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Off-Label Uses of Topical Calcineurin Inhibitors

Eric Wong, MD and Anil Kurian, MD

Division of Dermatology & Cutaneous Sciences, Department of Medicine, University of Alberta, Edmonton, AB, Canada

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ABSTRACT

Topical calcineurin inhibitors (TCIs) have been proposed as an alternative, long-term treatment option to topical corticosteroids, without the side effects commonly associated with steroid use. Currently, TCIs are only approved for treatment of atopic dermatitis in patients 2 years of age or older. This article reviews the off-label uses of TCIs and their efficacy in the treatment of cutaneous diseases. Studies show that TCIs may be effective in treating/managing a variety of skin conditions. The strongest evidence based support on clinical outcomes has been reported for allergic contact dermatitis, lichen planus, psoriasis, seborrheic dermatitis and vitiligo.

Key Words: immunosuppressive agents, off-label use, pimecrolimus, tacrolimus, topical calcineurin

Introduction

The potential side effects of long-term topical corticosteroid use have propelled the need for an alternative treatment option. Topical calcineurin inhibitors (TCIs) have been proposed as a potential substitution. There are two common topical drug forms available: tacrolimus 0.03% or 0.1% ointment and pimecrolimus 1% cream. Currently, the use of tacrolimus in Canada has been indicated for treatment of patients with moderate to severe atopic dermatitis in those 2 years of age or older. TCIs work by inhibiting the protein, calcineurin phosphatase, thus reducing cytokine production and T-cell activation. Their mechanism of action is attributed to immunomodulatory and anti-inflammatory properties. These medications have been thought of as a potential and viable alternative due to their mild cutaneous and minimal systemic side effects. Moreover, patient compliance may be enhanced as these are steroid sparing agents. In this article, we will discuss the off-label uses of TCIs with the greatest support.^{1,2}

Discussion

Allergic Contact Dermatitis

Allergic contact dermatitis (ACD), an often debilitating condition, can affect many individuals professionally, as well as personally. Varied results in the

many individuals professionally, as well as personally. varied results in the management of ACD with TCIs have been reported.

Bhardwaj et al. in 2007 showed in a double-blind study of 21 patients, who patch tested positive to 5% nickel sulfate, that there was no difference in treatment efficacy when comparing tacrolimus 0.1% ointment, pimecrolimus 1% cream, clobetasol propionate 0.05% ointment, and triamcinolone acetonide 0.1% ointment, but all treatments were noted to be better than the placebo in the treatment of nickel-induced ACD.³ Other cases and studies have reported favorable findings in regards to the efficacy of tacrolimus in the treatment of ACD.⁴ In a randomized, double-blind, vehicle-controlled study of 67 patients with chronic allergic dermatitis, tacrolimus ointment 0.1% was more effective and better tolerated than placebo.⁵ A double-blind study of 28 volunteers by Alomar et al. in 2003 showed that tacrolimus 0.1% under occlusion was equally as effective as mometasone furoate 0.1% with a greater decrease of erythema seen in the TCI group. Both treatments were significantly better than placebo in the patients with nickel induced ACD.⁶ These findings suggest that tacrolimus may be beneficial for the treatment of ACD.

Very few studies have shown evidence for pimecrolimus in the management of ACD.⁷ Therefore, further research of pimecrolimus is required for the treatment of ACD to determine whether it can be used as a substitute for steroids.

Cutaneous Lupus Erythematosus

A randomized, double-blind study of 18 patients with cutaneous lupus erythematosus (CLE) involving the face (malar rash, discoid lesions, and subacute cutaneous LE) showed tacrolimus 0.1% ointment was as safe and effective as clobetasol propionate 0.05% cream.⁸ Another double-blind study demonstrated that pimecrolimus 1% cream was comparable with betamethasone valerate 0.1% cream in discoid lupus.⁹ However, further research is warranted to determine if TCIs can be recommended as a potential therapeutic option for cutaneous lesions of lupus.

Lichen Planus

An idiopathic inflammatory disease, lichen planus (LP) is characterized by pruritic, violaceous papules on the skin, scalp, nails and mucous membranes. TCIs have been commonly studied in the treatment and efficacy of oral lichen planus (OLP). Multiple studies have shown significantly better results with the use of tacrolimus 0.1% ointment when compared to clobetasol propionate 0.05%, with one study reporting greater than 94% of patients with complete or partial resolution of OLP. In a randomized, prospective study in 2006, Laejendecker et al. compared the efficacy of tacrolimus 0.1% against triamcinolone acetonide 0.1% ointment in 40 patients with OLP. Although tacrolimus induced a better initial clinical response, relapses were common in both groups.¹²

Although less studied, pimecrolimus alone or combined with triamcinolone acetonide 0.1% paste demonstrated improvement from baseline compared to placebo in the treatment of OLP. This double-blind study showed substantial improvement in both treatments but no significant difference in efficacy between them.¹³ These results indicate that TCIs can be a suitable option for the treatment of LP, especially the oral type.

Lichen Sclerosus

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Lichen sclerosus (LS) is a chronic skin disorder of unknown etiology, characterized by pruritus, thickened white plaques, and scarring usually on or around the genital regions. High potency topical corticosteroids are generally considered the treatment of choice for LS.

Hengge et al. in 2006 found that of 84 LS patients who were treated with tacrolimus 0.1%, 43% exhibited clearance of active lesions at 24 weeks of treatment.¹⁴ Favorable results were mainly seen in patients with anogenital LS, but also extragenital. However, more research into the efficacy of pimecrolimus for LS is needed as little evidence and mixed results have been reported.^{15,16}

It is important to note that LS may be associated with the development of cutaneous squamous cell carcinomas and, therefore, examination to exclude a neoplasia is required prior to treatment with TCI.

Psoriasis

Psoriasis is a common skin condition, affecting approximately 2% of the world's population. This disease is a T-cell mediated inflammatory skin condition leading to epidermal hyperproliferation and differentiation.¹⁷ Current treatment options, including corticosteroids, vitamin D3 analogs, light therapy and coal tar, can be bothersome and uncomfortable.

A double-blind study of 167 patients found tacrolimus 0.1% ointment to be superior on the face and intertriginous areas compared to placebo, with clinical improvement seen as early as 8 days after treatment initiation.^{18M} Ortonne et al. also found that topical tacrolimus 0.3% gel and 0.5% cream were just as effective and safe as calcipotriol 0.05% ointment after 12 weeks in an open-label, randomized study of 124 patients with plaque psoriasis.¹⁹ Additionally, in 2007 Liao et al. showed that for facial/ genital-femoral psoriasis, tacrolimus 0.3% mg/g ointment was clinically superior to calcitriol 3 µg/g in 50 patients as measured by reduction of Target Area Score (TAS) and Physician's Global Assessment (PGA).²⁰ Multiple studies have shown tacrolimus is generally well tolerated and efficacious in psoriasis, particularly in the facial, inverse and genital regions. As topical steroids must be used cautiously in these sensitive skin areas, due to increased risk of cutaneous adverse events, treatment with TCIs offers a beneficial alternative that is not associated with skin atrophy.²¹⁻²⁶

In contrast, pimecrolimus was found to have better efficacy than placebo but demonstrated mixed results when compared to calcipotriol and corticosteroids in the treatment of inverse psoriasis.^{27,28} Limited cases have shown inconsistent findings with TCIs in the treatment of various subtypes of psoriasis, including acrodermatitis continua of Hallopeau, generalized pustular psoriasis, and palmar and plantar psoriasis.^{29,30}

Generally, tacrolimus appears to be a viable and valuable alternative in the treatment of psoriasis and can be particularly effective in the inverse type, but further studies are required to determine whether pimecrolimus is a better treatment option than current standard medications.

Rosacea

A study by Bamford et al. in 2004 of 24 patients with rosacea who were treated with 0.1% tacrolimus twice daily showed improvement in erythema after the 12-week study, however, therapy did not reduce papulopustular

signs.³¹ Others studies have shown that tacrolimus may be beneficial in steroid-induced rosacea.^{32,33} As evidence is sparse, it is recommended that TCIs should not be used as first-line treatment for rosacea.

Seborrheic Dermatitis

Seborrheic dermatitis (SD) is a chronic and relapsing skin condition characterized by scaly, itchy, and red to pink patches and plaques usually found on the face and scalp. It is believed that *Malassezia* yeasts play a causative role in SD pathogenesis.³⁴

Small pilot studies of 18 and 16 patients found that tacrolimus 0.1% ointment proved to be a safe and effective therapeutic option for SD.^{35,36}

Results from Warshaw et al. showed that there was a significant improvement with pimecrolimus 1% cream compared to vehicle in 96 patients treated, with maximum improvement observed after 2 weeks of use.³⁷ Various studies have shown improvement with pimecrolimus for facial SD, ranging from 63-83% complete clearance rates.^{38,39} Pimecrolimus 1% cream was shown to be as equally effective as ketoconazole 2% cream⁴⁰ and 1% hydrocortisone acetate cream,³⁸ as well as demonstrated improved efficacy over both topical metronidazole and topical methylprednisolone.⁴¹

There is convincing evidence to support the treatment of SD with topical pimecrolimus; however, more studies are required to assess the efficacy of tacrolimus as research is sparse.

Vitiligo

Vitiligo is an autoimmune, progressive disorder of depigmentation that is relatively benign, but its drastic appearance can be psychologically disabling to affected individuals. There is no defined and clearly effective treatment for vitiligo as response can be highly variable.

Multiple studies have shown mixed results in patients treated with TCIs and ultraviolet (UV) light. More than 50% of patients in two studies treated with tacrolimus 0.1% ointment plus excimer laser resulted in better repigmentation of areas of vitiligo as compared with excimer alone.^{42,43} Another study showed less encouraging results using narrow-band UV-B light plus tacrolimus or placebo, which did not produce noticeable clinical improvement between treatments.⁴⁴

A randomized, double-blind study with pediatric patients comparing tacrolimus 0.1% ointment with dobetasol propionate 0.05% cream showed that both treatments were equally effective.⁴⁵ Retrospective studies involving 57 children treated with either 0.03% or 0.1% tacrolimus ointment for at least 3 months demonstrated that it was an effective alternative therapy for vitiligo of the head and neck in pediatric patients.⁴⁶ Other studies have shown beneficial results when tacrolimus was applied alone especially for facial vitiligo, with significant repigmentation as high as 75%,

observed in 40% of patients.⁴⁷

Pimecrolimus has shown positive results with combination UV therapy for facial vitiligo.⁴⁸ Additional studies may help delineate the role of pimecrolimus in vitiligo.

The need for a range of treatment options in vitiligo is essential due to the variable patient-specific response rates to therapy. Topical tacrolimus may be a viable option, as results have been promising for children with facial vitiligo, either as monotherapy or combined with excimer laser in skin sensitive areas. It is important to note that there has been no decisive evidence from animal models implicating TCIs as potential photocarcinogens, however, further studies are warranted to provide insights for long-term management.⁴⁹

Conclusion

Although only receiving regulatory approval for one indication, TCIs have shown promise in the off-label treatment of other dermatological conditions. Most notably, studies have shown efficacy of tacrolimus and pimecrolimus in psoriasis, lichen planus, vitiligo, and allergic contact dermatitis, as well as other skin disorders. Finding alternatives to corticosteroids in order to limit side effects, including skin atrophy, striae, perioral dermatitis, rosacea and telangiectasia, is important for longterm management, and TCIs do not induce these adverse cutaneous effects. However, TCIs are not without their own side effects, which can include burning, stinging sensation, transient erythema and allergic contact dermatitis. The burning/stinging sensation is usually transient, subsiding in 7-10 days of daily use. There are several reports suggesting increased incidence and risk of infection while undergoing therapy with topical tacrolimus, but this finding has yet to be confirmed in clinical study.⁵⁰ It is important to note that concerns regarding possible adverse effects from systemic absorption remain to be observed clinically.

In 2005, the Food and Drug Administration's (FDA) Pediatric Advisory Committee announced a recommendation of a black box warning for tacrolimus and pimecrolimus, stating a possible risk of cancer from topical use, yet a causal link has not been clearly established. Despite the lack of evidence, this concern arose from studies of three species (monkeys, rats and mice), which developed cancer (lymphoma and skin malignancies) after treatment with large doses of oral (systemic) TCIs.

The Canadian Dermatology Association's (CDA) position on TCIs is that the FDA recommendation of the black box warning is not warranted, stating 'lack of clinical evidence and experience.' The CDA further states that there is no evidence to support an increased rate of lymphoma in those using TCIs when compared to the general population and 'clinical and histological patterns of lymphomas noted were not consistent with typical immunosuppression-related lymphomas.'⁵¹ The American Academy of Dermatology (AAD) held a similar position stating that 'there is no data that proves proper topical use of pimecrolimus and tacrolimus is dangerous in people.'⁵² Overall, TCIs have been shown to be effective in a variety of offlabel uses without the long-term side effects that come with corticosteroids and, therefore, may elicit improved treatment compliance. Further research may lead to a greater role and recognition for TCIs in autoimmune and inflammatory diseases. In addition, continued research could reveal other dermatological conditions that may benefit from these medications.

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