentration does not produce eczema, and a second or third application with the 2% solution is then necessary. To prevent photolysis, the patient's head should be covered with a hairpiece or scarf for at least 6 hours, but preferably for 48 hours after DPC is washed off. In successful cases, vellus hair usually appears within 8 to 12 weeks, and this becomes thicker and darker with continued treatment over 4-17 months. When unilateral regrowth is noted, DPC should be applied to the entire scalp. Treatment failure is considered if no regrowth occurs after 20 weeks. Treatment is stopped after 30 weeks of uninterrupted treatment after the first successful elicitation, since a good response later is unlikely.

Eyebrows should be treated with extreme caution with a concentration one-tenth of that used for the scalp. Eyelashes should not be treated.

In several open- and placebo-controlled trials, the reported response rates from India and abroad have varied from 6%-85% with a realistic estimate of 50%-60%.[38-41] In a retrospective analysis of the largest cohort of patients reported so far, 77.9% cases developed significant response (>75% terminal hair regrowth) at 32 months, with significant regrowth observed in 17.4% cases of alopecia totalis and universalis, in 60.3% cases of alopecia involving 75-99% scalp area, in 88% cases with 50-74% involvement and in 100% cases with <50% involvement.[42] Long-term follow-up data have shown that the median time to relapse (defined as loss of >25% of regrown hair) is 30.7 months.[42,43] The risk of relapse is unrelated to the extent of alopecia before treatment.

Warts: 0.1% to 3% DPC solution in acetone is used for the treatment of common warts.[44] The patient is sensitised on the arm with 2% DPC, which is occluded for 48 hours. Once the initial sensitisation reaction has settled, it is applied to the wart with increasing concentration until a reaction is elicited. The patients then continue at this dose until clearance. With this therapy, the clearance rate has been shown to vary from 8%-88%.

Buckley and associates used DPC 0.1% for digital warts and 2% for plantar warts with clearance of all lesions in 85% patients after a mean of 5 treatments (range 1 to 22), with median clearance time being 5 months (range 0.5 to 14 months).[44]

Metastatic melanoma: A 76-year-old woman with 400 cutaneous lesions of metastatic melanoma and considered too old for aggressive surgical or medical therapy, was successfully treated with oral cimetidine and DPC.[45] After 66 weeks, there was 'complete histological resolution'. The remission persisted for 70 weeks without evidence of distal spread.

Adverse effects include regional lymphadenopathy, eczema at treated site and impaired sleep.[46] The less common adverse effects are fever and chills, fainting spells and flu-like symptoms. Rarely, contact leucoderma, erythema multiforme, urticaria and contact urticaria occur. It is not mutagenic, teratogenic and has no organ toxicity. It is undetected in serum or urine despite 0.5ml of 1% DPC solution in acetone application to the scalp.

Tolerance i.e. the acquired inability to provoke an eczematous challenge reaction despite initial successful sensitisation, develops in 10-12% cases after an interval of 7-18 months.[39] This necessitates switching over to SADBE if further treatment is required.

Caution: Female patients of child-bearing age should have a negative pregnancy test before starting DPC and should use reliable contraception throughout the treatment period.[46] Many centres do not recommend its use in children <15 years of age due to lack of long-term toxicity data.

Available internationally @ $87.20 for 5 gm.

Squaric acid Dibutyl Ester (SADBE)

Mechanism of action: It is similar to DPC. However, long-term treatment of alopecia areata potentially leads to significant non-specific suppression of delayed hypersensitivity reaction.[47]

Topical uses

Alopecia areata: The treatment protocol is identical to DPC. In a study involving 129 patients, complete regrowth occurred in 81 patients (63%).[47] Of the 13 alopecia totalis patients, 11 experienced regrowth, while of two alopecia universalis patients, regrowth occurred in one case. However, in another series of 17 patients (11 with alopecia areata and 6 with alopecia totalis), terminal hair growth was not detected in any patient after one month, and in only 3 of 6 cases after 3 months of therapy.[48]

In some patients, regrowth occurs at sites distant from the site of SADBE application or denser and faster growth is observed over untreated sites.[49] This is termed 'castling phenomenon'. The mechanism is unclear, but a systemic effect of localized application has been proposed. It has also been observed in 1-2% cases after DPC treatment.[38]

Warts: Of the 20 subjects (14 with plantar warts, 4 with periungual warts and one each with warts on the hand and leg) treated with 0.1% or 0.01% solution once weekly or every other week to maintain mild contact dermatitis, lesions resolved in 12 patients after an average of 6 applications (range 2 to 12).[50]

Adverse effects are similar to DPC. Like DPC it is not mutagenic. It is not as stable in acetone as DPC and requires refrigeration.

Available internationally @ $149.50 for 5 gm.

Dinitrochlorobenzene (DNCB)

DNCB was the first topical sensitizer to be extensively studied for the treatment of alopecia areata and warts. It contains contaminants that are mutagenic and carcinogenic to animals. When applied locally, more than 40% of the drug is absorbed systemically. DPC and SADBE have now largely replaced DNCB.

Topical uses:
Alopecia areata and warts: Cure rates of up to 80% have been seen in warts.[51] However, in various placebo-controlled Indian studies, DNCB was not found to be superior to placebo in both alopecia areata and condyloma acuminata.[52-54]

Skin cancers: The mechanism of action is not clear. It is possible that the sensitising agent acts as a hapten and interacts with weak tumour antigens that by themselves are not sufficiently immunogenic to evoke an effective immune response. It has been used in Bowen's disease, BCC and actinic keratoses.
Melanoma: In a 71-year-old woman with acral lentiginous melanoma of the heel who was unsuitable for surgical treatment, continued application of DNCB led to disappearance of the lesion.[55]

HIV infection: Since DNCB modulates Langerhans cell function, which plays an important role in HIV infection, investigators have studied its use in this condition.[56,57] In a controlled trial from Brazil, the treatment was associated with improved immune function and decreased viral load.[56] However, more sensitive studies are required to better define this role.

Atopic dermatitis: In an open trial involving 9 patients, DNCB treatment led to a significant decrease in the total body surface area of the involved skin.[58]

DNCB has also been successfully used in isolated cases of SLE, lichen nitidus and chronic nodular prurigo.[59-61]

Adverse effects are similar to DPC.

Immunostimulators

Imiquimod

It is a synthetic molecule, which enhances both innate and acquired immune response, in particular, cell-mediated immune pathways, by stimulating monocytes and macrophages via binding to cell surface receptors, like Toll receptor 7, to produce several specific cytokines including IFN-α, IL-1, 6, 8, 10, 12 and tumour necrosis factor (TNF)-α, resulting in local antiviral, antitumour and immunoregulatory activity. It also stimulates natural killer and B cells and enhances migration of Langerhans cells.

Topical uses:
Warts: Imiquimod is a recommended safe and effective treatment.

Anogenital warts: In a randomised vehicle-controlled trial, anogenital warts treated with thrice weekly application of 5% imiquimod cream for 16 weeks, showed complete clearance in 50% patients.[62] Recurrences with this therapy are lower than with ablative modalities.

Common warts: In an open-labelled trial, 5% imiquimod cream applied once a day for 5 days per week for up to 16 weeks showed over 50% reduction in size to complete clearance in 56% patients.[63] The response was better for warts located on the trunk, face or hands as compared to those on the feet.

Keloids: It increases local levels of IFN-α which enhances keloidal collagenase activity, reduces keloidal fibroblast synthesis of collagen, reduces glycosaminoglycan synthesis and induces apoptosis, hence produces an antifibrotic and antikeloidal effect.[64] In an open trial on 12 patients, once daily treatment for 8 weeks was found to be safe and effective in minimizing keloidal recurrences following surgical excision.[65]

Molluscum contagiosum: Once daily application for 6-8 weeks was found effective in an open trial.[63]

Actinic keratosis: In 6 cases, the lesions resolved with thrice weekly treatment for 6 to 8 weeks, probably due to an increase in immune status and infiltration of CD4 lymphocytes. [66]

Bowen's disease: Complete resolution of lesions with no recurrences was achieved with once daily application for 6 weeks in an open-labelled study in 16 cases of biopsy-proven Bowen's disease.[67]
Lentigo maligna: It is considered a good treatment option for patients unwilling to undergo surgery. In a case report, complete clinical and histological resolution was observed with once daily application for 7 months with over 9 months of disease-free period.[68]

Extra mammary paget's disease: Once daily application for 14

weeks has been found useful in 2 recalcitrant cases.[69]

Basal Cell Carcinoma (BCC)

Once daily application of 5% imiquimod cream shows promising efficacy and reasonable safety. Imiquimod mimics the action of the body's natural immune response against BCC, which has been studied in spontaneously regressing lesions. In those lesions, cytokines such as IFN-γ are detectable, and act to increase the infiltration of CD4+ lymphocytes into the stroma and tumour islands.

Superficial BCC: In a double-blind study, patients were randomised into 12 weeks of one of four dosing regimens; twice daily, once daily, 5 days a week and 3 days a week application.[70] The clearance rate (87%) was highest in the once daily treated group. Clinical clearance of the tumour assessed by visual and tactile examination corroborated with histological clearance.

Nodular BCC: In an Australian study, of the 99 subjects of nodular BCC (face 33%, limbs 35%, and trunk 31%) treated for 6 weeks, 71% cases showed complete clearance with once daily application.[71]

Bowenoid papulosis (BP): A 38-year-old woman with podophylin-resistant BP was treated with 5% imiquimod cream on alternate days until the skin became visibly irritated, then once daily for 10 days, resulting in complete clinical and histological clearance.[72]

Adverse effects: It causes local skin reactions such as eythema, erosions and excoriation or flaking.

Available internationally as Aldara™, 5% cream, 250mg, 3M Pharmaceuticals, $219 for 12 packets.

Resiquimod

It is a more potent and soluble analogue of imiquimod.[73] Like imiquimod, it stimulates Th1 cell-mediated immune response and is found to be active against genital herpes in the guinea pig model. It has been successfully tried in recurrent genital herpes simplex infection.

Miscellaneous Agents

Topical calcipotriol

Calcipotriol is a synthetic vitamin D_3 (cholecalciferol) analogue, developed by modification of the side chain to enhance the antipsoriatic effect of vitamin D_3 and ameliorate its hypercalcemic action.

It performs anti-psoriatic action by binding to vitamin D receptors (VDR) present on the keratinocytes, and by inhibiting cellular proliferation and inducing cellular differentiation.[74] Various studies have demonstrated its potential use in several other dermatoses by its immunomodulatory effect.[75] It acts on monocytes, macrophages, B and T lymphocytes to inhibit thymocyte proliferation induced by IL-1 and the release of IL-6 and IFN-γ from activated mononuclear cells. It reduces the number of infiltrating neutrophils and causes progressive reduction in dermal cellular infiltrate with a shift from CD4+ helper cells to CD8+ suppressor cells.

Topical calcipotriol is available as 50ug/g ointment, cream and solution internationally, and in India, as cream form.

Indications

Psoriasis: It has been used to treat mild to moderate plaque psoriasis either alone or as an adjuvant to dithranol, topical steroids and phototherapy, as twice daily application with maximum weekly application of 100g in adults and 50g in children.[76] Significant improvement occurs after 6 weeks.

Vitiligo: Investigators have demonstrated the presence of VDR on melanocytes and have suggested that calcipotriol may regulate melanin synthesis.[77] Research has also revealed defective calcium homeostasis in melanocytes and keratinocytes in the depigmented skin, which is reversed with calcipotriol therapy. In a randomised, double-blind, right/left comparative study, combination therapy with PUVA produced marked improvement with faster repigmentation.[77]

Miscellaneous disorders: Both, case reports and large controlled trials have demonstrated its usefulness in keratinisation disorders including juvenile and adult-onset pityriasis rubra pilaris, inflammatory linear verrucous epidermal nevus, ichthyosis vulgaris, epidermolytic hyperkeratosis, lamellar ichthyosis, Sjogren-Larsson syndrome, ichthyosis linearis circumflexa, X-linked ichthyosis, hereditary palmoplantar keratoderma, acanthosis nigricans, keratosis pilaris and Darier's disease, with twice daily application for 1-4 months.[78-81]

It has been successfully used in morphea (open-label study), prurigo nodularis (randomized double-blind trial), lichen amyloidosis (double-blind pilot study), lichen sclerosis-et-atrophicans, recalcitrant Grover's disease, confluent and reticulate papillomatosis and keratosis lichenoides chronica (case reports).[82-87]

Side-effects: Topical calcipotriol causes skin irritation and rarely hypercalcemia after excessive or prolonged application in patients with concomitant renal impairment. It not recommended to patients with atopic dermatitis, neurodermatitis or nummular eczema.[75] It requires a relatively high pH for stability and should therefore not be mixed with other agents.

Advantages: It does not induce skin atrophy or photosensitization, is well tolerated in children and is not teratogenic. If a patient conceives during therapy, the drug should be stopped. However, elective abortion is not indicated.

Available in India as Daivonex, 50mg/g (0.005%) ointment, 30 gm, Rs. 860/-, Croslands.

Anthralin

It was originally used in 1876 in its natural form, chrysarobin,

obtained from the South American 'Araroba' tree. The first synthetic antipsoriatic preparation, anthralin, was developed in Germany in 1916 as a 0.05%-0.1% formulation in acetone or salicylic acid and liquor carbonis detergens. It is being used in the treatment of plaque psoriasis and alopecia areata because of its antimitotic, irritant and immunomodulatory properties.[88]

Mechanism of action: It exerts an antimitotic effect by inhibiting DNA synthesis, repair and replication within keratinocytes, lymphocytes and fibroblasts, inhibits nicotinamide adenine dinucleotide-dependent isocitrate dehydrogenase enzyme which is responsible for mitochondrial respiratory burst activity, reduces polyamine biosynthesis by inhibiting ornithine decarboxylase and decreases cGMP level to normal in psoriatic skin.[88]

In alopecia areata, it has been shown to elicit regrowth both as a result of its irritant property and due to a non-specific immunomodulatory action. [89]

Topical uses

Psoriasis: Anthralin is an effective therapeutic option for limited plaque psoriasis.[88] Since the development of Ingram's regimen in the 1930s, much effort has been expended in devising schedules that maximize efficacy and patient compliance but reduce the side-effects.[90] Various regimens including short contact therapy and 'minutes' therapy, use of low concentration anthralin (0.01-0.05%) and combination with topical steroids have been tried.[91] In the short contact regimen, 1%-3% anthralin ointment applied for 10-20 minutes or 0.1-1% ointment applied for 3 hours has shown encouraging results.

Alopecia areata: In an open-label trial in 66 patients, 1% cream applied daily at night, with initial contact time of 30 minutes and increased to tolerance, was shown to produce hair growth after 3 months and good cosmetic response after a mean of 6 months in 25% cases.[89] Fiedler et al[92] observed good cosmetic response in 11% of recalcitrant cases after 24 weeks of combination regimen of 0.5% anthralin cream applied at night and 5% minoxidil applied twice daily.

Zinc pyrithione shampoo is used to wash out the agent. Patients are cautioned to wash their hands after applying the cream and to protect the treated skin against sun exposure.

Side-effects: It can produce irritant and allergic contact dermatitis and staining of skin and clothes. It has been shown to precipitate bullous pemphigoid in psoriasis patients.[88]

Available in India as ointment (30 gm, Rs.31.50).

Topical Zinc

In a double-blind randomised controlled study on 291 cases of subacute and chronic eczema, lichen planus and limited psoriasis, topical zinc sulphate 2.5% in combination with 0.05% clobetasol propionate cream (Zincoderm cream, Apex laboratories) was found superior to topical steroid used alone, due to the antiinflammatory property of zinc sulphate to prevent release of keratinocyte-associated markers of inflammation.[93] It also causes re-epithelialization of partial thickness wounds and second degree burns in animal (domestic pig) models. Once daily application of zinc oxide cream (0.3 mg Zn/cm^2 or 17 mg/g) in polyvinyl pyrrolidone over 12 full thickness cutaneous wounds made on anaesthetized pigs, led to granulation tissue formation up to the level of surrounding normal skin by Day 11, which was significantly better than placebo-treated (polyvinyl pyrrolidone only) wounds.[94]

Topical Interferon (IFN)

It has been used in recurrent genital herpes simplex infection. In a double-blind placebo-controlled analysis, treatment with 10^5 IU/gm of IFN-α in hydrophilic ointment containing dimethyl sulfoxide led to rapid cessation of viral shedding when compared to placebo (66% culture negativity on Day 1 vs. 25% in placebo group; $P< 0.02$).[95] In the 90 days post-treatment period, IFN-treated cases had fewer recurrences than the placebo-treated counterparts (1.18 vs. 2.25) This reduction, while not statistically significant $(P<0.1)$ was encouraging. In actinic keratosis, in a placebo-controlled trial, topical IFN-α2b gel (30 x 10^6 IU/g) applied four times a day for 4 weeks did not show significantly better results.[96]

Intralesional interferon

IFN-α2b (5 x 10^5 IU/dose - 1.5 x 10^6 IU/dose) and recombinant IFNβ-1a (1.0 x 10^6 IU) administered intralesionally three times a week has been effectively used in cases of lentigo maligna, cutaneous leishmaniasis, condyloma accuminata, verruca plana, actinic keratoses, squamous and basal cell carcinoma, keloids and hypertrophic scars, recalcitrant plaques of DLE and 'alarming' hemangiomas, defined as lesions that compromise a patient's life or the functions of vital organs.[97-102]

Intralesional Bacillus Calmette-Guerin

A pooled analysis of the efficacy of intralesional Bacillus Calmette-Guerin(BCG) immunotherapy in malignant melanoma showed complete responses in 19% cases, partial responses in 26% and extended survival in 13% of patients with Stage III melanoma (metastatic disease).[103]

Topical immunomodulator therapy is emerging as the treatment of choice for several immune-mediated dermatoses. It carries the advantage of lesser side-effects than systemic agents, with equal to higher efficacy, provided the drug is dispensed in an appropriate vehicle. Further controlled studies are required to ascertain the optimal dosage, concentration, vehicle and duration of therapy of these agents, which would provide maximum therapeutic benefit.

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