# Efficacy and Safety of Tacrolimus Ointment in Pediatric Patients with Moderate to Severe Atopic Dermatitis

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***Background:*** *Atopic dermatitis (AD) is an immunological skin disease. It is common in pediatric populations and often requires topical steroid treatment. Moderate to severe AD may not respond to topical steroids. They often require systemic steroids, which may result in growth retardation. Protopic, a non-steroid, tacrolimus based ointment which is a calcinurin inhibitor has been proved to be effective in caucacian with AD.*
***Objective:*** *To evaluate safety and efficacy of 0.03% tacrolimus ointment (Protopic ) in moderate to severe AD in pediatric patients age 2-12 years.*
***Material and Method:*** *This was a one month multicenter open-label clinical trial using tacrolimus ointment twice daily in 61 subjects with moderate to severe AD from September to December 2004. Efficacy assessments were measured by Physician's Global Evaluation of Clinical Response (PhGECR), Eczema area and Severity Index (EASI), Patient's Global Evaluation of Clinical Response (PaGECR), and Quality of Life (QOL). Safety assessment was measured by incidence rate of adverse events.*
***Results:*** *Fifty-eight patients completed the studies. Twenty-two patients were male; thirty-nine patients were female. Twenty-nine patients had moderate AD. Thirty-two patients had severe AD. Three cases had discontinued treatment at the third week due to increase in severity. Over all PhGECR were significantly increased, 94% showed moderate improvement in PhGECR at week 4 or end of treatment (EOT)and 83% had better improvement in PaGECR at EOT. Within 7 days, tacrolimus demonstrated rapid onset in reduction of EASI score and itch in patients. Mean QOL were significantly decreased at the end of the present study. Incidence of adverse events included application site burning (21%), itching (17%), pruritus (9%), infections(3%), and erythema and folliculitis (2%) . Burning sensation, erythema, pruritus and itching were resolved after the first week.*
***Conclusion:*** *Topical tacrolimus ointment is effective and safe in moderate to severe AD. It significantly improved PhGECR, EASI, PaGECR, and QOL in pediatric patients after the first week of treatment and continued through the end of the study. The major adverse events were burning, itching, and pruritus, which were resolved within the first week of therapy.*

***Keywords****: Aptopic dermatitis, Tacrolimus ointment, Pediatric patient*

***J Med Assoc Thai 2006; 89 (11): 1915-22***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

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Atopic dermatitis[1-3] (AD) is an intensely pruritic, chronic, inflammatory, immunologically based skin disease with a genetic predisposition. The initial occurrence of atopic dermatitis is often during the first year of life, and although it may improve with age, it can continue or recur periodically. Patients whose disease continues beyond six years of age have a poor prognosis for outgrowing it. Atopic dermatitis is usually accompanied by respiratory allergy and a family history of asthma, hay fever, and dry skin.

Standard therapeutic modalities[3-6] are directed at controlling the predominant symptoms of the disease: xerosis, erythema, and pruritus. These therapies include the liberal use of emollients, minimizing contact with irritants, dietary intervention, antihistamines, and antibiotics. The use of a low-potency topical corticosteroid is often recommended. When more aggressive treatment is needed, mid- to high-potency topical corticosteroids are the therapy of choice, but can be associated with skin atrophy and are contraindicated for use on the face and in intertriginous areas. In pediatric patients, prolonged use of topical corticosteroids may also be associated with growth retardation[2].

Systemic immunomodulating therapy is reserved for those patients who are resistant to topical corticosteroids[3,7-13], and include systemic corticosteroids, UVA, UVB methoxypsoralen light treatments, cyclophosphamide, azathioprine, chloroquine, gamma interferon, interleukin-2 or cyclosporine. The inherent toxicities associated with such systemic administrations result in a negative benefits risk ratio for use in this non-fatal disease, particularly in pediatric patients. In this context, a topical formulation of cyclosporine has been tested but did not provide an acceptable clinical benefit[14-17].

Tacrolimus has been approved in major countries around the world to prevent and/or treat allograft rejection in organ transplantation. Its mode of action is similar to that of cyclosporine, which suppresses the activation and proliferation of antigen-specific T-cells. However, tacrolimus has a lower molecular weight and is more potent than cyclosporine[18-21]. Preclinical *in vitro* pharmacology evaluations and *in vivo* toxicology studies have indicated that tacrolimus ointment could be effective and safe for use in humans. Clinical studies of tacrolimus ointment showed promising results for the treatment of AD affecting the face, neck, and body[22,23]. This was an open-labeled, multi-center study to determine the efficacy and safety of tacrolimus ointment in pediatric patients with moderate to severe atopic dermatitis in Thailand.

**Material and Method**

This was an open-labeled, multi-center study. Enrolled patients (2-12 years old) applied the tacrolimus ointment 0.03% twice daily for 4 weeks or until one week after the affected areas defined for treatment at baseline were completely cleared, whichever was first. Scheduled study visits were conducted at pre-study (optional), baseline/day 1, week 1, week 2, week 3 and week 4/end-of-treatment. The end-of-treatment visit was conducted prior to week 4 for patients who discontinued treatment early for any reason. Additional visits were conducted if necessary.

Tacrolimus ointment was applied to the patients twice per day, approximately 10 to 14 hours apart, as a thin coating over the affected areas of atopic dermatitis defined for treatment by the investigator at baseline. The study ointment should be applied at least 2 hours prior to or at least 30 minutes after bathing, showering, 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.

The minimum length of treatment for all patients was 2 weeks. If the baseline treatment areas were "cleared" before or at 1 week, treatment with the study ointment should continue for at least a total of 2 weeks before stopping. In all other instances, therapy must continue for one week after areas of atopic dermatitis were cleared or for 4 weeks, whichever was first.

***Efficacy Assessments***

All the efficacy assessments were done by the same physician rater at baseline and at all subsequent study visits. A secondary rater may be present at the baseline evaluation and agree on the ratings. The secondary rater might then act as a backup rater in the event of an emergency or unavailability of the physician for subsequent visits.

Physician's Global Evaluation of Clinical Response (PhGECR) was recorded weekly from week 1 to week 4/end-of-treatment. This evaluation was rate change of the lesions of atopic dermatitis that were defined in the baseline treatment area only using the 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%) and worse (< 0%).

The physicians assessed the individual signs of the lesions of atopic dermatitis that were defined in the baseline treatment area only, in the following four body regions: head and neck, upper limbs, trunk and lower limbs.

Physician's Assessment of Individual Signs was rated for the following six signs (EASI score) at baseline/day 1 and weekly from week 1 to week 4/end-of-treatment: erythema, edema/ induration /papulation, excoriation, oozing / weeping / crusting, scaling and lichenification. Each individual sign was rated using the following scale: absent = 0, mild = 1, moderate = 2 and severe = 3.

The percentage of body surface area affected by atopic dermatitis was estimated by the physician for each of the four body regions at baseline/day 1 and every week from week 1 to week 4/end-of-treatment. This assessment was made on the affected lesions defined in the baseline treatment areas.

A composite index of area involved and severity of the signs of atopic dermatitis in the four designated regions were 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.

Patients made two assessments at each study visit. The patient evaluations were based on all affected areas. The Patient's Assessment of Overall Response was assessed global improvement of the patient's atopic dermatitis. The patient's assessment of itch was assessed by the amount and intensity of itch using a visual analog scale. Patients completed the patient's assessment page at baseline/day1 and once weekly from week1 to week4/end of treatment. The assessment should be done before the physician's assessments so that the patient's assessment was not biased.

***Patient Population***

In order for a patient to qualify for the present study, the patient must meet all of the following inclusion criteria on Baseline/Day 1 and the patients who exhibit any of the exclusion criteria will not be eligible for the study.

***Inclusion criteria***

Patient has a diagnosis of atopic dermatitis using Hanifin and Rajka Criteria[24], which is rated as moderate to severe using Rajka and Langeland Criteria[25] involving at least 10% of the body surface area.

Patient has given informed consent. For those patients under 18 years old, the parent/guardian has also given consent.

Patient is at least 2 years of age.

Female patients with child-bearing potential must have a negative pregnancy test and all patients will be advised not to get pregnant during the study.

Patient meets the following washout requirements and agrees to follow restrictions during the study

Patient and, if applicable, parent/guardian, agrees to comply with study requirements and is able to be at the clinic for all required study visits.

***Exclusion criteria***

Patient has a skin disorder other than atopic dermatitis in the areas to be treated.

Patient has pigmentation or extensive scarring or pigmented lesions in the areas to be treated which would interfere with rating of efficacy parameters.

Patient has clinically infected atopic dermatitis at baseline.

Patient may require systemic corticosteroids or more than 2 mg prednisone equivalent per day of inhaled and/or intranasal corticosteroids during the present study

Patient has a known hypersensitivity to macrolides or any excipient of the ointment.

Patient has a systemic disease, including cancer or history of cancer or HIV, which would contraindicate the use of immunosuppressants.

Patient has a chronic condition (e.g., diabetes, hypertension), which is either not stable or not well controlled.

Patient is pregnant or breast feeding an infant.

***Safety Assessments***

Safety was based on clinical adverse events reported by patients or observed by the physician. Adverse events were assessed by the physician during the study period and were recorded.

***Additional Assessments***

Patients completed a quality of life (QOL) questionnaire at baseline/day1 and week 4/end-of-treatment. The purpose of administering the quality of life questionnaire was to assess the physical and psycho-social aspects of the disease state, which might affect patient functioning and the patient's perception of the care that they were receiving. In diseases of a chronic nature, such as atopic dermatitis, the patient's long-term quality of life was adversely affected by the severity of the disease, which could limit daily functioning and comfort. The quality of life questionnaire that was used in the present study was the Thai Version of Childhood Dermatology Life Quality Index (DLQI)[3,7].

***Statistical analysis***

All statistical tests were two-sided, with the significance level of alpha = 0.05, unless otherwise specified. The 95% confidence interval was calculated for the primary outcome. For efficacy end points, the paired t test was used to evaluate effects before and after a treatment. The Wilcoxon signed-rank test was used for nonparametric analyses. Analysis of variance with repeated measurement was also applied for baseline.

**Results**

Sixty-one patients (mean age ± SD = 6.98 ± 2.81 years) were enrolled in the present study (Table 1). Fifty-eight patients had completed the studies, 22 were male and 39 were female. Twenty-nine patients had moderate AD and thirty-two patients had severe AD. Three cases had discontinued treatment at the third week due to increase in severity.

Overall, mean PhGECR score were significantly increased from 2.28 at first week to 2.42 at second week and 3.07 at week four ($p < 0.001$) (Fig.1). PhGECR at the end of treatment reviewed 7% clear, 26% excellent, 40% marked,21% moderate, and 4% slight improvement. Mean EASI had significantly decreased from 6.09 at base line to 3.72 at the end of week one to 2.09 at end of week four ($p < 0.001$) (Fig. 2).

**Table 1.** Demographic data at baseline (n = 61)

| | |
|---|---|
| Severity | |
| Moderate | 29 cases (47.5%) |
| Severe | 32 cases (52.5%) |
| Age(Year) Mean ± SD | 6.98±2.81 |
| Gender | |
| Male | 22 cases (36.1%) |
| Female | 39 cases (63.9%) |

Mean PaGECR score at first week of 1.91 had decreased slightly at the second week (1.79) and significantly increased at week four at 2.31 ($p = 0.018$) (Fig. 3). PaGCER at the end of treatment, reviewed 57% were much better, 26% were better, 12% slightly better, 3% were the same, and 2% were worse. Mean itch score was significantly decreased from 67.7 at base line to 44.7 at week one and to 26.4 at week four ($p < 0.001$) (Fig. 4). Mean QOL were significantly decreased from 1.19 at base line to 0.68 at the end of the present study ($p < 0.01$) (Fig. 5).

Incidence of adverse events included application site burning 14 cases (23%), erythema 2 cases (3.3%), itching 10 cases (16.4%), folliculitis one case (2%), and infection two cases(3%) Burning sensation, erythema, pruritus, and itching were resolved after the first week.

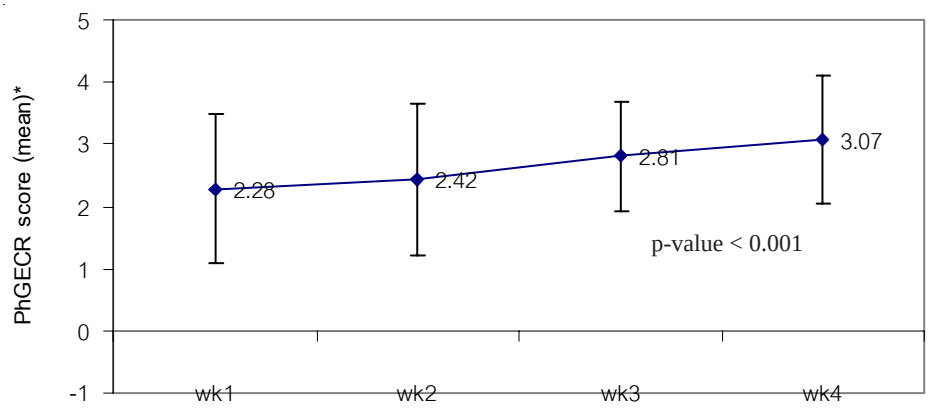


**Fig. 1** Mean PhGECR Score at week 1 to week 4
* Physician's Global Evaluation of Clinical Response (PhGECR)
5 = 100% Improvement = Clear
4 = 90-99% Improvement = Excellent Improvement
3 = 75-89% Improvement = Marked Improvement
2 = 50-74% Improvement = Moderate Improvement
1 = 30-49% Improvement = Slight Improvement
0 = 0-29% Improvement = No Appreciable Improvement
-1 = < 0 % = Worse

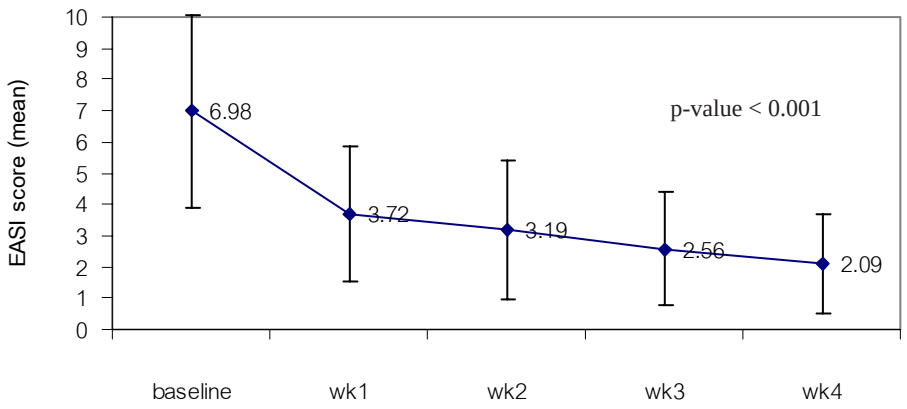


**Fig. 2** Mean EASI score over time at baseline and week 1 to week 4

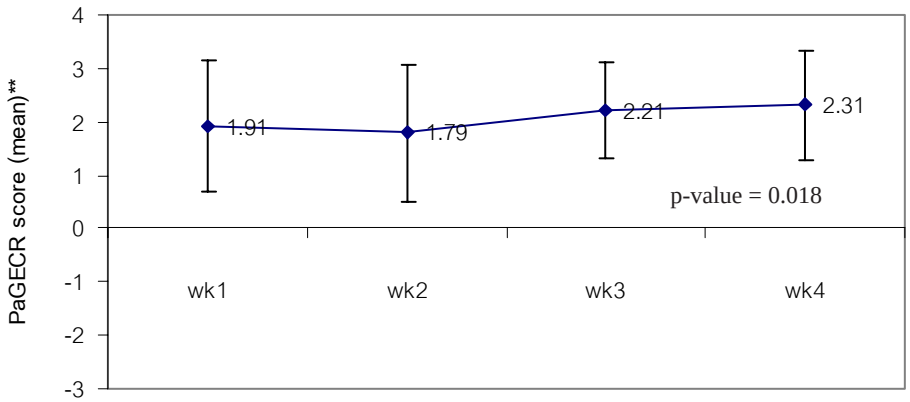


**Fig. 3** Mean PaGECR Score at week 1 to week 4
** Patient's Global Evaluation of Clinical Response (PaGECR)
3 = Much Better, 2 = Better, 1 = Slightly Better, 0 = Same, -1 = Slight Worse, -2 = Worse, -3 = Much Worse

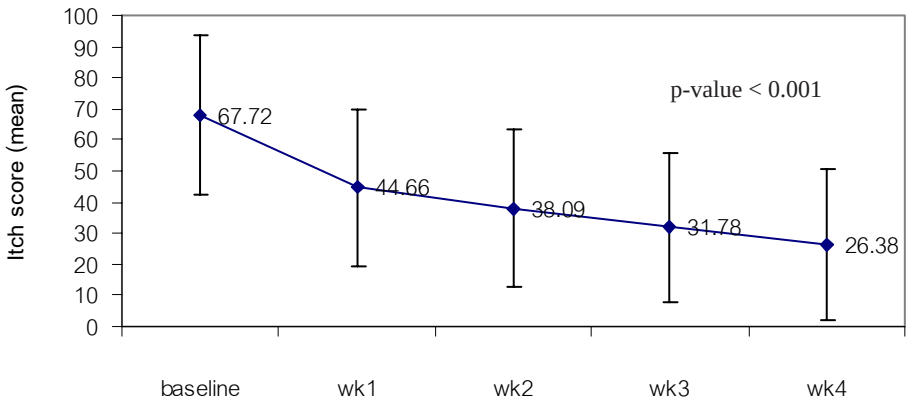


**Fig. 4** Itch over time at baseline, week 1 to week 4

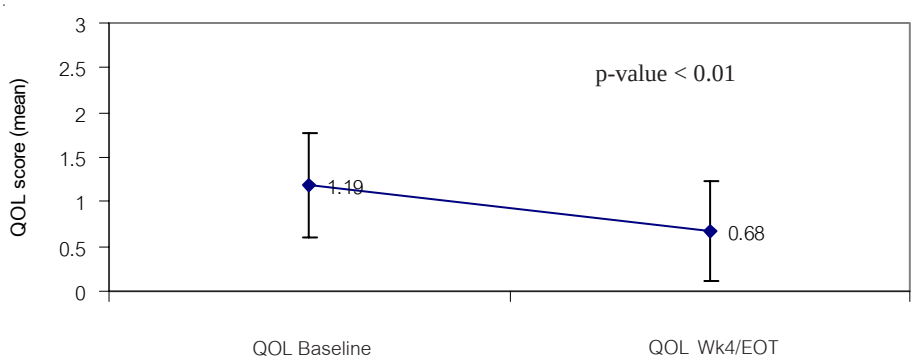


**Fig. 5** QOL of atopic dermatitis at baseline and week 4/end of treatment
The decrease in QOL score means reflects QOL improvement

The percentage of patients achieving ≥ 94% *moderate improvement* based on a Physician's Global Evaluation of Clinical Status and ≥ 83% *better improvement* based on a Patient's Global Evaluation of Clinical Status at the End of Treatment. The result of the present study showed rapid improvement and the authors can conclude that topical tacrolimus ointment is effective and safe in moderate to severe AD. It significantly improved PhGECR, EASI, PaGCR, and QOL in pediatric patients after the first week of treatment and continued through the end of the present study. For future research, a long-term study should be designed to evaluate the safety and efficacy of tacrolimus ointment in pediatric patients with moderate to severe atopic dermatitis in Thailand.

**Discussion**

Prior studies have investigated the effective and safety of Tacrolimus ointment in pediatric patients with moderate to severe atopic dermatitis[24,26,28-31]. According to the results of the many experiments performed over the decade, which were reviewed by Lisa AB[24], they exhibited most nearly the percentage of patients who cleared or showed excellent improvement (at least 90% improvement) with regard to the results of the present study, 36% and 33%, respectively. According to the study of Schachner et al[30], it was shown that tacrolimus 0.03% ointment generated a 54.8% improvement of EASI whereas the present study exhibits only 34.3% improvement (6.09 to 2.09). Moreover, the results of Kang et al's study also showed that although the improvement of efficacy was notable after the first week and was maintained till the end of the study, there was no indication that the effectiveness decreased with the continuing daily use[31]. Hanifin et al presented a study that evaluated the efficacy and safety of tacrolimus ointment, for up to 4 years, in patients with AD[26]. Its result exhibited the adverse events occurring during the treatment process in pediatric patients (2-15 years of age). Skin infection is the most common adverse event occurring among pediatric patients; followed by pruritus (itching), skin burning, rash, and erythema. Whereas, the results of the authors' short-term study display that the most common is skin burning and least common is infection and folliculitis. Additionally, the results from Phase I study of tacrolimus (FK506) ointment[27] summarized that the adverse events do not appear to be related to dose. Therefore, the safety and efficacy in a bigger population should be accounted for to make it clear about the long term usage of this study drug. Fortunately, the Koo et al[29] study had already investigated the 8,000 subjects in the terms of safety and effectiveness in AD patients in 2005. Regarding its results, the percentage of body surface affected (% BSA) was decreased by 91% at the end of the study (18 months). Skin infections, varicella zoster and shingles, were insignificantly found during the treatment period and also undiscovered in Chapman et al's[28]. According to the Chapman et al study in 2005, at the end of the study, tacrolimus ointment decreased the itching score significantly. This was also experienced in the authors' experiment.

60% of pediatric AD patients reported that QoL is affected by skin disease. Therefore, besides the effective and safety of the study drug, the impacts of tacrolimus ointment on the QoL of the patient need to be emphasized. In 2001, Drake's experiment was designed to evaluate this impact on a study drug comparing with vehicle ointment. Its result showed that

tacrolimus ointment could improve QoL of AD pediatric patients with greater improvement when compared with vehicle[25]. Moreover, Drake's study also showed that more than 80% of patients preferred to use tacrolimus ointment for continuing although the percentage of cleared patients at the end of study was lower (28.7%) than other experiments.

In conclusion, the authors can summarize that tacrolimus ointment exhibits an effective and safe profile in pediatric AD patients although adverse events were discovered but not significant. Moreover, the study drug can improve the quality of life in AD patients for which, additionally, there is a high preference to use it after completing the study. Although the drug profiles were cleared, a further experiment should investigate the long-term usage due to atopic dermatitis, the skin disease that can recur throughout one's lifetime.

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## *การประเมินประสิทธิภาพและความปลอดภัยของยาทาโคลิมุสชนิดขี้ผึ้ง ในผู้ป่วยเด็กโรคผื่นภูมิแพ้ผิวหนังอักเสบ ที่มีอาการในระดับปานกลางถึงรุนแรง*

***ศรีศุภลักษณ์ สิงคาลวณิช, นภดล นพคุณ, วนิดา ลิ้มพงศานุรักษ์, วาณี วิสุทธิ์เสรีวงศ์, กอบกุล อุณหโชค, อมรศรี ชุณหรัศมิ์, ศิริวรรณ วนานุกูล, รัศนี อัครพันธุ์***

***ที่มา:*** *โรคผื่นภูมิแพ้ผิวหนัง เป็นโรคผิวหนังที่เกี่ยวข้องกับระบบภูมิคุ้มกันของร่างกาย ที่พบได้บ่อยในผู้ป่วยเด็กและส่วนมากใช้ยาทาสเตียรอยด์ในการรักษาอาการแต่ในสภาวะที่โรคผื่นภูมิแพ้มีความรุนแรงในระดับปานกลางถึงรุนแรง การใช้สเตียรอยด์ชนิดทาอาจไม่ได้ผล และต้องเปลี่ยนไปใช้ยาสเตียรอยด์ชนิดออกฤทธิ์ทั่วร่างกายซึ่งอาจมีผลกดการเจริญเติบโตของเด็ก Protopic เป็นตัวยาทาโคลิมุสในรูปแบบขี้ผึ้ง ที่ไม่ใช่ยาสเตียรอยด์ ที่ออกฤทธิ์ในการยับยั้งแคลซินูรินที่ได้รับการอนุมัติว่ามีประสิทธิภาพในการรักษาโรคผื่นภูมิแพ้ผิวหนัง*

***วัตถุประสงค์:*** *การวิจัยในครั้งนี้มี วัตถุประสงค์เพื่อประเมินประสิทธิภาพและความปลอดภัยของการใช้ยาทาโคลิมุสชนิดขี้ผึ้งขนาด 0.03% ในการรักษาอาการของโรคผื่นภูมิแพ้ผิวหนังอักเสบ ในผู้ป่วยเด็กอายุ 2-12 ปี ที่มีความรุนแรงของโรคในระดับปานกลางถึงรุนแรง*

***วัสดุและวิธีการ:*** *การวิจัยในครั้งนี้เป็นการศึกษาแบบเปิดฉลาก ซึ่งเป็นการวิจัยร่วมหลายสถาบัน โดยใช้ระยะเวลา 1 เดือน ในผู้ป่วยเด็กจำนวน 61 คน ที่เป็นโรคผื่นภูมิแพ้ผิวหนังอักเสบ ที่มีอาการในระดับปานกลางถึงรุนแรง ระยะเวลาทำการวิจัยช่วงเดือนกันยายน พ.ศ. 2547 ถึง ธันวาคม พ.ศ. 2547 การประเมินประสิทธิภาพของยาจะประเมินผลการตอบสนองโดยรวมทางคลินิกโดยแพทย์ผู้ทำการวิจัย บริเวณที่มีการอักเสบของผิวหนัง และดัชนีความรุนแรงของโรค การประเมินผลการตอบสนองโดยรวมทางคลินิกโดยตัวผู้ป่วยเอง หรือ ผู้ปกครอง และการวัดคุณภาพชีวิตด้านความปลอดภัยจะประเมินจากอุบัติการณ์การเกิดอาการข้างเคียงที่พบจากโครงการวิจัย*

***ผลการศึกษา:*** *มีผู้ป่วยที่เข้าร่วมจนสิ้นสุดการวิจัยจำนวน 58 คน เป็นเด็กผู้ชาย 22 คน เด็กผู้หญิง 39 คน มีความรุนแรงของโรคในระดับปานกลางจำนวน 29 คน ระดับรุนแรง 32 คน ผู้ป่วย 3 คนออกจากการวิจัย ณ สัปดาห์ที่ 3 เนื่องจากมีอาการของโรครุนแรงมากขึ้น โดยรวม พบว่า 94 % ของผู้เข้าร่วมการวิจัยจากการประเมินโดยแพทย์ผู้ทำการวิจัย มีอาการดีขึ้นปานกลางจนถึงหายเป็นปกติ ณ สัปดาห์ที่4 หรือ สิ้นสุดการวิจัย และ 83% ของผู้เข้าร่วมการวิจัยรู้สึกว่าอาการดีขึ้นจนถึงดีขึ้นมาก เมื่อประเมินโดยตัวผู้ป่วยเอง หรือ ผู้ปกครอง ภายใน 1 สัปดาห์ ยาทาโคลิมุสชนิดขี้ผึ้งสามารถลดค่า EASI และระดับอาการคันในช่วงเวลาการรักษาได้อย่างรวดเร็ว ค่าเฉลี่ยคุณภาพชีวิตมีค่าลดลงอย่างมีนัยสำคัญทางสถิติหลังสิ้นสุดการวิจัย อุบัติการณ์การเกิดอาการข้างเคียง ได้แก่ อาการแสบร้อนบริเวณที่ทา 21% อาการคันบริเวณที่ทา 17% ผื่นแพ้ 9% อาการบวมแดง 2% ตุ่มน้ำพอง 2% และติดเชื้อ 3% และอาการข้างเคียง ส่วนใหญ่ หายไป หลังสัปดาห์แรก*

***สรุป:*** *ยาทาโคลิมุสชนิดขี้ผึ้งมีประสิทธิภาพและความปลอดภัยในการรักษาอาการของโรคผื่นภูมิแพ้ผิวหนังอักเสบในผู้ป่วยที่มีความรุนแรงของโรคในระดับปานกลางถึงรุนแรง ค่าการตอบสนองโดยรวมทางคลินิกที่โดยแพทย์ผู้ทำการวิจัย, ค่าแสดงบริเวณที่มีการอักเสบของผิวหนังและดัชนีความรุนแรงของโรค, การตอบสนองโดยรวมทางคลินิกโดยตัวผู้ป่วยเอง หรือ ผู้ปกครอง และคุณภาพชีวิต ดีขึ้นอย่างมีนัยสำคัญทางสถิติหลังจากการใช้ยาในสัปดาห์แรกและต่อเนื่องไปจนจบการวิจัย อาการข้างเคียงส่วนใหญ่ ได้แก่ อาการแสบร้อน อาการคันบริเวณที่ทาและผื่นแพ้ ซึ่งหายได้เองในช่วงสัปดาห์แรกของการรักษา*