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Original Article

Topical calcipotriol versus oral psoralen-UVA (PUVA) and topical calcipotriol in the treatment of vitiligo in type IV skin

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Abstract

Background The treatment of vitiligo is a challenging task. Several therapeutic modalities have been tried till date. Topical calcipotriol alone and in conjunction with PUVA have shown good results in various international studies in the treatment of type I & II vitiliginous skin.

Objective Our aim was to evaluate and compare the efficacy of topical calcipotriol alone and in combination with PUVA in the treatment of vitiligo in type IV skin.

Patients and methods Sixty patients of vitiligo (26 males & 34 females), aged 12-60 years and involving < 30% of the body surface area were enrolled and randomly divided into two equal groups. Group I patients were treated with twice daily application of topical calcipotriol for six months. In group II patients, in addition to topical calcipotriol, photochemotherapy (PUVA) was advised thrice a week for the same duration. Response was graded according to the degree of repigmentation.

Results In group I, only one sixth (16.7 %) of the cases responded and all of them had less than 50% repigmentation whereas **i**n group II, all the patients responded. Seventy percent of the cases in this group showed excellent response (> 75% of repigmentation).

Conclusion We conclude that topical calcipotriol alone has no role in the treatment of vitiligo in type IV skin but when combined with PUVA leads to an excellent response in greater than two third of the patients.

Key words
Vitiligo, topical PUVA, calcipotriol.

Introduction

Vitiligo is a common, autoimmune, acquired disorder characterized by well-circumscribed milky white macules and patches devoid of identifiable melanocytes. It carries a significant risk of associated disorders, particularly thyroid disease, diabetes mellitus, Addison's disease and pernicious anaemia.[1,2]

It occurs in approximately 1% of the world's population. It affects all the races and the frequency is same in both sexes.[3,4]

Although most of the patients are physically in good health, the cosmetic disfigurement caused by this disorder may lead to

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psychogenic turmoil. In severe cases it leads to depression and suicidal tendencies.[5]

Various modalities of treatment are useful in vitiligo including photochemotherapy and corticosteroids.[6] There remains a group which is resistant to most forms of conventional therapies.[7] Topical calcipotriol alone and in combination with PUVA has shown good results in the treatment of type I & II vitiliginous skin in recent international studies.[8] The present study was conducted to compare the two modalities of treatment in our population with vitiligo, the majority of which have type IV skin.

Patients and methods

The study was conducted at the Department of Dermatology, Unit II, Mayo Hospital, Lahore, from 1st June 2004 to 1st December 2005. Sixty patients of vitiligo, diagnosed clinically, were enrolled. They were of either sex, aged 12-60 years and had stable vitiligo with involvement of <30% of body surface area. Only those patients were included who showed no evidence of spontaneous repigmentation. The duration of their disease was <5 years and they had received no treatment for the last two months.

The patients with lip-tip type of vitiligo or mucosal involvement and those who had known hypersensitivity to calcipotriol or psoralen or had shown an abnormal reaction to UVA radiation in the past were excluded. Patients who had history of photosensitivity, cataract, hypertension or any systemic disorder, arsenic exposure, pregnancy, lactation, concomitant use of vitamin D, calcium and any other drug that can affect calcium homeostasis were also excluded. Patients with hypercalcemia, hypercalciuria or urolithiasis was found on investigations were not included in the study.

An informed consent was taken. All the relevant details regarding history, examination, treatment, type of vitiligo, sites of involvement and extent of the disease were recorded on a pro forma. The surface area involved was measured according to the rule of 9. Involved skin was photographed before the start of therapy. The patients were divided into two groups. In group I, thirty patients were treated with twice daily application of topical calcipotriol ointment. In group II, thirty patients were put on combination therapy with twice daily application of topical calcipotriol ointment and ingestion of 8-methoxypsoralen followed by UVA exposure three times a week. The dose of 8-methoxypsoralen was 0.5 to 0.6 mg/kg body weight two hours before UVA (Waldmann 1000 equipment) exposure. The UVA treatment was initiated at 0.5 Joules/cm^2 (J/cm^2) with subsequent increase of 0.5 to 1.0 J/cm^2 at every third visit to achieve and maintain moderate erythema in vitiliginous lesions. The patients were advised to wear UVA protective glasses when exposed to ultraviolet light (natural or artificial) for next 24 hours. Liver and renal function tests and serum calcium level were performed before treatment and repeated monthly. Ophthalmological examination was carried out before commencement and at the end of treatment.

The patients were assessed weekly during the first month and then fortnightly for the next five months to monitor improvement and adverse effects. Photographs of

vitiliginous skin were taken after 3 and 6 months. At each visit pigmentation and adverse effects were noted. The improvement was evaluated by comparing the treated areas with pretreatment photographs. Responses were graded on a scale form 0-4, depending on degree of repigmentation, as follows: G0 - no response (0%), G1 - poor response (1-25%), G2 - fair response (26-50%), G3 - good response (51-75%), G4 - excellent response (76-100%).

Statistical analysis

Chi-square test with Yate's correction was used to analyze the results. A 0.05 level of significance in two tails was considered as significant.

Results

Sixty patients, 30 in each group, suffering from vitiligo with Fitzpatrick skin type IV completed the study. There were 14 males and 16 females in group I and 12 males and 18 females in group II, respectively, showing slight female preponderance. Group I and group II were found to be similar in age distribution which ranged from 12-60 years. The mean age in group I was 21.2±10.8 years, while in group II it was 25.3±11.9 years with no statistically significant difference. The duration of illness was <5 years in both groups. The mean duration was 1.7±1.5 years in group I and 1.8±1.4 years in group II. The two groups were well matched in terms of pretreatment parameters. The mean cumulative UVA dose in group II was 11.24 J/cm^2.

When topical calcipotriol alone was applied,

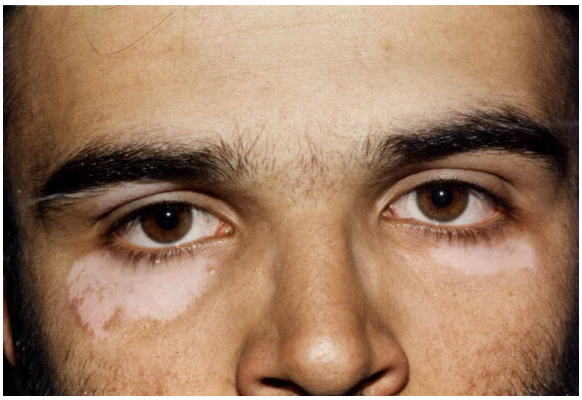

Figure 1 A 29-year-old man with vitiligo involving infraorbital regions bilaterally .

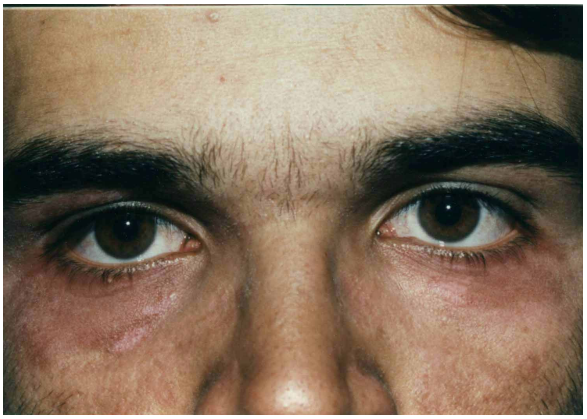

Figure 2 Patient after 3 months of dual therapy with topical calcipotriol and oral PUVA, showing 70% improvement.

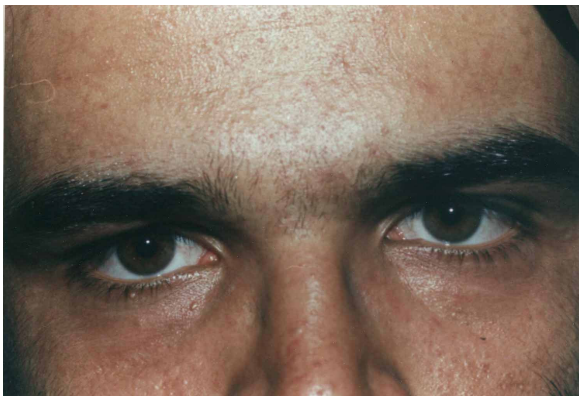

Figure 2 Patient after 6 months of treatment, showing > 90% improvement.

25 (83.3%) of the patients did not show any improvement and none of the patients had complete recovery (grade 0). Three (10%) patients fell in grade 1, while 1 (3.3%) case

each was seen in grade 2 and grade 3, respectively.

When topical calcipotriol was used along with PUVA, all the patients responded and 21 (70%) had grade 4 improvement (**Figure 1**, **2** and **3**). Six (20%) patients fell in grade 3 and 3 (10%) in grade 2. When the two groups were compared, the results of combination therapy were significantly better than calcipotriol alone, p <0.05 (**Table 1**).

The cutaneous side effects were relatively less in case of group I as compared to group II, but the difference was not statistically significant with p >0.05 (**Table 2**). Nausea and vomiting were reported by 3 patients belonging to group II.

Table 1 Comparison of results in patients treated with topical calcipotriol alone and topical calcipotriol plus PUVA

*Grade**	*Calcipotriol (n=30)*	*Calcipotriol + PUVA (n=30)*	*P-value*
0	25 (83.3%)	0	<0.001
1-3	5 (16.7%)	9 (30.0%)	>0.05
4	0	21 (70.0%)	<0.05

* 0=0% repigmentation; 1=1-25% repigmentation; 2=26-50% repigmentation; 3=51-75% repigmentation; and 4=76-100% repigmentation

Table 2 Comparison of side effects in patients treated with topical calcipotriol alone and topical calcipotriol plus PUVA

Side effects	*Calcipotriol (n=30)*	*Calcipotriol + PUVA (n=30)*
Pruritus & burning	3 (10.0%)	5 (16.7%)
Erythema	2 (6.7%)	4 (13.3%)
Xerosis	2 (6.7%)	Xerosis
Nausea & vomiting	0	3 (10.0%)

Discussion

This kind of study has been carried out for the first time in Pakistan. We found combination therapy of calcipotriol plus PUVA effective in our patients. However, calcipotriol alone was not found to be useful in type IV skin. The treatment was well-tolerated whether calcipotriol was used alone or in combination with PUVA, with no significant side effects.

The results of our combination therapy (topical calcipotriol and PUVA) are comparable with the results of a randomized left-right comparison study, carried out by Ermis *et al.*[9] (**Table 3**). The latter study which was conducted on type I and type II skin showed that concurrent topical calcipotriol potentiates the efficacy of PUVA in the treatment of vitiligo. Complete repigmentation was seen in 63% of their patients while 70% of our patients showed similar results. However, the mean cumulative dose was less (8.6 J/cm^2) in achieving complete repigmentation as compared to our study in which the mean cumulative UVA dose was 11.2 J/cm^2. Another study in which calcipotriol was given with PUVAsol showed good results in patients with type IV skin.[10] Their results also support our observation regarding the beneficial effects of combined treatment of calcipotriol with PUVA.

Comparing our results of combination therapy (calcipotriol plus PUVA) with those of Parsad[11] in which PUVA alone was used, our cases showed better results in terms of recovery (>50% improvement in 80% of cases). Only 23.6% of cases showed >50% of improvement in the study carried out by Parsad. It appears that the combined therapy

Table 3 topical calcipotriol with PUVA: comparison of results between type IV skin and type I & II skin.

	Present study 2002 (n=30)	*Ermis et al.*[9] *2001 (n=27)*
Type of skin	IV	I & II
Mean cumulative UVA dose (J/cm^2)	11.24	8.62
Complete repigmentation	21 (70.0%)	17 (63.0%)

Table 4 Topical calcipotriol alone: comparison of results between type IV skin and type I & II skin.

	Present study 2002 (n=30)	Ameen *et al.*[8] 2001 *(n=27)*
Types of skin	IV	I & II
<50% repigmentation	29 (96.7%)	10 (45.4 %)
>50% repigmentation	1 (3.3%)	12 (54.6 %)

in type IV skin results in a significantly higher percentage of repigmentation and may shorten the duration of UVA exposure, leading to decrease in the dose-dependent side effects related to PUVA. It is known that PUVA promotes the synthesis of tyrosine by stimulating the cAMP activity. Calcipotriol augments the effectiveness of PUVA by synthesis of tyrosine and melanin production. The explanation of the latter mechanism is due to the ability of calcipotriol to increase intracellular calcium leading to decrease in reduced thioredoxin concentration which is known to stimulate tyrosine activity.[8] The other reason may be that both topical calcipotriol and PUVA immunologically mediate the repigmentation process by decreasing the antigenic potential of antibodies directed against melanocytes and Langerhans cells.[12,13]

Though our results of combined therapy are comparable with the previous studies, our experience regarding monotherapy (calcipotriol alone) differs. Fifty five percent of the patients in a study by Amin *et al.*[8] showed >50% of improvement whereas only 3.3% of our patients had similar degree of response (**Table 4**). It is difficult to understand the reason for this difference. Defective calcium up take has been demonstrated in both melanocyte and keratinocyte cell cultures from vitiliginous skin leading to high intracellular concentration of reduced thioredoxin.[14,15] This inhibits tyrosinase activity and decreases the synthesis of tyrosine and melanin.[14] Also vitamin D3 receptors are present on melanocytes.[16] It has been suggested that vitamin D3 is involved in the regulation of melanin synthesis.[17] Calcipotriol enhances vitamin D3 receptors in psoriatic skin,[18] suggesting its possible mode of action in vitiligo. Though the number of melanocytes is same in all types of skin it could be due to a fault at the receptor level in type IV vitiliginous skin. The defect may be in the number or function of vitamin D3 receptors.

We conclude from our study that topical calcipotriol alone has no role in the treatment of vitiligo in type IV skin, but has a beneficial effect when added to PUVA. Further studies regarding monotherapy with either PUVA or calcipotriol and their comparison with combination therapy (calcipotriol+PUVA) may help in clarifying the role of calcipotriol in vitiligo in different types of skin.

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