Once-Daily Application of Calcipotriene 0.005%–Betamethasone Dipropionate 0.064% Ointment for Repigmentation of Facial Vitiligo

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Vitiligo vulgaris is an autoimmune pigmentary disorder with no universally efficacious therapeutic options. Separate applications of calcipotriene ointment 0.005% and topical corticosteroid ointments have been successful in the repigmentation of vitiligo. We sought to examine the efficacy of a combination calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment in the repigmentation of vitiligo. An institutional review board–approved retrospective chart review was conducted in 13 pediatric and adult patients with vitiligo treated with calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment once daily for at least 2 months. Two of 3 children had 76% to 100% repigmentation of facial vitiligo with once-daily usage after 2 months. Of the 10 adults (aged 28–55 years), 1 had 100% facial repigmentation in 3 months, 1 had 76% to 99% facial repigmentation in 5 to 9 months, and 2 had 26% to 50% repigmentation in 3 months. Twelve patients developed some facial repigmentation. No patients experienced atrophy, telangiectases, or lesion enlargement during treatment. Combination calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment shows promise as a once-daily vitiligo therapy. Adult and pediatric facial vitiligo patients may see repigmentation as early as 2 months after initiation of therapy. Children may experience a better response, but larger studies are needed.

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Vitiligo vulgaris is a disorder of pigmentary loss caused by autoimmune destruction of melanocytes. Vitiligo affects 0.4% of the worldwide population and has a considerable psychosocial impact. It is associated with autoimmune diseases including diabetes mellitus, alopecia areata, pernicious anemia, Hashimoto thyroiditis, and Addison disease.[1] A single mutation in the NACHT leucine-rich–repeat protein 1 gene, *NALP1*, has been identified in patients with vitiligo and familial autoimmunity.[2] This gene is believed to regulate cutaneous immune functioning.

Although no topical therapies have been specifically approved for vitiligo vulgaris, available off-label topical treatments include corticosteroids, calcipotriene ointment with or without corticosteroids, calcineurin inhibitors, and pseudocatalase.[3] However, these therapies are not universally effective; carry side-effect profiles; and have high rates of noncompliance, especially because they require twice-daily application for efficacy. As a result, alternative vitiligo therapies are necessary.

A small case series of children treated with calcipotriene ointment 0.005% in combination with a low- to mid-potency topical corticosteroid has been published, demonstrating good repigmentation of vitiligo, even in patients who were previously

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resistant to corticosteroids. The published protocol required morning application of topical corticosteroids and night application of topical calcipotriene.[4] The present study examined the efficacy of once-daily application of a stable combined preparation of calcipotriene 0.005%–betamethasone dipropionate 0.064% in the repigmentation of vitiligo.

Materials and Methods

Thirteen patients (10 female, 3 male) with vitiligo, ranging in age from 4 to 55 years (3 children, 10 adults), were included in this study. An institutional review board–approved chart review was performed on patients with vitiligo. For inclusion in this report, patients with facial vitiligo treated for at least 2 months with calcipotriene 0.005%–betamethasone dipropionate 0.064% were included. None of the patients included in the chart review demonstrated prior spontaneous repigmentation within the 3 months preceding treatment and none were on therapy at the time of study medication initiation.

Patients were instructed to apply a thin layer of combined calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment to affected facial areas nightly before bed. The patients were examined every 6 to 8 weeks by the investigators while using this therapy. Treated areas of vitiligo were inspected under standard lighting as well as under a Wood lamp (365-nm UV light). The percentages of depigmentation and repigmentation were determined based on body surface area measurements of the lesions using the rule of nines. Treatment was terminated after complete repigmentation was achieved or at least 2 months of therapy without repigmentation.

Table 1.

Patient Demographics

	Pediatric Patients, n (n=3)	Adult Patients, n (n=10)
Age, y		
Mean	6.3	38.4
Range	4–9	28–55
Race		
White	2	7
Hispanic	1	1
Southeast Asian	0	2
Sex		
Male	1	2
Female	2	8

Results

Table 1 shows demographic characteristics of the vitiligo patients who were evaluated. Table 2 shows clinical response to therapy. Side effects of therapy are shown in Table 3. Of the 4 patients with more than 75% repigmentation (2 children and 2 adults), tacrolimus ointment treatment failed in 4 patients and clobetasol propionate ointment failed in 1 patient as prior therapies. None of the patients experienced development of atrophy or telangiectases; 2 patients (adults) each reported facial acne and localized erythema. The adults with side effects were on therapy for more than 3 months prior to experiencing changes. None of the patients reported lesion enlargement in treated areas.

Comment

The etiology of vitiligo includes autoimmune, autocytotoxic, neural, genetic, and environmental hypotheses.[5] Most data support an autoimmune reaction against melanocytes. Vitiligo is associated with autoimmune disease. Antimelanocyte and antityrosinase antibodies have been detected in patients with vitiligo.[1] These antibodies have the potential to cause the accumulation of toxic peroxidation by-products in the melanogenesis pathway. Additionally, melanocytes and keratinocytes within vitiliginous lesions have shown decreased calcium uptake.[6] An intracellular calcium deficit can increase concentrations of reduced thioredoxin, thereby inhibiting tyrosinase in the production of melanin, which results in clinical depigmentation.

Topical calcipotriol, a $1,25(OH)_2D_3$ analog, as monotherapy or in combination has been found to be effective in the treatment of vitiligo. Calcipotriol exerts its response via immunomodulation and the modification of defective calcium homeostasis. Vitamin D_3 receptors have been localized to melanocytes, keratinocytes, fibroblasts, and immunocytes.[7] These vitamin D_3 receptors allow for calcipotriol to regulate melanocyte and keratinocyte growth and differentiation as well as cytokine production and secretion. Calcipotriol also downregulates the production of IL-8, which is believed to enhance inflammatory destruction of melanocytes. Additionally, calcipotriol increases IL-10, which reduces the number of Langerhans cells and their ability to function as

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Table 2.

Clinical Response to Therapy

	Pediatric Patients, n (n=3)	Adult Patients, n (n=10)
Overall Repigmentation		
0%	0	1
1%–25%	1	5
26%–50%	0	2
51%–75%	0	0
76%–99%	1	1
100%	1	1
Overall Repigmentation by Clinical Type		
Vulgaris		
0%	0	1
1%–25%	1	3
26%–50%	0	0
51%–75%	0	0
76%–99%	0	0
100%	1	1
Acrofacial		
0%	0	0
1%–25%	0	2
26%–50%	0	1
51%–75%	0	0
76%–99%	0	1
100%	0	0
Segmental		
0%	0	0
1%–25%	0	0
26%–50%	0	1
51%–75%	0	0
76%–99%	1	0
100%	0	0
Type of Repigmentation		
Follicular	0	2
Diffuse	3	8

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Table 3.

Side Effects of Therapy

Side Effects	Pediatric Patients, n	Adult Patients, n
Acne	0	2
Atrophy	0	0
Erythema	0	2
Telangiectases	0	0

antigen-presenting cells in the epidermis. Thus vitamin D_3 analogs such as calcipotriol quell the autoimmune inflammatory reaction immune response that characterizes vitiligo.

Several studies have demonstrated the efficacy of topical corticosteroids and calcipotriene in the repigmentation of vitiligo. In a study of 12 pediatric patients who were treated with morning application of topical steroids and nightly application of topical calcipotriene, 83% (10/12) of patients responded to therapy, with an average of 95% repigmentation by body surface area.[7] Prior monotherapy with the same topical corticosteroids had failed in 4 patients. Response was greatest in the periocular and facial locations.[7]

Our study employed a stable preparation of combined calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment, which was applied once daily for the treatment of vitiligo. The greatest repigmentation was demonstrated in the pediatric population with facial vitiligo. Notably, more than 75% repigmentation was observed in patients who were treatment resistant to traditional therapies including tacrolimus and topical steroids. Moreover, the side-effect profile of calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment was limited to facial acne and localized erythema in adults on therapy for more than 3 months. Cutaneous atrophy and telangiectases were not observed in our study, which is likely a result of the once-daily application and lower concentrations of calcipotriene and steroid in the combined preparation.

Although larger randomized controlled trials are needed to further evaluate the efficacy and safety of calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment, based on these data we believe combination calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment shows promise as a once-daily vitiligo therapy with a minimal side–effect profile. Adult and pediatric facial vitiligo patients may see repigmentation as early as 2 months into therapy. Furthermore, calcineurin inhibitor–resistant and corticosteroid-resistant vitiligo may respond to this medication as a first- or second-line treatment.

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