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Original Article

Effect of Topical Tacrolimus on Vitiligo in Children

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Abstract

***Background**: Considering safe treatment modalities for children with vitiligo, search for newer therapeutic agents continues. Hence, new immunomodulatory agents such as calcineurinantagonists, frequently referred to as topical immunomodulators (TIMs) have recently been introduced as new promising tools to treat acquired hypopigmentary disorders. Tacrolimus is safe in treating children due to lack of skin atrophy and less data are available on effect of topical tacrolimus on vitiligo.* ***Objective**: To see the effect of topical tacrolimus on vitiligo in children.* ***Materials and Methods**: This prospective study was done in outpatient department of Dermatology and Venereology, Chittagong Medical College Hospital (CMCH), Bangladesh. Clinically diagnosed vitiligo patients of up to 12 years age visiting Skin & VD OPD, CMCH during study period were the study population (total 30). The study was carried out from November 2007 to April 2008.* ***Results**: A total of 30 patients, 13 (43.33%) males and 17 (56.66%) females with focal, segmental or generalized vitiligo were studied. Seventy percent of study subjects were from 7–12 years of age. Topical tacrolimus 0.03% ointment was administered twice daily for 12 weeks to each patient. Repigmentation was complete (>75%) in 43.33% cases (13/30), was moderate (50–75%) in 33.33% (10/30), mild (<50%) in 13.33% (4/30). Clinical adverse effects were noted in 6.67% (2/30) of cases where pruritus was in 3.33% (1/30) and burning in 3.33% (1/30). None of the reactions was severe, all were mild and well-tolerated and most occurred within the first month of initiation of treatment and resolved with continued use of drug and completely cured after the treatment completed. Nobody had to discontinue the therapy for side effects.* ***Conclusion**: In conclusion, tacrolimus ointment may be a rapidly efficacious and safe option for the treatment of vitiligo in children. The ease of topical self-administration with minimal side effects makes this novel immunomodulatory agent a promising addition to the therapeutic armamentarium for vitiligo in children.*

***Key words**: Vitiligo; Tacrolimus; Macules; Patches; Immunomodulator; Topical*

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Introduction

The word vitiligo is derived from Greek word 'vitilus' which means spotted calf.[1] Vitiligo is a specific, common, often heritable acquired disorder characterized by well circumscribed milky white cutaneous macules and patches devoid of identifiable melanocyte.[2]

Vitiligo, which is benign and noninfectious in nature, involves 1–2% of the world population. Patients

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affected by vitiligo have a vast reduction of quality of life caused by the color contrast between healthy pigmented skin and the depigmented vitiliginous patches that give the patients psychological problems.[3] All races are affected. Both sexes are affected equally; the female prevalence in some studies can probably be attributed to greater concern and greater willingness to express concern about a cosmetic defect.[2]

Vitiligo may develop at any age. Onset has been reported from birth to 81 years age. Congenital vitiligo is very rare. Vitiligo usually begins in childhood. The prevalence of the disease in the United States has been estimated at 1%, although large studies in other countries have shown a prevalence of 0.38% in Denmark, 1.13% in Surat, India and 0.46% in Kolkata, India.[1] The peak age of onset in all series was between 10 to 30 years approximately. One-half of those with vitiligo acquire the disease before the age of 20 years.[2]

In vitiligo, a number of treatment modalities have been employed in the past 30 years. These include phototherapy such as psoralens with exposure to ultraviolet A (PUVA) radiation therapy, narrow band UVB, surgical skin grafts, micropigmentation and immunomodulators that can be applied alone or in combination.

Abnormalities in both humoral and cell mediated immunity have been documented in vitiligo patients and they present a basis for using immunomodulating agents such as corticosteroids and immunomodulators in the treatment of vitiligo.[4] Among the immunomodulators, corticosteroids have been used both topically and systemically over the past 3 decades for the treatment of disseminated vitiligo. Again topical immunomodulators (TIMs), agents that regulate the local immune response of the skin, are now emerging as the therapy of choice for several immune mediated dermatoses such as atopic dermatitis, contact allergic dermatitis, alopecia areata, psoriasis, vitiligo, connective tissue disorders such as morphea and lupus erythematosus, disorders of keratinization and several benign and malignant skin tumors because of their comparable efficacy, ease of application and greater safety than their systemic counterparts. They can be used on a domiciliary basis for longer periods without aggressive monitoring.[5] Topical corticosteroid was eventually found suitable for the treatment of only acrofacial and localized forms because of adverse effects. Considering the lack of uniformly effective and safe treatment modalities for children with vitiligo, search for newer therapeutic agents continues. Hence, new immunomodulatory agents such as calcineurinantagonists, frequently referred to as TIMs have recently been introduced as new promising tools to treat acquired hypopigmentary disorders.[5]

TIMs inhibit T-cell activation and the production of the various cytokines; this is considered as the working mechanism of action of TIMs in vitiligo till now. Tacrolimus achieves better results on the face and neck than on the other body areas. Particular advantages of TIMs are safety in treating these areas because of lack of skin atrophy and good tolerance. The incidence of application site adverse events in vitiligo seems to be lower than in the treatment of atopic dermatitis. On the face and neck, TIMs may become a useful tool in the treatment of adults and children with vitiligo despite possibly lower efficacy than topical corticosteroids.[4] In this study, we evaluate the effects of tacrolimus in children with vitiligo.

Materials and Methods

This prospective study was carried out from November 2007 to April 2008 at the Skin & Venereal Diseases outpatient department, Chittagong Medical College Hospital(CMCH), Chittagong. Clinically diagnosed vitiligo patients of up to 12 years age visiting Skin & VD OPD, CMCH during study period were the study population (total 30).

Data-collecting instruments included structured questionnaire, observation check list, photographic camera and measuring tape. Each patient was treated with twice daily topical application of tacrolimus 0.03% ointment to target lesions for 12 weeks. Patients who had not received any treatment for vitiligo (both systemic and topical) in the previous 2 months prior to inclusion were included. Patients aged more than 12 years, patients who refused to be included in the study, known cases of tacrolimus sensitivity, patients taking or requiring any steroids, patients with extensive vitiligo, with albinism and hypopigmented nevus were excluded from the study. Data of all the selected patients were recorded. At the baseline visit, history of vitiligo regarding age of onset, duration, pattern of presentation (focal, segmental, generalized), affected sites, presence of leukotrichia, Koebner phenomenon, halo nevus, concomitant infection, history of trauma or skin infection or sun exposure or exposure to chemical, drug ingestion were taken. Patients were asked about

previous use of tacrolimus and any hypersensitivity to these agents. They were searched for any associated diseases like diabetes mellitus, thyroid disorders, alopecia areata, Addison' s disease and polyglandular syndrome. Family history of vitiligo was taken. Efficacy and safety were evaluated in every follow-up visit at one month interval and finally evaluated at the 4th visit.

In addition to the required data on patients' history and diagnosis, also clinical responses were documented during visits and by pre-tacrolimus and post-tacrolimus photography. Representative lesions of vitiligo excluding mucosal sites were selected in each patient and photographed at baseline. The efficacy of the preparations were documented by counting the grading number of repigmentations, status of site of the lesions at the start and at the end by using a 4 point score [0=none, 1=mild or <50% repigmentation, 2=moderate or 50–75% repigmentation, 3=complete or >75% repigmentation]. The repigmentations were labeled as marginal, perifollicular, diffuse or combined.

Safety of the medication of treatment was assessed by observing the side effects such as itching, tingling, hyperesthesia, erythema, irritation, burning, telangiectasias and atrophy of the skin. Safety parameters (itching, erythema, irritation) were evaluated in the same way using a 4 point score (categories: absent, mild, moderate, severe).

Statistical methods

Each individual patient had a separate code number. All data were collected in the structured questionnaire and entered into a personal computer. Analysis of the data was done by Microsoft Office Excel program.

Results

The study was carried out on 30 vitiligo patients (age up to 12 years) for a period of 12 weeks. Majority of the patients suffering from vitiligo were in the age group of 7–12 years (Table I) and majority were females (56.66%); 16.67% of cases had family history of vitiligo. Eighty per cent cases had no history of previous skin lesions (Table I), 6.67% had associated diseases, among them one had thyroid disorder and another had alopecia areata. Generalized vitiligo was the most common (46.67%) presentation followed by focal type (43.33%) (Table I). In 73.33% cases vitiligo lesions were symmetrical; 23.33% cases had lesions of face, head and neck areas (Table I). Among the cases marginal type of repigmentation was the most common (40%) followed by perifollicular type (33.33%) among repigmented cases (Table I). Repigmentation was observed in 4 cases (13.33%) on the 1st follow-up visit at the end of 4 weeks. At the next visit, it was observed in 22 cases (73.33%) and after 12 weeks of therapy with tacrolimus ointment 27 cases (90%). Among those who had repigmentation, 43.33% (13/27) had >75% repigmentation, 33.33% (10/27) had 50–75% repigmentation and 13.33% (4/27) had <50% repigmentation (Table II). In generalized type 92.86% had at least some pigmentation, in focal type 92.31% had at least some pigmentation and in segmental type 66.66% had some pigmentation. Side effects were minimum. Pruritus was observed in 3.33% of cases and burning in 3.33% cases; but overall side effects (6.67%) were statistically insignificant. The majority of the patients seemed to be without any side effects during the whole course of therapy (Fig 1).

Table I: Distribution of the study patients by age, skin lesions before developing vitiligo, types of vitiligo, site of lesions and pattern of repigmentation (n=30)

Variables	Number	Percentage
Age group		
0–6 yrs	9	30
7–12 yrs	21	70
Skin lesions before vitiligo		
Dermatoses	3	10
Trauma (fall, burn etc.)	2	6.67
Drug reaction	1	3.33
No lesion	24	80
Types of vitiligo		
Generalized	14	46.67
Focal	13	43.33
Segmental	3	10
Involved body sites		
Face, head & neck	7	23.33
Trunk & extremities	10	33.33
Combined	13	43.33
Repigmentation pattern		
Marginal	12	40
Perifollicular	10	33.33
Diffuse	2	6.67
Combined	3	10
No pigmentation	3	10

Table II: Response after 12 weeks in different types of vitiligo

Types of vitiligo	Response			
	Complete	Moderate	Mild	None
Generalized (n=14)	6 (42.86%)	5 (35.71%)	2 (14.29%)	1 (7.14%)
Focal (n= 13)	7 (53.85%)	4 (30.77%)	1 (7.69%)	1 (7.69%)
Segmental (n=3)	0	1 (33.33%)	1 (33.33%)	1 (33.33%)

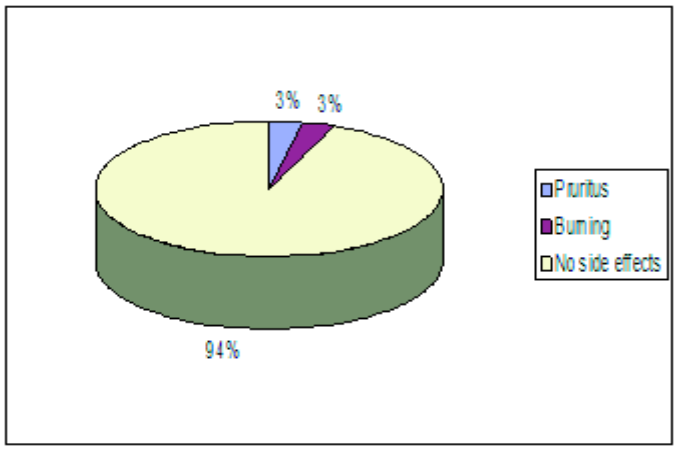

Fig 1. Side effects during therapy in the study subjects

Discussion

Topical immunomodulatory agents such as tacrolimus and pimecrolimus have come into focus for several reasons. These agents are extremely well-tolerated in children and adults and can be used for long duration without evidence of atrophy or telangiectasias, the common complications associated with long term use of corticosteroids. This is an advantage in treating a chronic disease such as vitiligo. As long term data about use of these agents for treatment of vitiligo in children are currently lacking, this study is relevant in this perspective.

In our study majority (56.67%) of vitiligo patients were of female sex. This finding correlated with the study done by Kanwar et al[6] who found female 59.09%. The incidence of a positive family history has variously been reported with a range between 6.25% to 38%.[7] In our study positive family history was found in 16.67% cases; this corroborates with the study done by Jarallah et al[8] who found it in 12% cases.

Prior to the development of vitiligenous lesions, finding of history of dermatoses (10%) and trauma (6.67%) in our study also correlates with the findings of the study conducted by Chowdhury et al[9] where they found 10% cases with history of preexisting dermatoses and 6% with trauma.

In our study few of the cases (6.67%) were found to have an association with systemic diseases, one had thyroid disorder and another had alopecia areata. This corroborates with the study done by Jarallah et al.[8]

In this study generalized, focal and segmental types of vitiligo were in 46.67%, 43.33%, and 10% cases. These findings correspond with the study done by Kanwar et al[6] where these were 54.5%, 40.9% and 4.5% respectively.

In our study vitiligo lesions were on face, head and neck areas in 23.33% cases. This is almost similar with the study conducted by Jarallah et al[8] where the researchers showed it 25.1%. The lesions were symmetrically distributed in most of the cases (73.33%) which is supported by the findings in the study done by Chowdhury et al[9] where they found it 60%.

In this study overall response to topical tacrolimus in the treatment of vitiligo in children has been observed. Ninety percent cases (27/30) had at least mild repigmentation. Among those who had repigmentation, 43.33% (13/27) had >75% repigmentation (complete), 33.33% (10/27) had 50–75% repigmentation (moderate) and 13.33% (4/27) had <50% repigmentation (mild). These results closely correlate with the study done by Kanwar et al[6] where 86.4% children showed some pigmentation at the end of 3 months. Repigmentation was complete, moderate and mild in 57.9%, 26.3%, 15.7% cases respectively.

The types of repigmentation were marginal in majority of cases (40%), perifollicular in 33.33% and diffuse in 6.67% cases. No repigmentation was seen only in 10% cases. It differs from the study done by Silverberg et al[10] where the diffuse pattern was in 57% and follicular pattern in 32% cases.

The speed of repigmentation was more marked within eight weeks. In 4^{th} week 13.33% repigmentation occurred, in 8^{th} week it was 73.33%. This result is supported by the study conducted by Grimes et al[11]; they demonstrated moderate and excellent repigmentation within eight weeks of treatment.

The present study further documents the safety of tacrolimus for the repigmentation in vitiligo in

children. Because of the need for an effective therapy with a positive benefit risk profile, the results of the study are quite promising. Twice daily tacrolimus (0.03%) ointment therapy was well-tolerated. Report of side effects from this study was only 6.67% and were transient and mild; no patient discontinued therapy due to adverse effects. In this study 93.33% patients were free from any kind of side effects like pruritus and burning. This result is supported by the study done by Silverberg et al[10] and Grimes PE et al[11].

In conclusion, it is proposed that tacrolimus ointment may be a rapidly efficacious and safe option for the treatment of vitiligo in children. The ease of topical self-administration with minimal side effects makes this novel immunomodulatory agent a promising addition to the therapeutic armamentarium for vitiligo in children.

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