

# Treatment of Mild to Moderate Plaque Psoriasis with Pimecrolimus, Clobetasol, or Calcipotriol Cream: A comparative study

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## Abstract:

**Background:** a number of studies have shown that application of topical calcineurin inhibitors is effective for a broad spectrum of inflammatory skin disorders.

**Objective:** to compare the efficacy and safety of 1% of pimecrolimus cream versus 0.05% of clobetasol cream and 0.005% of calcipotriol cream in psoriatic patients.

**Patients and methods:** adults on stable plaque psoriasis were randomized to three treatment groups (pimecrolimus, clobetasol, and calcipotriol group). The criteria of inclusion involve affected BSA of  $\leq 10\%$ , with a local psoriasis severity index (LPSI) score of  $\geq 5$ . The main assessment of clinical efficacy was the percent changes in LPSI. The quantitative determination of cytokine levels (IL -6, s IL-2R, TNF- $\alpha$ ), skin biopsies, and creams safety were also evaluated.

**Results:** the median percent changes in LPSI for pimecrolimus, clobetasol and calcipotriol groups were 51%, 56% and 59%, respectively ( $p > 0.05$ ). Pimecrolimus cream decreased cytokines levels and improved pathological features of psoriatic lesion. Mild skin burning was the most frequent adverse event reported by pimecrolimus (40%;  $p < 0.05$ ) versus 8% in clobetasol and 12% in the calcipotriol gr.

**Conclusion:** pimecrolimus cream demonstrated efficacy comparable with that of clobetasol and calcipotriol for the treatment of mild to moderate plaque psoriasis.

**Key words:** psoriasis; pimecrolimus; clobetasol; calcipotriol; efficacy; safety.

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## Introduction:

Psoriasis is a chronic inflammatory skin disorder, which is clinically characterized by circumscribed red plaques covered with white scales on the surface (1). Histological features show proliferation of epidermis with parakeratosis, dilation of superficial blood vessels, polymorphonuclear leukocyte infiltration in the stratum corneum, and perivascular infiltration of mononuclear cells in the upper dermis (2).

A growing body of evidence has shown that immunologic mechanisms are involved, and activated T-cells play a crucial role, via an array of proinflammatory cytokines, in the pathogenesis of psoriasis (3). Interleukin - 2 (IL -2), interleukin - 6 (IL - 6), and tumor necrosis factor alpha (TNF -  $\alpha$ ) are the hallmark cytokines in a psoriatic cytokine network. Several investigators have suggested the possible use of TNF -  $\alpha$ , IL - 6, IL - 8 and soluble interleukin - 2 receptor (s IL - 2R) as markers of disease severity in psoriasis (4,5,6).

While no cure is available for psoriasis, many treatment options exist. Current topical treatments for psoriasis include coal tar, anthralin/dithranol, corticosteroids, calcipotriol, retinoids and ultraviolet light, and although these medications can provide some relief and control of the symptoms, they can be associated with unwanted side effects (7). Therefore, there is a need for a new topical treatment that can quickly and effectively improve

the clinical signs and symptoms of psoriasis and can be applied safely for prolonged periods of time (8,9).

Tacrolimus and pimecrolimus (topical calcineurin inhibitors) are a macrolide molecules isolated from the fermentation broth of *Streptomyces tsukubaensis*, which have immunosuppressive property and approved for the treatment of atopic dermatitis for adult and children. (10). A number of studies have shown that topical application of these drugs is effective for a broad spectrum of inflammatory skin disorders (11). Here, the objective of this study was to compare the efficacy and safety of 1% of pimecrolimus cream versus 0.05% of clobetasol cream and 0.005% of calcipotriol cream in the treatment of mild to moderate plaque psoriasis in adults.

## Patients and Methods

This was a 12-weeks observer-blinded study, conducted in AL-Karama Teaching Hospital and private dermatologic clinics, under supervision of specialist physicians, during 2014-2015. The study was designed in accordance with the Ethics Committee approval before the start of the treatment. A screening visit was carried out at baseline and a target lesion was identified at week 12 (end of treatment). All patients received a consecutive unique number for randomization and stratified in the dermatology clinic. This number was also fixed on the sealed box containing the studied cream tubes.

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Patients were asked not to show their study medication to the investigator (observer-blinded study). All tubes were returned in a sealed box at the end of the study, and the tubes were weighed to calculate the amount of medication used. Male and female patients aged 20 years or above, having stable plaque psoriasis for at least 3 months prior to the start of the study, were randomized to treatment, and a written informed consent from each patient was achieved. In this study, the target lesions of our patients were located on the trunk or extremities. The criteria of inclusion involved a total affected body surface area (BSA) of  $\leq 10\%$ , one target lesion located on the trunk or extremities sized between 50 and 250 cm<sup>2</sup>, with a local psoriasis severity index (LPSI) score of  $\geq 5$ . Eighty three patients were distributed randomly into three groups as follow:

1-Pimecrolimus group (n=27): applied 1% pimecrolimus cream (Elidel®).

2-Clobetasol group (n=27): applied 0.05% clobetasol cream (Dermovate®).

3-Calcipotriol group (n=29): applied 0.005% calcipotriol cream (Daivonex®).

Each of these creams were applied twice daily (at the morning and evening) to all affected body areas, and for up to 12 weeks. Clearance of lesion was defined as no scaling, thickening, or redness of the skin.

Exclusion criteria during the study include those patients on systemic dosage form of corticosteroids, UV-light treatments, antipsoriatics (anthralin, tar, topical retinoids, salicylic acid, psoralens, tazarotene), immunosuppressive and chemotherapeutic agents, drugs that alter calcineurin inhibitor concentration (cytochrome P450 3A4 isoenzyme inhibitors/inducers, like clotrimazole, barbiturates), and drugs that can exacerbate psoriasis (antimalarials, lithium salts).

The main assessment of clinical efficacy was the % of change between day 1 (baseline) and week 12 (end of treatment) in the local psoriasis severity index (LPSI) of the target lesion. The LPSI, which reflect the severity score of the target lesion, was determined by summation the grade of severity (0 up to 4) for redness, thickness, and scaling, using the scoring system from the psoriasis area severity index (PASI), where LPSI score ranged from 0 to 12 (i.e.  $4 \times 3=12$ ). (12)

According to the British Association of Dermatology, the PASI examines four body regions: a) the head and neck, b) the hands and arms, c) the chest, abdomen and back (trunk) and d) the buttocks, thighs and legs. Each region is given a score to show how much of the region is affected by psoriasis (area score) and a score to record how bad the psoriasis is (severity score). The area score can range from 0 (no psoriasis) to 6 (all of the skin affected). The severity score for each region determined by adding scores for redness, thickness and scale, each of which is graded from 0 to 4, giving a maximum of 12. Thus, PASI score can be ranged from 0 (no disease) to 72

(maximal disease) (i.e.  $6 \times 12=72$ ). (12)

Additional clinical assessments included the physician's and patient's assessment of clinical response, and the cosmetic acceptability for each treatment. For the physician's and patient's assessment, the rating of the score was graded by: worse; no change; slightly better; better, and much better.

Safety assessments during the study included the monitoring of the local and systemic adverse events, which defined as any untoward occurrence in a patient during the study.

Blood samples (5 ml) for serum cytokines measurements were collected from just patients that will receive 1% of pimecrolimus cream at baseline, after 6 weeks, and after 12 weeks of treatment, where clobetasol and calcipotriol were approved to decrease serum cytokines levels. Sera were separated and immediately stored at  $-80^{\circ}\text{C}$  until analysis. The quantitative determination of IL -6, s IL-2R, and TNF- $\alpha$  level were conducted by an Enzyme-Linked Immunosorbant Assay (ELISA) technique based on the sandwich principle, using a commercial available kit [Diaclone research, (URS) – France]. Every sample was run in duplicate, and the mean value was calculated and used for statistical analysis. Punch biopsies (3 mm) were taken under local anaesthesia from trunk and extremities skin lesion for just 10 patients on pimecrolimus cream, immediately before the start of treatment and at the end of the study. The biopsies were immediately fixed in formalin for histopathological examination. Sections were stained with the standard Haematoxylin and Eosin stain using standard histological laboratory methods for evaluation of morphological changes. This study was planned to have a sample size that would be sufficient to detect any significant difference among patient groups. Data were expressed as mean  $\pm$  standard error of mean (SEM) or proportions (number or percentage of patients). Excel program of Microsoft Office 2010 was applied, where analysis of variance (ANOVA), chi-square ( $\chi^2$  analysis), and Wilcoxon rank-sum test were used for statistical analysis of our data. In the exploratory analysis of the endpoints, all p-values  $<0.05$  were considered significant.

## Results

There were no major differences among the treatment groups regarding the reasons for discontinuation; systemic adverse effects were the main reasons for the withdrawal in the pimecrolimus (2 patients; 7.4% due to the dizziness) and clobetasol group (2 patients; 7.4% due to the face and mouth swelling). In the calcipotriol group, 2 patients (6.9%) withdrew from the study because of arthralgia, while 2 further patients (6.9%) were withdrawn because lack of efficacy. So, virtually, only (25) patient for each group completed this study.

Patients in the three groups of this study were well matched in their demographic data (age, gender) and evenly distributed in their baseline characteristics (duration of psoriasis and

current stable disease, site of lesion, affected BSA, and scores that reflect the severity of psoriasis) (table 1). These approached and comparable mean values (not individual values) of demographic and baseline characteristics, in spite of randomized distribution among the different groups, can be attributed to the normal distribution curve concept, in addition to the good sample size for each group (n=25).

Table (1): demographic and baseline characteristics.

Variables	Pimecrolimus cream (1%) N=25	Clobetasol cream (0.05%) N=25	Calcipotriol cream (0.005%) N=25
Age (years) Mean ± SEM Range	46.5±14.7 20-73	47.6±16.2 23-80	49.8±13.8 21-78
Gender Male Female	20(80%) 5(20%)	17(68%) 8(32%)	20 (80%) 5(20%)
Psoriasis duration (yr) mean± SEM range	7.6±2.8 1.4-15.2	8.5±1.7 1.2-17.1	8.2±2.1 1.3-16.4
Stable duration(months) mean± SEM range	12.3±4.5 6.0-18.1	10.8±3.6 6.2-14.5	11.6±5.7 6.7-17.3
Site of lesion Trunk Extremities	8(32%) 17(68%)	10(40%) 15(60%)	7(28%) 18(72%)
% affected BSA mean± SEM range	6.3±2.2 2-10	6.6±2.3 1-10	6.4±2.1 2-10
LPSI score mean± SEM range	7.1±1.7 6-11	7.3±1.6 5-12	7.6±1.4 6-12
PASI score mean± SEM range	6.9±3.6 1.5-12.0	7.6±4.0 1.6-11.7	7.0±3.2 1.7-11.9

Data expressed as mean± SEM, ranges, or number of patients (%).

Statistically, no significant difference was present among the treatment groups (p>0.05). BSA, body surface area; LPSI, local psoriasis severity index; PASI, psoriasis area severity index.

The median percent of change in the LPSI of the target lesion between baseline and end of treatment was slightly lower in the pimecrolimus and clobetasol treatment groups (51% and 56%, respectively) compared with the calcipotriol group (59%). There was no statistically significant difference in these percentages among treatment groups (p>0.05) (figure 1).

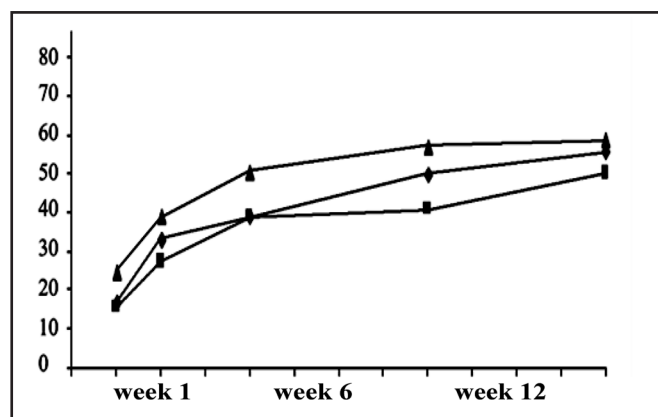


Figure (1): percentage changes from baseline along the study time in local psoriasis severity index (LPSI) of the psoriatic lesion.

■ 1% pimecrolimus cream; ◆ 0.05% clobetasol cream; ▲ 0.005% calcipotriol cream

Clinical improvement in the median percent of change in LPSI was observed in all groups after about ten days of treatment. This improvement continued to increase during the study, being fastest and greatest in the patients applying calcipotriol cream (figure 1). A greater decrease in total affected BSA during the treatment period was observed in patients on pimecrolimus compared with other groups (figure 2). The median percent of change in total affected BSA between baseline and the end of treatment was 41%, 38% and 35% for the pimecrolimus, clobetasol and calcipotriol group, respectively (p>0.05).



Figure (2): psoriatic lesion before and after treatment with pimecrolimus cream.

Regarding the physician's assessment of clinical response at the target lesion, 44%, 46% and 49% of the patients in the pimecrolimus, clobetasol and calcipotriol groups, respectively, achieved a result of 'much better' at the end of study (figure 3a). Considering the patient's assessment of clinical response at the target lesion, 48%, 52% and 55% of patients in the respective treatment groups scored their psoriasis as 'much better' (figure 3b).

Along the study period which prolonged for 3 months, the median daily drug consumed amount was approach among the three treatment groups (4.9 g, 4.5 g, and 4.3 g, respectively for pimecrolimus, clobetasol and calcipotriol cream).

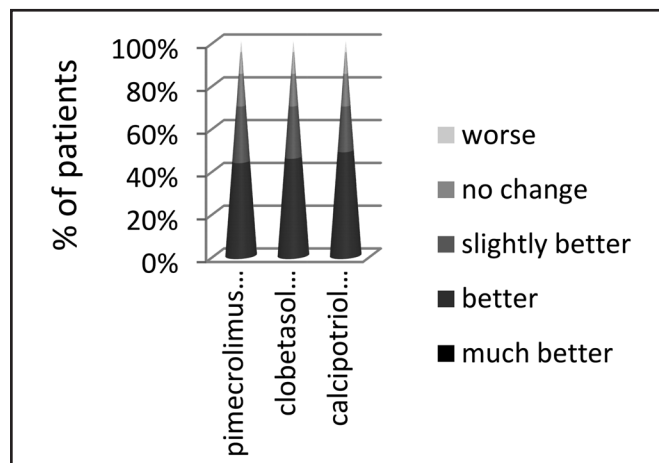


Figure (3a): Physician's assessment at the target lesion.

Considering cytokines, table (2) clarified that, after treatment with 1% of pimecrolimus cream, there is a statistically significant reduction ( $p < 0.05$ ) in the serum levels of the proinflammatory cytokines (IL-6, sIL-2R, and TNF- $\alpha$ ) compared with their levels at the baseline.

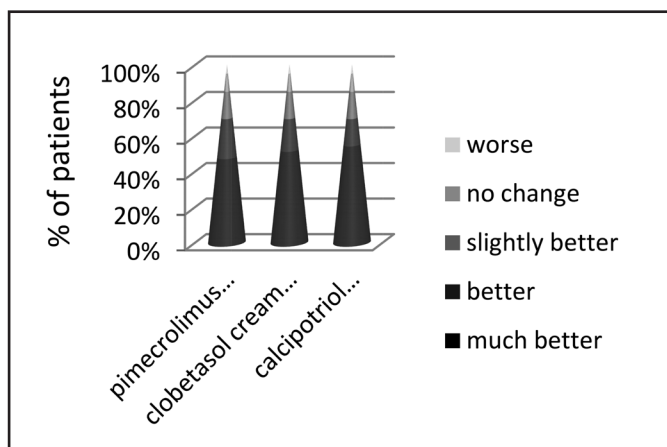


Figure (3b): Patient's assessment at the target lesion.

Table (2): Levels of serum cytokines in psoriatic patients before and after treatment with 1% of pimecrolimus cream.

Cytokines	Baseline levels	After 6 weeks of treatment	After 12 weeks of treatment
IL-6 (pg/ml)	34.76 ± 12.34 a	16.24 ± 9.58 b	6.99 ± 2.34 c
s IL - 2R ( pg / ml)	475.45 ± 45.45 a	355.32 ± 40.21 b	144.65 ± 38.44 c
TNF- $\alpha$ (pg/ml)	174.23 ± 36.45 a	122.24 ± 20.35 b	31.85 ± 16.45 c

Values are mean ± SEM (pg/ml). Data with non identical superscript letters within the same parameter considered differ statistically ( $p < 0.05$ ).

At the baseline, the histopathologic features of psoriatic lesion for pimecrolimus patients involved a uniform parakeratosis, regular acanthosis in the mild intracellular and slight intercellular oedema, scattered mitosis of basal and prickle cells, papillomatosis, dilatation and tortuosity of the loops of capillaries and mild perivascular infiltration with lymphocytes (figure 4a). Migration of leucocytes from capillaries in the tips of papillary bodies through epidermis occurs to form the so called microabscesses, which is another confirmatory sign. However, all the characteristic features may not be present in one section alone. Also, it is important to note that dermis was affected earlier than epidermis in psoriasis. After topical application of pimecrolimus cream for 3 months, there was

a significant improvement in the above histopathological features as a general. In the psoriatic lesions, and as an effect of pimecrolimus cream, there was no parakeratosis, no oedema or infiltration of cutis, but some degree of acanthosis and mild hyperkeratosis was seen. Mild infiltrate, dilated capillaries and mild acanthosis, continued to persist in few number of specimens even in this healed stage (figure 4b). Also, it was seen that the granular cell layer and parakeratosis seemed to alternate with each other.

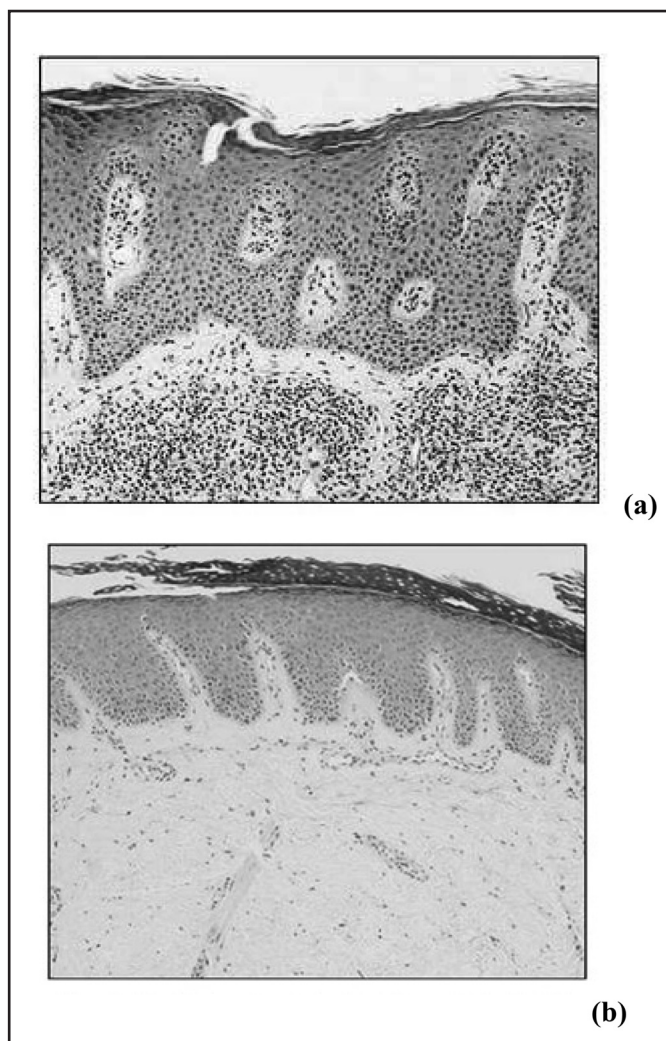


Figure (4): microscopic appearance of psoriatic lesion before (a) and after (b) treatment with pimecrolimus cream.

Regarding the safety, 15 patients (60%) in the pimecrolimus group, 17 patients (68%) in the clobetasol group, and 18 patients (72%) in the calcipotriol group experienced adverse events during the study. Most of these events occurred at the site of treatment application and were mild to moderate in their intensity (table 3).

Table (3): Adverse effects of the treatment groups.

Variables	Pimecrolimus cream (1%) N=25	Clobetasol cream (0.05%) N=25	Calcipotriol cream (0.005%) N=25
Total effects	15(60)	17(68)	18(72)
Local effects			
Burning sensation	10(40)*	2(8)	3(12)
Itching & irritation	9(36)*	2(8)	4(16)
Warm feeling	2(8)	1(4)	0(0.0)
redness	0(0.0)	2(8)	3(12)
Dryness	1(4)	3(12)	2(8)

Dermatitis	2(8)	0(0.0)	3(12)
Skin atrophy and striae	0(0.0)	5(20)*	0(0.0)
Skin discoloration	0(0.0)	2(8)	3(12)
Skin infections	0(0.0)	1(4)	0(0.0)
exacerbation of psoriasis	0(0.0)	0(0.0)	1(4)
Systemic effects			
Face and mouth swelling	2(8)	2(8)	0(0.0)
Flu-like symptoms	3(12)	0(0.0)	0(0.0)
dyspnea	1(4)	0(0.0)	0(0.0)
dizziness	2(8)	0(0.0)	3(12)
arthralgia	0(0.0)	0(0.0)	2(8)

Data expressed as number of patients (%).

\* Significant difference compared with other two groups ( $p < 0.05$ ).

Skin burning was the most frequent adverse event reported by the patients applying pimecrolimus (40%;  $p < 0.05$ ) versus 8% in clobetasol and 12% in the calcipotriol group, followed by itching and irritation for patients using pimecrolimus (36%;  $p < 0.05$ ) versus 8% in clobetasol and 16% in the calcipotriol group. Most cases of skin burning and itching were mild in their intensity and decreased greatly in prevalence after ten days of treatment as the clinical condition of skin improved. Skin burning and irritation led to the withdrawal of two patients for each of pimecrolimus and clobetasol group. In the calcipotriol group, two cases of skin irritation and two case of psoriasis exacerbation led to withdrawal from the study. Five patients on clobetasol (20%) suffering from skin softening and thinning ( $p < 0.05$ ). As a cosmetic acceptability, the odour of the studied medications was acceptable for most patients in the three treatment groups. However, most patients applying calcipotriol unlike the staining of clothes caused by the topical application (24% versus 3% for pimecrolimus and 2% for clobetasol;  $p < 0.05$ ).

### Discussion

Pimecrolimus is an immunophilin ligand, which binds specifically to the cytosolic receptor, immunophilin macrophilin-12. This pimecrolimus-macrophilin complex effectively inhibits the protein phosphatase calcineurin, by preventing calcineurin from dephosphorylating the nuclear transcription factor of activated T cells (13). This results in the blockage of signal transduction pathways in T cells and the inhibition of the synthesis of inflammatory cytokines, specifically Th1, Th2, and mast cell- type cytokines (14, 15). Several studies have evaluated the effectiveness of calcineurin inhibitors as a treatment for inflammatory skin diseases, including dermatitis, eczema and psoriasis. In animal models of allergic contact dermatitis, topical pimecrolimus was found to be effective. In human studies of allergic contact dermatitis

pimecrolimus demonstrated significantly more efficacy than the control treatment (16). As well, the effectiveness of pimecrolimus 0.6% cream was comparable to 0.1% betamethasone-17-valerate. Pimecrolimus is effective and safe in both children and adults with atopic dermatitis. When pimecrolimus 1% cream has been applied to adult atopics, improvement has been observed as early as the first week, with a 72% reduction in severity after 3 weeks (17). Topical application of pimecrolimus has been shown to be effective in the treatment of several inflammatory skin disorders other than atopic dermatitis (18). A number of therapeutic usefulness of topical pimecrolimus were documented, particularly for T-cell mediated skin diseases, such as eczema, seborrheic dermatitis, pyoderma gangrenosum, lichen planus, lichen sclerosus, cutaneous lupus erythematosus, vitiligo, and alopecia areata, with a favorable adverse effects profile, which includes little effect on the systemic immune response (19,20). Studies reported that topical tacrolimus (a prototype calcineurin inhibitor) shows dramatic effect for facial, intertriginous, and genital lesions. These lesions are usually not covered by thick scales, and thus the penetration is simple (21, 22). So, we expect that if we select our patients with facial, genital, or intertriginous lesions (rather than trunk or extremities), clinical improvement of psoriasis may be more significant because these areas are thin and their penetration usually easier and faster. Patients on calcipotriol had the fastest improvement, although when we approach to the end of study, there was little difference among the three treatment groups, suggesting that a longer course may be necessary to achieve optimal efficacy with these therapies. As a whole, this study showed that after 3 months of treatment, the clinical efficacy of the 1% pimecrolimus cream was comparable to that of 0.05% clobetasol and 0.005% calcipotriol. In the present study, Local Psoriasis Severity Index (LPSI) was selected because the evaluation of a local target lesion was considered to be a more sensitive measurement for treatment efficacy. The basic characteristics of psoriasis lesions (redness, induration, and scaliness) provide a means of assessing the severity of psoriasis. Accordingly, a gold standard for assessment of extensive psoriasis has been the Psoriasis Area Severity Index (PASI) (12). Considering the amount of creams consumed along this study, the median daily drug usage was comparable among the treatment groups (4.9 g, 4.5 g and 4.3 g for pimecrolimus, clobetasol and calcipotriol cream, respectively). This approximately equivalent amount of the consumed pimecrolimus gives another indication about its potency and clinical efficacy for treatment of psoriasis. From pharmaceutical point of view, trying the occlusion method (by use of dressing) or salicylate formula to improve absorption and permeation of pimecrolimus through the thickened scales, and consequently its clinical efficacy, may be suggested as a recommendation for future work, but also may associated with higher systemic drug exposure, and then

higher risk of systemic side effects (23, 24). The association of some proinflammatory cytokines in vivo and the effect of pimecrolimus cream on their levels were evaluated. All mean values of patients were significantly decreased after application of pimecrolimus cream compared with baseline values. Also, there was a significant relationship between serum levels of TNF -  $\alpha$ , sIL - 2R, IL - 6 and the severity of the disease for each patient (25). These results were in agreement with previous studies which reported a significant increase in the levels of serum IL - 6, IL - 8, IL - 2R, IL - 12, TNF -  $\alpha$ , and IFN -  $\gamma$  in psoriatic patients as compared with healthy control, suggesting that proinflammatory cytokines directly related to the clinical symptoms, PASI and disease severity. Furthermore, these cytokine levels were decreased after psoriasis treatment (26, 27, 28). In particular, TNF- $\alpha$  stimulates keratinocyte proliferation, T-cell and macrophage cytokine production, and expression of adhesion molecules on vascular endothelial cells. In the involved skin of psoriasis, TNF, TNF-receptor 1, -receptor 2 are upregulated in dermal blood vessels. Biological therapies targeting TNF have been achieved beneficial effects and improved quality of life of patients (5,6). It was shown that, in vitro, tacrolimus can down regulate IL-8R expression in normal keratinocytes, and also decrease IL-8 binding to freshly separated human keratinocytes (29, 30). Our results showed such in vivo down-regulation of sIL-2R, IL-6, and TNF- $\alpha$  level for pimecrolimus treated patients. Also, we observed that in patients on pimecrolimus treatment, circulating levels of IL-6, sIL-2R, along with TNF- $\alpha$ , decreased with progression of treatment course. This is in agreement with another study, which found that cyclosporine A (an immunosuppressant agent that also inactivate T-cell function) inhibited epidermal expression of both IL-6 and IL-1 $\beta$  in psoriatic lesions after relatively short term therapy (31). The characteristic histological features of psoriasis are epidermal hyperproliferation and infiltration of both dermis and epidermis by inflammatory cells including neutrophils, lymphocytes, macrophages and mast cells, establishing a vicious cycle of events associated with increased keratinocyte divisions and complex cytokine network (32, 33, 34). In the present study, pimecrolimus may cut this vicious cycle by down regulation of cytokines and inactivating T-cells, leading to improvement in the histopathologic features of psoriatic lesion. Very few studies have been conducted regarding the histopathologic changes in psoriasis before and after treatment (35). In this study, it was seen that in the active lesions, parakeratosis was more uniform, microabscesses were larger and more numerous. There were dilated capillaries in the papillary bodies which were engorged with erythrocytes and leucocytes. The infiltrate was composed predominantly of polymorphonuclear leucocytes. Pimecrolimus significantly relieve most of these morphologic abnormalities, making skin layers approach to normal and healthy tissues. In the present study, the regression

of histopathologic changes of psoriatic lesions under pimecrolimus treatment were first seen in the epidermis, especially in stratum corneum and granulosum, and the changes in dermis persisted for a much longer time. The presence of these changes in clinically cleared psoriatic lesions point to an important question, of how long a psoriatic skin lesion needs to be treated in order to postpone recurrence as long as possible and achieve a permanent remission. Local side-effects of topical calcineurin inhibitors commonly reported by patients are feelings of warmth, burning, stinging, increase of erythema or irritation, and increased itching (36). In the long-term study conducted in adults, application site reactions of pimecrolimus were experienced by 46% of patients. In general, these events were of mild to moderate severity in most cases and occurred early in the treatment phase (37). In 50-60% of cases, application site reactions started during the first 4 days of pimecrolimus application, resolved within 7 days and were most frequently localized on the face and neck. The most common application site reactions was burning sensation, which occurred in 26% of the adult patients treated with pimecrolimus (38). Comparing the incidence of infections in adult patients treated with pimecrolimus or vehicle, bacterial and fungal infections occurred at similar frequencies in both groups (39). In the current study, the higher incidence of drug-related adverse effects observed in the patients applying the pimecrolimus cream can be attributed mainly to the skin burning and irritation; otherwise, there was no difference among the three treatment groups in the probability of most adverse effects. Transient skin burning at the site of application is a common adverse effect associated with the prototype "tacrolimus" ointment and this appears to be true for the pimecrolimus cream formulation (36). Skin burning normally lasts about 15 min, discomfort was not sufficient for discontinuation of drug therapy for most patients, and the prevalence of skin burning decreased gradually as the clinical state of the skin lesion improved (37). Apart from corticosteroids, topical calcineurin inhibitors (like tacrolimus and pimecrolimus) do not cause either skin atrophy, striae, or telangiectasia even by long-term use, which considered as advantage of these drugs. One of the possible explanations is that they does not affect endothelial cells, keratinocytes and fibroblasts, and thus does not affect collagen synthesis and skin thickness (38). Pharmacologically, pimecrolimus inhibits the upstream signal of mainly IL-2-mediated T-cell proliferation, while everolimus (a member of mTOR inhibitor family) block its downstream signals (40). Therefore, and as a recommendation for future work, this combination therapy is a logical regimen for refractory cases of psoriasis, and may have a synergistic therapeutic effect. Beneficially, with this combination, one can reduce the dose of both drugs, resulting in less adverse reactions, while achieving better therapeutic effects. A limitation of this study was the possibility of observer bias. The patients were asked

not to show their type of topical therapy used, but it is possible that the patients may have unwittingly given some clue to the investigator. Moreover, the higher incidence of burning observed in the pimecrolimus group may also give indication to the observer about its adverse effects. From above, pimecrolimus cream is a promising immunomodulatory agent, providing e psoriasis, and may prevent the disease progression. It may reduce or eliminates the need for topical corticosteroids and can provide an excellent treatment alternative for steroids, and steroid-sparing therapies. Further studies which prove the efficacy and safety of pimecrolimus cream for psoriasis will be necessary and pimecrolimus await additional investigations to determine the ideal formulations for particular body sites in the treatment of psoriasis.

### **Conclusion**

In summary, pimecrolimus cream demonstrated efficacy comparable with that of clobetasol and calcipotriol, giving a possible therapeutic option for the treatment of mild to moderate plaque psoriasis in adults.

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