

## Pimecrolimus – A Safe and Effective Local Immunomodulator in the Treatment of Inflammatory Skin Diseases

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Received: September 5, 2004

Accepted: February 9, 2005

**SUMMARY** Pimecrolimus (SDZ ASM 981), an ascomycin derivative, as one of the new classes of immunomodulating macrolactams, is specifically effective in the treatment of inflammatory skin diseases. The interest in pimecrolimus is highly important for its significant anti-inflammatory activity, cell-selective inhibition of inflammatory cytokines, immunomodulatory capabilities, and low systemic immunosuppressive potential. The mechanism of action of pimecrolimus is the blockage of T cell activation, blocking signal transduction pathways in T cells, and inhibition of the synthesis of inflammatory cytokines, specifically Th1- and Th2-type cytokines. Several studies have evaluated the effectiveness of pimecrolimus as the treatment of choice for inflammatory skin diseases.

**KEY WORDS:** Elidel®; ascomycin; pimecrolimus; immunosuppression

### INTRODUCTION

Topical immunological modulators (TIMs) (tacrolimus and pimecrolimus) are new exciting agents in the treatment of inflammatory skin diseases, particularly for the treatment of atopic dermatitis (AD) (1-14). Since the first use of tacrolimus in patients in the mid 1990s, and of pimecrolimus thereafter, extensive clinical experience has shown them to be an effective, well tolerated alternative to topical steroids in the treatment of AD. Both TIMs showed good safety profile with longterm use in clinical setting. Pimecrolimus (SDZ ASM 981), an ascomycin derivative, is one of the new classes of immunomodulating macrolactams and is specifically effective in the treatment of inflammatory

skin diseases. Pimecrolimus 1% cream (Elidel®) is currently the most advanced ascomycin macrolactam under development. The mechanism of action of pimecrolimus is the blockage of T cell activation. Like all ascomycins, pimecrolimus is an immunophilin ligand, which binds specifically to the cytosolic receptor, immunophilin macrophilin-12. This pimecrolimus-macrophilin complex effectively inhibits the serin phosphatase calcineurin, by preventing calcineurin from dephosphorylating the nuclear factor of activated T cells (NF-AT), a transcription factor. The results with pimecrolimus shows the blockage of signal transduction pathways in T cells and the inhibition of the synthesis of inflammatory cytokines, specifically Th1- and

Th2-type cytokines. Pimecrolimus has also been shown to prevent the release of cytokines and proinflammatory mediators from mast cells. Several studies have evaluated the effectiveness of pimecrolimus as a treatment for inflammatory skin diseases such as AD, allergic contact dermatitis (ACD), autoimmune diseases, psoriasis, seborrheic dermatitis, etc. (1,2,8,14,15).

Pimecrolimus 1% cream is approved in the United States for the treatment of AD. Pimecrolimus is a calcineurin inhibitor that functions as a topical immunosuppressant (1,2). Topical pimecrolimus has proved safe and effective in children with moderate AD. It has also proved effective in other inflammatory skin diseases.

### PIMECROLIMUS IN PSORIASIS

In the treatment of psoriasis, topical use of pimecrolimus has proved promising (3). As oral agents, both tacrolimus (4) and pimecrolimus (5) were shown in pilot studies to be effective in the treatment of moderate to severe plaque psoriasis. Some have stated that given orally, pimecrolimus is as potent or superior to tacrolimus in treating ACD in mice and rats (6). However, no trial comparing these medications systemically in humans has yet been performed.

Neither tacrolimus ointment (7) nor pimecrolimus (3,8) cream appear effective in treating plaque-type psoriasis when simply applied in the commercially available form. In a dose-binding pilot study by comparing five doses of oral pimecrolimus in the treatment of moderate to severe plaque psoriasis (5 mg o.d., 10 mg o.d., 20 mg o.d., 20 mg b.i.d. and 30 mg b.i.d.) were compared with placebo, the agent effectiveness was proven in 38 patients (8). However, neither medication has yet been approved by the US Food and Drug Administration (FDA) for this indication. In case of tacrolimus, this is so although higher percutaneous drug absorption has been demonstrated in diseased skin than in healthy skin (9). In a pilot study of 70 patients, 23 of them in the calcipotriol (0.05%) twice-daily group, 24 in the tacrolimus (0.3%) ointment once-daily group, and 23 in the placebo group, tacrolimus was not effective in the treatment of psoriasis (10-13).

Occlusion is also associated with increased effectiveness of pimecrolimus in treating psoriasis (14,15). Pimecrolimus (0.3% and 1.0% cream) under occlusion was used to treat ten patients with chronic plaque-type psoriasis (16). For control treatment, the corresponding ointment base

(placebo) and open-labeled clobetasol-17-propionate ointment (0.05%) were used. The trial was designed as a randomized, double-blind, within-subject comparison over 2 weeks using the microplaque assay. Evaluation was performed by daily determination of clinical scores for erythema and induration. The results of the study showed that after 2 weeks of treatment, total scores decreased by 92 percent for clobetasol, by 82 percent for pimecrolimus (0.1%), by 63 percent for pimecrolimus (0.3%), and by 18 percent for the ointment base (placebo) (3).

A significant therapeutic effect of pimecrolimus in treating psoriasis without occlusion, where pimecrolimus had greater efficacy than the vehicle, although being less efficacious than calcipotriol and clobetasol ointment, has been reported by Gupta and Chow in their review including the study of Mrowietz *et al.* (8). Changing the formulation of pimecrolimus to increase its penetration is also a promising means to increase its efficacy in treating psoriasis (3).

While the role of pimecrolimus in the treatment of psoriasis remains to be defined, its use is likely to increase. Additional investigations are needed to determine ideal formulations of pimecrolimus for particular body sites in the treatment of psoriasis.

Pimecrolimus (Elidel<sup>®</sup>, SDZ ASM 981), a new macrolactam ascomycin derivative, was highly effective in treating plaque-type psoriasis when applied under Finn-chamber occlusion. A two-center, randomized, double-blind, vehicle- and positive-control patient study was therefore conducted in 23 adult psoriasis patients. Pimecrolimus 1% in an experimental ointment formulation was applied twice daily, along with a corresponding vehicle, 0.005% calcium ointment, and 0.05% clobetasol-17-propionate ointment to test the sites without occlusion, for 21 days. Erythema, induration and scaling (score: 0 [absent] to 4 [severe]) were evaluated. The total sign score was defined as the sum of the erythema, induration and scaling scores (range 0-12). Pimecrolimus 1% ointment was significantly ( $p=0.03$ ) more effective than the corresponding vehicle, with an improvement in total sign score of 51.4% compared with 36.7% for the corresponding vehicle. Improvements with calcipotriol and clobetasol-17-propionate were 71.5% and 88.3%, respectively. No local or systemic drug side effects were observed in the study. The authors concluded that pimecrolimus 1% cream experimental ointment formulation was significantly more effective than the correspond-

ing vehicle but less effective than calcipotriol and clobetasol cream (3,8). The first study reporting a significant therapeutic effect of pimecrolimus in an ointment formulation applied without occlusion to psoriatic plaques was that performed by Mrowietz *et al.* (17). Topical calcineurin inhibitor (pimecrolimus 1% cream) provided control of inflammation without causing longterm adverse effects such as skin atrophy and striae. Pimecrolimus 1% cream is a safe and effective treatment for intertriginous psoriasis (18).

### PIMECROLIMUS IN ATOPIC DERMATITIS

There have been several human studies evaluating the efficacy of pimecrolimus in AD. Pimecrolimus is effective and safe in both children and adults with AD. When pimecrolimus 1% cream was applied for adult AD, improvement was observed as early as the first week, with a 72% reduction in severity after 3 weeks. Transient irritation may occasionally be experienced at the site of pimecrolimus cream application. Similar results have also been described in children aged 3 months and older following the application of pimecrolimus 1% cream (8). Pimecrolimus has an enormous potential as a new treatment of inflammatory skin diseases; it has proved effective in atopic and allergic contact dermatitis, with no unfavorable adverse effect profile, including little effect on the systemic immune response (8). Luger *et al.* (19) assessed the use of topical pimecrolimus in AD patients who had 5% to 30% total body surface area involvement (n=260). Subjects were randomly assigned to treatment with pimecrolimus cream 0.05%, 0.2%, 0.6% or 1.0% vehicle cream, or with 0.1% betamethasone-17-valerate cream applied twice daily for 3 weeks. Pimecrolimus 1% and 0.6% cream were both effective, whereas pimecrolimus 0.05% had no significant effect (19). In their review including the study of Harper *et al.*, Gupta and Chow (8) conclude that pimecrolimus was well tolerated and effective in pediatric patients, even as young as 3 months, regardless of the extent of body surface involvement or duration of treatment.

Topical applications are indicated for treating AD. In this indication, it represents an alternative or an adjuvant to topical corticosteroids. Pimecrolimus may also prove beneficial in the treatment of other dermatoses (20). When applied at the first signs or symptoms of AD, Elidel® prevents flare progression and improves longterm disease control. Pimecrolimus cream 1% (Elidel®) applied twice daily showed greatest efficacy and was se-

lected for subsequent studies in adults, children and infants with AD. Elidel® is a steroid-free cream containing 1% strength of the topical immunomodulator pimecrolimus. Elidel was specifically developed as a treatment for AD and is approved for use in children as young as 2 years of age. The production of inflammatory cytokines by activated T cells in skin is thought to play an important role in the pathogenesis of AD. Elidel® potently suppresses cytokine production by dermal T cells without significantly impairing systemic immune responses. Elidel® does not cause steroid-associated local effects such as dermal atrophy, striae, or telangiectasias. In randomized controlled clinical studies, twice-daily application of Elidel® was shown to significantly improve the signs and symptoms of AD in infants, children and adults (21). The clinical effect of Elidel® on pruritus, the most troublesome symptom of AD, can be observed within 1 week of therapy and is maintained for the duration of treatment. Elidel® is well tolerated; the risk of application-site reactions such as itching or burning is comparable with that of the vehicle. Adverse effects were generally mild in patients receiving Elidel® and occurred at rates comparable with those in patients receiving vehicle treatment. In a 1-year study, Elidel® significantly reduced the incidence of flares when used at the first signs and symptoms of acute AD. As the result, the overall corticosteroid use to treat flares was significantly lower in patients using Elidel® for early intervention (21).

Meurer *et al.* (22) compared the safety and efficacy of pimecrolimus cream 1%-based treatment versus conventional therapy in adults with moderate AD. Patients were randomized to receive pimecrolimus cream 1% (n=62) or vehicle (n=68) at the first signs/symptoms of AD, for 24 weeks as required. A moderately potent topical corticosteroid (prednicarbate 0.25% cream) was allowed in both groups to treat flares. Corticosteroids were required on fewer days in the pimecrolimus group compared with the vehicle group (9.7 vs. 37.8%, p<0.001). Furthermore, 59.7% of pimecrolimus-treated patients experienced no flares during the study period compared with 22.1% of vehicle-treated patients (p<0.001). Pimecrolimus cream 1% was well tolerated throughout the study. For adults with moderate AD, pimecrolimus cream 1% is well tolerated, reduces the incidence of flares, reduces/eliminates corticosteroid use, improves longterm disease control, and enhances the patients' quality of life (22). Systemic absorption is very low and no accumulation is observed (8).

Luger *et al.* (23) performed a randomized, double-blind, multicenter study comparing the long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids (TCS) in 658 adults with moderate to severe AD. Patients applied either pimecrolimus or TCS (i.e. 0.1% triamcinolone acetonide cream and/or 1% hydrocortisone acetate cream) twice daily to all affected areas until complete clearance or for up to 1 year. A majority of patients treated with either pimecrolimus or TCS used the drug on a continuous basis over 1 year. In patients who had >30% of body surface involved by AD, the incidence of all skin infections was significantly lower in the pimecrolimus group than in the TCS group (95% CI of treatment difference, -25.3% to -3.4%). The most frequent application site reaction was burning (25.9% of patients on pimecrolimus and 10.9% on TCS), which was transient and mild to moderate in most cases. Three TCS-treated patients reported skin striae. There were no treatment-related serious or clinically significant systemic adverse events. The efficacy was better in patients on continuous TCS therapy, although patients completing the study were similarly well-controlled in both groups. About 42% of the pimecrolimus-treated patients were maintained for 1 year without TCS. Pimecrolimus demonstrated a favorable safety profile when used to treat adult patients with moderate to severe AD for up to 1 year. A significant proportion of patients could be maintained without TCS for a year (23).

Allen *et al.* (24) measured pimecrolimus blood concentrations and evaluated tolerability and efficacy in children and infants treated topically for AD with pimecrolimus cream 1% for three weeks. Three open-label, noncontrolled, multiple topical dose studies were conducted in children aged 8-14 years (study A, ten patients), and in infants aged 8-30 months (study B, eight patients) and 4-11 months (study C, eight patients). Pimecrolimus blood concentrations were determined on days 4 and 22 of treatment, and at end of study. Efficacy was assessed using the Eczema Area and Severity Index (EASI). Pimecrolimus blood concentrations were consistently low, typically (81%) below 1 ng/ml, with more than half of the measurements below the assay limit of quantitation (0.5 ng/ml) in studies A and B. The highest blood concentration measured throughout the three studies was 2.6 ng/ml. The cream was well tolerated, locally and systemically. The most common adverse event suspected to be related to study medication was a transient mild to moderate stinging sensation at the application site in 5/26 patients.

There was no indication of any systemic adverse effect. The patients responded well to therapy with a rapid onset of action, usually within four days. Median reductions of EASI from baseline at day 22 were 55% (study A), 63% (study B), and 83% (study C). Three-week treatment with pimecrolimus cream 1% twice daily in children and infants with extensive AD is well tolerated and results in minimal systemic exposure. Therapy with Elidel®/pimecrolimus cream applied twice daily proved safe and effective for significantly reducing the severity of symptoms in 251 children (aged 3-23 months) with mild to moderate AD in studies of up to one-year duration (25,26). Early intervention with pimecrolimus to prevent progression to disease flare proved significantly more effective than conventional management of AD (25). Early treatment of AD may alter the so called atopic march, as studies have suggested that AD might be a risk factor for the development of allergic diseases of the respiratory tract. The efficacy of topical corticosteroids directly correlates with safety concerns: as potency increases, so does the potential for side effects. There is a significant need for pimecrolimus in AD therapies, particularly for the treatment of moderate to severe disease. Optimal AD therapy should be at least as effective as conventional treatment, have an excellent safety profile, and offer the potential to prevent flares and modify the disease (25). Pimecrolimus monotherapy provides a real alternative for treatment challenges associated with conventional AD therapy. Analysis of flare-prevention rates observed in several clinical trials indicates that more children remain flare-free with pimecrolimus compared with other TIMs (25,26). Pimecrolimus combines high anti-inflammatory activity in the skin with a low potential to impair systemic immune reactions. Multicenter studies demonstrated the efficacy and safety of pimecrolimus cream in patients with AD and confirmed it to be suitable for short-term treatment and longterm management of AD in adults, children and infants as young as 3 months. Topical application in humans is not associated with atrophogenic side effects observed with corticosteroids. Pimecrolimus blood levels remained consistently low after repeated topical application and no clinically relevant drug-related systemic adverse events have been reported among 8000 patients treated in clinical trials so far. Short-term, phase I/II and phase II trials of pimecrolimus administered orally in psoriasis and AD have shown that this drug is highly effective in a dose-dependent manner in patients with these diseases,

and has a favorable safety profile. This finding is confirmed by pharmacogenomic blood analysis. Available data indicate that pimecrolimus, in both cream and oral formulations, may represent a new option for the treatment of inflammatory skin diseases (27). Pimecrolimus cream 1% is an efficacious and well-tolerated treatment for infants and children with mild and moderate AD, which makes it a promising new therapy for the clinical care in pediatric AD patients (28-31).

### **PIMECROLIMUS IN CHRONIC HAND ECZEMA**

A multicenter, randomized, vehicle-controlled, 3-week study was conducted in patients with chronic hand dermatitis (HD) of various etiologies and locations to identify subgroups particularly responsive to twice-daily application of pimecrolimus cream 1% with overnight occlusion (32). A total of 294 patients were randomized to the study. By the final visit on day 22, there was a trend towards greater clearance in patients who received pimecrolimus than in those treated with vehicle cream. The analysis of treatment success by various stratification factors revealed that palmar involvement had notable impact on the response ( $p=0.33$ ). Patients in the pimecrolimus group continued to improve throughout the study; however, in the vehicle group, improvement plateaued after 15 days. Pimecrolimus was well tolerated, with a low rate of application-site reactions such as burning. Pimecrolimus cream 1%, when used twice daily with overnight occlusion, may be of benefit in the management of chronic HD (32).

### **PIMECROLIMUS IN ALLERGIC CONTACT DERMATITIS**

In human studies of ACD, pimecrolimus 1% cream proved to be significantly more effective than control treatment. Also, efficacy of pimecrolimus 0.6% was comparable to that of 0.1% betamethasone-17-valerate, however, pimecrolimus was not associated with any of the side effects characteristic of topical steroids. Topical application of pimecrolimus is not associated with skin atrophy (8).

Contact dermatitis is a common clinical problem, with prevalent sensitizers being cosmetics, metals, medicines, and plants. Plants of the genus *Toxicodendron* cause ACD in 50% to 70% of the population (33). There are studies supporting the effectiveness of macrolactams when administered

before antigen challenge, but there are no studies describing the effectiveness of these drugs in the treatment of established human ACD. To investigate the effect of topical pimecrolimus in the treatment of *Toxicodendron*-induced ACD once rash is evident, poison ivy tincture was applied bilaterally to anterior forearms of 12 subjects with Finn chambers (Allerderm Diagnostic Products, Petaluma, CA) (33). After dermatitis had become evident, the volunteers treated each arm twice daily with either 1% topical pimecrolimus cream or placebo in a blinded fashion. The outcomes measured were a dermatitis grading score and time to rash and itch resolution. The median  $\pm$  SEM time for rash resolution was  $16.55 \pm 1.59$  days in the treatment group and  $16.27 \pm 1.82$  days in the placebo group ( $p=0.601$ ). The median time for itch resolution was  $4.73 \pm 1.56$  days in the treatment group and  $4.91 \pm 1.59$  days in the placebo group ( $p=0.167$ ). The mean dermatitis score was  $2.26 \pm 0.17$  in the treatment group and  $2.32 \pm 0.15$  in the placebo group ( $p=0.62$ ). The application of topical pimecrolimus was ineffective in the treatment of ongoing *Toxicodendron*-induced ACD (33). The study by Quelle-Rousset *et al.*, reviewed by Gupta and Chow (8) was the first controlled trial where pimecrolimus (0.2% and 0.6% cream) demonstrated efficacy in 66 nickel ACD during 12-day twice daily treatment with both concentrations. The wide array of inflammatory skin diseases treated successfully with pimecrolimus cream 1% has been demonstrated by Professor Luger, i.e. psoriasis, Netherton's syndrome, hand eczema, perioral eczema, dyshidrotic eczema, seborrheic dermatitis, perioral dermatitis, chronic actinic dermatitis, steroid induced rosacea, vitiligo, pyoderma gangrenosum, granuloma annulare, lichen sclerosus et atrophicus, oral and genital lesions in Crohn's disease, and discoid lupus erythematosus (34).

### **CONCLUSION**

Pimecrolimus 1% cream has a promising immunomodulatory potential as topical treatment for inflammatory skin disease and is ideal treatment option for AD. Pimecrolimus provides safe and effective longterm management for moderate to severe AD, and to prevent the disease progression, then for ACD and other inflammatory skin diseases as well as psoriasis. It reduces or eliminates the need of topical corticosteroids. Pimecrolimus 1% cream provides an excellent treatment alternative to topical corticosteroids and steroid-sparing therapies. Elidel® is an agent for pre-emptive

patient self-management, for use in all age groups and safely applied to all skin surface and even on sensitive areas including face, neck, intertriginous lesions and skin folds.

At last, pimecrolimus improves the quality of life of patients with AD, and of their families.

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