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SHORT COMMUNICATION

Efficacy of the Topical Calcineurin Inhibitors Tacrolimus and Pimecrolimus in the Treatment of Vitiligo in Infants Under 2 Years of Age: A Randomized, Open-Label Pilot Study

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Abstract

Background The efficacy of topical calcineurin inhibitors (TCIs) for the treatment of infants with vitiligo aged less than 2 years remains to be fully determined.

Objective This aim of this pilot study was to assess the efficacy and tolerability of the TCIs tacrolimus and pimecrolimus in infants with vitiligo aged under 2 years.

Methods Infants with vitiligo aged < 2 years were randomly assigned to receive either tacrolimus ointment 0.03% or pimecrolimus cream 1% for a period of 6 months. During this period, topical treatment was applied twice daily. The proportion of body surface area of the treated lesions, locations, and possible adverse effects were recorded. In addition, the overall satisfaction scores of the patients' parents was evaluated by virtue of the visual analog scale (VAS).

Results Forty-six infants with vitiligo were enrolled in this study. The overall response rate (> 0% repigmentation) was 100%, while the effective rate (> 50% repigmentation) of the tacrolimus and pimecrolimus groups was 69.6% and 65.2%, respectively. Meanwhile, the effective rates for vitiligo located on the head and neck, trunk, and extremities were 70%, 64.3% and 50%, respectively, while the response rates for non-segmental and segmental vitiligo were 74.4% and 28.6%, respectively. Only a low incidence of local adverse reactions (including mild redness and skin picking) was reported during the treatment process.

Conclusions Topical tacrolimus ointment 0.03% or pimecrolimus cream 1% have efficacy for vitiligo in infants, which serves to achieve an appropriate level of safety and tolerability during the 6-month period of applications. Thus, TCIs proved to be a therapeutic option for vitiligo in infants under 2 years of age.

Key Points

Topical tacrolimus ointment 0.03% and pimecrolimus cream 1% for treating vitiligo attained favorable efficacy, with a low adverse reactions rate and good tolerance.

Calcineurin inhibitors carry a boxed warning for risk of malignancies, and clinicians should be extremely prudent in the long-term external use of tacrolimus and pimecrolimus.

More data are required to support the efficacy and safety of tacrolimus and pimecrolimus for infants with vitiligo (particularly systemic adverse reactions).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40261-019-00845-x) contains supplementary material, which is available to authorized users.

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1 Introduction

Vitiligo is an acquired depigmenting disorder that has affected 0.38–2% of the global population, from all age groups, with half of these cases beginning in childhood [1]. Various treatments are currently available to treat vitiligo. Treatment guidelines have recommended topical calcineurin inhibitors (TCIs; tacrolimus 0.03% and 0.1% ointment for adults, 0.03% for children aged ≥ 2 years, and pimecrolimus cream 1% for patients ≥ 2 years) as second-line options for the short-term intermittent treatment of vitiligo [2]. According to existing literature, topical tacrolimus and pimecrolimus have been reported to exhibit favorable therapeutic efficacy without inducing any corticosteroid-related adverse events [3–5]. In the last decade, several clinical studies have demonstrated their off-label safety by applying TCIs to infants aged < 2 years diagnosed with dermatosis. For instance, Sigurgeirsson et al. suggested that topical pimecrolimus or topical corticosteroids (TCSs) are well tolerated for the long-term management of infants with mild-to-moderate atopic dermatitis (AD), which would not affect the immune system [6]. In metabolomic studies, compared with TCS studies, pimecrolimus cream 1% could attain comparable efficacy and exceptional safety relative to the desonide cream 0.05% used in infants with AD aged < 2 years [7]. Moreover, Mandelin et al. treated 50 AD infants (< 2 years of age) with tacrolimus 0.03% for 2 years, and it proved to be well tolerated among the studied population of infants [8]. Taken together, these studies suggest that it is viable to apply TCIs in infants with vitiligo aged under 2 years.

A number of child patients have been recruited in several studies to examine the effects of TCIs on vitiligo; however, these studies were mostly performed on children older than 2 years of age. As such, the therapeutic efficacy of TCIs in vitiligo infants has not been specifically examined as yet. Herein, this study aimed to investigate the therapeutic effects of tacrolimus ointment 0.03% and pimecrolimus cream 1% in infants with vitiligo aged under 2 years.

2 Patients and Methods

2.1 Patients

From February 2017 to May 2018, 46 infants with vitiligo aged 6–24 months were recruited. Inclusion criteria were patients who had been diagnosed with vitiligo by senior physicians and for whom no systemic application of corticosteroids was required. Parents were informed of the potential benefits and risks of topical applications of corticosteroids or TCIs, and had agreed to apply the TCIs. In addition, parents had signed the informed consent. Patients with a history of spontaneous repigmentation of vitiligo lesions, malignant diseases, or autoimmune disorders were excluded from this study.

2.2 Treatment Method

The present study was designed as a randomized, open-label clinical trial. Infants were divided into two groups as per a simple randomized method, including 23 patients in the tacrolimus group and 23 in the pimecrolimus group. Infants were chosen randomly by means of a random number (taken from http://www.randomizer.org), with even numbers representing pimecrolimus and odd numbers representing tacrolimus. Infants were offered topical treatment of tacrolimus ointment 0.03% (Protopic, Astellas Pharma, Japan; batch no. J20140148) or pimecrolimus cream 1% (Elidel®, MEDA Manufacturing, France; batch no. H20170004), based on their grouping, twice daily for 6 months.

2.3 Assessment and Analysis

Relevant data were extracted, including the patients' age, area of the lesion, and adverse effects (either reported by parents or physicians).

After completion of the treatment, all patients were then subsequently followed-up and assessed by the same dermatologists at 4-week intervals until 24 weeks, and related data and information regarding improvements were recorded. The repigmentation rate was graded as excellent (> 75% repigmentation), good (> 50 to 75% repigmentation), fair (> 25 to 50% repigmentation), poor (> 0 to 25% repigmentation), and no response [9]. At the same time, the overall response rate was defined as the presence of any degree of repigmentation (> 0% repigmentation), while the rate of effectiveness was defined as at least > 50% repigmentation. The effective rate = (good case number + excellent case number)/total case number.

Moreover, the satisfaction of patients' parents was evaluated using a visual analog scale (VAS), ranging from 0 (not satisfied at all) to 10 (extremely satisfied). Additionally, local adverse drug reactions, including erythema, atrophy, telangiectasia, pigment changes, and folliculitis were observed throughout the study period.

Within the tacrolimus and pimecrolimus groups, the proportion of patients with different degrees of repigmentation was calculated and was compared at baseline and 24 weeks. Fisher's exact test was used to compare the categories representing the degree of repigmentation among treatments, lesion areas, and clinical types. p values < 0.05 were considered statistically significant. For statistical analyses, SPSS statistical software (IBM Corporation, Armonk, NY, USA) was used.

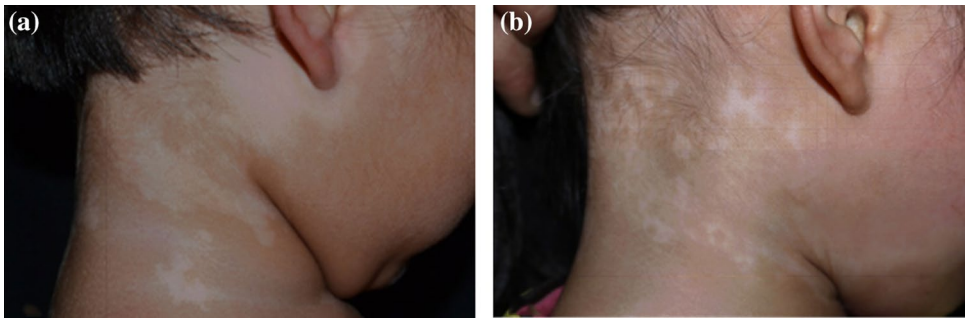

Fig. 1 Symptom changes in infants before and after treatment (6 months). A significant clinical improvement of depigmentation lesions was observed. Vitiligo on the face and neck **a** before treatment, and **b** in patients treated with tacrolimus ointment 0.03%

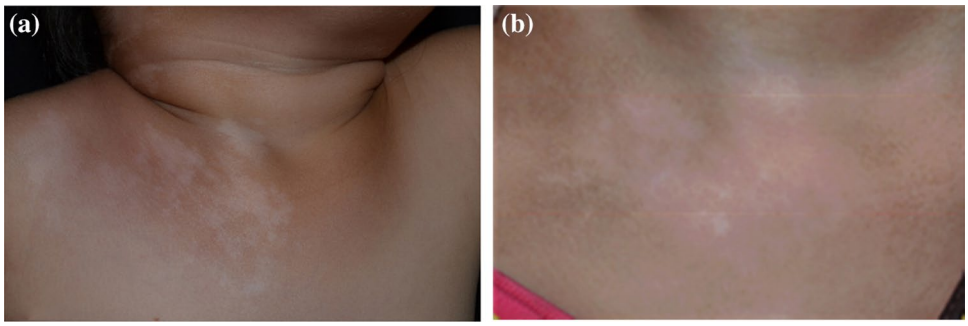

Fig. 2 Symptom changes in infants before and after treatment (6 months). A significant clinical improvement of depigmentation lesions was observed. Vitiligo on the trunk **a** before treatment, and **b** in patients treated with tacrolimus ointment 0.03%

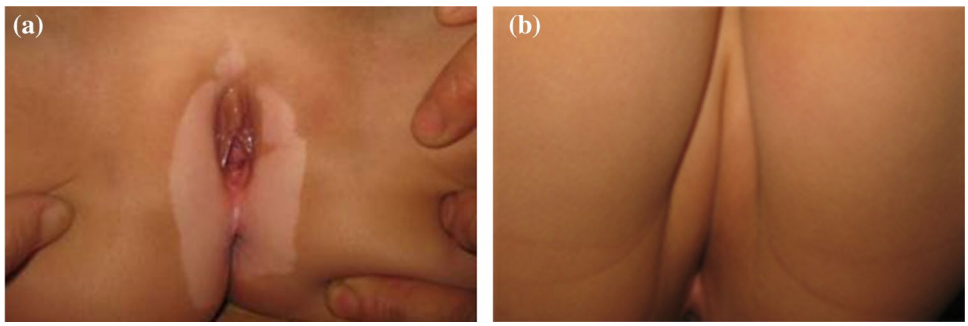

Fig. 3 Symptom changes in infants before and after treatment (6 months). A significant clinical improvement of depigmentation lesions was observed. Vitiligo on the vulva **a** before treatment, and **b** in patients treated with pimecrolimus cream 0.1%

3 Results

3.1 Patients and Treatment

Baseline demographics of the 46 infants enrolled in this trial were recorded, all of whom had completed the 6-month study. All patients and their parents were contacted regarding follow-up visits, to which their parents agreed. Patients included 18 boys and 26 girls, with a mean age of 14.6 months (0.2–7 months). Seven infants had segmental vitiligo and 39 had non-segmental vitiligo. The average course was 2.0 ± 1.5 months, and the Vitiligo Area Scoring Index (VASI) score ranged from 0.035 to 1.5, with an average of 0.83 ± 0.43.

3.2 Response Rate for Treatment

The overall response rate, defined as some degree of repigmentation, was 100%. The effective rates (> 50% repigmentation) in the tacrolimus and pimecrolimus groups were 69.6% and 65.3%, respectively. In addition, the degree of improvement was not statistically different between the two medications (Chi-square 0.99, $p > 0.05$) (Figs. 1, 2, 3).

3.3 Treatment Response for Different Lesion Areas

The effective rates of vitiligo located on the head and neck (70%), trunk (64.3%), and perineum (100%) were markedly higher than that of the extremities (50%; Chi-square 8.00, $p < 0.05$) (Fig. 4, Table 1).

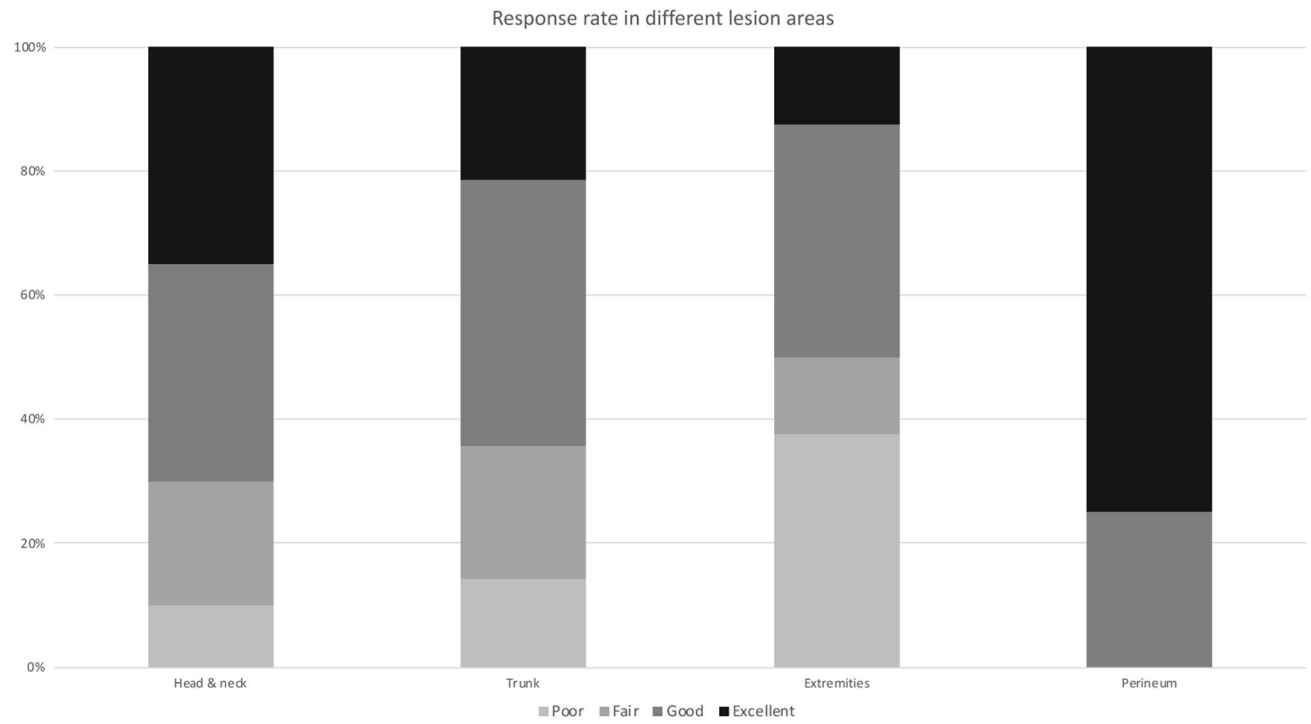

Fig. 4 Response rate in different lesion areas

Table 1 Response rate in different medication, location, and type of vitiligo groups

Factor	No response	Poor	Fair	Good	Excellent
Total [$n=46$]	0	15.2 (7)	17.4 (8)	37.0 (17)	30.4 (14)
Medication					
Topical tacrolimus 0.03% [$n=23$]	0	17.4 (4)	13.0 (3)	34.8 (8)	34.8 (8)
Topical pimecrolimus 1% [$n=23$]	0	13.0 (3)	21.7 (5)	39.2 (9)	26.1 (6)
Location					
Head and neck [$n=20$]	0	10 (2)	20 (4)	35 (7)	35 (7)
Trunk [$n=14$]	0	14.3 (2)	21.4 (3)	42.9 (6)	21.4 (3)
Extremities [$n=8$]	0	37.5 (3)	12.5 (1)	37.5 (3)	12.5 (1)
Perineum [$n=4$]	0	0	0	25.0 (1)	75.0 (3)
Type					
Segmental [$n=7$]	0	42.8 (3)	28.6 (2)	28.6 (2)	0
Non-segmental [$n=39$]	0	10.3 (4)	15.4 (6)	38.5 (15)	35.9 (14)

Data are expressed as % (n)

3.4 Treatment Response for Different Clinical Types

The effective rates of non-segmental vitiligo (74.4%) were significantly higher than those of segmental vitiligo (28.6%; Chi-square 5.66, $p<0.05$) (Table 1).

3.5 Satisfaction Scores for Patients' Parents

The median scores for tacrolimus and pimecrolimus were 7.0 ± 2.17 (range 4–10) and 7.0 ± 2.3 (range 3–10).

3.6 Local Adverse Events

Mild redness and scratch occurred in two patients in the pimecrolimus group and three patients in the tacrolimus

group. No serious local adverse reactions were detected by their parents.

4 Discussion

Generally speaking, parents can promptly discover the skin changes in their infants, and relevant consultations with physicians are required at the early stage of disease. Therefore, patients in this study only had small skin lesions within a short time after disease onset. Judging from the guidelines and clinical experiences, systemic medication is often not the preferred choice, but topical drug therapy is suitable for infants. External application of corticosteroid preparation is one of the preferred treatments for vitiligo; but most parents of vitiligo infants have excessive concerns and phobias regarding TCSs in clinical practice. As a result, identifying the appropriate treatment for infants is difficult, therefore it is necessary to assess the efficacy and safety of tacrolimus ointment 0.03% and pimecrolimus cream 1% in the long-term treatment of patients with vitiligo aged under 2 years.

In their study, Udompataikul et al. [10] included both children and adults treated with topical tacrolimus 0.1% twice daily for 6 months, and demonstrated that the response rate was 94.44% in children, which was significantly higher than in adults. Additionally, Kanwar et al. [11] suggested that the topical application of tacrolimus proved an effective treatment for Asian children with vitiligo, and resulted in a repigmentation rate of 86.4%. On this basis, the present study is the first to include infants aged < 2 years and indicates a satisfactory result. Moreover, we discovered that evident efficacy has been attained in the vulvar region; however, after inquiry, it was found the infants had used diapers, which might enhance drug absorption. Furthermore, no adverse reaction to vulvar swelling was observed in patients who had used diapers after medication, and the satisfaction scores in over half of the parents of these patients was above 7, indirectly suggesting good tolerance of the topical application.

The reasons for good curative effect are likely to be associated with timely treatment, the small area of skin involved, and good compliance of the parents. The most common adverse effects of TCIs were pruritus, burning, and irritation. Moreover, no serious local adverse reactions were identified in this study, which may be related to the integrity of the skin barrier in lesional vitiligo skin, thus revealing the safety and reliability of the 6-month treatment.

The main limitations of our research were that the description of medication discomfort may be milder than the actual levels since the feedback regarding treatment for infants was from the parents instead of the infants themselves. In addition, systemic absorption and safety following 6 months of TCIs have yet to be confirmed. It is noteworthy that in January 2006, a public health advisory issued a warning regarding the long-term safety and risk of malignancies of treatment, and a medication guide was issued for TCIs. Moreover, the systemic absorption of TCIs is of particular concern in the pediatric age group, whose ratio of body surface area to weight is the highest. We recommends that sun protection and regular follow-up visits are necessary in infants with vitiligo. On this basis, we propose that topical tacrolimus ointment 0.03% or topical pimecrolimus cream 1% are effective and well tolerated for infants with vitiligo.

5 Conclusions

According to our observations, TCI treatment (both topical tacrolimus and pimecrolimus) appears to be an efficient and safe modality for infants with vitiligo; however, additional data on the long-term risks of this treatment for infants are still warranted. In addition, sample size should be expanded to conduct further research on the changes in blood metabolites to evaluate the systemic effects of TCIs in infants.

Compliance with Ethical Standards

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Conflict of interest Wenting Hu and Yongping Xu contributed equally to this work. Wenting Hu, Yongping Xu, Yangyang Ma, Jiehao Lei, Fuquan Lin, and Ai-E Xu declare they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the study protocol, the Ministerial Ordinance on GCP for Drugs, and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Institutional Review Board at Anhui University Hospital on 12 February 2016.

Informed consent Informed consent was obtained from parents of all individual participants included in this study.

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