

Comparison of topical 0.03% tacrolimus with 0.05% clobetasol in treatment of vitiligo

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Abstract

Objective To compare the efficacy and safety of topical tacrolimus ointment with topical clobetasol ointment in vitiligo patients.

Methods This quasi-experimental study was carried out in outpatient, Department of Dermatology Unit-II, KMEU/ Mayo Hospital, Lahore. Sixty patients above 12 years were selected by non-probability purposive sampling method and were divided into two equal groups. Patients having lesions of less than 2 years of duration were included. After obtaining an informed consent, patients in group I were treated with twice daily application of 0.1% tacrolimus ointment and group II with clobetasol ointment for a period of six months. If no response was obtained, treatment was stopped after three months.

Results Repigmentation was seen in 15 (50%) patients in tacrolimus group and 27 (90.0%) in clobetasol group. Contact dermatitis was noted in one patient in each group and acneiform eruption was recorded in one patient in the clobetasol group.

Conclusion Topically, clobetasol remains to be an effective therapy in vitiligo. Topical tacrolimus was not effective in our patients. Intermittent use of clobetasol is as safe as continuous use of tacrolimus.

Keywords

Vitiligo, depigmentation, tacrolimus, clobetasol.

Introduction

Vitiligo is a common, acquired idiopathic skin disorder characterized by milky white macules and patches caused by the destruction of cutaneous melanocytes due to self-destructive, genetic, neural, biochemical, viral and autoimmune mechanisms.¹

It may be associated with other autoimmune disorders like hyperthyroidism, hypothyroidism, pernicious anemia, diabetes mellitus and

Addison's disease.² The prevalence of vitiligo in various populations ranges from 1 to 2%.³ Different therapeutic modalities are being used currently with varying success rates. The rationale of these treatment options is to induce repigmentation in the lesions and to stabilize the disease i.e. arrest the progression of disease.^{4,5} The choice of therapy depends on age of the patient, type of vitiligo, stage, site and distribution of lesions.⁵

Current topical treatment options include camouflage, cosmetics, sunscreens, topical corticosteroids, vitamin D analogues, topical calcineurin inhibitors, and depigmentation with p-benzyl-phenol. Systemic treatment options include corticosteroids, ciclosporin and other

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immunosuppressives. Phototherapy e.g. broadband UVB, narrowband UVB, UVA, psoralen with ultraviolet A (PUVA) is used alone in combination with topical preparations. Surgical therapies include full-thickness and split-skin grafting, mini (punch) grafts, suction blister grafting, micro-pigmentation, autologous melanocyte transplantation).⁶

New treatment modalities include 308-nm excimer laser, immunomodulators (tacrolimus), super oxide dismutase and catalase and grafting of cultured melanocytes.⁷

Abnormalities in humoral and cell-mediated immunity in vitiligo patients form a basis for using immunomodulating agents, such as corticosteroids and macrolide immunomodulators. The purpose of this study was to assess the efficacy of topical macrolide tacrolimus in the treatment of vitiligo. It inhibits calcineurin and consequently T-cell activation and the production of various cytokines.⁸

We compared the efficacy and safety of clobetasol 0.05% ointment and tacrolimus 0.03% ointment in vitiligo.

Methods

Patients presenting to the outpatient clinic, department of dermatology, Mayo Hospital, Lahore with age > 12 years, belonging to either sex, with disease duration of < 2 years and no evidence of repigmentation were enrolled. Patients with lip-tip type of vitiligo and mucosal involvement and involvement of body surface area >25%, patients who received systemic or topical treatment for 4 weeks prior to study, pregnant and lactating women and patients with hypersensitivity to tacrolimus or steroid were excluded.

Table 2 Demographic and clinical data of study groups.

	<i>Group I - Tacrolimus</i>	<i>Group II - Clobetasol</i>	<i>Both groups</i>
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A total of sixty patients of vitiligo (diagnosed clinically) were divided randomly in two groups by using random permuted block technique. Prior informed written consent regarding the study and photographs from the patients was taken. Demographic information of the patient along with detailed history and examination was recorded on a specially designed proforma. Patients were photographed before commencement, after three months and at the end of therapy.

Patients in group I applied topical tacrolimus 0.03% over vitiliginous patches twice daily for a period of six months. Patients in group II applied topical clobetasol 0.05% ointment for three weeks in one month. After every 3 weeks application of clobetasol, it was withheld for one week. Patients were followed up every month for a period of six month. In those patients where no response was obtained, therapy was stopped after three months.

Efficacy of tacrolimus and clobetasol was measured by area of repigmentation (reduction in number and size of vitiliginous patches) and response was graded as shown in **Table 1**. Safety was measured by evaluating the side effects e.g. burning, itching, blistering, atrophy, telangiectasia and acneiform eruption on treated skin. In patients with any side effect due to either drug, therapy was discontinued.

The outcome qualitative variables i.e. areas of repigmentation and side effects were compared

Table 1 Grades of response of treatment.

<i>Grade</i>	<i>Percentage of area of repigmentation</i>
0	No response
1	Poor (1-25)
2	Fair (26-50)
3	Good (51-75)
4	Excellent (76-100)

	N=30	N=30	
<i>Age (years)</i>			
Range	13-50	13-70	13-70
Mean	22.27 ± 9.22	24.97 ± 11.12	23.62 ± 15.12
<i>Age groups (years)</i>			
<20	16 (53.3%)	17 (56.7%)	33 (55%)
20-40	13 (43.3%)	9 (30%)	22 (36.7%)
>40	1 (3.3%)	4 (13.3%)	5 (8.3%)
<i>Sex</i>			
Male	16 (53%)	14 (47%)	30 (50%)
Female	14 (47%)	16 (53%)	30 (50%)
<i>Duration of disease</i>			
1-6 month	14 (46.7%)	10(33.3%)	24 (40%)
6month -1 year	14 (46.7%)	14 (46.7%)	28 (46.7%)
1-2 year	2 (6.7%)	6(20%)	8 (13.3%)
<i>Sites of involvement</i>			
Face	1 (3.3%)	6 (20%)	7 (11.7%)
Neck	2 (6.7%)	0	2 (3.3%)
Trunk	4(13.3%)	1 (3.3%)	5 (8.3%)
Upper limb	5 (16.7%)	8 (26.7%)	13 (21.7%)
Lower limb	18 (60%)	15 (50%)	33 (55%)
<i>Distribution of lesions</i>			
Symmetrical	8 (26.7%)	15 (50%)	23 (38.3%)
Asymmetrical	16 (53.3%)	2 (6.7%)	18 (30%)
Focal	6 (20%)	13 (43.3%)	19 (31.7%)

by using chi-square test. A P value of ≤ 0.05 was considered statistically significant.

Results

Sixty patients suffering from vitiligo were included in the study. Out of these 30 (50%) patients were in the tacrolimus group and 30 (50%) patients were in the clobetasol group.

There were 30 (50%) female and 30 (50%) male patients, with an overall female to male ratio of 1:1. Age and sex distribution in the tacrolimus group and the clobetasol group is shown in **Table 2**. Age of the patients ranged from 13 to 70 years with the mean age of 23.62 ± 12.49 years. Duration of disease ranged from 1 month to 2 years in both groups. Majority of patients i.e. 28 (93.3%) in the tacrolimus group and 24 (80%) in the clobetasol group had vitiligo for <1 year. Sites of involvement are shown in **Table 2**. In both groups lower limbs were the most involved site.

An excellent degree of repigmentation was recorded in 10 (16.7%), good in 7 (11.7%), fair in 11 (18.3%) and poor in 14 (23.3%) patients. Repigmentation did not occur in 18 (30.0%) patients. Two (3.3%) patients were lost to follow-up.

Repigmentation in both groups is compared in **Figure 1**. 14 (46.7%) patients with clobetasol and 3 (10%) patients with tacrolimus showed $\geq 50\%$ repigmentation ($p < 0.01$) i.e. significantly better results with clobetasol than tacrolimus in treatment of vitiligo.

In 57 (93.3%) patients, side effects of treatment did not occur (**Figure 2**). Acneiform eruption was noted in 1 patient in clobetasol group. Contact dermatitis was recorded in 1 patient in both groups.

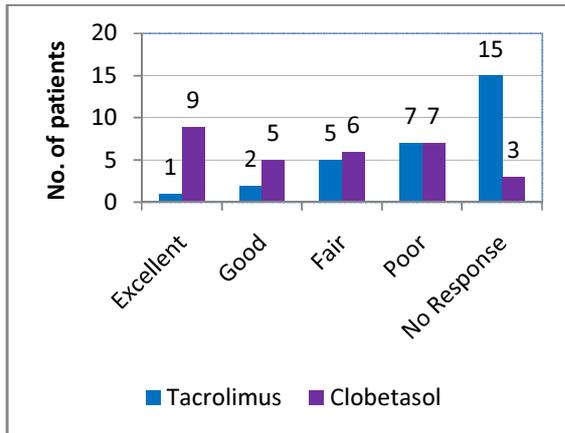


Figure 1 Comparison of repigmentation in the tacrolimus and clobetasol group. Excellent (76-100% improvement), good (51-75% improvement), fair (26-50% improvement), Poor (1-25% improvement), no response (0% improvement).

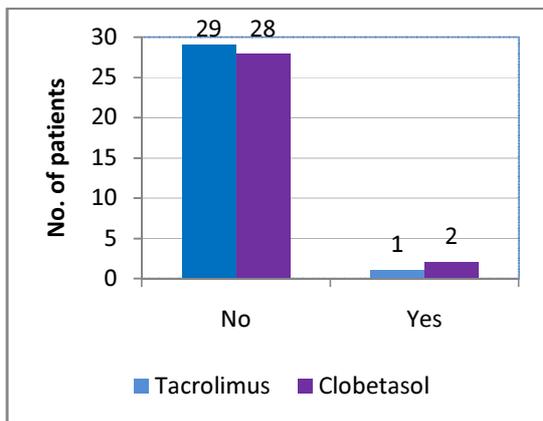


Figure 2 Comparison of side effects in the two treatment groups.

Table 3 Comparison of present study with that of Lepeet *et al.*¹⁶ regarding repigmentation in the tacrolimus group

Repigmentation	Lepe <i>et al.</i> study	Present study
No response	2 (10%)	15 (50%)
Poor	4 (20%)	7 (23.3%)
Fair/moderate	5 (25%)	5 (3.3%)
Good	4 (20%)	2 (6.7%)
Excellent	5 (25%)	1 (3.3%)

Discussion

Treatment of vitiligo is indeed a great challenge for any physician or dermatologist despite recent advancements made in the various therapeutic modalities for this disease in the last few

decades. The currently available therapies are largely unsatisfactory and vary widely between cultures and within health systems.⁹

Defects in cell-mediated and humoral immunity have been postulated and documented in the pathogenesis of vitiligo.^{8,10} Therefore, most updated therapeutics have focused mainly on immunomodulators. Topical immunomodulating agents, such as corticosteroids have been widely used in the treatment of vitiligo and over the last few years, macrolides have been added to the list to treat various disorders with underlying defects in immunity involved in pathogenesis, including vitiligo. It is suggested that an imbalance in local cytokine expression may play a role in the pathogenesis of vitiligo. Suppression of TNF-alpha may be associated with repigmentation in the vitiliginous lesion.¹⁰ Direct interaction between topical tacrolimus FK506 and keratinocytes creates a favourable milieu for melanocytes growth and melanoblast migration, a possible mechanism of repigmentation in patients with vitiligo.¹¹ It has also been observed that tacrolimus increases the melanogenesis and cell migration on human A375 cells.¹²

Topical tacrolimus ointment (0.1% or 0.03%) when applied twice daily for six months, is an effective, well-tolerated and safe therapy for head and neck vitiligo particularly in children.¹³

It may be used as an alternative in the treatment of vitiligo in face and neck where the patients are unable to receive regular phototherapy and fear the side-effects of topical steroid in long-term use.¹⁴

Oral, topical and intralesional corticosteroids are used in vitiligo due to their anti-inflammatory and immune suppressive properties.¹⁵ Localized vitiligo is conveniently treated by topical steroid and oral steroid dose regimen. Mild or lower potency corticosteroids are usually preferred.

Patients should be closely monitored for side effects like atrophy, acneiform eruption, striae, telangiectasia etc.

Present research is a comparative study between two topical immunomodulating agents, clobetasol and tacrolimus. With tacrolimus only half (50%) of the patients showed repigmentation while in the clobetasol group, most of the patients (90.0%) had positive response. 10% of the patients in the clobetasol group did not show any pigmentation.

A similar study was carried out by Lepe *et al.*¹⁶ for the treatment of childhood vitiligo. In this study it was seen that tacrolimus was equally effective as topical steroid in vitiligo. Kanwar *et al.*¹⁷ studied tacrolimus in children with vitiligo and had similar results. Good (50%-75%) to excellent (>75%) repigmentation was observed in facial vitiligo after six months of treatment with tacrolimus in a study by Almeide *et al.*¹⁸

Significant differences were found between the results of our study and that of Lepe *et al.*¹⁶, **Table 3**. Certain factors may be responsible for different results. Our patients were skin type IV and V, while Lepe *et al.*¹⁶ included Mexicans patients with skin type II to type V. Majority of their patients had lesions on face and upper trunk while in our patients legs were involved in the majority. Face and neck regions usually respond better as compared to legs.

Results in our patients treated with clobetasol are comparable with those of other international studies. Nearly one third of our patients showed excellent response especially on legs. Likewise similar results were seen on legs and abdomen with clobetasol in the study by Lepe *et al.*¹⁶ Both therapies failed to produce result on the dorsum of hand or areas devoid of hair follicles in our study and also in the study of Lepe *et al.*¹⁶ In another study by Kumari, repigmentation

occurred with clobetasol in 90% to 100% of the area involved in more than 80% of patients with vitiligo of the face and more than 40% of patients with vitiligo on other parts of the body.¹⁹ More studies in greater number of patients in different geographical regions may clear this discrepancy of results in the studies.

In majority of patients (93.3%), side effects of treatment did not occur. Acneiform eruption and dermatitis were noted in 2 (6.7%) patients, respectively in clobetasol group and dermatitis was recorded in 1 patient (3.33%) in tacrolimus group. Results in our study indicated that there was no significant difference in safety i.e. side effects of tacrolimus and clobetasol in the treatment of vitiligo. Side effects like burning, itching or erythema and peeling have been observed in the studies by Agrawal *et al.*²⁰ and Tsiskarishvili.²¹ Such side effects were not reported by our patients. Though atrophy is an important side effect of clobetasol when used for longer periods, we did not see any such effect in our patients. This may be due to the fact that we did not use it in continuity and one week drug free interval was given after every three weeks. As response with tacrolimus was not comparable with other international publications, more studies may be required to assess the efficacy of the product in our patients.

Conclusion

We may conclude that topical tacrolimus may not be an effective therapy for vitiligo in our patients. Topical clobetasol remains to be an effective topical therapy in treating patients of vitiligo with skin type IV and type V. Intermittent use of clobetasol was as safe as continuous use of tacrolimus.

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