The efficacy, safety, and stability of tacrolimus 0.03% ointment in treatment of nonsegmental vitiligo

Nagwa E. AbdElazim, Haidy A. Yassa, Ayman M. Mahran

Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Assuit University, Assiut, Egypt

Correspondence to Haidy A. Yassa, Master Degree in Dermatology, Venereology and Andrology, Faculty of Medicine, Assuit University, Assiut, Egypt.
Zip Code: 71111;
Tel: 01020735904.
e-mail: haidyjoseph2012@yahoo.com

Received 16 April 2018
Revised 16 April 2018
Accepted 12 May 2019
Published 05 February 2020

Journal of Current Medical Research and Practice
2020, 5:41–45

Background
Topical immunoarm adulators have been successfully used as a monotherapy or in combination with other therapeutic modalities in vitiligo treatment. Topical tacrolimus has been reported to promote melanoblast differentiation and groth. Additionally, it promotes a favorable environement that enhances the proliferation of melanocytes/ melanoblasts through an interaction with keratinocytes, and thereby repopulating vitigiginous skin lesions.

Aim
To detect the effect of tacrolimus ointements in treatment of nonsegmental vitiligo.

Method
A total of 35 patients with vitiligo were enrolled in Tacrolimus this randomized placebo-controlled study. Two vitiliginous patches were chosen in each patient. The first lesion (A) was treated by tacrolimus 0.03% ointment, and the second lesion (B) was treated by panthenol cream as a placebo. Treatment course was 3 months, and follow-up was done for three extra months. Vitiliginous patches were assessed at baseline and monthly for 6 months.

Results
Moderate to excellent response was observed in 25.7% of lesions A compared with 0% of lesions B (P = 0.002). Disease duration has a negative effect on therapeutic response. No adverse effects were noted to tacrolimus ointment except for mild erythema in 6% of the patients.

Coclusion
Given its immunomodulatory properties and lack of cutaneous adverse effects, tacrolimus is a potential therapeutic alternative for vitiligo, with an improved benefit-risk ratio.

Keywords:
immunomodulatory, tacrolimus, vitiligenous

J Curr Med Res Pract 5:41–45

2357-0121

Introduction

Vitiligo is an acquired pigmentary skin disorder with an estimated incidence of ~1% of world population affecting both sexes equally [1]. It is a disfiguring disease causing great psychosocial stress and is characterized clinically by the development of depigmented macules and patches that correspond histologically to decreased or absent cutaneous melanocytes.

There are various hypotheses included in the mechanism of vitiligo; it is a result of interactions between oxidative stress and autoimmunity in patients with genetic background [2,3].

Many treatment modalities have been used in vitiligo, but there is still no effective and safe treatment for this disease. Vitiligo therapeutic options include topical agents, phototherapy, combination therapy, and surgery. However, there are many problems of the current treatments such as resistance to therapy, treatment complications, and recurrence after treatment [4,5]. As there are numerous clues to the autoimmune nature of the disease, the role of topical immunomodulatory drugs, calcineurin inhibitors, like tacrolimus and pimecrolimus on T cells and mast cells, inhibiting T-cell activation and production of cytokines and preventing the release of pro-inflammatory mediators in mast cells by degranulation, has been investigated in vitiligo [6]. Tacrolimus ointment does not cause atrophy, telangiectasia, or potential adverse ocular effects of topical corticosteroids [7]. The present study was conducted to assess the effect, safety, and stability of tacrolimus 0.03% ointment in treating vitiligo.

Patients and methods

This is a single-blind, randomized placebo-controlled study. The study was carried out in the Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Assiut University, Egypt, during the period of July 2015 to July 2017.The study was approved by the Institutional Review Board, Faculty of Medicine,

Assiut University. Informed consent was obtained from all patients or guardians.

Thirty five patients with the clinical diagnosis of stable vitiligo vulgaris were enrolled in this study. Exclusion criteria were patients aged less than 6 years and more than 60 years, unstable vitiligo (the patient who showed neither extension of the existing lesions nor occurrence of new lesions within the past year was considered stable [8]), patients on topical or systemic therapy on any site and any size of lesion during the past 3 months, pregnancy and lactation, and patients with any apparent concomitant systemic or dermatological disease.

All patients were subjected to complete history taking plus general and dermatological examinations. In addition, vitiligo lesions were classified as recent if the disease duration was less than 4 years.

Two almost equal vitiliginous lesions in the same anatomical area were chosen for treatment in each patient. Allocated lesions were grouped by block randomization. Lesion A was treated by tacrolimus 0.03% ointment (tacrolimus; Al-Andalous, Cairo, Egypt) once daily for 3 months. On the second lesion (lesion B), placebo in the form of panthenol cream was applied once daily for 3 months.

Patients were followed up monthly for 3 months and for another 3 months to assess the response rate and the stability of pigmentation.

The dimensions of the treated lesions were measured in transverse and longitudinal axes at the time of enrollment and every month for 6 months. Lesions were measured by an observer who was blinded to the line of treatment.

According to the Vitiligo Global Assessment Scale and depending on the percentage of repigmentation, treatment response was graded as follows: no response (0%), mild (<25%), moderate (25 to <50%), good (≥50–75%), and excellent (≥75–100%) response (Oh *et al.*, 2012). [9] Percentage of repigmentation was calculated according to the following formula:

$$\text{Repigmentation percentage} = \frac{\text{Area before} - \text{Area after treatment}}{\text{Area before treatment}} \times 100$$

Photography was taken using a digital camera (Lumix digital camera, DMC-FH2, 14 mega pixels; Panasonic Corporation, Japan). Photographs were evaluated by two dermatologists.

At the end of the study, patient satisfaction was assessed according to the criteria of Wong and Vasconez [10] as follows: dissatisfied, neutral, somewhat satisfied, moderately satisfied, and very satisfied.

Statistical analysis

Data were analyzed by version 16, SPSS (SPSS Inc., Chicago, Illinois, USA). Simple frequencies were used for data checking and cleaning.

Statistical methods were applied as follows: descriptive statistics such as mean, SD, frequencies, and percentages. χ^2 was used to compare the difference in distribution of frequencies among different groups, but if the number of cells was small, we used Fisher's exact test. Independent sample *t* test was used to compare the difference in means among different groups. We tested the effect of the three treatments and the time of measurements on the mean of change in lesions' size. The effects of other factors on the treatment response like age, sex, family history, and duration of disease were included as covariates in this model. Statistical significance was defined by a *P* value of less than 0.05.

Results

The present study was carried out on 35 patients with stable vitiligo vulgaris attending the outpatients' clinic of the Department of Dermatology, Venereology and Andrology, Assiut University Hospitals, Assiut, Egypt. Patients were treated by tacrolimus ointment (0.03%) once daily on lesions A and panthenol cream once

Table 1 Demographic and clinical data of patients with vitiligo

Data	Patients with vitiligo (*n*=35) [*n* (%)]
Age (years)	
Mean±SD	36±11
Range	8-59
Sex	
Male	10 (25.7)
Female	25 (74.3)
Duration of disease (years)	
Mean±SD	5±4.3
Range	1-10
Marital status	
Single	18 (51.4)
Married	17 (48.6)
Special habits	
Smoker	6 (17.1)
Nonsmoker	29 (82.9)
Family history	
Yes	14 (40)
No	21 (60)
Size of treated areas (cm^2)	
Mean±SD	50±15.7
Range	120

cm^2: Range value (34.3 - 65.7)

daily on lesions B for 3 months and followed up for another 3 months.

Among the studied population, 10 (25.7%) were males and 25 (74.3%) were females. The patients' age ranged between 8 and 59 years. The disease duration ranged between 1 and 10 years. The demographic and clinical data are shown in Table 1.

There was a statistically significant difference between the size of the treated lesions before and after 3 months of treatment in lesions A ($P = 0.041$) (Table 2). Overall, 2.8% of lesions showed more than or equal to 50% repigmentation (moderate to excellent response) at the end of 3 months. At the same time, 22.9% of lesions showed 25–50% repigmentation whereas 48.6% showed mild response to treatment (Table 3).

Sex did not have any significant effect on the treatment responses of lesions A or B.

Regarding disease duration in lesions A, there was a significant difference in treatment response according to disease duration ($P = 0.005$). Patients with disease duration less than 4 years showed better moderate and good responses (20%=17.1% moderate + 2.9% good) compared with those with long-standing cases (5.7%). However, long-standing cases showed better mild response than recent cases (28.6 vs. 20%) (Table 4).

Treatment response was significantly negatively correlated with disease duration in lesions A (r=–0.671, $P = 0.005$).

According to site distribution in lesions A, there were high significant differences in treatment responses according to site ($P = 0.001$). Mild response was the best in the limbs (70%) followed by hands and feet (35.7%) and then neck and trunk (25%). Moderate response was the best in neck and trunk (25%) followed by hands and feet (21.4%) and then the limbs (17.6%). Neck and trunk only showed good response (25%).

According to stability of repigmentation, no significant differences could be detected in treatment responses after 3 and 6 months of follow-up in both lesions A ($P = 0.0825$).

At the end of the follow-up period, 20% of patients who were treated with tacrolimus showed neutral satisfaction to treatment response and 25.7% of patient showed somewhat satisfaction.

No adverse effects were noted to tacrolimus ointment except for mild erythema in 6% of the patients.

Regarding treatment response in areas treated with placebo (lesions B), no repigmentation could be detected in lesions B, which were treated by panthenol cream as placebo (Fig. 1).

Table 2 Size of treated lesions A before and after treatment

Size of lesions A	At first visit	After 3 months of treatment	*P*
Mean (cm^2)	31.27±18.75	27.34±15.23	0.041*
Range (cm^2)	5-125	1.1-98.44	

*P value less than 0.05, significant.

Table 3 Percentage of repigmentation after 3 months of treatment according to global assessment scale in lesions A

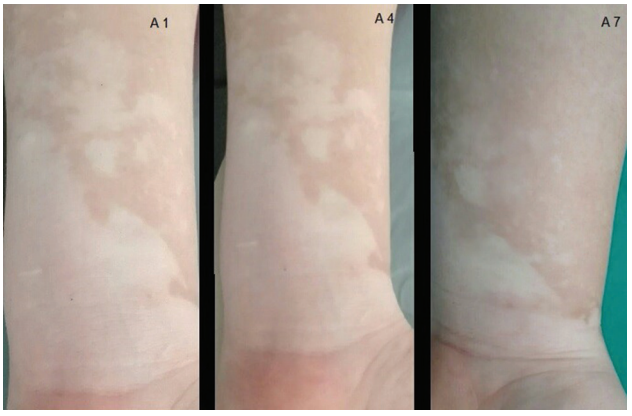
Percentage of repigmentation	Lesions A [*n* (%)]
No effects (0%)	9 (25.7)
Mild (<25%)	17 (48.6)
Moderate (≥25 to <50%)	8 (22.9)
Good (≥50 to <75%)	1 (2.8)
Excellent (≥75 to 100%)	0
Total number of lesions	35 (100)

Table 4 Percentage of repigmentation in recent and long-standing cases in lesions A

Duration of the disease			
Percentage of repigmentation	Recent ≤4 years	Long-standing >4 years	*P*
No effects (0%)	2 (5.7)	7 (20)	0.005*
Mild (<25%)	7 (20)	10 (28.6)	
Moderate (≥25 to <50%)	6 (17.1)	2 (5.7)	
Good (≥50 to <75%)	1 (2.9)	0	
Excellent (≥75 to 100%)	0	0	
Total	16	19	

*P value is significant < 0.05

Figure 1



A patient with lesions over the wrist of left hand treated with tacrolimus ointment 0.03% once daily. AI lesion at the beginning of the study, A4 lesion after 3 months of treatment, and A7 lesion at the end of the study that showed moderate repigmentation.

Discussion

The primary objective of this study was to explore the efficacy, safety, and stability of tacrolimus 0.03% ointment as a treatment for stable vitiligo vulgaris.

Topical immunomodulators have been successfully used as monotherapy or in combination with other therapeutic modalities in vitiligo. They inhibit calcineurin action, thus preventing T-cell activation and the production of various inflammatory cytokines [11].

In our study, we found that lesions A (treated by single daily application of tacrolimus 0.03% ointment) showed moderate response (>25–50%) in 22.9% of lesions and good response (≥50–75%) in 2.8% of lesions.

Xu *et al.* [12] reported moderate to complete repigmentation in 40% of patches treated with tacrolimus twice daily for 4 months. However, higher percent of repigmentation was previously reported. Moreover, Kanwar *et al.* [5] described marked to complete repigmentation in 57.9% of 25 children with vitiligo treated with tacrolimus ointment. The better response in these studies might be because both studies were done on children's skin, which may respond better to treatment.

On the contrary, Husain *et al.* [13] used topical tacrolimus (0.03%) ointment twice daily in the treatment of localized vitiligo for 24 weeks, and they found that 83.3% of patients responded positively to treatment. However, excellent repigmentation was noted in only 3.3% of patients.

In several previous studies, tacrolimus ointment was applied twice daily [4,12–14]. If we had done so, it might have augmented the tacrolimus effect. However, because of the self-regulatory property of tacrolimus, as the patient's skin will absorb progressively lower quantities of the agent as the lesion heal, we thought that once daily application would be enough.

We found that lesions treated with placebo did not show any improvement in terms of the size and repigmentation changes.

In lesions A, the percent of repigmentation in early lesions (≤4 years) was significantly higher than those in long-standing lesions (P = 0.005). Moreover, there was a statistically significant difference in treatment response in recent and long-standing lesions A (P = 0.005). A significant negative correlation was reported between disease duration and the percent of repigmentation in lesions A (≤4 years r=−0.574, P = 0.019 and > 4 years r=−0.604, P = 0.013). So, this means that disease duration had a negative effect on the therapeutic responses in our study.

Nordal *et al.* [15] found that repigmentation was difficult to achieve in patients with long-term vitiligo. Similarly, Xu *et al.* [12] reported that repigmentation for patients with long-term vitiligo is notoriously difficult to achieve. Moreover, Hartmann *et al.* [16] mentioned that the patients who proceed early for treatment had higher chance of cure. In addition, Udompataikul *et al.* [17] reported a better therapeutic response in patients with vitiligo with disease duration less than 5 years.

When therapeutic response was evaluated according to the anatomical site of the lesions, we found higher percent of repigmentation in lesions on the neck and trunk (>50% repigmentation in 75% of the lesions), followed by limbs (>50% repigmentation in 41% of the lesions) and lastly hands and feet patches (>50% repigmentation in only 7% of the lesions).

Certain areas are known to resist repigmentation, including hands and feet, lip-tip vitiligo, association with leucotrichia and segmental vitiligo. Few reasons for resistance of the acral areas were suggested. The most popular theory is the relatively lower density or absence of pilosebaceous follicles and the reservoirs from which the melanocytes migrate. Relatively, less melanocytes density as well as higher chances of koebnerization over this friction and injury-prone anatomical sites may be other possible mechanisms [18].

Our findings are supported by Olsson and Juhlin [19] who reported that irrespective of the therapeutic modality, fingers and elbows were the most difficult areas to repigment whereas the trunk and limbs (not including elbows and knees) responded better. In the studies by Kawalek *et al.* [20], Fai *et al.* [21], and Xu *et al.* [12], the response in patients with vitiligo depended mainly on the site. It was better in facial lesions and poor on the extremities and genital areas.

To assess the durability of our novel therapeutic approach, we extended the follow-up period for another 3 months after the end of the treatment protocol. We found that the repigmentation obtained in lesions A was stable in all patients, as no significant difference was found between the size of the treated lesions at the end of 3 and 6 months in A (P = 0.825). So, this means that our therapeutic approach can provide consistent and stable response for at least 6 months.

Regarding adverse effects, we noted only temporary erythema with tacrolimus ointment in 6% of patients. Rokni *et al.* [22] reported that the adverse effects were unremarkable except for slight irritation in three out of 30 patients with vitiligo after treatment with tacrolimus ointment 0.1%.

At the end of the study period, 20% of patients who were treated with tacrolimus showed neutral

satisfaction to treatment response and 25.7% of patient showed somewhat satisfactions.

Conclusion

In conclusion, we are offering a safe therapeutic option for treatment of vitiligo. This treatment is almost completely safe, easy, and relatively cheap and cost effective. So, tacrolimus ointment 0.03% can be very attractive in treating such a devastating illness.

Acknowledgements

A single-blind, randomized placebo-controlled study was conducted.

The study was carried out in the Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Assiut University, Egypt, during the period from July 2015 to July 2017.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Speeckaert R, Marijin M, Van Geel N. Why treatments do (n×t) work in vitiligo: An autoinflammatory perspective. Autoimmunity Reviews 2015; 14:332–340.

2 Hofny E, Bamatral M, Hassan H, Mahran A, Mohamed N. Serum and tissue levels of total antioxidant capacity in nonsegmentalvitiligo. Journal of the Egyptian Women's Dermatologic Society 2018; 15:35–39.

3 Xie H, Zhou F, Liu L, Zhu G, Gao T. Vitiligo: How do oxidative stress-induced autoantigens trigger autoimmunity? J DermatolSience 2015; 163:1186–1193.

4 Grimes PE, Soriano T, Dytoc MT. Topical tacrolimus for repigmentation of vitiligo. J Am AcadDermatol 2002; 47:789–791.

5 Kanwar AJ, Dogra S, Parsad D. Topical tacrolimus for treatment of childhood vitiligo in Asians. Clinical Experimental Dermatol 2004; 29:589–592.

6 Tharp MD. Calcineurin inhibitors. DermatologicTherapy 2002; 15:325–332.

7 Paller AS. Use of nonsteroidal topical immunomodulators for the treatment of atopic dermatitis in the pediatric population. J Pediatr 2001; 138:163–168.

8 Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CE, *et al.* Revised classification/nomenclature of vitiligo and related issues: the Vitiligo global issue Consensus Conferenc. Pigment Cell Melanoma Res 2012; 25:E1–E13.

9 Oh TS, Lee O, Kim JE, Son SW, Oh CH. Quantitative method for measuring therapeutic efficacy of the 308 NM excimer laser for vitiligo. Skin research and technology; 2012; 18:347–355.

10 Wong L, Vasconez H. Patient satisfactionafter Nd: YAG laser-assisted lipolysis. Ann PlastSurg 2011; 5:561–563.

11 Wong R, Lin AN. Efficacy of topical calcineurin inhibitors in vitiligo. Int J Dermatol 2013; 52:491–496.

12 Xu AE, BS, Zhang DM, Wei XD, Huang B, Lu LJ. Efficacy and safety of tarcrolimus cream 0.1% in the treatment of vitiligo. Int J Dermato 2009; 48:86–90.

13 Husain MA, Alam MN, Rahim R, Joarder Y, Wahidujjaman, Ferdous M. Efficacy and safety of topical tacrolimus 0.03% in the treatment of localized vitiligo. Medicine Today 2017; 29:1–5.

14 Grimes PE, Morris R, Avaniss-Aghajani E, Soriano T, Meraz M, Metzger A. Topical tacrolimus therapy for vitiligo: therapeutic responses and skin messenger RNA expression of proinflammatory cytokines. J Am Acad Dermatol 2004; 51:52–61.

15 Nordal E, Guleng G, Ro¨nnevig J. Treatment of vitiligo with narrowband-UVB (TL01) combined with tacrolimus ointment (0.1%) vs. placebo ointment, a randomized right/left double blind comparative study. J EurAcadDermatolVenereol 2011; 25:1440–1443.

16 Hartmann A, Bröcker EB, Hamm H. Occlusive treatment enhances efficacy of tacrolimus 0.1% ointment in adult patients with vitiligo: Results of a placebo-controlled 12-month prospective study. ActaDermVenereol 2008; 88:474–479.

17 Udompataikul M, Boonsupthip P, Siriwattanagate R. Effectiveness of 0.1% topical tacrolimus in adult and children patients with vitiligo. J Dermatol 2011; 38:536–540.

18 Seleit I, Bakry OA, Abdou AG, Dawoud NM. Immunohistochemical expression of aberrant Notch-1 signaling in vitiligo: an implication for pathogenesis. Ann DiagnPathol 2014; 18:117–124.

19 Olsson MJ, Juhlin L. Long-term follow-up of leukodermapatientstreated with transplants of autologous cultured melanocytes, ultrathin epidermal sheets and basal cell layer suspension. Br J Dermatol 2002; 147:893–904.

20 Kawalek AZ, Spencer JM, Phelps R. Combined Excimer laser and Topical Tacrolimus for the treatment of vitiligo: a pilot study. DermatolSurg 2004; 30:130–135.

21 Fai D, Cassano N, Vena GA. Narrow-band UVB phototherapy combined with tacrolimus ointment in vitiligo: a review of 110 patients. J EurAcadDermatolVenereol 2007; 21:916–920.

22 Rokni GR, Golpour M, Gorji AH, Khalilian A, Ghasemi H. Effectiveness and safety of topical tacrolimus in treatment of vitiligo. Advanced Pharmaceutical Technology and Research 2017; 8:1–7.