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ORIGINAL ARTICLE

A Pilot Study of 1% Pimecrolimus Cream for the Treatment of Childhood Segmental Vitiligo

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Background: There is as yet no effective and safe treatment for vitiligo. One percent pimecrolimus cream, a topical calcineurin inhibitor, has been tried for the treatment of vitiligo, with its therapeutic efficacy having mostly been reported in non- segmental vitiligo. However, questions about the therapeutic efficacy of 1% pimecrolimus cream have remained unanswered regarding segmental vitiligo. **Objective:** The aim of this study was to study the therapeutic efficacy and safety of 1% pimecrolimus cream for segmental childhood vitiligo. **Methods:** Nine childhood patients with segmental vitiligo were treated with 1% pimecrolimus cream twice daily for three months, after which good responders were scheduled to continue with the 1% pimecrolimus cream monotherapy. The efficacy and safety of this treatment were determined by the levels of repigmentation, initial response time and the presence of adverse events including burning, dryness, stinging and itching. **Results:** Four of nine patients achieved mild to moderate responses after three months of treatment and thus continued with treatment. Among these four patients, three achieved an excellent response and one patient achieved a moderate response, with a mean treatment duration of 7.3 months. Transient local burning sensation was the most common adverse event. In comparison with the patients with poor response, those patients with good response showed a shorter disease duration (8.5 ± 10.5 mo vs. 13.4 ± 10.1 mo), more frequent facial involvement (4/4 patients vs. 3/5 patients) and earlier initial response after treatment (1.0 ± 0.0 mo vs. 2.0 ± 1.0 mo). **Conclusion:** This study suggests that 1% pimecrolimus cream is an effective and well-tolerated treatment for segmental childhood vitiligo. **(Ann Dermatol 25(2) 168～172, 2013)**

Key words: Pimecrolimus, Vitiligo

INTRODUCTION

Vitiligo is an acquired pigmentary disorder characterized by white macules that result from a loss of functioning melanocytes[1]. Clinical forms of vitiligo are classified into two subtypes: non-segmental and segmental vitiligo[1]. The former accounts for 85% to 95% of cases and usually presents with symmetrical lesions. By contrast, segmental vitiligo is characterized by unilateral lesions with a dermatomal distribution and tends to occur at an earlier age than does the non-segmental form. Although the etiology of vitiligo is poorly elucidated, there are four major hypotheses: the autoimmune hypothesis, the neural hypothesis, the biochemical hypothesis and the impaired redox status hypothesis[1].

Various therapeutic modalities are available for the treatment of vitiligo, but these therapeutic modalities are reported to have limited therapeutic efficacy and a relatively high occurrence of adverse events. Thus, there remains a demand for new therapies. Calcineurin inhibitors (tacrolimus and pimecrolimus) have been reported to show a good therapeutic efficacy for vitiligo without glucocorticoid-induced adverse events[2-9]. Although a

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small number of patients with segmental vitiligo have been included in several studies examining the effect of pimecrolimus on vitiligo[5,10], these reported studies were performed mostly for non-segmental vitiligo. As such, the therapeutic efficacy of pimecrolimus for segmental vitiligo has not as yet been specifically studied. Herein, we report the result of 1% pimecrolimus cream monotherapy for the treatment of childhood segmental vitiligo.

MATERIALS AND METHODS

Patients

Children with segmental vitiligo were recruited and informed consent was obtained from their parents. Patients with segmental vitiligo affecting less than 10% of their body surface were included and those who completed at least three months of 1% pimecrolimus cream monotherapy were evaluated. Patients were excluded if they had a history of spontaneous repigmentation of vitiligo lesions, malignant diseases or autoimmune disorders such as thyroid disorders, diabetes mellitus, pernicious anemia, Addison's disease, alopecia areata or lupus erythematosus. Any concomitant treatment for vitiligo was restricted for four weeks before this study commenced.

Treatment methods

All patients were instructed to apply 1% pimecrolimus cream twice daily over the vitiligo lesions for three months. Patients with mild to excellent responses after three-month treatment of topical pimecrolimus persisted with a further three-month use of this treatment, whereas patients with no or minimal responses were moved to receive combined therapy of 1% pimecrolimus cream and phototherapy such as excimer laser treatment (data not shown). The final assessment of therapeutic efficacy was performed when the patient discontinued with the 1% pimecrolimus cream monotherapy. Patients were instructed to use sunscreen on their vitiligous lesions during the treatment.

Response to treatment

The extent of repigmentation was evaluated monthly by a single dermatologist by comparing photographs taken before and during the treatment. Treatment responses were graded as excellent (76～100%), moderate (51～75%), mild (26～50%), minimal (1～25%) or no response, according to the extent of repigmentation.

Adverse effects

Treatment-related adverse events such as burning, dryness,

Table 1. The basic characteristic and response rate of patients

Number	Age	Sex	Involved site	Koebner phenomenon	Poliosis	Duration of disease (mo)	Previous treatment	Past history	Family history	Treatment period (mo)	Onset of repigmentation (mo)	Response rate at 3 months	Response rate at the final assessment	Subsequent treatments	Side effect
1	8	F	Face	-	-	5	None	None	None	11	1	Mild	Excellent	None	Itching
2	10	M	Face	+	-	1	None	Tic disorder	None	6	1	Moderate	Excellent	None	None
3	16	M	Face	-	-	24	None	None	None	6	1	Moderate	Excellent	None	Burning
4	6	M	Face	-	+	4	None	None	None	6	1	Mild	Moderate	None	Burning
5	8	F	Face	-	-	24	None	None	None	3	2	Minimal	Minimal	Excimer laser	None
6	11	M	Buttock	-	-	2	Topical glucocorticoid	None	None	5	1	Minimal	Minimal	None	None
7	6	M	Lt. arm	-	-	7	None	None	None	3	1	Minimal	Minimal	None	None
8	8	M	Face	-	-	24	None	Atopic dermatitis	None	3	3	Minimal	Minimal	Excimer laser	None
9	4	M	Face	-	-	10	None	None	None	3	3	No	Minimal	Excimer laser	None

F: female, M: male, Lt.: left.

stinging or itching were assessed throughout this study.

RESULTS

Patients

Of the nine patients enrolled in this study, seven were male and two were female with a mean age of 8.6±3.5 (range 4~16 yr). The mean duration of disease was 11.2±9.9 months (range 1~24 mo) and the involved sites were the face (n=7), arm (n=1) and buttocks (n=1). One patient had poliosis associated with vitiligo and another patient experienced the Koebner phenomenon. With respect to the treatment history, one patient had experienced treatment failure with topical glucocorticoid. None of the children had any associated autoimmune disease but one had atopic dermatitis and another had a tic disorder. There was no family history of vitiligo in their first- or second-degree relatives. All laboratory results were within normal parameters in all patients. The basic characteristics and response rates of patients are summarized in Table 1.

Response to treatment

All of the nine patients treated with 1% pimecrolimus cream for more than three months qualified for evaluation. Three months after the treatment, two showed moderate response, two showed mild response, four had minimal response (Fig. 1) and one patient had no response. The four patients with mild to moderate responses after three months of treatment continued with the 1% pimecrolimus cream monotherapy and achieved an excellent response (n=3, 75.0%) (Fig. 2) or a moderate response (n=1, 25.0%) at the final assessment. The mean treatment duration of these four patients was 7.3 months. Meanwhile, one patient (case 6) who showed minimal response after three months of treatment continued to receive two more months of topical therapy, because he could not visit the clinic for phototherapy and wanted to continue the 1% pimecrolimus monotherapy. However, in this patient the vitiligo lesions did not show any greater

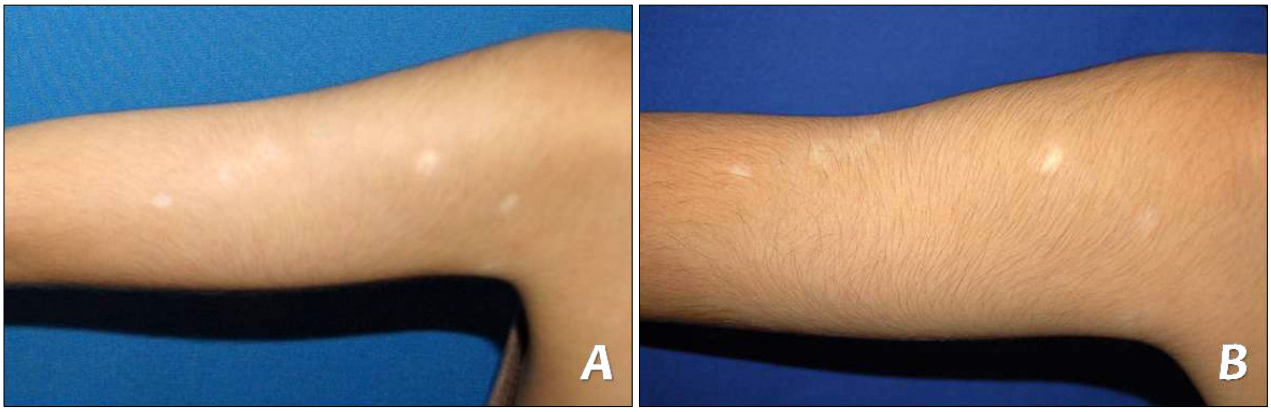

Fig. 1. Six-year-old male patient with minimal response to 1% pimecrolimus cream in vitiligo. (A) Before treatment, (B) after three months of treatment.

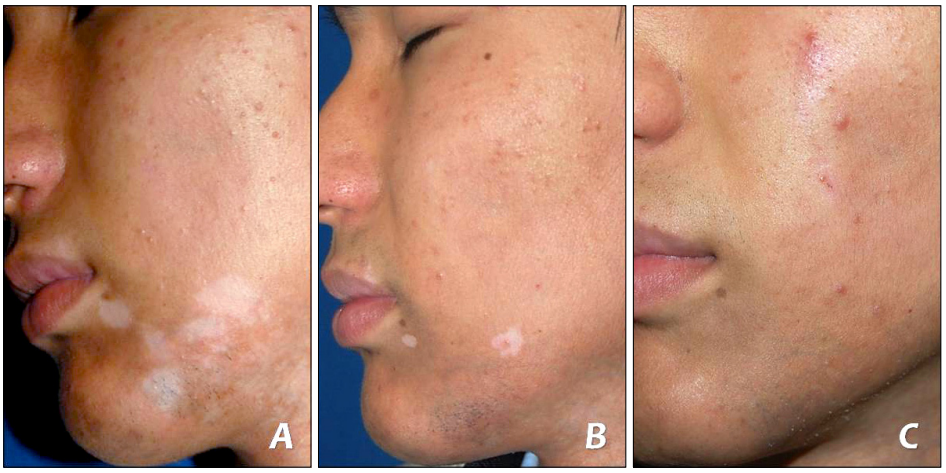

Fig. 2. Sixteen-year-old male patient with excellent response to 1% pimecrolimus cream in vitiligo. (A) Before treatment, (B) after three months of treatment, (C) after six months of treatment.

Table 2. The epidemiologic and therapeutic factors of two groups, classified by the treatment response after 3 months of treatment

Variable	Mild to moderate response	No or minimal response
Number of patients	4	5
Sex		
Male	3	4
Female	1	1
Age (yr)	10±4.3	7.4±2.6
Involved site		
Face	4	3
Arm	0	1
Buttock	0	1
Disease duration (mo)	8.5±10.5	13.4±10.1
Onset of response (mo)	1.0±0.0	2.0±1.0
Response at the final assessment	3 excellent 1 moderate	5 minimal

response in spite of his prolonged topical therapy.

In this study, there were some differences between the four patients with mild to moderate responses and the five patients with no or minimal responses after three months of treatment. Specifically, the former patient group had a comparatively shorter disease duration (8.5±10.5 mo vs. 13.4±10.1 mo), more frequent facial involvement (4/4 patients vs. 3/5 patients) and an earlier initial response after treatment (1.0±0.0 mo vs. 2.0±1.0 mo). Statistical analyses were not performed due to the small number of patients included in this study (Table 2).

Adverse effects

The treatment-related adverse events were local burning, which was reported by two patients, and itching, which was reported by one patient. These adverse events were mild and transient, and did not require the cessation of treatment.

DISCUSSION

Pimecrolimus, a calcineurin inhibitor, has been introduced for the treatment of vitiligo, showing good therapeutic efficacy and a lack of glucocorticoid-related side effects such as skin atrophy and telangiectasia[2-9]. However, the effect of pimecrolimus has to date mostly been studied in patients with non-segmental vitiligo[2-9]. Thus, we investigated the therapeutic efficacy of 1% pimecrolimus cream for children with segmental vitiligo.

In this study, four of the nine patients studied showed mild to moderate response after three months of treatment and therefore continued with 1% pimecrolimus cream monotherapy. With a mean treatment duration of 7.3 months, they achieved moderate to excellent responses (51～100%).

In a previous study that examined 0.05% clobetasol propionate cream for the treatment of segmental vitiligo, 34.2% of patients experienced more than 50% repigmentation after 4.5 months of treatment[11]. Considering this previous report, the 1% pimecrolimus cream achieved a satisfactory therapeutic efficacy for childhood segmental vitiligo in this study. Choi et al.[9] reported that pimecrolimus-treated vitiligo achieved more rapid repigmentation than did topical glucocorticoid-treated vitiligo. They emphasized the melanocyte-stimulating effect of pimecrolimus as the cause of this more rapid repigmentation. Kang and Choi[12] supported this by demonstrating that tacrolimus has a direct effect on melanocyte migration and melanogenesis *in vitro*. Moreover, Lan et al.[13] recently proved that combined treatment of tacrolimus and endothelin induces the mobility of melanoblasts *in vitro*. They also proposed that follicular repigmentation in the vitiligo lesions treated by tacrolimus could be explained by melanoblast migration. Furthermore, calcineurin inhibitors are known to inhibit the production of reactive oxygen species[1,14]. Thus, it could be proposed that calcineurin inhibitors maintain cellular homeostasis by reducing reactive oxygen species and consequently prevent the destruction of vulnerable melanocytes.

There were fewer adverse events in this study than was the case in previous studies examining topical glucocorticoid, although this study differed in that it was conducted on pediatric patients.

Segmental vitiligo is distinct from non-segmental vitiligo with respect to its age of onset, the distribution of lesions, clinical course and treatment strategies[1]. Unlike non-segmental vitiligo, segmental vitiligo is not closely associated with autoimmunity, but is more likely explained by the neural hypothesis[1]. The therapeutic efficacy of 1% pimecrolimus cream for non-segmental vitiligo has mostly been explained by 'suppression of autoimmunity' in previous studies[5]. Considering that a recent study reported more than 50% repigmentation in 32.1% of non-segmental vitiligo lesions treated by 1% pimecrolimus cream, the therapeutic efficacy found in this study showed a satisfactory result[7]. As an autoimmune mechanism is lacking in the pathogenesis of segmental vitiligo, mechanisms other than immune suppression should be investigated. As mentioned above, we think that the melanocyte-stimulating effect and the inhibition of reactive oxygen species shown by pimecrolimus are probable causes for the good therapeutic results in this study.

Although the small number of patients restricts statistical analysis, the good responders to 1% pimecrolimus cream

tended to have facial lesions, shorter disease duration and earlier initial responses compared to those with poor response. The time duration until initial response ranged from one to three months. Thus, treatment responses to 1% pimecrolimus cream for segmental vitiligo should be evaluated at least three months after treatment. Similar results were obtained in a previous study using pimecrolimus and tacrolimus for the treatment of non-segmental vitiligo[15]. Therefore, 1% pimecrolimus cream was scheduled to be combined with phototherapy for those patients who displayed no or minimal responses after three months of treatment in this study.

In conclusion, since 1% pimecrolimus cream showed good efficacy without glucocorticoid-associated adverse events, it could be a good therapeutic option for the treatment of segmental childhood vitiligo.

There are several limitations to this study that should be noted: it was not double-blinded, the treatment duration was not controlled, and it included only a small number of patients. Nevertheless, the primary clinical importance of this study is that it is the first to investigate the therapeutic efficacy of pimecrolimus exclusively for segmental vitiligo.

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