

Original Article

Efficacy of tacrolimus plus narrowband ultraviolet B phototherapy versus narrowband ultraviolet B phototherapy alone in the treatment of vitiligo

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Abstract *Objective* To compare the efficacy of tacrolimus plus narrowband ultraviolet B (NB-UVB) phototherapy versus NB-UVB phototherapy alone in the treatment of vitiligo .

Methods A total of 94 patients were randomized into two equal groups A and B. Patients in group A were managed with combined treatment i.e. NB-UVB three times a week plus topical tacrolimus 0.1% once daily application while patients in group B will be subjected to NB-UVB alone three times a week alone for three months. The efficacy was determined in term of repigmentation by measuring vitiligo area severity score.

Results 41 (87.2%) patients in group A achieved efficacy while group B showed efficacy in 32 (68.1%) patients ($p=0.022$). Efficacy was unrelated to age, sex, severity and duration of vitiligo.

Conclusion Combination therapy is more effective than monotherapy in the treatment of vitiligo.

Key words

Efficacy, tacrolimus, narrowband ultraviolet B, vitiligo.

Introduction

Vitiligo is a common acquired, idiopathic pigmentary disorder characterized by progressive circumscribed depigmented macules or patches that corresponds histologically with reduced or absent cutaneous melanocytes. It affects 1% of world's population,¹ though the prevalence has been reported as high as 4% in some South Asian, Mexican and American populations.² It is considered as one of the most prevalent depigmentary condition affecting 3-4% of Indian population.³ In Pakistan the reported prevalence is 4.4-7.5 %.⁴

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The exact cause of vitiligo is unknown. It occurs at any age, irrespective of race, ethnic group or skin colour. Both sexes are affected equally though female predominance has been reported.⁵ Vitiligo is divided into generalized or non-segmental vitiligo characterized by white patches, often symmetrical, usually increasing in size with time and localized or segmental vitiligo characterized by white patches with unilateral distribution that may totally or partially match a dermatome but not necessarily.¹

There is no universally effective therapy specific for vitiligo. Different treatment options currently available are directed towards stopping progression of the disease and achieving repigmentation.^{1,4,6} Therapies include topical corticosteroids, topical immunomodulators,

calcium modulators, phototherapy, surgery, lasers, combination therapies, depigmentation of normally pigmented skin and adjunctive therapies like sunscreen and camouflage.⁷ Among the available therapies, narrowband ultraviolet B (NB-UVB) phototherapy is considered as the 'gold standard' for the treatment of diffuse vitiligo due to its simplicity, safety and efficacy.^{8,9} Many studies have reported the efficacy and safety of tacrolimus ointment in vitiligo inducing repigmentation especially when located on head and neck.^{1,10} Combination of NB-UVB with tacrolimus is the most effective with the least side effects.^{6,9,11}

Tacrolimus (FK-506) is an immune modulator inhibiting T cell activation and the production of proinflammatory cytokines, whose levels are higher in vitiligo lesional skin. It also enhances the proliferation of melanocytes.^{1,7,12} NB-UVB radiation with an emission spectrum of 310-312 nm induces local immunosuppression and stimulates the proliferation of melanocytes in the skin and the outer root sheath of hair follicles. There is a stimulatory effect on melanogenesis by increased production of melanocyte stimulating hormone and tanning.²

As melanogenesis is a complex, multi-stage process and different topical agents act at different stages of the process, thus providing a rationale for combinations of agents i.e. topical with phototherapy to act in synergism for better therapeutic results.¹³

The present study was undertaken to compare the efficacy of tacrolimus plus NB-UVB phototherapy versus NB-UVB phototherapy alone in the treatment of vitiligo.

Methods

This randomized controlled trial was conducted at department of dermatology, Lady Reading

Hospital, Peshawar from September, 2013 to March, 2014.

Sample size Total sample size was 94 patients i.e. 47 in each group with 5% level of significance and 90% power of test, efficacy in combination group taken as 74.35% and in NB-UVB alone group, the efficacy taken as 45.3%¹³ using WHO software for sample size determination.

Patients with pregnancy and lactation, history of skin malignancy or pre malignant skin lesions, history of photosensitivity and erythroderma, Other forms of treatment for vitiligo within the previous 3 months, diabetes mellitus, thyroid disease, herpes simplex, bacterial and fungal infection were excluded from the study as these factors act as confounders and effect the study results.

Data collection procedure After approval from hospitals ethical and research committee, all patients meeting the inclusion criteria were included in the study through OPD. Patients were subjected to detailed history, examination, taking note of the number of depigmented macules and approximate percentage of body surface area by using "rule of nine". Relevant hematological and biochemical investigations were carried out. All patients were randomly allocated into two groups by lottery method. Patients in group A were subjected to combined treatment i.e. NB-UVB phototherapy three times a week plus topical tacrolimus 0.1% once daily application while patients in group B were subjected to NB-UVB treatment three times a week alone for three months. The starting dose of NB-UVB was based on the minimum erythema dose. The efficacy in either group was considered successful if there was repigmentation $\geq 75\%$ in vitiligo lesions. Efficacy was measured in the form of percentage of repigmentation of target lesion/lesions, and

was measured at the end of 12 weeks with responses analyzed with vitiligo area and severity index (VASI) repigmentation score.

Results

Out of 47 patients in group A, 16 (34%) were males and 31 (66%) were females while group B comprised of 19 (40.4%) males and 28 (59.6%) females. Male to female ratio was 0.59:1. Sex distribution among the groups was insignificant ($p = 0.522$).

Mean age was 28.59 ± 8.86 years with range of 15-51 years. In group A 14 (29.8%) patients were ≤ 25 years, 27 (57.4%) 26-40 years and 6 (12.8%) patients between the ages >40 years. While in group B, 17 (36.2%) patients were ≤ 25 years, 26 (55.3%) in 26-40 years and 4 (8.5%) patients with age >40 years. The age distribution among the groups was also insignificant ($p = 0.701$).

Regarding efficacy, 41 (87.2%) patients in group A gained efficacy while treatment was ineffective in 6 (12.8%) patients. Similarly, group B showed efficacy in 32 (68.1%) patients while treatment was not effective in 15 (31.9%) patients. The combination therapy had greater efficacy than monotherapy ($p=0.022$).

In both groups, A and B, the age of the patients did not affect the treatment efficacy in both groups, $p=0.748$ and 0.610 , respectively (Table 1).

When efficacy was stratified according to gender, in both groups it did not differ significantly (Table 2). In group A, 93.7% males improved as compared to 83.9% females ($p=0.336$). Similarly, efficacy in males and females in group B was 63.1% and 71.4%, respectively ($p=0.551$).

Table 1 Comparison of efficacy in two treatment groups in different age groups.

			Age (years)						p-value	
			≤25		26-40		≥41			
			N	%	N	%	N	%		
Groups	A	Efficacy	Yes	13	13.8%	23	24.5%	5	5.3%	0.748
			No	1	1.1%	4	4.3%	1	1.1%	
	B	Efficacy	Yes	11	11.7%	19	20.2%	2	2.1%	0.610
			No	6	6.4%	7	7.4%	2	2.1%	

Group A: narrowband UVB and tacrolimus, group B: narrowband UVB alone.

Table 2 Comparison of efficacy in two treatment groups in males and females.

			Gender				p-value	
			Male		Female			
			N	%	N	%		
Groups	A	Efficacy	Yes	15	93.7%	26	83.9%	0.336
			No	1	7.3%	5	16.1%	
	B	Efficacy	Yes	12	63.1%	20	71.4%	0.551
			No	7	36.9%	8	28.6%	

Group A: narrowband UVB and tacrolimus, group B: narrowband UVB alone.

Table 3 Stratification wise distribution of efficacy

		Groups								p values
		A				B				
		Efficacy				Efficacy				
		Yes		No		Yes		No		
		N	%	N	%	N	%	N	%	
Baseline VASI Score	≤ 10.00	30	31.9%	3	3.2%	26	27.7%	10	10.6%	0.271
	>11.00	11	11.7%	3	3.2%	6	6.4%	5	5.3%	
Duration of vitiligo (years)	≤5.00	4	4.3%	0	0%	4	4.3%	0	0%	0.152
	>6.00	37	39.4%	6	6.4%	28	29.8%	15	16.0%	
Fitzpatrick skin type	II	10	10.6%	4	4.3%	9	9.6%	3	3.2%	0.310
	III	9	9.6%	0	0%	5	5.3%	6	6.4%	
	IV	9	9.6%	1	1.1%	8	8.5%	2	2.1%	
	V	13	13.8%	1	1.1%	10	10.6%	4	4.3%	

Group A: narrowband UVB and tacrolimus, group B: narrowband UVB alone.

When stratification was made over baseline VASI score, duration of vitiligo and Fitzpatrick skin type in both the groups, efficacy did not show significant difference in both the groups (Table 3).

Discussion

Vitiligo is the most common depigmentation disorder of the skin affecting around 0.5% of the population worldwide. The British Association of Dermatologists clinical guidelines for the management of vitiligo recommend narrowband ultraviolet light B (NB-UVB), (311 to 312 nm), tacrolimus, and topical steroids to treat the condition.¹⁴

The Cochrane systematic review update concluded that light combination interventions were superior to monotherapies. However, larger studies are needed to provide stronger evidence for the many combination interventions that have shown promise in treating vitiligo.¹⁵

NB-UVB has been used in combination with different topical agents to increase its efficacy and thus shorten the total duration of treatment. Treatment options that have been used with NB-

UVB in vitiligo till date include topical tacrolimus.^{16,17}

Several factors appeared to affect the degree of treatment response, including site of disease, darker skin color, and age. Patients who had casual, daily sun exposure to the application site during treatment experienced the greatest benefit from tacrolimus ointment 0.1%. Patients with darker skin tones, especially those with disease involvement of the head and neck, had the best response. The younger patients in this series also appeared to respond particularly well.^{18,19}

Tacrolimus does not cause skin atrophy even in the long term therapy.¹⁹⁻²²

Regarding topical corticosteroids, one randomized controlled study compared 0.1% tacrolimus and 0.05% clobetasol cream in 20 children with vitiligo. The level of repigmentation was 49.3% with clobetasol and 41.3% with tacrolimus.²³ Despite the best answer, the side effects associated with corticosteroids, mainly in the acrofacial lesions, are relevant. Dawid *et al.*²⁴ performed a double-blind, intra-patient comparison of 1% pimecrolimus cream with placebo cream in 20

patients with vitiligo predominantly situated on the extremities and not on the face and found no significant change in mean target lesion.²⁴

According to patients evaluation the level of repigmentation of 50% was considered cosmetically satisfactory. Among the established therapies phototherapy and photochemotherapy have limited use for adverse reactions, difficult access to the sources of light and time spent during treatment.

In a recent study Ordal *et al.*²⁶ found combination of NB-UVB and tacrolimus ointment to be more effective than UV monotherapy in patients with vitiligo.²⁵ However, NB-UVB was administered for a minimum period of 3 months. Other studies with smaller sample size have found better pigmentation in NB-UVB and tacrolimus arm although the difference was not statistically significant.^{26,27} In our study 28% of patients had >75% repigmentation. This is in contrast to the previous studies where higher pigmentation rate was achieved.^{17,28} This can be attributed to the fact that in our study 50% of the lesions were at resistant sites, where as in the previous studies the proportions of lesions at resistant sites were less,²⁶ or such sites were excluded from the analysis.^{28,29} Grade of pigmentation completely depended on the site of lesions. The pigmentation was more on lesions over face, trunk and limbs. Similar results were obtained in the study by Fai *et al.*¹⁷

Conclusion

Treatment of vitiligo with tacrolimus ointment 0.1% and narrowband ultraviolet B phototherapy produced repigmentation in the majority of patients in this series. Further clinical studies are warranted to determine which vitiligo patients are most likely to benefit from topical tacrolimus therapy, and whether the best response is

attained with topical tacrolimus monotherapy or with combination therapy using additional treatment modalities. Studies investigating the safety of topical tacrolimus in combination with natural sunlight, UV light, excimer laser, and PUVA also are warranted.

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