THE EFFICACY AND SAFETY OF TACROLIMUS OINTMENT IN PEDIATRIC 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 0.03% in treatment of moderate to severe AD in pediatric patients from Vietnam Nation Institute of Dermatology.

- Assess the safety of Tacrolimus ointment 0.03% in treatment of AD.

2. SUBJECTS AND METHODS

2.1. SUBJECTS:

Pediatric patients had diagnosis of moderate to severe atopic dermatitis who was treated at Vietnam Nation Institute 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.

- Pediatric, at least 2 years of age.

- Male and female patients.

- Patients didn't have other skin disorders and severe heart, liver, kidney and lung diseases.

- Patients had given informed consent. The parent/guardian has also given consent.

*** Exclusion criteria**:

- Patients below 2 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.

2.2. MATERIALS

Tacrolimus ointments, 0.03%, 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 comparation trial.

- Sample size: randomized, 30 pediatric AD patients from 2-12 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:

Pediatric patients were applied tacrolimus ointment 0.03% 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 gardian 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 site:

Vietnam Nation Institute 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), 30 pediatric patients were enrolled in the present study in Vietnam Nation Institute of Dermatology.

3.1 General informatic of patients

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

Patients	**Subject (n=30)**	
Gender	**n**	**%**
Male	16	53.3
Female	14	46.7

Age (year) Min Max	 3 12	
Average age (year) Mean ± SD	7.021 ± 3.568	
AD onset Min Max Not defined	 0 11	
Average onset of AD (year)	2.33 ± 2.58	
Average area of lesion (Mean ± SD)	41.16 ± 22.54	
Itch (Mean ± SD)	82.89 ± 14.07	
Severity Moderate Severe	 13 17	 43.3 56.7

Table 1's observation:

- Number of AD female patients is same as male (53.3% vs. 46.7%). The min AD onset age is in the first month, the max is 11 years old. Average onset age of pediatric patient is slightly low, happened in 2 first years (Mean ± SD: 2.33±2.58) and the lesion area is much (Mean ± SD: 41.16±22.54)

- Before treatment: the itching index is high (82.89%) and severe severity AD-acquired is higher than at moderate severity (56.7% vs 43.3%).

3.2 Efficacy assessment:

Table 2: **Physician's Global Evaluation of Clinical Response**

Time / **Subject**		**Clinical Improvement***				
		Cleared (100%)	**Excellent improvement (90-99%)**	**Marked improvement (75-89%)**	**Moderate improvement (50-74%)**	**Total**
Subject (n=71)	Week 1 (n=27)	0	6.9	37.9	44.8	89.7
	Week 2 (n=23)	0	13.0	43.5	34.8	91.3
	Week 3 (n=21)	0	14.3	61.9	19.0	95.2
	Week 4 (n=20)	0	5.0	10.0	65.0	80.0

*** 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 (6.9%). However, if consider that 50-74% is "Clinical success", the successful improve of treatment was 89.7%. The

result was improved in second and third week (over 90%). In forth week, the "Clinical success" was 80.0%.

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

Eczema Area and Severity Index (EASI)						
Time / Subject		**Baseline (1)**	**Week 1 (2)**	**Week 2 (3)**	**Week 3 (4)**	**Week 4 (5)**
EASI (Mean ± SD)		17.7±11.9	8.0±5.7	5.88±3.9	3.7±2.5	2.1±1.7
EASI score differentiation		p1'với p2' < 0.001; p2' với p3'< 0.001; p3' với p4'< 0.0; p4' với p5' < 0.01				
The Patient's Assessment of Treatment Effects						
Time / Subject		*Much better*	*Better*	*Slightly better*	*Same*	*Slight worse*
Size (n=18)	Week 1	11.1	27.8	44.4	16.7	
	Week 2	5.6	44.4	38.9	5.6	
	Week 3	5.6	50.0	33.3	11.1	
	Week 4	11.1	55.6	16.7	16.7	

Table 3's observation:

- In children, Eczema Area and Severity Index (EASI) was rapidly decreased from baseline (week 0 =17.7±11.9) to end of treatment (week 4 =2.1±1.7). These differences were significantly p1'<0.001and p2'<0.001

- The Patient's Assessment of Treatment Effects: in first week, the better ratio was 38.9%; slightly better was 44.4%. After 4 weeks, the clinical improvement ratio was increased (better – 66.7% + slightly better – 16.7% = 83.4%). The ratio of no change was 16.7%.

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)**	82.89±14.07	60.28±16.1	45.89±15.6	45.3±18.55	34.9±17.1
Itch score differentiation	p1'với p2' < 0.001. p2' với p3' < 0.001. p3' với p4' < 0.02. p4' với p 5' < 0.02				
Quality of life's score					
Subject		**Before treatment**		**After treatment**	
Subject **(Mean ± SD)**		27.81±7.71		37.2±3.07	
Differentiation		p < 0.001			

Table 4's observation:

-At baseline (week 0), patients had high itch score (82.89±14.07). However, in 2nd week, the itch score was significantly decreased (45.89±15.6). In week 4, the itch score was moderate level (34.9±17.1). Level of itch between weeks was significantly reduced ($p < 0.001$).

- Quality of life's score was significantly increase ($p<0.001$) from baseline (week 0 = 27.8±7.71) to end-of-treatment (week 4 = 37.2±3.07).

3.3 Safety assessment

In 30 pediatric AD patients, adverse events did not occur.

4. DISCUSSION:

4.1. General characteristics of AD patients

In 2 years (2007-2009), there is 30 cases of pediatric AD patients were enrolled into this study taken place at Vietnam Nation Institute of Dermatology. We have some observations:

- Number of AD-acquired patient is same in female than in male (53.3% vs 46.7%)

- Lowest age is 3 years old and highest age is 12 years old, correspondent with inclusion criteria.

- Min AD onset age is first month, max is 11 years old. Average onset age of pediatric patient is slightly low, happened in 2 first years (Mean ± SD: 2.33± 2.58).

- Ratio of lesion in children (Mean±SD: 30.41±16.32), correspondent with ratio of severe level (56.7%)

4.2. Assessment of treatment effects

4.2.1 Physician's Global Evaluation of Clinical Response (PhGECR):

In first week, the cleared response was very low (6.9%). However, if consider that 50-74% is "Clinical success", the successful improve of treatment was 89.7%. The result was improved in second and third week (over 90%). In forth week, the "Clinical success" was 80.0%. This result is correspondent with these of **Cheer SM**, **Plosker GL** (6) double-blind in 304 adult AD patients and 351 pediatric patients showed clinical improvement ≥ 90% (assessment based on group using ointment 0.1% and 0.03% compared with placebo usage group).

4.2.2. Eczema Area and Severity Index (EASI):

In children, EASI score was rapidly decreased from baseline (week 0 =17.7±11.9) to end of treatment (week 4 =2.1±1.7) indicate the effect of tacrolimus ointment in AD treatment. These differences were significantly p1'<0.001 and p2'<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 ($p<0.001$) from baseline (week 0 = 27.8±7.71) to end-of-treatment (week 4 = 37.2±3.07).

4.2.4 Patient's Assessment of treatment effects:

After 4 weeks, the clinical improvement ratio was increased; better and slightly better ratio is 83.4%. The ratio of no change was 16.7%.

4.2.5 Assessment of Itch:

-At baseline (week 0), patients had high itch score (82.89±14.07). In 2nd week, the itch score was significantly decreased (45.89±15.6). In week 4, the itch score was in moderate level (34.9±17.1). 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, there was no adverse events occurred during treatment.

5. CONCLUSION:

- Tacrolimus ointment exhibits an effective treatment in pediatric AD patients. Ph GECR showed clinical improvement is 80.0%. EASI index is rapidly decrease from baseline (week 0) to end of treatment (week 4). Patient's Global evaluation of clinical response showed significantly increasing of clinical improvement (over slightly better = 83.4%). Itching assessment is significantly reduced. Quality of life measurement increased until end of treatment (week 4).

- Safety assessment: there was no adverse events occurred in study group.

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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 agent which 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 pediatric patients.*

Material and Method:

30 subjects with moderate to severe AD pediatric patients from 2007-2009.

- Design: open-label clinical trial, comparision before and after treatment.

- Administration: applied ointment 0.03% 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 80.0%. EASI index is rapidly decrease from baseline (week 0 = 17.7±11.9) to end of treatment (week 4 = 2.1±1.7). Patient's Global evaluation of clinical response showed significantly increasing of clinical improvement (over slightly better = 83.4%). Itching assessment is significantly reduced (week 4, moderate itch = 34.9±17.1). Quality of life measurement increased until end of treatment (week 4). There was no adverse events occurred in study group.

Conclusion : Tacrolimus ointment 0.03% is effective and safe in moderate to severe pediatric AD patients.

Keywords: Atopic dermatitis, pediatric patient, Tacrolimus ointment 0.03%

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