

THE EFFICACY AND SAFETY OF TACROLIMUS OINTMENT IN ADULT PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

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1. INTRODUCTION

Atopic dermatitis (AD), was called “endogenous eczema” or “atopic eczema”, is the most common chronic inflammation skin disease. It occurs in every age but mostly seen in childhood before 2 years old, long-lasting and may persist into adulthood. Clinical images change on each stage or age. In infant, the condition causes oozy bumps on forehead, cheeks while adults are more likely to develop thick, leathery and lichenification lesions with a persistent itch. It may involve in history of allergy disorders like asthma, hives, hay fever....

Today, treatment for AD is still difficult. The most common therapy is the control of dry, red and itchy skin. Application of topical corticosteroids is indicated but patients can have side effects like skin atrophy, striae, acnes.... Especially in children, long-term use of topical corticosteroids can affect on their growth.

Tacrolimus is an immunosuppressive agent which has same pharmacology action of cyclosporine. Tacrolimus has more effect because of its low molecular weight. In vitro and in vivo clinical trials reveal that tacrolimus ointment has efficacy and safety effect in human. Worldwide clinical trials showed that tacrolimus is efficacy and safety in atopic dermatitis treatment. However, Vietnam has no trials on determine the effect of tacrolimus in AD treatment yet. The present study was undertaken to:

- Assess the efficacy of Tacrolimus ointment 0.1% in treatment of moderate to severe AD in adult patients from Vietnam Nation Institute of Dermatology and HCM Hospital of Dermatology.

- Assess the safety of Tacrolimus ointment 0.1% in treatment of AD.

2. SUBJECTS AND METHODS

2.1. SUBJECTS:

Adult patients had diagnosis of moderate to severe atopic dermatitis who was treated at Vietnam Nation Institute of Dermatology and HCM Hospital of Dermatology from 2007 to 2009.

* **Diagnosis criteria:**

Patient had diagnosis of AD using Hanifin and Rajka, including 4 major characteristics and 23 minor characteristics. Patients must have 3 or more of each characteristics to be enrolled (see Apendix I)

* **Inclusion criteria:**

- Patients had a diagnosis of moderate to severe AD Rajka and Langeland Criteria (Appendix II) involving at least 10% of the body surface area.
- Patients were at least 18 years of age.
- Female patients with child-bearing potential must have had a negative pregnancy test and all patients were advised not to pregnancy during the study.
- Patients didn't have other skin disorders and severe heart, liver, kidney and lung diseases.
- Patients had given informed consent.

*** Exclusion criteria:**

- Patients below 18 years old.
- Patients had a skin disorder other than AD in the areas to be treated.
- Patients had pigmentation or extensive scarring or pigmented lesions in the areas to be treated which would interfere with rating of efficacy parameters.
- Patients had clinically infected atopic dermatitis at baseline.
- Patients were used exclude drugs (*see Appendix 5*)
- Patients had a known hypersensitivity to macrolides or any excipient of the ointment.
- Patients had a systemic disease, including cancer or history of cancer or HIV, which would contraindicate the use of immunosuppressants.
- Patients had a chronic condition (e.g. diabetes, hypertension), which is either not stable or not well controlled.
- Patients were pregnant or breast feeding an infant.

2.2. MATERIALS

Tacrolimus ointments, 0.1%, containing propylene carbonate, white wax, mineral oil, paraffin and white petrolatum were supplied by Janssen - Cilag Vietnam

2.3. METHODS

- **Study design:** prospective, open-labeled, before and after usage comparison trial.

- **Sample size:** randomized, 74 adult AD patients \geq 18 years old

- **Study procedures:**

+ ***Patient enrollment*** (*section 2.1*)

+ ***Documented Case Report Form (CRF)***

* Obtain information: Name, age, gender, weight, medical history of patient and patient's family

* Performed physical exam:

. Determined the severity of the patient's atopic dermatitis using the grading system of Rajka and Langeland (*Appendix 2*). Three levels of severity: Mild (3-4 points), Moderate (4,5-7,5 points) and Severe (8 - 9 points). This study had just enrolled moderate to severe AD patients.

. Determined primary treated area for 4 signs AD in the defined body regions: Head/Neck; Upper limbs; Trunk; Lower Limbs (*Appendix 4*)

. Assess the severity of AD lesions like erythema, edema, excoriation, oozing, scaling, lichenification (*Appendix 3*)

* Recorded in CRF (*Appendix 7*)

* Obtained height, weight, respiration rate, pulse rate, blood pressure and temperature

* Test (if needed): Pregnancy test, sugar blood test, AD lesions photos.

- Dose and Administration:

Adult patients were applied tacrolimus ointment 0.1% twice per day, as a thin coating over the affected areas, approximately 10 to 14 hours apart in 4 weeks. The study ointment should be applied at least 2 hours prior to or at least 30 minutes after bathing, showering, shaving, use of sauna, or heavy exercise (i.e. causes sweating). On study visit days, the study ointment should be applied at least 2 hours prior to the visit. If the Baseline Treatment Areas are “Cleared” before or at 1 week, treatment with the study ointment will continue for at least a total of 2 weeks before stopping.

Interim visits on week 1, 2, 3 and week 4/End-of treatment

- **Efficacy assessments***: Patients were assessed if applied at least 3 continuous days of treatment (equivalent to 5 times of drug applied) from the first day of study.

Assessment criteria:

+ **Physician's Assessment of Individual Signs**: based on changes of signs erythema, edema/induration/papulation, excoriation, oozing/weeping, scaling, lichenification. Each sign was rated using the following scale: Absent = 0, Mild = 1; Moderate = 2; Severe = 3.

+ **Physician's Global Evaluation of Clinical Response**: based on rate change of lesions of treated areas using following scale: cleared (100%), excellent improvement (90-99%), marked improvement (75-89%), moderate improvement (50-74%), slight improvement (30-49%), no appreciable improvement (0-29%), worse (<0%).

+ **Eczema Area and Severity Index (EASI) for each of 4 body regions**: calculated using the Physician's Assessment of Individual Signs and the Affected Area Assessment of the lesions of atopic dermatitis that were defined in the Baseline Treatment Area only.

Calculation of EASI score:

Total EASI score = Head/Neck (Subtotal) x 0.1 + Upper Limbs (Subtotal) x 0.2 + Trunk (Subtotal) x 0.3 + Lower Limbs (Subtotal) x 0.4

Area score:

Score	0	1	2	3	4	5	6
Area (%)	0	1-9	10-29	30-49	50-69	70-89	90-100

+ **The Patient's Assessment of Treatment Effects**: Patients will make two assessments at each study visit (before and after treatment) based on all affected areas (ratio of 100%). The

assessment rates include; much better, better, slightly better, same, slightly worse, worse. Much better and better is considered good.

+ **The Patient's Assessment of Itch:** using a Visual Analog, patient or guardian crossed the rule to assess the amount and intensity of itch. The itch assessment using following scale from 0 to 100: 0-19 : no or slight itch; 20-39: mild itch; 40-59: moderate itch; 60-79: severe itch; 80-100: worst itch

- **Quality of life measurement:** Patients completed a Quality of Life questionnaire at before and after treatment. Improving of life quality is scored to 40. Low score expressed the more affect on AD on patient. 40 is consider as "not affection".

- **Safety assessment**:** Safety were based on clinical adverse events reported by patients or observed by the physician.

Note:

* All the efficacy assessments should be done by the same physician rater at baseline and at all subsequent study visits.

** Patients will be evaluable for safety if they have received at least one application of the study drug.

2.4. Statistical analysis

All statistical tests will be two-sided, with the significance level of $\alpha = 0.05$, unless otherwise specified. The 95% confidence interval will be calculated for the primary outcome. For efficacy end points the Paired t test will be used to evaluate effects before and after a treatment. The Wilcoxon signed-rank test will be used for nonparametric analyses.

2.5 Study sites:

Vietnam Nation Institute of Dermatology and HCM Hospital of Dermatology

2.6 Study duration: 2007-2009

2.7 Ethical study:

- Beside the aim of benefit on patient, this study doesn't serve any other purposes.
- The protocol was based on internal standards and supplied by Janssen-Cilag. The study was supervised by South-East Asia researcher.

2.8 Limitation:

- Because of short-time assessment, this study can not follow-up the relapse cases if occur.
- This study just assessed the monotherapy of tacrolimus ointment.

3. RESULTS

In 2 years (2007-2009), 74 adult patients were enrolled in the present study in Vietnam Nation Institute of Dermatology and HCM Hospital of Dermatology.

3.1 General informatic of patients

Table 1: Demographic data at baseline (n=74)

Patients		Adult(n=74)	
Gender		n	%
	Male	29	39.2
	Female	45	60.8
Age (year)			
	Min	18	
	Max	80	
Average age (year) Mean ± SD		41.01 ± 15.72	
AD onset			
	Min	2	
	Max	69	
	Not defined	5	
Average onset of AD (year)		20.23 ± 17.25	
Average area of lesion (Mean±SD)		30.41 ± 16.32	
Itch (Mean±SD)		77.86 ± 18.47	
Severity			
	Moderate	58	78.4
	Severe	16	21.6

Table 1's observation:

- Number of AD female patients is 2 times more than male (60.8% vs. 39.2%). Average age of adult patient is slightly high (Mean ± SD: 41.01±15.72), however the onset age is soon (Mean ± SD: 20.23±17.25). The lesion area is not much (Mean ± SD: 30.41±16.32)

- Before treatment: the itching index is high in adult (77.86±18.47) and at moderate severity 78.4%.

3.2 Efficacy assessment:

Table 2: Physician's Global Evaluation of Clinical Response

Time		Clinical Improvement*				
		Cleared (100%)	Excellent improvement (90-99%)	Marked improvement (75-89%)	Moderate improvement (50-74%)	Total
Subject (n=71)	Week 1 (n=71)	0	1.4	60.6	23.9	85.9
	Week 2 (n=68)	0	7.4	52.9	32.4	92.6
	Week 3 (n=62)	0	19.4	48.4	24.2	91.9
	Week 4 (n=58)	10.3	24.1	34.5	20.7	89.7

* **Clinical improvement was calculated on % ratio:** Patients with Moderate improvement (50-74%) were considered as “Clinical success”

Table 2's observation: in first week, the cleared response was very low (1.4%). However, if consider that 50-74% is “Clinical success”, the successful improve of treatment was 85.9%. The result was improved in second and third week (over 90%). In forth week, the “Clinical success” was 89.7%.

Table 3: EASI score, The Patient's Assessment of Treatment Effects

Eczema Area and Severity Index (EASI)						
Time		Baseline (1)	Week 1 (2)	Week 2 (3)	Week 3 (4)	Week 4 (5)
Subject						
EASI (Mean ± SD)		16.25±6.8	9.27±5.12	4.85±3.27	3.02±2.26	1.89±1.98
EASI score differentiation		p1' vs p2' < 0.001; p2' vs p3' < 0.001; p3' vs p4' < 0.001, p4' vs p5' < 0.001				
The Patient's Assessment of Treatment Effects						
Time		<i>Much better</i>	<i>Better</i>	<i>Slightly better</i>	<i>Same</i>	<i>Slight worse</i>
Subject						
Size (n=57)	Week 1	22.8	24.6	40.4	10.5	1.8
	Week 2	22.9	35.1	26.3	12.3	3.5
	Week 3	23.6	38.2	29.1	7.3	1.8
	Week 4	40.0	27.3	21.8	10.9	0.0

Table 3's observation:

- Eczema Area and Severity Index (EASI) was rapidly decreased from baseline (week 0 =16.25±6.8) to end of treatment (week 4 =1.89±1.98). These differences were significantly p1'<0.001 and p2'<0.001

- The Patient's Assessment of Treatment Effects: in first week, the better ratio was 47.4%; slightly better was 40.4%. In second and third week: the better ratio was increased (week 2 = 58.0%; week 3 = 61.8%). After 4 weeks, the clinical improvement ratio was increased (better - 67.3% + slightly better – 21.8% = 89.1%). The ratio of no change was 10.9%.

Table 4: Assessment of itch, quality of life's score

Itch over time					
Subject	Baseline (1)	Week 1 (2)	Week 2 (3)	Week 3 (4)	Week 4 (5)
Subject (Mean± SD)	77.8±18.47	59.9±23.0	46.9±24.17	36.2±24.48	27.46±23.6
Itch score differentiation	p1' vs p2' < 0.001; p2' vs p3' < 0.001; p3' vs p4' < 0.001; p4' vs p5' < 0.02				
Quality of life's score					
Subject	Before treatment		After treatment		
Subject (Mean ± SD)	28.54±7.5		36.31±6.05		
Differentiation	p < 0.003				

Table 4's observation:

-At baseline (week 0), patients had high itch score (77.8 ± 18.47). However, in 2nd week, the itch score was significantly decreased (59.9 ± 23.0). In week 4, the itch score was moderate level (27.46 ± 23.6). Level of itch between weeks was significantly reduced ($p < 0,001$).

- Quality of life's score was significantly increase ($p < 0.003$) from baseline (28.54 ± 7.5) to end-of-treatment (week 4 = 36.31 ± 6.05).

3.3 Safety assessment

In 74 adult AD patients, adverse events occurs at low incidence (9/74 cases =12.2%), itching is the most common adverse event (12.2%), follow by skin burning at applied area (5.4%). Other cases are dryness and redness (1.4%). These events just occurred in the first week and disappeared without change or discontinue of drug usage.

4. DISCUSSION:

4.1. General characteristics of AD patients

In 2 years (2007-2009), there is 74 cases of adult AD patients were enrolled into this study taken place at Vietnam Nation Institute of Dermatology and HCM Hospital of Dermatology. We have some observations:

- Number of AD-acquired patient is higher in female than in male (60.8% vs 39.2%)
- Lowest age is 18 years old and highest age is 80 years old, correspondent with inclusion criteria.
- AD-acquired average age is high (Mean \pm SD: 41.01 ± 15.72) while the onset age is extremely early (Mean \pm SD: 20.23 ± 17.25).
- Ratio of lesion in adult is less than in pediatric patients (Mean \pm SD: 30.41 ± 16.32), correspondent with ratio of moderate severity in adult patients (78.4%)

4.2. Assessment of treatment effects

4.2.1 Physician's Global Evaluation of Clinical Response:

In first week, the cleared response was very low (1.4%). The Clinical improvement result was increase in second and third week (over 90%). In forth week, the "Clinical success" was 89.7% (>50% improvement). This result is correspondent with these of [Cheer SM, Plosker GL](#) (6) double-blind in 304 adult AD patients showed clinical improvement $\geq 90\%$ (assessment based on group using ointment 0.1% and 0.03% compared with placebo usage group). [Breneman D, Fleischer AB Jr](#) et al (5) showed that 90% patients had clinical improvement in first week of treatment.

4.2.2. Eczema Area and Severity Index (EASI):

In adult, EASI score was rapidly decreased from baseline (week 0 = 16.25 ± 6.8) to end of treatment (week 4 = 1.89 ± 1.98) indicate the effect of tacrolimus ointment in AD treatment. These differences were significantly $p_1 < 0.001$ and $p_2 < 0.001$. This result is correspondent with these of [Cheer SM, Plosker GL](#) (6) showed clinical improvement appeared early in the first week. Moreover, according to the study of [Boguniewicz M, Fiedler VC](#) (7), multi-center, double-blind in pediatric patients from 7-16 years old showed the improvement of sign, clinical symptoms of AD, increase EASI score.

4.2.3 Quality of life's assessment before and after treatment:

Quality of life's score was significantly increase ($p < 0.003$) from baseline (28.54 ± 7.5) to end-of-treatment (week 4 = 36.31 ± 6.05).

4.2.4 Patient's Assessment of treatment effects:

After 4 weeks, the clinical improvement ratio was increased; better and slightly better ratio is 89.1%. The ratio of no change was 10.9%.

4.2.5 Assessment of Itch:

-At baseline (week 0), patients had high itch score (77.8 ± 18.47). In 2nd week, the itch score was significantly decreased (59.9 ± 23.0). In week 4, the itch score was in moderate level (27.46 ± 23.6). Level of itch between weeks was significant reduced ($p < 0,001$). According to [Boguniewicz M, Fiedler VC](#) (7), multi-center, double-blind study on pediatric patients from 7-16 years old, itching ratio reduced from 74%-89% compared with before treatment.

4.2.6 Safety assessment:

In this study, adverse events occurs at low incidence (12.2%), itching is the most common adverse event (12.2%), follow by skin burning (5.4%), dryness and redness (1.4%). These events just occurred in the first week and disappeared after 2-3 days. These cases were consulted so that there was no change, concomitant usage or discontinue of drug usage.

5. CONCLUSION:

- **Tacrolimus ointment exhibits an effective treatment in adult AD patients.**

- **Adverse events** occurs at low incidence (12.2%), itching is the most common adverse event (12.2%), follow by skin burning (5.4%). Other cases are dryness and redness (1.4%). There was no change, concomitant usage or discontinue of drug usage.

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Abstract

Atopic dermatitis (AD) is the most common chronic inflammation skin disease, long-lasting and difficult in treatment. In the world, Tacrolimus is an immunosuppressive agents was used for AD treatment resulting in safety and efficacy result. However, there is no study in Vietnam.

Objective: *To evaluate safety and efficacy of tacrolimus ointment in moderate to severe AD in adult patients.*

Material and Method:

74 subjects with moderate to severe AD adult patients from 2007-2009.

- Design: open-label clinical trial, comparision before and after treatment.
- Administration: applied ointment 0.1% twice per day, approximately 10 to 14 hours apart in 4 weeks or 1 more week until clear treatment.
- Result assessment: based on Physician's assessment of individual signs (PhGECR); Physician's global evaluation of clinical response; Eczema area and severity Index (EASI) of four body regions; Patient's Assessment of treatment effects; Patient's assessment of Itch; Quality of life measurement and Safety assessment. Data analysis is based on statistical tests.

Results:

- In week 4, PhGECR showed clinical improvement is 89.7%. EASI index is rapidly decrease from baseline (week 0 = 16.25 ± 6.8) to end of treatment (week 4 = 1.89 ± 1.98). Patient's Global evaluation of clinical response showed significantly increasing of clinical improvement (over slightly better = 89.1%). Itching assessment is significantly reduced (week 4, moderate itch = 27.46 ± 23.6). Quality of life measurement increased until end of treatment (week 4). Adverse events occurs at low incidence (12.2%), itching is the most common adverse event (12.2%), follow by skin burning (5.4%). Other cases are dryness and redness (1.4%). There was no change, concomitant usage or discontinue of drug usage.

Conclusion : Tacrolimus ointment is effective and safe in moderate to severe adult AD patients.

Keywords: Atopic dermatitis, adult patient, Tacrolimus ointment 0.1%

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