Effectiveness of Proactive Therapy in Pediatric Atopic Dermatitis Patients with 0.03% Tacrolimus Ointment versus 0.02% Triamcinolone Acetonide Cream: A Prospective Randomized Split-Side Single-Blinded Controlled Trial

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ABSTRACT:

SUNANTAWANICH K, LEKHAVAT C, SRIMUANG A, SUKSAWANG N, BOONPUEN N. EFFECTIVENESS OF PROACTIVE THERAPY IN PEDIATRIC ATOPIC DERMATITIS PATIENTS WITH 0.03% TACROLIMUS OINTMENT VERSUS 0.02% TRIAMCINOLONE ACETONIDE CREAM: A PROSPECTIVE RANDOMIZED SPLIT-SIDE SINGLE-BLINDED CONTROLLED TRIAL. THAI J DERMATOL 2022;38:45-53.

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Background: Along with reactive treatment aiming to control disease flares, atopic dermatitis (AD) patients can use proactive treatment to halt subclinical inflammation of normal-appearing skin and prevent exacerbation.

Objectives: To determine and compare the effectiveness and adverse effects of 0.03% tacrolimus ointment and 0.02% triamcinolone acetonide (TA) cream twice weekly as proactive therapy.

Materials and Methods: This 4-month prospective single-blinded randomized controlled trial included thirty-eight patients, aged 2-14 years old, with moderate AD (SCORAD 25-50). In the first two months, the patients applied a cream base twice daily and 0.02% TA cream as reactive therapy. In the next two months, 0.03% tacrolimus ointment and 0.02% TA cream were additionally given as proactive therapy to be applied twice weekly at selected normal-appearing areas on each side, randomly assigned between left and right sides of the antecubital or popliteal fossae. The patients were evaluated every four weeks. Outcome measures included number of disease exacerbations, disease-free days, duration to first exacerbation, and adverse effects.

Results: Thirty-eight patients completed the study. In contrast to 0.02% TA, twice weekly 0.03% tacrolimus ointment helped to reduce the number of disease exacerbations with a p-value of 0.029 and increased the total number of disease-free days by 1.5 days ($p = 0.02$). Both agents as proactive treatment significantly delayed the next disease flare. No adverse reaction was reported during the study.

Conclusion: We suggest using proactive therapy with 0.03% tacrolimus ointment in moderate AD patients, while 0.02% TA cream may be considered in cases of limited budget.

Key words: Atopic dermatitis, proactive therapy, tacrolimus ointment, triamcinolone acetonide cream

Introduction

Along with reactive treatment aiming to control acute exacerbation and inflammation, proactive treatment has been used to prevent further exacerbation of atopic dermatitis (AD). The twice weekly or thrice weekly application of topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) on normal-appearing areas that had a history of frequent recurrences were recommended for moderate to severe AD patients[1,2]. Disease exacerbation is believed to be caused by on-going subclinical inflammation and subclinical epidermal barrier defects. The intermittent use of topical anti-inflammatory agents or proactive therapy aims to halt these subclinical events[3]. Long-term control with intermittent low-dose anti-inflammatory agents should reduce the risk of treatment-related adverse events, especially with TCS, improve patients' and caregivers' quality of life, and reduce the total cost of the disease.

Both TCS and TCI had been studied for their efficacy as proactive treatments. A systematic review of clinical trials, aimed to determine the efficacy to prevent AD flares and the tolerability of the agents, suggested that TCS and TCI were more effective to prevent disease flares than vehicles and showed that topical fluticasone propionate was more efficacious than topical tacrolimus[4]. In the aspect of subclinical events, 0.1% tacrolimus ointment delivered greater skin integrity, overall hydration, and reduction of epidermal protease activity than 0.1% betamethasone valerate cream which improved the epidermal barrier but also elevated the surface pH level[3].

In Thailand, most patients cannot afford TCI despite their concern about the side effects of TCS as the cost of TCI is much higher. Our study is a head-to-head study that aimed to compare the effectiveness between 0.03% tacrolimus ointment and 0.02% triamcinolone acetonide cream (TA), and to compare the safety profiles of the agents.

Material and methods

This prospective randomized controlled single-blinded split-body clinical trial was conducted at the Institute of Dermatology, Bangkok. The study was approved by the ethics committee of the Institute of Dermatology. Written informed consent was obtained from all subjects and their caregivers prior to enrollment.

The sample size was calculated to be 38 patients by the n4studies application[5] based on a 12-month prospective study of twice-weekly 0.03% tacrolimus ointment in AD children[6]. The inclusion criteria included AD patients, diagnosed by Hanifin and Rajka's criteria[7], aged 2 to 15 years old and having a baseline scoring atopic dermatitis index (SCORAD) of 25 to 50, which indicated moderate severity[1]. Exclusion criteria included subjects who were pregnant or lactating.

Every subject should have a controlled disease without applying topical anti-inflammatory agents and systemic immunosuppressants for at least 1 week or 4 weeks, respectively, before entering the study. A site of interest, either the antecubital fossae or popliteal fossae, was chosen for each patient from a history of equally affected right and left sides and the history of most frequent exacerbation. Every patient had been followed up for 16 weeks, divided into 2 phases: the first 8 weeks of the reactive phase and the last 8 weeks of proactive phase. Home record forms were given to their parents or caregivers for marking when they applied 0.02% TA to the assigned areas during disease exacerbation (DE). The patients were evaluated every 4 weeks. Number of DE, duration of exacerbation, first day of the exacerbation, and adverse events were evaluated. Each subject was randomized into the A or B group, based on their order of enrollment using Microsoft Excel. In the proactive phase, subjects in group A would receive agent 1 to be applied on their right side and agent 2 to be applied on the left side. Meanwhile, group B would receive agent 1 to be applied on their left side and agent 2 on the right side. In the reactive phase, every subject received a cream base for twice daily use and 0.02% TA cream twice daily for disease exacerbation until lesions had cleared. After that, the subjects would enter the proactive phase only when they were free from disease exacerbation and had at least a 1-week TCS-free period. Proactive treatments with 0.03% tacrolimus ointment and 0.02% TA cream were additionally given for twice weekly use on the assigned right or left side, based on the random number the patient received, along with a twice daily cream base application. If the subjects had a disease flare episode during the proactive phase, they were advised to apply 0.02% TA twice daily until the lesions resolved and to stop using both proactive agents. They could resume applying proactive agents only after the lesions had cleared. The investigators were unaware of the identity of the proactive agents as they were simply marked as agent 1 and agent 2.

The primary outcome was the effectiveness of proactive therapy with 0.03% tacrolimus ointment and 0.02% TA cream, in the aspect of number of DE, disease-free days, and duration until the next exacerbation, which was the duration between the first day of each phase to the first day of disease flare. Adverse reactions were monitored throughout the study.

Statistical analysis

The demographic data and baseline characteristics were analyzed via descriptive analysis. The number of exacerbations and number of disease-free days were compared with the Wilcoxon Signed Ranks test. Time to first relapse was analyzed by using Kaplan-Meier survival estimates and the differences were

compared with the log-rank test. The McNemar test was used to compare the number of no-flare areas before and after proactive treatment. The statistical analysis was performed using IBM SPSS version 26. A p-value (p) of < 0.05 indicates statistical significance.

Table 1 Demographic data

	Mean ± SD.	**Min – Max**
Age (years)	7.53 ± 3.45	2 - 14
Sex		
Female, n (%)	26 (68.4%)	
Male, n (%)	12 (31.6%)	
Baseline SCORAD	35 ± 7	25 - 49
Selected site		
Antecubital fossae	32 (84.2%)	
Popliteal fossae	6 (15.8%)	
Duration of AD (years)	4.31 ± 2.54	0.5 - 10
2-month treatment cost (baht)	3,941 ± 3,164	200 – 13,600
Family income (baht/month)	46,611 ± 35,749	10,000 – 200,000

Table 2 Reactive and proactive therapy (Wilcoxson Signed Ranks test)

	0.03% tacrolimus side (n=38) Median (IQR)	**0.02% triamcinolone acetonide side (n=38)** Median (IQR)	**p-value**
Number of disease exacerbations (times)			
Reactive phase	2 (0, 5)	1 (1, 4)	0.390
Proactive phase	0 (0, 3)	1 (0, 3)	0.305
p-value	0.029*	0.167	
Disease-free days (days)			
Reactive phase	49 (42, 56)	49.5 (43, 55)	0.593
Proactive phase	54.5 (48, 56)	54.5 (47, 56)	0.591
p-value	0.009*	0.066	
Adverse events			
Reactive phase	0 (0%)	0 (0%)	1
Proactive phase	0 (0%)	0 (0%)	1
p-value	1	1	

Table 3 Number of no-flare areas* (McNemar test)

	0.03% tacrolimus side (n=38)	0.02% triamcinolone acetonide side (n=38)	p-value
	n (%)	Median (IQR)	
Reactive phase	10 (26.3%)	9 (23.7%)	1
Proactive phase	20 (52.6%)	18 (47.4%)	1
p-value	0.006*	0.022	

*No-flare area is the area that had no disease exacerbation during the 8-week period of time in the reactive or proactive phases.

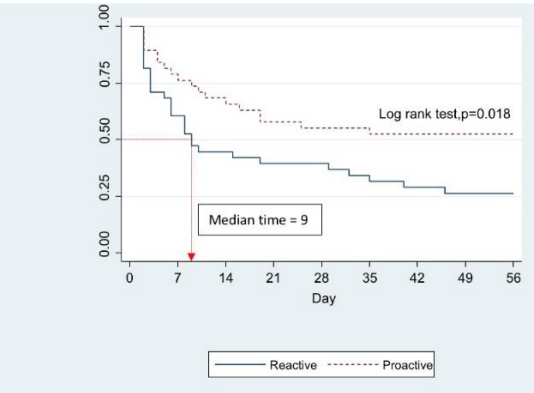

Figure 1 Shows the probability of disease relapse of the 0.03% tacrolimus side, reactive versus proactive phase

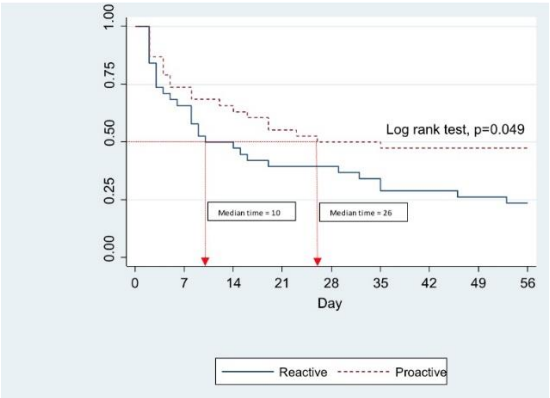

Figure 2 Shows the probability of disease relapse of the 0.02% TA side, reactive versus proactive phase

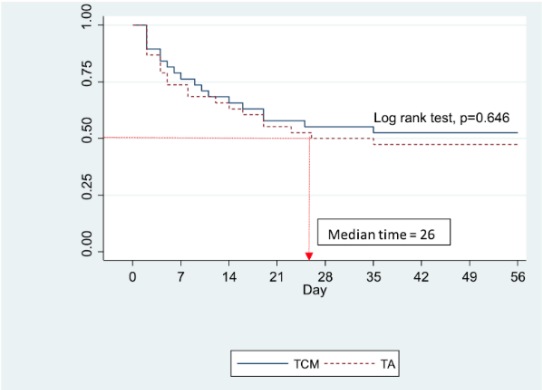

Figure 3 Shows the probability of disease relapse of proactive therapy, 0.03% tacrolimus ointment versus 0.02% TA cream

Demographics and characteristics of patients

A total of 38 subjects completed the study. The background characteristics and demographic data are described in Table 1. There were 26 females (68.4%). The mean age of the patients was 7.53 years. The duration of AD ranged from 6 months to 10 years. The mean baseline SCORAD was 35. The most common assigned area of interest was the antecubital fossae (84.2%).

Table 2 shows both reactive and proactive phase results as median and interquartile range (IQR) as the data were in a non-normal

distribution. In the reactive phase, the median numbers of exacerbations of tacrolimus and TA side were 2 and 1 times, respectively, p = 0.390. The number of disease-free days for tacrolimus and TA side were 49 and 49.5 days, respectively, p = 0.593.

In the proactive phase, 0.03% tacrolimus ointment showed improvement in almost all parameters. The number of disease exacerbations was significantly reduced, and the number of disease-free days was significantly increased. On the other hand, there was no significant improvement in either the number of exacerbations nor the number of disease-free days for the 0.02% TA cream side. The median time to first relapse was longer in the proactive phase for both agents. Proactive therapy with 0.03% tacrolimus ointment significantly prolonged the first day of relapse from a median day of 9 to more than 56, p = 0.018, (Figure 1). Twice weekly 0.02% TA cream also prolonged the median day of first relapse from 10 to 26, p = 0.049, (Figure 2). There was no statistically significant difference between the agents in the aspect of prolongation of the first relapse, (Figure 3).

The areas without any disease flare were increased from 26.3% to 52.6% for the tacrolimus side, p-value of 0.006, and 23.7% to 47.4% for the TA side, p-value of 0.022, (Table 3).

There was no adverse reaction reported in either the reactive or proactive periods.

Discussion

Our study shows similar benefits to proactive therapy for the prevention of atopic dermatitis exacerbation to many previous studies[4,6,8], but this is the first study to compare the effectiveness of topical tacrolimus and topical corticosteroids as proactive therapy in Thailand. In 2020, a prospective study compared the efficacy and safety between 0.005% fluticasone ointment and 0.03% tacrolimus ointment in the active and maintenance phases in moderate AD children[9], showing that both agents had similar efficacy. However, in the acute treatment phase, tacrolimus was prescribed for use once daily. In Thailand, the cost of 0.03% tacrolimus ointment per gram was about 150 times higher than 0.02% TA cream. A study in Germany in 2010 showed that the application of 0.03% tacrolimus ointment twice weekly helped to prevent AD exacerbation without adding to the cost of the treatment for moderately severe AD children, and possibly reducing the cost for severe AD children[6]. A 12-month trial in adult AD patients[10] showed that twice weekly 0.1% tacrolimus ointment also effectively reduced the number of DE, delayed the first exacerbation, and decreased the percentage of disease flare. The study included mild, moderate, and severe cases.

Our study showed that, proactive therapy with 0.03% tacrolimus significantly increased the number of disease-free days and reduced the number of DE. Both agents significantly prolonged the duration to the next disease flare with better data for the tacrolimus side, but there was no significant difference between both arms. Twice-weekly use of 0.03% tacrolimus ointment also significantly increase probability of no DE in 8-week period of time, (Table 3). In contrast to our study, a systematic review showed indirect evidence that TCS, fluticasone propionate, might be more efficacious than tacrolimus ointment[4]. But the evaluating period was shorter for the fluticasone group, so over longer periods, tachyphylaxis of the agent could be induced.

Cutaneous and systemic adverse reactions from long-term TCS use are more concerning for physicians, patients, and parents than is the case from TCI. Skin infection, impetigo, and varicella were reported to be similar for vehicle and TCI and for TCI and TCS. There was no report of skin atrophy from TCI and low potency TCS, but there was inconclusive data for mid-potency TCS. Systemic infections, like influenza-like illness, were reported from the long-term use of TCI. Growth rate and immune system function were similar for the TCS and TCI groups. There were no reports of TCI or TCS-induced lymphoma from a 5-year study[11]. There was no adverse event report from our subjects, in terms of burning sensation, skin atrophy, or skin infection.

Our study has several limitations. As we started this study during the COVID-19 pandemic era, the number of patients visited and eligible to be enrolled was limited. The short period of follow-up time is another limitation. We suggest a longer and larger trial to evaluate the cost-effectiveness of the agents, and non-inferiority trial of 0.02% TA cream to 0.03% tacrolimus ointment.

In conclusion, we encourage proactive therapy in moderate-severity patients with either 0.03% tacrolimus ointment or 0.02% TA cream to prevent AD flares. The greater improvement in the tacrolimus side may suggest the higher efficacy of the agent. The higher price of the former and the higher possibility of side effects of the latter should be considered for each patient case-by-case. No adverse effect was found in our 8-week proactive period.

Conclusion

This prospective study was the first in Thailand to compare the effectiveness of 0.02% TA cream and 0.03% tacrolimus ointment as proactive therapy. Both agents help to delay the next atopic flare, and 0.03% tacrolimus ointment further helps to decrease the frequency of exacerbation and to increase the number of disease-free days. No adverse reaction was observed throughout the 8-week proactive

period. We suggest using proactive therapy with 0.03% tacrolimus ointment in moderate AD patients, while 0.02% TA cream may be considered in cases of limited budget.

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