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Topical Calcineurin Inhibitors in the Treatment of Vitiligo

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1. Introduction

Vitiligo is the most common depigmenting disorder, with a prevalence of approximately 0.5% in the world population. Almost half of the patients with vitiligo present before 20 years of age. The two sexes are affected equally, and there are no apparent differences according to skin type or race.[1,2] On histology, vitiligo is identified by the loss of epidermal melanocytes with absence of inflammation.

Commonly used repigmentation therapies whose efficacy is supported by data from randomized controlled trials include ultraviolet light (for whole body or targeted lesions) and topical agents (corticosteroids and calcineurin inhibitors). Narrow-band ultraviolet B radiation (NB-UVB), which delivers peak emission at 311nm, is currently the preferred treatment for adults and children with vitiligo. Topical therapies may be effective in cases of localized disease. Combination therapy is often considered when there has been no response to phototherapy alone after three months or when the goal is to accelerate the response and reduce cumulative exposure to UV light.[3] This chapter will review the literature on the topical use of pimecrolimus and tacrolimus in the treatment of vitiligo alone as well as when combined with other common therapies.

2. Pimecrolimus

Topical calcineurin inhibitors have shown promise in the repigmentation of affected areas in patients with vitiligo without causing the adverse effect profile associated with other common treatments for this disease.[4] Pimecrolimus has been approved for the treatment of atopic dermatitis and has shown a very low incidence of side effects. In comparison, corticosteroids can cause thinning of the skin as well as epidermal atrophy at the application site, and PUVA has an associated skin cancer risk.[5] Thus far, pimecrolimus has shown a very low incidence of mild, temporary adverse effects including erythema and irritation at the application site,[6] which makes this modality a safe treatment option. It appears that pimecrolimus may offer a considerable advantage in cases where the side effects of other therapies are of greater concern as in vitiligo occurring in pediatric patients or disease affecting facial, intertriginous, and genital regions, as neither epidermal atrophy nor telangiectasia are major concerns.[2]

There are several hypotheses about the pathogenesis of vitiligo, but there is increased evidence of an auto-immune mechanism involving both humoral and cellular immunity.

This has been supported by the frequent detection of circulating auto-antibodies, cytoplasmatic antigens of melanocytes, and activated T-cells in the periphery of actively progressing lesions in vitiligo patients.[7] An analysis of 19 vitiligo patients for 24 weeks showed that, at baseline, patients expressed a significant increase in the expression of interferon-γ, tumor necrosis factor alpha (TNF-α) expression, and IL-10 in involved and uninvolved skin as compared to healthy patients. After treatment, TNF-α expression decreased in involved and adjacent uninvolved skin, illustrating a relationship between cytokine imbalance and the depigmentation process of vitiligo.[8]

Pimecrolimus inhibits the production of T-cells and prevents mast cells from releasing pro-inflammatory mediators.[9] The structure of pimecrolimus has higher lipophilicity than that of tacrolimus and binds to macrophilin 12 with high affinity.[10] This complex inhibits calcineurin resulting in the suppression of pro-inflammatory cytokine[1] secretion by activated T-cells, specifically that of interferon-γ, IL-1, IL-2, IL-3, IL-4, IL-5, GM-CSF, and TNF-α[11,12] which are believed to be responsible for the damage to melanocytes that results in vitiligo. *In vitro* research on the effect of calcineurin inhibitors on melanocytes affected by vitiligo may further support the hypothesis that the pathogenesis of vitiligo involves an auto-immune response as well as autocytotoxic components. It has been observed *in vitro* that the interaction between calcineurin inhibitors and keratinocytes induces the release of stem cell factor and enhancing matrix metalloproteinase-9 activity, allowing melanocytes to grow.[13]

A study evaluating the efficacy of topical 0.05% clobetasol propionate versus 1% pimecrolimus ointment indicated that pimecrolimus is just as effective as clobetasol propionate in repigmenting skin without producing the side effects that often result in the discontinuation of steroid treatment. The study group included 10 patients ranging in age from 12-66 years old with generalized vitiligo ranging in duration from two to 40 years. Affected regions varied from extremities, trunk, or acral regions. There was no statistically significant difference in the degree of repigmentation resulting from pimecrolimus versus clobetasol propionate, but atrophy and telangiectasia were reported in the clobetasol propionate treatment group, indicating that pimecrolimus has a more favorable safety profile than clobetasol. Two patients being treated with pimecrolimus reported experiencing a mild burning sensation that was not severe enough to result in the discontinuation of treatment.[14] Topical corticosteroids are indicated in the treatment of vitiligo and have been a common treatment for approximately 30 years.[15] Recurrence of symptoms of vitiligo and the relatively high incidence of adverse effects including atrophy, telangiectasia, striae, and contact dermatitis are limiting factors particularly for children and sensitive areas of the skin.[10,16]

Because of the low-toxicity of pimecrolimus, it may be a treatment of particular interest in more sensitive areas affected by vitiligo such as the periocular and genital regions and in pediatric patients. In a case study conducted by Leite et al.[7] an eight-year old patient showed near-complete remission of symptoms of vitiligo in the periocular area after four months of treatment and with no relapse one year thereafter. In another case study presented in Leite et. al. study, an eleven-year-old boy achieved almost complete repigmentation of all vitiligo lesions in the genital region after three months of treatment. Both patients showed good tolerability to the treatment regimen indicating that pimecrolimus may be a safer option for the skin of children and adolescents whose skin shows greater predilection for local side-effects.[7]

In a study conducted by Mayoral et al., eight adults presenting with facial vitiligo were treated with pimecrolimus 1% cream twice a day for at least three months. The average length of the study was eleven months from baseline to the final follow-up visit. Patients showed a statistically significant response, averaging 72.5% improvement in pigmentation of the facial region.Every patient showed a response to study treatment regardless of length of disease, extent of disease, or previous treatment regimen, including patients who had not responded to previous therapies including PUVA and Melagenina®. It was observed that the greatest improvement in surface area correlated with the longest duration of disease at baseline and had no significant association with longer treatment duration. Treatment was well tolerated.[8]

The combination of pimecrolimus with other common treatment modalities for vitiligo has been studied to determine whether the degree of response to treatment could be improved or the response time could be accelerated. Esfandiarpour et al. conducted a double-blind, placebo-controlled study to determine the efficacy of pimecrolimus 1% cream combined with NB-UVB in the treatment of vitiligo.[1] NB-UVB has been recently introduced as a similar, safer treatment option than PUVA. Although these photochemotherapy (NB-UVB and PUVA) do have some local immunomodulatory effects, these treatment methods are effective most likely because of the stimulation of melanocyte proliferation.[17,18] It was hypothesized that the addition of pimecrolimus 1% cream to treatment with NB-UVB would better address the autoimmune components of the disease. In this study, 68 patients were randomized into one of two groups: NB-UVB plus pimecrolimus 1% cream or NB-UVB plus placebo for three months. After 12 weeks of treatment, statistically significant repigmentation occurred in more than 50% of facial lesions in 64.3% of patients in the group that received NB-UVB plus pimecrolimus 1% versus 25.1% of patients in the group that received NB-UVB plus placebo. There was no significant difference in the repigmentation rate of other body areas between the two groups.[1]

Another study explored the addition of microdermabrasion in the treatment of nonsegmental vitiligo in children with pimecrolimus 1% cream. It is believed that microdermabrasion may modulate the immune response and autoinoculation of melanocytes as well as enhance the absorption of topical immunomodulators through the inflammation and erosion of the skin. The purpose of this study was to determine if microdermabrasion would be effective in enhancing the efficacy and decreasing the treatment time. Results indicated a positive response to treatment, as 60.4% of lesions treated by combined therapy showed a clinical response, with 43.4% of lesions treated by combined therapy showing complete repigmentation after a three month treatment period, compared with 32.1% repigmentation of lesions treated with pimecrolimus alone, and 1.7% for placebo.[19]

3. Tacrolimus

Topical tacrolimus is a potential therapeutic option for the management of vitiligo. Despite this drug's clinical efficacy, the underlying mechanism of topical tacrolimus in the management of vitiligo is not well understood and has been rarely studied. Tacrolimus is a non-steroidal anti-inflammatory agent used in the treatment and management of many skin disorders and was initially formulated for atopic dermatitis. Similarly to pimecrolimus, tacrolimus exerts its therapeutic effects by targeting and inhibiting calcineurin in the skin, which regulates T-cell division and activation, and in turn inhibits

pro-inflammatory cytokines.[20] Systemically administered tacrolimus is an effective immunosuppressant that is used as an anti-rejection agent in organ transplantation, and due to its effective immunosuppression, systemic tacrolimus increases the risk for skin cancer.[21] Topical tacrolimus, however, has not been associated with systemic immunosuppression or increased risk for malignancies in long-term clinical research.[22,23,24] The avoidance of natural and/or artificial light during tacrolimus therapy and application of sunscreen daily is advised.

Multiple studies have documented the stimulatory effects of UV light on melanogenesis and melanocyte proliferation.[25,26] The therapeutic effects of psoralen photochemotherapy and phototherapy with NB-UVB for the repigmentation of vitiliginous skin have also been documented.[27,28] The suppression of pro-inflammatory cytokines via tacrolimus may facilitate the stimulatory effects of ultraviolet light on the repigmentation of vitiliginous skin. Evidence suggests a suppression of TNF-α after application of tacrolimus, which may play a role in repigmentation.[21] TNF-α has been shown to inhibit melanocyte proliferation and melanogenesis, which has allowed for speculation that epidermal cytokines may be a part of a negative feedback that negates the stimulus of melanocytes.[29] Additionally, a number of cytokines, including TNF-α are shown to up-regulate the expression of intercellular adhesion molecule-1 (ICAM-1) on melanocytes, which may trigger a lymphocyte-melanocyte attachment and play a role in the destruction of melanocytes.[30,31] Because tacrolimus inhibits T-cells and therefore cytokines, including TNF-α, tacrolimus may help prevent the aforementioned negative feedback loop as well as the expression of ICAM-1 on melanocytes.

Studies have shown that topical corticosteroids and topical tacrolimus are similarly efficacious in the repigmentation of both facial and nonfacial vitiliginous lesions.[32,33] However, long-term use of topical corticosteroids is contraindicated due to their serious side effects. Therefore, topical tacrolimus offers many advantages over topical corticosteroids for the management of chronic skin disorders including vitiligo. In contrast to topical corticosteroid treatment which results in a predominantly diffuse pattern of repigmentation,[34] topical tacrolimus often induces follicular repigmentation. This indicates the involvement of melanoblast in the repigmentation process, namely the proliferation of inactive melanocytes (melanoblasts), which migrate to the nearby epidermis to differentiate and form perifollicular pigment islands.[35,36,37] Topical tacrolimus induces follicular repigmentation better in sun-exposed anatomical sites. Keratinocytes are known to secrete endothelin, a prodifferentiation factor of melanoblasts, after exposure to UVB radiation.[38] Therefore, sun-exposed keratinocytes most likely provide the necessary endothelin for optimal melanoblast differentiation effect induced by topical tacrolimus.[10]

Topical tacrolimus has been reported to promote melanoblast differentiation and growth. Additionally, topical tacrolimus promotes a favorable environment that fosters the proliferation of melanocytes/melanoblasts through an interaction with keratinocytes, and thereby repopulating vitiliginous skin lesions.[10] In another study by Kang et. al.,[39] topical tacrolimus was seen to induce tyrosinase, which eventually leads to melanin biosynthesis, activity, and expression.

Studies have shown mixed results for combination therapy, consisting of topical tacrolimus and UVB.[40,41,42,43] The use of topical tacrolimus in association with phototherapy gives rise to concern about the possibility of an increased risk to skin malignancies.[44] However, the results of a 2005 study on hairless mice suggest that topical

tacrolimus prevents DNA photodamage due to a filter effect of both active and vehicle components in topical formulation but does not affect the clearance of DNA photoproducts.[45] Fai et. al., employed combined therapy, and indicated a rapid and relevant improvement of facial vitiligo, followed by lesions on the limbs and trunk (including the neck), whereas the overall response of vitiligo in other skin areas (extremities and genital areas) was poor.[46] This fact has been attributed to the greater density of hair follicles in the head and neck areas, and thus, greater melanocyte reservoirs.[47] Further long-term efficacy and safety data and randomized controlled trials on a large number of study participants are required.

Combined therapy of topical tacrolimus and 308-nm excimer laser in the management of vitiligo has been evaluated as well. Unlike topical tacrolimus and UVB phototherapy, combination treatment of topical tacrolimus and 308-nm excimer laser has been reported to be more effective and faster than that of excimer laser in monotherapy.[48,49] In comparison with NB-UVB, phototherapy with excimer laser has the advantaged of a targeted treatment, thereby limiting the delivery of radiation only to affected vitiligo skin areas. However, NB-UVB may be more useful for the treatment of extensive vitiligo and is more advantageous than excimer phototherapy with regards to cost, session duration, and patient compliance.[42]

Occlusive treatment has been reported to enhance topical tacrolimus efficacy in treating vitiligo. As mentioned earlier, it has been shown that when applying tacrolimus openly on extremities, there was negligible effect. However, Hartmann et. al.[50] used polyurethane foil or hydrocolloid dressings for overnight occlusive treatment, and moderate to excellent repigmentation was achieved, depending on the dressing utilized. It was suggested that since hydrocolloid dressings lead to higher stratum corneum water holding capacity compared with polyurethane foil[51], the hydrocolloid dressings may be more suitable for enhancing the transcutaneous penetration of the topically applied agent. Moreover, the Hartmann et. al. study had also measured serum concentrations of tacrolimus. All study subjects had tacrolimus serum levels below the detection limit after 12 months, indicating the long-term topical treatment with additional long-term occlusion of areas up to 150 cm^2 does not lead to accumulation of tacrolimus in the blood.[47] Still, larger placebo-controlled studies using topical tacrolimus in combination with occlusion, penetration enhancers, or phototherapy, or in higher concentrations, are required to determine the exact role of topical tacrolimus in the treatment of vitiligo and its optimal mode of use.

4. Conclusion

In conclusion, topical pimecrolimus and tacrolimus are effective and well tolerated treatment options for both adults and children with vitiligo. Moreover, it has been documented that topical tacrolimus has better outcomes for the treatment of vitiligo in children[52] and in patients of skin of color.[53] Topical calcineurin inhibitors are a great alternative for persons with vitiligo but with poor compliance to phototherapy and/or with fear of the side-effects of using topical corticosteroids long-term. Further randomized controlled studies are needed to enhance the understanding of how these topical medications work. Additionally, combination therapy utilizing NB-UVB or eximer laser with topical calcineurin inhibitors should be evaluated in larger trials so that safety and efficacy data can help guide clinicians in managing vilitigo when presented with refractory cases.

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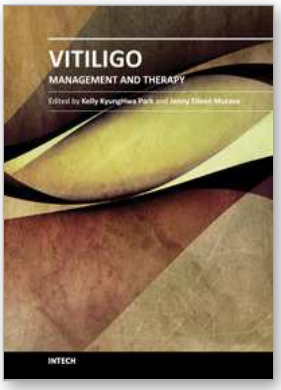

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