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Pimecrolimus Cream 1% for Treatment of Vulvar Lichen Simplex Chronicus: An Open-Label, Preliminary Trial

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Key Words
Pimecrolimus cream 1% · Pimecrolimus cream, efficacy and safety · Vulvar lichen simplex chronicus

Abstract
Background: To evaluate efficacy and safety of pimecrolimus cream 1% twice daily for treatment of vulvar lichen simplex chronicus (LSC). ***Methods:*** Patients in this 12-week, open-label study had biopsy-proven vulvar LSC. Inclusion criteria were patient-reported Visual Analog Scale for Pruritus Relief ≥3 (VAS-PR, 0 cm = no itching to 10 cm = severe itching) and Investigator's Global Assessment ≥2 (IGA, 0 = no disease to 3 = severe disease). Safety was evaluated by adverse event reports and pimecrolimus blood level measurements. ***Results:*** Twelve women aged 25–53 years were enrolled. The median pruritus score (VAS-PR) decreased from 6 (min. 4.9, max. 9.0) at baseline to 0 cm at week 4 (max. 4.2), week 8 (max. 3.1) and week 12 (max. 2.1). Seven patients reported complete resolution of pruritus by week 4. Median IGA decreased from 2.5 (min. 2, max. 3) at baseline to 0 (min. 0, max. 2) at week 12. Erythema, excoriation, and lichenification improved for all patients. Pimecrolimus blood concentration for all samples was below the limit of quantification, 0.3 ng/ml. No adverse events were reported. ***Conclusions:*** In this exploratory study, signs and symptoms of vulvar LSC improved for all women and pimecrolimus cream showed a favorable safety profile. Larger prospective studies are needed to further evaluate pimecrolimus for treatment of vulvar LSC.

This research was presented at the 2006 Annual Meeting of the American Academy of Dermatology and also accepted as a poster presentation for the 2006 Annual Clinical Meeting of the American College of Obstetricians and Gynecologists.

Introduction

Lichen simplex chronicus (LSC) of the vulva is an eczematous disorder characterized by itching, scratching and lichenification [1]. The condition is the end stage of an itch-scratch-itch cycle and is also known as neurodermatitis, pruritus vulvae, squamous hyperplasia, and hyperplastic dystrophy. The etiology of initiating pruritus that leads to LSC includes atopic dermatitis, contact dermatitis, and eczema, though the underlying pathophysiology is unknown [1]. The intense, chronic itching caused by these conditions leads the patient to repetitively rub and scratch the affected area. The skin responds by thickening and developing a coarse texture, with increased

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skin markings called lichenification. The skin may also have variable pigmentation and feel leathery. Histopathological examination shows hyperkeratosis, spongiosis, acanthosis, and a chronic dermal inflammatory infiltrate [2].

There are few treatment options available for treatment of LSC, especially for patients with long-standing disease [3]. The current gold standard treatment for vulvar LSC is local application of potent or ultra-potent topical corticosteroids [1, 2]. Although these treatments are efficacious, topical corticosteroids have serious local and systemic side effects, including dermal thinning, skin atrophy, superimposed fungal infections, rebound dermatitis, and adrenal insufficiency [3–7]. Due to these side effects, long-term use of corticosteroids for the treatment of vulvar LSC may be inadvisable. Therefore, a safe and effective alternative intervention is needed for this disorder.

Pimecrolimus cream 1% (Elidel®, Novartis Pharmaceuticals Corp., East Hanover, N.J., USA) is a topical calcineurin inhibitor that binds to macrophilin-12 and inhibits cytokine synthesis by T cells. It is approved in the USA for the treatment of mild to moderate atopic dermatitis of children, adolescents, and adults [8] and additional clinical studies suggest efficacy for pimecrolimus cream 1% as a treatment for seborrheic dermatitis [9] and other inflammatory skin conditions, such as inverse psoriasis [10]. The documented efficacy of pimecrolimus cream 1% includes a quick time to reduction of pruritus [11]. Pimecrolimus cream 1% also has a well-established local safety profile [12, 13]. Unlike ultra-potent corticosteroids, pimecrolimus cream 1% does not affect keratinocytes or inhibit collagen synthesis and therefore does not cause skin atrophy [14].

As the histopathology of LSC demonstrates a chronic lymphocytic infiltrate and because pimecrolimus is effective in controlling pruritus, pimecrolimus should be an effective treatment for LSC. Theoretically, this would be a distinct advantage of pimecrolimus over the ultra-potent corticosteroids for the treatment of LSC as recurrences are common, and long-term treatment is often required. Taken together, the pathophysiology of vulvar LSC and the efficacy of pimecrolimus for treatment of other inflammatory dermatologic conditions support the theory that pimecrolimus cream 1% may effectively treat LSC without the potentially serious side effects that are associated with corticosteroids. This report includes the results of an exploratory study designed to evaluate the efficacy and safety of pimecrolimus cream 1% for the treatment of vulvar LSC.

Materials and Methods

This clinical study protocol was approved by the Anne Arundel Medical Center Investigational Review Board, and was submitted to the FDA for a third-party IND. The study was conducted from October 2004 to August 2005 in accordance with Good Clinical Practices and the Declaration of Helsinki (2000). Written informed consent was obtained from each patient in the study prior to any study procedure being performed.

Study Design

This was an exploratory, single-center, investigator-initiated, open-label, uncontrolled, single-arm study of patients with biopsy-proven LSC of the vulva. The study consisted of a 2-week screening period followed by a 12-week treatment period with pimecrolimus cream 1%. Scheduled clinic visits were performed at screening, baseline, and weeks 4, 8, and 12 following enrollment. A physical examination was performed by the same investigator at all visits without consultation to prior visit data. A digital photograph of the affected area was obtained at each visit and was stored electronically.

Patients were instructed that gentle washing of the target treatment area was permissible prior to application of study medication and that skin was to be dry before applying treatment. Pimecrolimus cream 1% was applied by the patient twice daily (every 12 h) as a thin coat over the affected area. Treated areas were not to be washed for at least 3 h after application of study medication. The investigator reviewed proper hygiene with the patient at each study visit.

Patients

Eligible subjects for the study were women at least 18 years of age. A 4-mm punch skin biopsy sample collected from each patient at screening was studied to confirm the diagnosis of LSC of the vulva and to rule out concomitant diagnoses of lichen sclerosus, lichen planus, psoriasis, candidiasis, or vulvar intraepithelial neoplasia. Pruritus at baseline was required to be at least mild ($\geq$3 on 10 cm continuous scale; 0 = no itching to 10 = severe itching), as assessed by the patient on the Visual Analog Scale for Pruritus Relief (VAS-PR) and disease activity at baseline was required to be at least moderate ($\geq$2 on a 4-point Likert scale; 0 = none to 3 = severe), as assessed by the investigator on the Investigator's Global Assessment (IGA). Prior to enrollment, the study required a 2-week washout period of topical medication and a 4-week washout of oral or systemic medication. Women of childbearing potential consented to practice two forms of effective birth control during the study period. A urine pregnancy test was administered to each patient at every visit. Pregnant and nursing women were excluded from participation in the study. Additionally, subjects were excluded from participation if they had a known hypersensitivity to any components of pimecrolimus cream 1%; a diagnosis of cancer, diabetes mellitus, Netherton's syndrome, or an immunosuppressive condition; poorly controlled chronic conditions; or systemic bacterial, viral, or fungal infections.

Outcome Assessments

The primary efficacy variable was the change from baseline of the patient's assessment of pruritus using a 10-cm VAS-PR [15]. At the screening, baseline, and week 4, 8 and 12 visits, patients

Table 1. Results of efficacy assessments show improvement of vulvar LSC over 12 weeks

Assessment (n = 12)	VAS-PR median (range)	Erythema median (range)	Lichenification median (range)	Excoriation median (range)	IGA median (range)
Scale	0–10	0–3	0–3	0–3	0–3
Baseline	6 (4.9–9.0)	3 (2–3)	2.5 (1–3)	2 (1–3)	2.5 (2–3)
Week 4	0 (0–4.2)	2 (0–3)	1 (0–3)	0 (0–2)	NA
Week 8	0 (0–3.1)[1]	1 (0–1)	0 (0–3)	0 (0–1)	NA
Week 12	0 (0–2.1)	1 (0–1)	0 (0–3)	0 (0–1)	0 (0–2)

[1] VAS-PR score for 1 patient was missing at week 8. The week 4 score of 3.1 was used for the week 8 calculation. Excluding this value, the median (range) of VAS-PR scores at week 8 was 0 (0–1.5).

reported their pruritus level (0 = no itching and 10 = severe itching) on the VAS-PR for itching felt over the 3 days prior to the visit.

Secondary efficacy variables included change from baseline of investigator assessments of treatment effect. Efficacy assessments were performed by the same investigator at all scheduled visits. The IGA of disease severity was scored at each visit using a 4-point scale of: 0 (no disease – no inflammatory signs), 1 (mild disease – mild erythema, papulation/infiltration, lichenification, excoriation), 2 (moderate disease – moderate erythema, papulation/infiltration, lichenification, excoriation), and 3 (severe disease – severe erythema, papulation/infiltration with oozing/crusting, hyperkeratosis) [16]. Evaluations of erythema, vulvar lichenification, and vulvar excoriations were performed by the investigator using a 4-point scale of: 0 (none), 1 (mild), 2 (moderate) to 3 (severe) for each criterion evaluated.

At each visit, safety assessments included recording of all spontaneously reported adverse events and evaluation of standard laboratory tests, including urinalysis, blood chemistry, and hematology. Measurements of pimecrolimus in blood at weeks 4, 8 and 12 was performed by a high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS) analytical method with a limit of quantitation of 0.3 ng/ml using a 250-μl blood sample. The concentration of pimecrolimus in the blood was not measured at baseline since patients had not been previously exposed to pimecrolimus.

Statistical Considerations

This small study was designed as an exploratory trial and the sample size was chosen based on the ability of the investigator to recruit patients and not according to a statistical sample size calculation. Descriptive statistics were used to analyze the data. Because the sample size was small and the scales of the efficacy assessment variables were ordinal, the median, range, and percentiles of the data for these variables were calculated. For all variables, the score at each follow-up visit was compared to baseline and the proportion of patients with improvement at each visit was analyzed.

Results

The study screened and enrolled 12 women between 25 and 53 years of age (median 36 years). All patients were Caucasian and no patient was exposed to pimecrolimus cream 1% prior to entering the study. All patients completed the full planned treatment period of the 12-week study. At baseline, the level of pruritus reported by most patients on the VAS-PR was moderate (median 6, min. 4.9, max. 9.0) and the data were normally distributed. In addition, the median level of disease severity assessed by the investigator on the IGA was moderate to severe (median 2.5, min. 2, max. 3) and the median level of erythema, lichenification, and excoriation was each assessed ≥ 2 (moderate to severe) (table 1).

Efficacy

Improvement was reported for all efficacy assessments evaluated during the course of the study (table 1). At each follow-up visit, the overall level of improvement for all variables for the study population increased as compared to the prior assessment (fig. 1).

The median score of the primary variable, the pruritus score (VAS-PR), decreased from 6 cm (min. 4.9, max. 9.0) at baseline to 0 cm at weeks 4 (max. 4.2), 8 (max. 3.1) and 12 (max. 2.1). The VAS-PR score for 1 patient (No. 11), was inadvertently not recorded at week 8. The week 4 score of 3.1 for this patient was used in calculation of the summary data for week 8. Excluding this value, the median (range) of VAS-PR scores at week 8 was 0 (0–1.5). This patient reported complete resolution at week 12. By week 12, 9 patients (75%) with a median baseline score of 5.8 cm (range 4.9–9) had complete resolution of pruritus at week 12 (fig. 1). The remaining 3 patients (25%) had

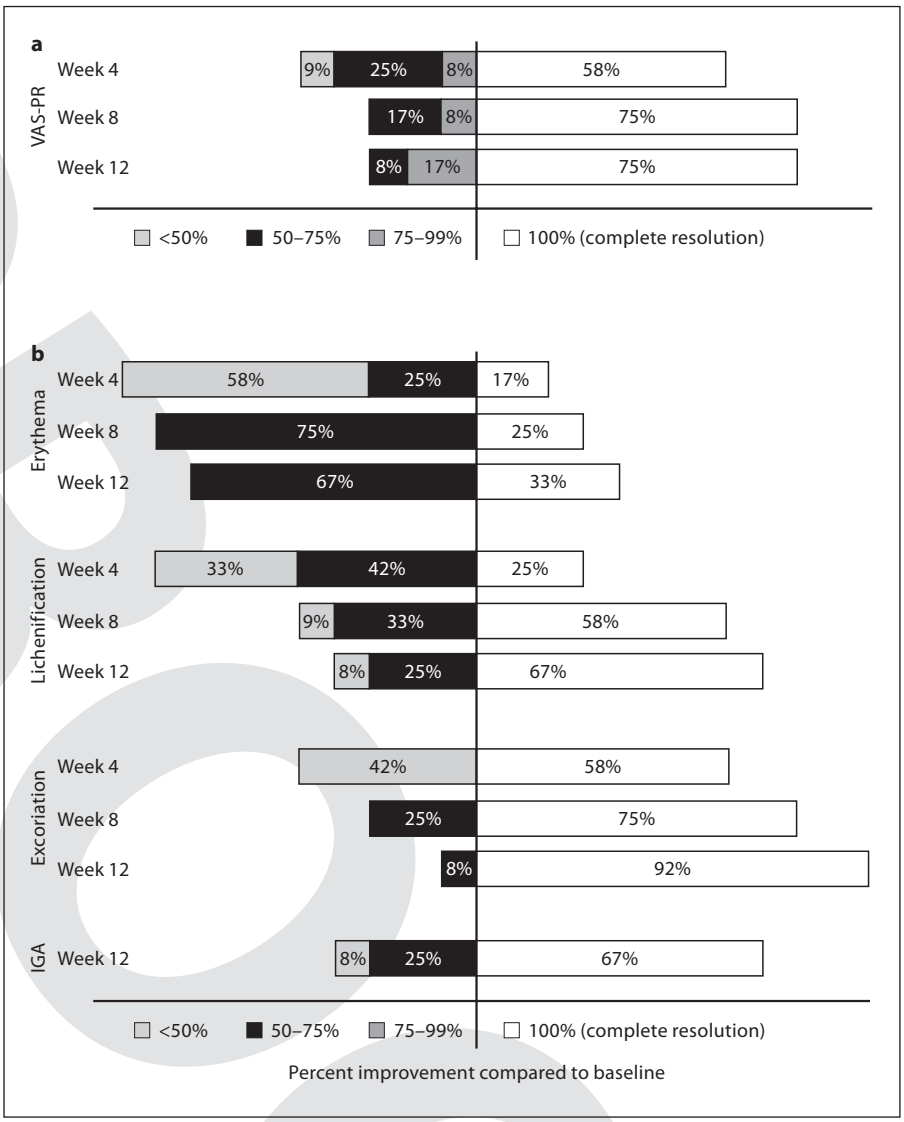

Fig. 1. Proportion of patients with improvement of vulvar LSC symptoms and signs over 12 weeks. **a** Primary efficacy variable: VAS-PR (0–10 scale). **b** Secondary efficacy variables: IGA (0–3 scale). * Improvement for the patient with a missing week 8 VAS-PR was calculated using a week 4 score.

decreased pruritus (6.7 cm [range 5.1–7.5] at baseline to 1.4 cm [range 1–2.1] at week 12). By week 4, 7 patients (58%) with median baseline score 5.6 cm (range 4.9–7.8) reported complete resolution of pruritus; complete resolution for these patients was maintained until week 12. In addition to the data collected per protocol, spontaneous patient reports of improvement of vulvar itching were noted as early as 2 weeks after beginning pimecrolimus cream 1% treatment.

The results of the secondary variables followed a similar pattern to the results of the patient-assessed pruritus score (table 1). IGA scores decreased from a moderate-to-severe median baseline score of 2.5 (min. 2, max. 3) to 0 (min. 0, max. 2) at study end. Erythema and excoriation reported as moderate-to-severe at baseline improved for all patients by week 12. Lichenification reported as moderate-to-severe at baseline was improved for all but 1 patient by the end of the study.

Representative improvement of LSC of the vulva from baseline to week 12 is presented in photographs of study patient number 3 (fig. 2). The profound hyperkeratosis of her left labia majora that was present at baseline was almost completely resolved by week 12.

Safety Results

No adverse events were reported or observed for any patient in the clinical study. In addition, no pregnancies were reported or detected. For all patients, there were no

significant alterations from baseline of standard laboratory tests. In all patients at all study visits, pimecrolimus blood concentration was below the lower limit of quantification, 0.3 ng/ml, of the HPLC/MS assay. Determination of pimecrolimus level in the blood was not possible for five scheduled time-points in the study: four samples were not stored appropriately after blood collection and 1 patient missed the week 8 blood collection.

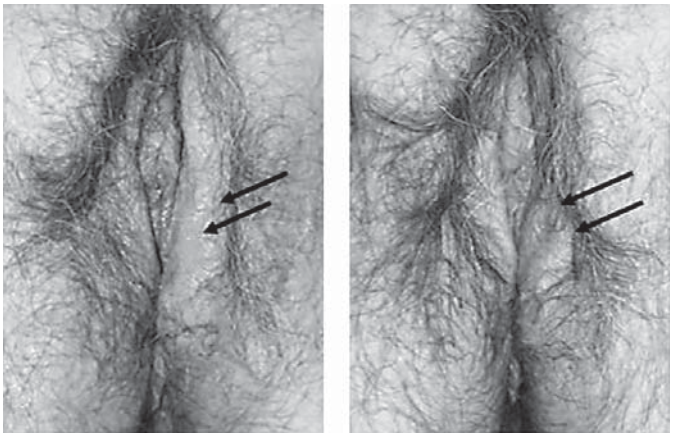

Fig. 2. Photographic observation of efficacy of pimecrolimus cream 1% for treatment of LSC of the vulva. For patient 3, the arrows indicate hyperkeratosis at baseline and almost complete resolution at week 12.

Discussion

The current gold standard of treatment for vulvar LSC is potent or ultra-potent topical corticosteroids. Although topical corticosteroids are effective for the treatment of many different dermatologic conditions including LSC, there are well-known potential complications associated with the inappropriate use of corticosteroids. These complications include dermal atrophy and stria formation, rebound reactions, hypothalamic-pituitary axis suppression, and secondary infections. To date, there have been no published reports of these steroid-induced side effects in patients with vulvar LSC. However, improper use of ultra-potent corticosteroids has the potential to significantly increase the risk of these side effects and may limit their usefulness.

Pimecrolimus inhibits T-lymphocyte activity by inhibiting calcineurin-dependent dephosphorylation-activation of specific nuclear factors, thus preventing transcription of pro-inflammatory cytokines including IL-2, IL-4, and IL-10, and interferon-γ. Given the mechanism of action of pimecrolimus cream 1%, its prior documented efficacy for treatment of pruritus associated with other dermatologic conditions, and the presence of chronic lymphocytic infiltrates at the histopathological level for patients with LSC, it was postulated that pimecrolimus should be an effective treatment for this condition. In addition, since pimecrolimus does not affect keratinocytes or inhibit collagen synthesis, it has not been shown to cause dermal atrophy [17]. Theoretically, this would be a distinct advantage of pimecrolimus over the ultra-potent corticosteroids for the treatment of LSC as recurrences are common, and long-term treatment is often required. Lastly, pimecrolimus cream 1% has been shown to be effective and well tolerated for the treatment of other vulvar dermatoses such as lichen sclerosus and erosive lichen planus [18–20].

The results of this study suggest that pimecrolimus cream 1% may be effective for the treatment of vulvar LSC. The early resolution of pruritus recorded in this study for the majority of patients following just 4 weeks of treatment and the spontaneous patient reports of improvement of vulvar itching observed as early as 2 weeks after initiation of treatment are consistent with previously published results of the time to resolution of pruritus associated with the evaluation of pimecrolimus cream 1% for atopic dermatitis [12, 16, 21, 22]. In addition, the improvement observed for all investigator assessments in this study, including evaluations of disease severity, erythema, lichenification, and excoriation, mirrored the more subjective, patient-assessed pruritus measurement, a pattern that is similar to that seen in previous studies of pimecrolimus [12, 16, 21, 22]. Since most patients in this small, exploratory study obtained optimum control of their condition after 8 weeks of treatment, consideration should be given to planning a twice-daily pimecrolimus cream 1% treatment regimen for 8 weeks for patients with mild or moderate severity disease. For patients with long-standing disease or a more severe condition, extending the treatment period to 12 weeks may be reasonable since improvement continued to be recorded for this period in the study.

In this small series of patients, pimecrolimus was an effective and well-tolerated treatment for vulvar LSC. Previous studies of pimecrolimus cream 1% have reported transient, mild to moderate cutaneous side effects described as a feeling of warmth at the application site [21, 22]. Although the skin area treated in this study was permeable and sensitive, there were no adverse reactions of

any type reported in this study. In addition, there is a theoretical risk of systemic absorption of pimecrolimus through the modified squamous epithelium of the vulva. However, in this trial all 31 blood samples collected at various time intervals over 12 weeks were measured with HPLC/MS and had levels of pimecrolimus lower than the limit of quantification. This finding supports that pimecrolimus applied to the vulva did not measurably accumulate in the blood of the patients.

A concern when considering use of topical calcineurin inhibitors for vulvar conditions is the report of increased herpes simplex viral breakouts. In this study, no patient had a viral breakout during the study. However, in a much larger 12-month trial evaluating pimecrolimus cream 1% (n = 328) vs. triamcinolone cream 0.1% (n = 330), a mid-potency topical corticosteroid, for the treatment of atopic dermatitis, the rate of viral skin infections was similar for both groups [21, 23]. In addition, the risk of immunosuppression-related lymphoma associated with profound and sustained immunosuppression has been cited as a concern when considering use of topical calcineurin inhibitors or topical corticosteroids. However, this remains a theoretical risk because the level of immunosuppression thought to be associated with development of lymphoma has not been observed at the recommended dosing regimens of these treatments [22, 24]. Additionally, it is important to note that the patients in this study had no measurable systemic exposure to pimecrolimus.

An important component of patient care is education and review of proper hygiene, since the irritative symptoms of LSC can be aggravated by contact with irritants or patient behavior. Patients may be advised to use 100% cotton underwear, use mild soap to wash their body and their undergarments, use a large amount of lubrication during sexual intercourse, or apply ice water compresses for vulvar irritation [3, 17]. Although these are essential points for patients to be aware of, for many women with vulvar conditions, these are insufficient for a cure and supplemental medications to treat the disease are necessary.

In conclusion, clinically noticeable improvement in pruritus associated with vulvar LSC was observed for most patients by 4 weeks of treatment with pimecrolimus cream 1% and was maintained throughout the study. Over the 12 weeks of treatment, the overall level of improvement for all investigator-assessed signs of LSC increased consistently compared to prior assessments. Over the treatment period, pimecrolimus cream 1% was well tolerated.

The results of this exploratory study therefore suggest that pimecrolimus cream 1% may represent an effective alternative treatment for vulvar LSC and provide the basis for a larger, randomized, active comparator-controlled study to evaluate and compare the efficacy and safety of pimecrolimus cream 1% vs. the current first-line therapy for women with this disorder.

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References

1 Lynch PJ: Lichen simplex chronicus (atopic/neurodermatitis) of the anogenital region. Dermatol Ther 2004;17:8–19.
2 Edward J, Wilkinson IKS: Atlas of Vulvar Disease. Baltimore, Williams & Wilkins, 1995.
3 Foster DC: Vulvar disease. Obstet Gynecol 2002;100:145–163.
4 Pierard GE, Pierard-Franchimont C, Ben Mosbah T, Arrese Estrada J: Adverse effects of topical corticosteroids. Acta Derm Venereol Suppl (Stockh) 1989;151:26–30, 47–52.
5 Lubach D, Rath J, Kietzmann M: Steroid-induced dermal thinning: discontinuous application of clobetasol-17-propionate ointment. Dermatology 1992;185:44–48.
6 Cherian MP, Abduljabbar M: Cushing's syndrome and adrenal suppression from percutaneous absorption of clobetasol propionate in infants. Saudi Med J 2001;22:1139–1141.
7 Hugues J, Rustin M: Corticosteroids. Clin Dermatol 1997;15:715–721.
8 Furue M, Terao H, Rikihisa W, Urabe K, Kinukawa N, Nose Y, et al: Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. Br J Dermatol 2003;148:128–133.
9 Stuetz A, Grassberger M, Meingassner J: Pimecrolimus (Elidel®, SDZ ASM 981): preclinical pharmacologic profile and skin selectivity. Semin Cutan Med Surg 2001;20:233–241.
10 Hultsch T, Muller KD, Meingassner JG, Grassberger M, Schopf RE, Knop J: Ascomycin macrolactam derivative SDZ ASM 981 inhibits the release of granule-associated mediators and of newly synthesized cytokines in RBL 2H3 mast cells in an immunophilin-dependent manner. Arch Dermatol Res 1998;290:501–507.
11 Zuberbier T, Chong SU, Grunow K, Guhl S, Walker P, Grassberger M: The ascomycin macrolactam pimecrolimus (Elidel®, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils. J Allergy Clin Immunol 2001;108:275–280.

12 Eichenfield LF, Lucky AW, Boguniewicz M, Langley RG, Cherill R, Marshall K, et al: Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol 2002;46: 495–504.
13 Warshaw E, Wohlhuter J, Drake D, Zeller S, Wenner R, Bowers S, et al: Randomized, double-blind, vehicle-controlled efficacy trial of pimecrolimus cream 1% for the treatment of moderate to severe facial seborrheic dermatitis. J Invest Dermatol 2005;125:A3.
14 Gribetz C, Ling M, Lebwohl M, Pariser D, Draelos Z, Gottlieb AB, et al: Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. J Am Acad Dermatol 2004;51:731–738.
15 Drake LA, Millikan LE: The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. Arch Dermatol 1995;131:1403–1408.
16 Kaufmann R, Fölster-Holst R, Hoger P, Thaci D, Loffler H, Staab D, et al: Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. J Allergy Clin Immunol 2004;114:1183–1188.
17 Queille-Roussel C, Paul C, Duteil L, Lefebvre MC, Rapatz G, Zagula M, et al: The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. Br J Dermatol 2001; 144:507–513.
18 Lonsdale-Eccles AA, Velangi S: 'Topical pimecrolimus in the treatment of genital lichen planus: a prospective case series.' Br J Dermatol 2005;153:390–394.
19 Goldstein AT, Marinoff SC, Christopher K: Pimecrolimus for the treatment of vulvar lichen sclerosus in a premenarchal girl. J Pediatr Adolesc Gynecol 2004;17:35–37.
20 Goldstein AT, Marinoff SC, Christopher K: Pimecrolimus for the treatment of vulvar lichen sclerosus: a report of 4 cases. J Reprod Med 2004;49:778–780.
21 Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A, et al: Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics 2002;110:e2.
22 Meurer M, Fartasch M, Albrecht G, Vogt T, Worm M, Ruzicka T, et al: Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis. Dermatology 2004;208:365–372.
23 Luger TA, Lahfa M, Folster-Holst R, Gulliver WP, Allen R, Molloy S, et al: Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis. J Dermatolog Treat 2004;15:169–178.
24 Fonacier L, Spergel J, Charlesworth EN, Weldon D, Beltrani V, Bernhisel-Broadbent J, et al: Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2005; 115:1249–1253.