ORIGINAL ARTICLES
SPECIAL TOPIC
Journal of Drugs in Dermatology

Topical Tacrolimus Is More Effective for Treatment of Vitiligo in Patients of Skin of Color

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ABSTRACT

Background: Vitiligo vulgaris is a chronic autoimmune depigmenting disorder affecting individuals of all skin colors. Lesions are commonly noted in the periorificial face and over the upper and lower extremities in areas of friction. Although there have been many published reports of successful therapies for vitiligo, few have assessed differential response based on skin color.
Objective: To determine if topical tacrolimus is more effective at treating vitiligo in individuals of color.
Methods: An IRB-approved chart review of patients with a diagnosis of vitiligo was conducted including patients seen between May 2001 and April 2006. Patients with vitiligo were treated with tacrolimus 0.03% for children ages 2–15 years of age and tacrolimus 0.1% ointment for individuals 16 years of age or older, applied twice-daily to all hypopigmented or depigmented lesions. A review of clinical features, Fitzpatrick skin type and response to topical tacrolimus were recorded.
Results: Topical tacrolimus was effective in all Fitzpatrick skin types, with superior efficacy on body lesions in individuals of Fitzpatrick types 3–4 (Fisher exact test, P=0.03). Further, individuals with Fitzpatrick type 3–4 skin had shorter interval to >75 percent improvement of lesions on the body (Kaplan-Meier Log-rank, P=0.03) and head and neck (P=0.016).
Conclusion: Topical tacrolimus is an effective treatment for vitiligo irrespective of skin tone, with greatest benefit in Fitzpatrick type 3–4 skin. Repigmentation of lesions on the head and neck is superior to repigmentation of the body and extremities in all racial subgroups.

J Drugs Dermatol. 2011;10(5):507-510.

INTRODUCTION

Vitiligo vulgaris affects 0.4–1 percent of the world population.[1] Pockets of areas of high incidence (as high as 8%) have been reported in India.[2] While vitiligo vulgaris affects all races and ethnicities, lesions are more noticeable in individuals of color, due to the greater differential in skin tone between normally pigmented skin and hypo- or depigmented skin.[1] Effective skin therapy in all races and Fitzpatrick skin types is needed. If untreated vitiligo may become progressively more cosmetically disfiguring; it may interfere with work or personal relationships and may become less amenable to therapy.[1,3]

The comparative study of response to agents by race or skin tone has been noted in some past clinical reports of therapies for vitiligo vulgaris. Cockayne et al. reviewed the fact that their pediatric population demonstrated better results with topical corticosteroids than their adults with vitiligo, but noted that the children were primarily of color.[4] Published data on efficacy of ultraviolet light therapies has demonstrated that narrowband UVB and excimer laser are more effective on the head and neck in individuals of color.[5,6]

A number of the original reports of topical tacrolimus for adults and children have documented good repigmentation in patients of color,[1,7] including patients from India[8] and Asia.[9] Differential repigmentation by skin tone or ethnicity has not been previously explored for topical tacrolimus. The aim of this report is to provide comparative data on response of individuals of all colors to therapy for vitiligo using tacrolimus ointment topically.

METHODS

An IRB-approved review of charts of individuals with the diagnosis of vitiligo vulgaris (international classification of diseases version 9 code 709.01) was conducted at the Department of Dermatology of the St. Luke's-Roosevelt Hospital Center, New York, NY. Individuals included in this review are those individuals who had used prescribed topical tacrolimus for at least a three month trial for vitiligo vulgaris. Clinical data reviewed included demographic data (age, sex, ethnicity), Fitzpatrick skin type, medical and family history, site of usage of tacrolimus, time at which first response was noted, length of medication usage to achieve maximum repigmentation and percentage of repigmentation (reflected as none, 100% or quartiles: 1–24%, 25–49%, 50–74% and 75–99%) as determined by a dermatologist (NS) during clinical visits. A standard prescribing protocol was followed for vitiligo. Tacrolimus was prescribed using 0.03% ointment for children ages 2–15 years and 0.1% ointment for patients ages 16 years and older.

Age and BSA were not normally distributed and were analyzed as ordinal variables. All categorical variables were examined by

Although there have been many published reports of successful therapies for vitiligo, few have assessed differential response based on skin color.

FIGURE 1. Interval to achievement of 75 percent repigmentation in individuals of Fitzpatrick types 1–2, 3–4 and 5–6 during the first six months of therapy

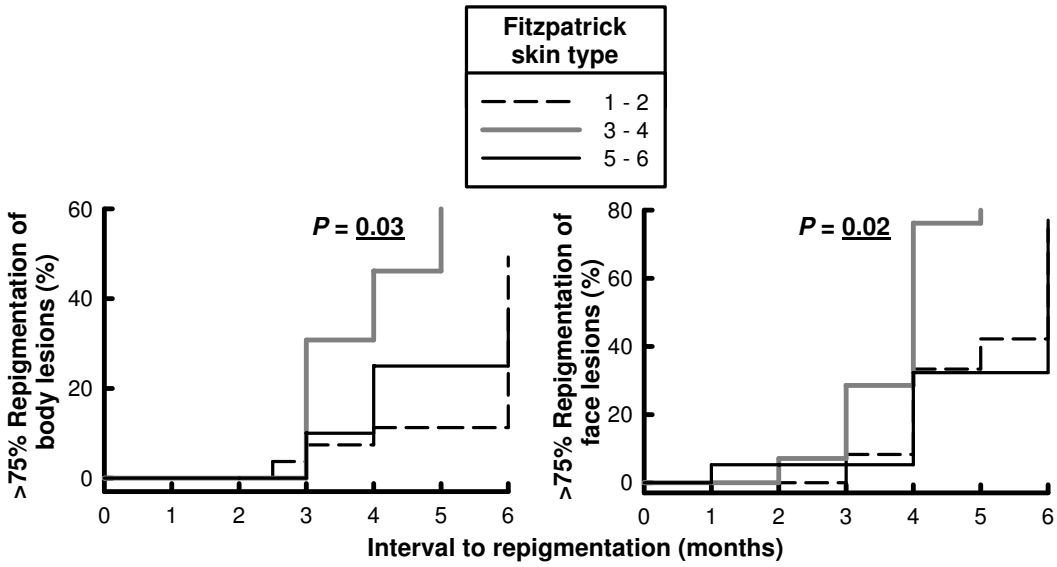

TABLE 1.

Demographics and Response of Individuals With Body Vitiligo Lesions							
Variable – no. (%)	Clinical Response (% Repigmentation)						*P*-value*
	None	1 – 25	26 – 50	51 – 75	76 – 99	100	
Sex							
Male	3 (11.1)	8 (29.8)	2 (7.4)	3 (11.1)	9 (33.3)	2 (7.4)	0.82
Female	8 (20.5)	11 (28.2)	3 (7.7)	4 (10.3)	8 (20.5)	5 (12.8)	
Age (yr)							
0 – 15	5 (19.2)	4 (15.4)	2 (7.7)	3 (11.5)	7 (26.9)	5 (19.2)	0.44
15 – 30	3 (20.0)	8 (53.3)	2 (13.3)	1 (6.7)	1 (6.7)	0 (0.0)	
30 – 45	2 (11.8)	4 (23.5)	1 (5.9)	2 (11.8)	7 (41.2)	1 (5.9)	
> 45	1 (12.5)	3 (37.5)	0 (0.0)	1 (12.5)	2 (25.0)	1 (12.5)	
Personal History of Autoimmune Disease#							
No	8 (16.3)	14 (28.6)	5 (10.2)	6 (12.2)	11 (22.5)	5 (10.2)	0.78
Yes	3 (17.7)	5 (29.4)	0 (0.0)	1 (5.9)	6 (35.3)	2 (11.8)	
Family History of Autoimmune Disease#							
None	5 (12.8)	12 (30.8)	3 (7.7)	4 (10.3)	9 (23.1)	6 (15.4)	0.84
First Degree only	2 (15.4)	4 (30.8)	0 (0.0)	2 (15.4)	5 (38.5)	0 (0.0)	
Second Degree only	2 (22.2)	2 (22.2)	1 (11.1)	1 (11.1)	2 (22.2)	1 (11.1)	
Both	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	
Fitzpatrick Skin Type							
1 – 2	2 (7.4)	11 (40.7)	1 (3.7)	4 (14.8)	8 (29.6)	1 (3.7)	0.03
3 – 4	1 (6.3)	4 (25.0)	1 (6.3)	0 (0.0)	6 (37.5)	4 (25.0)	
5 – 6	8 (34.8)	4 (17.4)	3 (13.0)	3 (13.0)	3 (13.0)	2 (8.7)	

*Fisher exact test.
#Autoimmune history includes systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, Grave's disease, alopecia areata and inflammatory bowel disease.

TABLE 2.

Demographics and Response of Individuals With Head and Neck Vitiligo Lesions

Variable – no. (%)	Clinical Response (% Repigmentation)						P-value*
	None	1 – 25	26 – 50	51 – 75	76 – 99	100	
Sex							
Male	1 (3.9)	1 (3.9)	2 (7.7)	2 (7.7)	14 (53.9)	6 (23.1)	0.19
Female	4 (10.3)	8 (20.5)	0 (0.0)	3 (7.7)	16 (41.0)	8 (20.5)	
Age (yr)							
0 – 15	2 (7.4)	3 (11.1)	1 (3.7)	3 (11.1)	10 (37.0)	8 (29.6)	0.92
15 – 30	1 (6.7)	3 (20.0)	1 (6.7)	1 (6.7)	6 (40.0)	3 (20.0)	
30 – 45	2 (12.5)	2 (12.5)	0 (0.0)	0 (0.0)	10 (62.5)	2 (12.5)	
> 45	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	4 (57.1)	1 (14.3)	
Personal History of Autoimmune Disease#							
No	4 (8.2)	4 (8.2)	2 (4.1)	4 (8.2)	23 (46.9)	12 (24.5)	0.34
Yes	1 (6.3)	5 (31.3)	0 (0.0)	1 (6.3)	7 (43.8)	2 (12.5)	
Family History of Autoimmune Disease#							
None	5 (13.2)	5 (13.2)	0 (0.0)	5 (13.2)	15 (39.5)	8 (21.1)	0.13
First Degree only	0 (0.0)	4 (21.1)	1 (5.3)	0 (0.0)	11 (57.9)	3 (15.8)	
Second Degree only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	2 (40.0)	
Both	0 (0.0)	0 (0.0)	1 (50.)	0 (0.0)	0 (0.0)	1 (50.0)	
Fitzpatrick Skin Type							
1 – 2	0 (0.0)	5 (19.2)	2 (7.7)	1 (3.9)	12 (46.2)	6 (23.1)	0.37
3 – 4	1 (5.6)	2 (11.1)	0 (0.0)	1 (5.6)	9 (50.0)	5 (27.8)	
5 – 6	4 (19.1)	2 (9.5)	0 (0.0)	3 (14.3)	9 (42.9)	3 (14.3)	

*Fisher exact test.
#Autoimmune history includes systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, Grave's disease, alopecia areata and inflammatory bowel disease.

fisher exact tests. Analysis of interval until ≥75 percent clinical improvement was performed using Kaplan-Meier survival analysis over a six month treatment period. Log-rank statistics and corresponding *P* values were calculated. Data were analyzed with SAS 9.2 Software (SAS Institute Inc., Cary, NC). All tests of significance were two-sided and *P* values of less than 0.05 were considered significant.

RESULTS

One hundred and one subjects were selected for the study (out of 151 charts that were reviewed); 11 were excluded due to incomplete follow up. Thirty five (38.9%) were male and 37 (42.5%) had a positive family history of autoimmune diseases. Age at initial treatment was 25.6 ± 18.9 years (mean age ± standard deviation). Sixty-six subjects had vitiligo lesions on the body; sixty-five on the face. Of subjects with body lesions, 53 had generalized and 13 segmental or localized disease. Of subjects with head and neck lesions, 55 had generalized and 10 segmental or localized disease.

Of subjects with Fitzpatrick skin types 1 and 2, 32 were Caucasian (94.1%), one Hispanic (2.9%) and one Asian (2.9%). Of types 3 and 4, one was Caucasian (4.2%), 21 Hispanic (87.5%), one Asian (4.2%) and one African American (4.2%). Of types 5 and 6, five were Hispanic (15.6%), eight Indian (25%), four Middle Eastern (12.5%), and 15 African American (46.9%).

Repigmentation with usage of topical tacrolimus was good in all Fitzpatrick skin types on the body (Table 1), as well as the head and neck (Table 2), with greater repigmentation of lesions on the body in individuals of Fitzpatrick skin types 3–4, over types 1–2 and 5–6 (Fisher exact test, *P*=0.03). More than 75 percent repigmentation of body lesions was noted in 62.5 percent of subjects with Fitzpatrick types 3–4, compared with only 33.3 percent of Fitzpatrick 1–2 and 21.7 percent of Fitzpatrick types 5–6 (Table 1). More than 75 percent repigmentation of head and neck lesions was noted in 69.3 percent, 77.8 percent and 57.2 percent of individuals of Fitzpatrick types 1–2, 3–4 and 5–6, respectively

(Table 2). However, these differences were not statistically different (P=0.37). Gender, age, family history of vitiligo and history of autoimmunity were not statistically significant for both head and neck or body lesions (Tables 1 and 2).

Rapidity of repigmentation, as judged by the interval until achievement of 75 percent repigmentation, was fastest for subjects with Fitzpatrick types 3–4, when compared with types 1–2 and 5–6 (Kaplan-Meier survival analysis). This was true for both body (Log-rank P=0.03; Figure 1A) and head and neck lesions (Log-rank P=0.02; Figure 1B). By 6 months, 75 percent or more repigmentation of body lesions was achieved in 49.3 percent, 64.1 percent and 37.5 percent of subjects with Fitzpatrick types 1-2, 3-4 and 5-6, respectively (Figure 1a). For head and neck lesions, 82.7 percent, 88.1 percent and 74.6 percent of lesions achieved 75 percent or more repigmentation, respectively (Figure 1b).

DISCUSSION

Vitiligo vulgaris is an autoimmune condition in which pigmentation is lost from the skin and mucous membranes. Patients of all colors can be affected by vitiligo.[1,3] One of the clinical difficulties in vitiligo therapy is identifying the best initial therapy for any one patient, as there is fair evidence in favor of a number of agents.[10] Our findings here suggest that topical tacrolimus is a beneficial therapy in all Fitzpatrick skin types, but may be especially effective for individuals of intermediate color (types 3–4). Studies looking comparatively at individual response to topical agents in vitiligo based on skin tone are lacking in the literature. This is the first study to demonstrate superior response in individuals of color and specifically individuals of intermediate pigmentation. Although our data suggests that the darkest skin types may not be as responsive to topical tacrolimus in atopic dermatitis, we found responses of individuals with Fitzpatrick types 5–6 (mostly African American and Indian individuals) to be non-inferior to that of Fitzpatrick types 1–2 (mostly Cacasian individuals), but inferior to responses in individuals in the Fitzpatrick 3–4 range (mostly Hispanic individuals).

Topical tacrolimus was initially developed as a topical agent for atopic dermatitis in Asia. Studies have suggested that individuals of African American descent may require higher concentrations than 0.03% tacrolimus topically for atopic dermatitis.[11] Factors that could affect response include genetic variations in ability to absorb products through the intact skin barrier, vitamin levels (e.g., vitamin D levels, which are lowest in individuals of Fitzpatrick types 5–6),[12] and immunological differences between racial groups. Furthermore, genetic studies have demonstrated that vitiligo is heterogeneous.[13-15] There may be different pathological bases for disease in different ethnic groups that could account for variations in response to topical agents.

In conclusion, our data demonstrates differences in clinical response to topical agents that support biological differences in individuals of different skin tones and ethnicities. Further research into comparative responses by skin tone and ethnicity are needed to aid in development of ideal therapeutic protocols for vitiligo in individuals of all skin types and ethnicities.

DISCLOSURES

The authors have no conflict of interest to disclose.

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