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REVIEW ARTICLE

Pimecrolimus: A review

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ABSTRACT

Pimecrolimus (SDZ ASM 981), an ascomycin derivative, is one of the new classes of immunomodulating macrolactams and was specifically developed for the treatment of inflammatory skin diseases. The interest in pimecrolimus has been substantial because of its significant anti-inflammatory activity and immunomodulatory capabilities and its low systemic immunosuppressive potential. The mechanism of action of pimecrolimus is the blockage of T cell activation. Pimecrolimus (like all ascomycins) 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 factor of activated T cells (NF-AT), a transcription factor. This results in 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 pro-inflammatory mediators from mast cells. Several studies have evaluated the effectiveness of pimecrolimus as a treatment for skin diseases. 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. As well, the effectiveness of pimecrolimus 0.6% cream was comparable to 0.1% betamethasone-17-valerate; however, pimecrolimus was not associated with any of the side effects characteristic of a topical steroid. Topical application of pimecrolimus is not associated with skin atrophy. 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. Pharmacokinetic studies have shown very low blood levels of pimecrolimus following topical application, with no accumulation after repeated applications. Following application of pimecrolimus cream occasional transient irritation may be experienced at the application site. Similar results have also been found in children aged 3 months and older following application of pimecrolimus 1% cream. Topical pimecrolimus in psoriasis appears to exhibit a dose-dependent therapeutic effect under semi-occlusive conditions. Pimecrolimus has an enormous potential as a new treatment of inflammatory skin diseases. It has been shown to be effective in atopic and allergic contact dermatitis, with a favorable adverse-effects profile, which includes little effect on the systemic immune response.

Key words: pimecrolimus, SDZ ASM 981

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Introduction

Pimecrolimus (SDZ ASM 981) is one of the new class of novel ascomycin immunomodulating macrolactams, and was developed for the treatment of inflammatory skin diseases. Ascomycin, first isolated as a fermentation product of *Streptomyces hygroscopicus* var. *ascomycetus* in the early 1960s,[1] was initially researched primarily for its antifungal properties. However, it was more than 20 years later that ascomycin was investigated for its structural and immunomodulatory

properties.[1] Two major derivatives were shown to be topically effective in treating inflammatory skin diseases: SDZ ASM 981 and SDZ 281-240. Pimecrolimus (SDZ ASM 981) is currently the most advanced ascomycin macrolactam under development. Pimecrolimus is a colourless, solid compound[2] with a molecular weight of 810.48 daltons.[2]

Interest in pimecrolimus has been intensive because of its significant anti-inflammatory activity and immunomodulatory capabilities and its low systemic immunosuppressive potential.

Mechanism of action

The mechanism of action of pimecrolimus is the blockage of T cell activation. Ascomycin macrolactams are immunophilin ligands that bind to a specific cytosolic receptor. Pimecrolimus binds to immunophilin macrophilin-12, also known as FK506 binding protein, and FKBP-12. Tacrolimus (FK506) and rapamycin also bind to macrophilin-12.[2] Like tacrolimus and cyclosporin A,[3] the mechanism of action of pimecrolimus involves its binding to macrophilin-12.[2] The pimecrolimus-macrophilin complex then binds to the cytosolic enzyme calcineurin phosphatase.[4] Calcineurin is a Ca^{2+}/calmodulin-dependent protein phosphatase that regulates the translocation of cytosolic components of nuclear factors, which in turn regulate the promoter activities of several mediators during mRNA transcription.[4] By inhibiting the action of calcineurin, the pimecrolimus-macrophilin complex prevents the dephosphorylation of the cytoplasmic component of the nuclear factor of activated T cells (NF-AT).[1] NF-AT regulates the mRNA transcription of a number of inflammatory cytokines; therefore, pimecrolimus blocks this transcription, especially Th1 (IL-2, IFN-γ) and Th2 (IL-4, IL-10) type cytokines.[4] Other cytokines, including IL-5, IL-10 and TFNα, are decreased in production by pimecrolimus in a dose-dependent manner.[4]

Pimecrolimus also targets mast cells which play an important role to anti-inflammatory activities.[5] Pimecrolimus inhibits not only the transcription and synthesis of cytokines from mast cells, but also the release of preformed mediators serotonin and β-hexosaminidase[1] by the inhibition of Fc$\in$-RI-mediated degranulation and secretion.[2] It is important to note that all the inhibition processes occur only when pimecrolimus is bound to macrophilin-12.[2] It is of interest that, during a study of murine mast cell line CPII,[2] it was found that pimecrolimus did not inhibit the transcription of a reporter gene which was under the control of the human TFNα promoter in the murine dendritic cell line, and had no effect on IL-8 release from keratinocytes, fibroblasts and endothelial cells. This is an indication of the specificity of the pharmacologic activity of pimecrolimus.[2]

The first study of the gene expression analysis of blood cells was performed on seven patients with psoriasis, who had been treated with oral pimecrolimus 30 mg twice daily.[6] Blood samples were taken from the patients prior to treatment and after 13 or 14 days of treatment. Gene chips were used for gene expression analysis and 7129 genes were surveyed. Kehren *et al.*[6] found a genomic profile of pimecrolimus of approximately 100 genes. As well, it was demonstrated that pimecrolimus treatment caused a strong down-regulation of the expression of mRNA for genes associated with the macrolactam target pathway and inflammation. However, no changes were found in the mRNA for genes which generally reflect drug related side effects, like those associated with apoptosis, stress induction and enzymatic induction. Therefore, Kehren *et al.*[6] concluded that the genomic analysis of blood cells from psoriatic patients treated with pimecrolimus supports the specific anti-inflammatory nature of the therapy.

Studies

Animal Models

Animal models have been used to evaluate the effectiveness of both topical and systemic pimecrolimus. Meingassner *et al.*[7,8] performed several studies in mouse, rat and pig models with allergic contact dermatitis, in which topical pimecrolimus displayed a very high level of effectiveness. In the pig model a statistically significant anti-inflammatory effect was observed at concentrations as low as 0.04%.

The atrophogenic effects of clobetasol-17-propionate 0.05%, a potent topical corticosteroid, and pimecrolimus 0.3% topical formulation on pig skin (which has similar qualities to human skin) were compared. Corticosteroids are known to cause skin atrophy after repeated topical or systemic use, affecting both the dermis and epidermis. Meingassner *et al.*[7] applied the corticosteroid and pimecrolimus formulations for 13 days under the same conditions. Pimecrolimus had no effect on skin texture or thickness, which suggests that it lacks an atrophogenic ability while displaying an effectiveness similar to potent corticosteroids in treatment of allergic contact dermatitis.

Oral therapy with cyclosporine A, tacrolimus and pimecrolimus for allergic contact dermatitis has been evaluated in mouse and rat models.[7,8] In the mouse model, pimecrolimus was found to be as effective as cyclosporine A following oral ingestion and slightly superior after subcutaneous administration.[7] As well, it was found that pimecrolimus at doses up to 4×90 mg/kg does not impair sensitization, unlike cyclosporine A or tacrolimus at doses of 4×60 mg/kg and 4×30 mg/kg, respectively.[8] In addition, pimecrolimus contrasts cyclosporine A and tacrolimus by inhibiting ongoing secondary inflammatory response, but not impairing the primary immune response in allergic contact dermatitis.[8]

Systemic immune reactions were also studied by Meingassner *et al.*[7] in two rat models, a graft-versus-host reaction and an allogenic kidney transplantation. In the graft-versus-host model the right hind foot pad of the rat was injected subcutaneously with spleen cells from allogenic rats. Pimecrolimus was administered by subcutaneous injection the same day as the

spleen cell injection, and 1, 2, and 3 days later. Pimecrolimus was inactive at low subcutaneous doses of 0.1 and 0.3 mg/kg, and had only a minimal effect at higher doses of 3 and 9 mg/kg. In the allogenic kidney transplantation model, following the transplant of the kidney from the donor rat to the recipient rat, pimecrolimus of 20% concentration in solid dispersion was administered daily to the recipient for the first 14 days after transplant. It was found that pimecrolimus prevented organ rejection at oral doses of 15.6 mg/kg and higher. Cyclosporin A was effective at dosages three times lower than this. Meingassner *et al.*[7] concluded that pimecrolimus, unlike cyclosporine A, has a large therapeutic window, within which treatment of skin inflammation is possible with no adverse effects on the immune system.

Neckermann *et al.*[9] performed a study to examine the effectiveness of systemic and topical pimecrolimus on hypomagnesaemic hairless rats compared with its vehicle. The magnesium deficiency in rats produces a pruritic rash, which resembles the clinical features of atopic dermatitis. The oral administration of pimecrolimus was in the form of a solid solution of 20% active drug. Daily doses of 4.0 or 12.5 mg/kg body weight were administered on three consecutive days by gavage (5 mL/kg body weight) following the development of clinical signs. Treatment with pimecrolimus 12.5 mg/kg cleared up the eruption, with pronounced reduction within the first day following the start of therapy. Complete inhibition was observed within 4 days; however, signs of recurrence appeared 2 days after the last dose and continued to be present until the end of the study period.[9] The vehicle-treated rats demonstrated no changes in the extent of pruritus or skin lesions.

Neckermann *et al.*[9] also evaluated the utility of pimecrolimus as a prophylactic agent using hypomagnesaemic hairless rats. Seven daily doses of either pimecrolimus 12.5 mg/kg body weight or vehicle were administered beginning from day 3 of the diet until day 9. The use of pimecrolimus using the prophylactic regimen almost completely suppressed the onset of the erythematous pruritic eruption with only one of seven pimecrolimus-treated rats developing slight erythema on day 9.[9] None of the rats treated in a prophylactic manner with systemic pimecrolimus exhibited any signs of pruritus during the study period; however, all vehicle treated rats developed severe erythematous lesions.

The topical administration of pimecrolimus to hypomagnesaemic hairless rats was conducted by dissolving the pimecrolimus 0.4% in ethanol/propylene glycol.[9] Topical treatment was applied to one ear and vehicle to the other. The ear treated with the active drug displayed significant reduction in erythematous swelling within one day of the start of therapy with the inflammation being suppressed for 3 days after the last dose; however, recurrence was noted 4 or 5 days after therapy had been discontinued. The use of topical pimecrolimus in a prophylactic manner was also effective with suppression of the inflammation of the ears of five rats treated. It is important to note that topical treatment of the ear with pimecrolimus did not affect the erythematous lesions on the trunk, and the degree of pruritus did not differ between the active drug and vehicle treated groups. Neckermann *et al.*[9] indicate that topical pimecrolimus at the concentration used in this study did not appear to have a systemic effect. Both the therapeutic and prophylactic treatment of the rats resulted in an inhibition of histamine levels; however, when there was clinical evidence of erythema, histamine blood levels in the pimecrolimus treated animals were similar to the vehicle treated rats.

Human Studies

Atopic dermatitis (Table 1 and Table 2)

There have been several human studies that have evaluated the efficacy of pimecrolimus in atopic dermatitis. Van Leent *et al.*[10] studied the topical application of 1% pimecrolimus twice daily versus once daily for 3 weeks on two comparative target areas (one on the left arm, one on the right arm), and compared efficacy with a placebo cream in 34 adult patients. Patients treated twice daily displayed significant improvement as early as 2 days of starting treatment, and within 3 weeks there was a mean reduction of 71.9% in the severity of atopic dermatitis. The median time for partial clearance of the disease at the treated sites was 8 days. By the end of the treatment period, 12 of 16 patients achieved partial clearance and three patients were totally clear.[10] The efficacy in those patients treated once daily was less than in the group receiving twice daily applications. In the once daily group, the mean reduction of severity of atopic dermatitis was 37.7% and none of the patients reached complete clearance by the end of the study period; only three of 18 patients achieved partial clearance.[10] The 1% pimecrolimus cream was significantly more effective than the placebo cream, with no skin irritation or any local adverse effects observed. After the completion of therapy, symptoms of atopic dermatitis returned gradually, without rapid rebound.

Laboratory studies were performed on all the patients with no relevant changes being observed. The concentration of pimecrolimus in whole blood was measured and only two of 129 samples exceeded the limit of quantification (0.1 ng/mL). The authors suggest that it is safe to assume that these two samples were contaminated, as they were taken from separate patients on two separate occasions.[10] Van Leent *et al.*[10] concluded that 1% pimecrolimus cream applied twice daily to the body surface is an effective and safe treatment of atopic dermatitis, with a dose dependent trend.

Luger *et al.*[11] assessed the use of topical pimecrolimus in patients with atopic dermatitis who had 5% to 30% total body surface area involvement ($n = 260$). Subjects were randomly assigned treatments of pimecrolimus cream 0.05%, 0.2%, 0.6%, or 1.0%, vehicle cream or 0.1% betamethasone-17-valerate cream. The 0.1% betamethasone-17-valerate cream is a potent corticosteroid, which was used as an internal control. The

Table 1 Use of topical pimecrolimus on adult patients with atopic dermatitis

Author	Study Type	Participants	Treatment Regime	Efficacy	Pimecrolimus Blood Level Concentrations	Safety
Van Leent *et al.*[10]	randomized, double blind, placebo controlled, right-and-left comparison study	34 adult patients daily vs. placebo cream for	pimecrolimus 1% cream applied twice daily or once 3 weeks on two comparative target areas (one on the left arm, the other on the right arm	patients with partial clearance ($0 < ADSI \leq 2$): 75% (pimecrolimus twice daily), 13% (placebo twice daily), 17% (pimecrolimus once daily), and 0% (placebo once daily; patients with complete clearance (ADSI = 0): 19% (pimecrolimus twice daily), and 0% (all other treatments)	only two of 121 blood samples were above the limit of quantification (0.1 ng/mL) – authors suspect the two samples were the result of contamination	no clinically significant adverse effects observed
Luger *et al.*[11]	double-blind, randomized, parallel-group, multicentre dose-finding study	260 adult patients (ages 18 years or older)	four concentrations of pimecrolimus cream (0.05%, 0.2%, 0.6%, 1.0%), vehicle cream, or 0.1% betamethasone-17-valerate (BMV) cream applied twice daily to affected areas for 3 weeks	patients with moderately clear or better (>50% improvement): 88.1% (BMV), 16.3% (vehicle), 53.3% (1.0% cream), 54.8% (0.6% cream), 32.6% (0.2% cream), and 0.05% cream failed to show significant therapeutic effect	systemic exposure was consistently low with 72% of measurements below limit of quantification	mild to moderate application site reactions were the most common adverse events reported, with the majority of reactions beginning on the first day and resolving within 3 days; next most common adverse events were pruritus and worsening of atopic dermatitis
Van Leent *et al.*[32]	two non-controlled, open-label, multiple topical dose study	total 52 adult patients (ages 18 years or older)	pimecrolimus 1% cream applied twice daily for 3 weeks, followed by twice daily application on an 'as-needed' basis for up to 1 year	not reported	blood concentration levels lower than limit of quantification (0.5 ng/mL) at 3 weeks: 78%; individual maximum concentrations ranged from < 0.5 to 1.4 ng/mL, with a single isolated value at 4.6 ng/mL – authors suspect this sample was contaminated blood concentration levels lower than limit of quantification (0.5 ng/mL) over 1 year: 98%; maximum concentration seen over the 1 year period was 0.8 ng/mL	well tolerated both locally and systemically

Table 2 Use of topical pimecrolimus on pediatric patients with atopic dermatitis

Author	Study Type	Participants	Treatment Regime	Efficacy	Pimecrolimus Blood Level Concentrations	Safety
Kapp *et al.*[12]	multicentre, parallel group, double-blind, controlled study	251 pediatric patients (ages 3–23 months)	pimecrolimus 1% cream or vehicle applied twice daily according to need for 1 year; emollients and medium-high potency topical corticosteroids were allowed to be used for flares not controlled by study medication	patients without incidence of flares at 6 months: 70.1% (pimecrolimus 0.1%), 32.6% (vehicle with emollients and corticosteroid use)	not reported	no significant difference in the incidence of adverse events between the two treatment groups
Harper *et al.*[13]	four open-label pharmaco-kinetic studies	total of 58 paediatric patients (ages 3 months to 14 years)	pimecrolimus 1% cream applied twice daily for 3 weeks; 11 patients continued treatment over 1 year on an 'as-needed' basis	not reported	blood concentration levels lower than 2 ng/mL: 93%; blood concentration levels lower than 5 ng/mL: 60%	no evidence of accumulation over time; no systemic side effect observed
Morris *et al.* in Paller[14]		pediatric patients (ages 5–16 years)	pimecrolimus 1% cream applied twice daily for 3 weeks	mean reduction in dermatitis: 70%	blood concentration levels below limit of detection (0.4 ng/mL): 60%	transient mild to moderate warmth or burning
Harper *et al.*[15]	open and non-controlled study	10 pediatric patients (ages 1–4 years) started	pimecrolimus 1% cream applied twice daily for 3 weeks	average EASI decreased by 12.8, with a range of improvement of 8–89% from baseline score at the end of treatment period	blood concentration levels lower than 0.5% ng/mL: 63%; individual maximum concentrations ranging from < 0.5 to 1.8 ng/mL	no serious adverse events occurred
De Prost *et al.*[25]	multicentre, double-blind study	713 pediatric patients (ages 2–17 years)	pimecrolimus 1% cream or current standard of care, including use of emollients (SoC) applied twice daily for 12 months; medium-high potency topical corticosteroids were allowed if flares occurred	patients without incidence of flares at 6 months: 61% (pimecrolimus 1%), and 34% (SoC); patients without incidence of flares at 12 months: 51% (pimecrolimus 1%), 28% (SoC); proportion of patients who did no use corticosteroids within 12 months: 57% (pimecrolimus 1%), and 32% SoC	not reported	systemic immune response not affected
Wahn *et al.*[26]	multicentre, controlled, double-blind study	713 pediatric patients (ages 2–17 years)	pimecrolimus 1% cream or vehicle applied twice daily for 1 year	patients without incidence of flares at 6 months: 61% (pimecrolimus 1%), and 34.2% (vehicle); patients without incidence of flares at 12 months: 50.8% (pimecrolimus 1%), and 29.3% (vehicle); patients treated with pimecrolimus had a longer time to first flare than vehicle and significantly reduced the use of corticosteroids	not reported	mild and transient feelings of warmth/ burning were reported by 10.5% of pimecrolimus treated patients

Table 2 *Continued*

Author	Study Type	Participants	Treatment Regime	Efficacy	Pimecrolimus Blood Level Concentrations	Safety
Whalley *et al.*[28]	two randomized, double-blind clinical trials	total of 403 pediatric patients (ages 2–17 years)	pimecrolimus 1% cream or vehicle applied for 6 weeks	significant improvement in quality of life scores in both treatment groups, however pimecrolimus treated group showed significantly greater improvements over vehicle treated group	not reported	not reported
Boguniewicz *et al.*[29]	two randomized, multicentre studies, followed by an open-label study	total of 403 pediatric patients (ages 2–17 years)	pimecrolimus 1% cream or vehicle applied twice daily for 6 weeks, followed by twice daily application on an 'as-needed' basis for 20 weeks	patients with clearance or almost clearance (IGA score = 1 or 0): 34.8% (pimecrolimus 1%), and 18.4% (vehicle)	not reported	most common reports of mild to moderate application site burning, which resolved early in treatment (18.1%)
Wahn *et al.*[30]	non-controlled, open-label, multiple topical dose, multicenter study	20 pediatric patients (ages 3–23 months)	pimecrolimus 1% cream or vehicle applied twice daily or 3 weeks	median reduction of EASI from baseline to day 22: –78%; marked eduction of EASI was observed as early as day 4	blood concentration levels lower than limit of quantification (0.1 ng/mL): 31%; blood concentration levels lower than 0.5 ng/mL: 71%; individual maximum concentrations ranged from < 0.1 to 2.29 ng/mL	adverse application site reactions reported, however the reactions were considered not to affect the well-being of the patients
Ho *et al.*[31]	double-blind, multicenter, vehicle controlled study, followed by an open label extension	186 pediatric patients (ages 3–23 months)	pimecrolimus 1% cream or vehicle applied twice daily for up to 6 weeks, followed by continuation of treatment of pimecrolimus patients twice daily for 20 weeks	patients with clearance or almost clearance (IGA score = 1 or 0) at 6 weeks: 54.5% (pimecrolimus 1%), and 23.8% (vehicle); mean reduction of EASI: –61.78% (pimecrolimus 1%), and +7.25% (vehicle); patients with no or minimal pruritus: 72.4% (pimecrolimus 1%), and 33.3% (vehicle)	not reported	well tolerated throughout study and extension

assigned treatment was applied twice daily for 3 weeks to all affected areas, except for the face. The greatest efficacy was observed with betamethasone-17-valerate over all other treatments. Pimecrolimus 1.0% and 0.6% cream were both effective treatments; pimecrolimus 0.05% treatment had no significant therapeutic effect, which was expected. All treatments helped to improve the pruritus. By the end of the study period signs of atopic dermatitis appeared to be moderately clear or better (> 50% improvement) with pimecrolimus 1.0% (53.3%) and 0.6% creams (54.8%) compared with only 16.3% improvement with the vehicle.[11]

Very few systemic adverse effects were observed and none were considered to be related to the treatment.[11] Local reactions at the application site included burning, warmth, stinging, smarting, pain and soreness. These occurred most frequently with pimecrolimus 1% cream, were of mild to moderate severity, and most reactions were transient, beginning on day 1 of treatment and resolving within the first 3 days. Luger *et al.*[11] concluded that topical application of pimecrolimus was well tolerated and effective in treating atopic dermatitis, displaying a dose-response trend, with 1.0% cream being the most effective concentration of pimecrolimus. It is possible that a treatment period exceeding 3 weeks would have resulted in a greater therapeutic effect.[11]

Topical pimecrolimus has been found to be safe and effective in children. Studies have been performed in children as young as 3 months. Kapp *et al.*[12] conducted a 6 month double-blind randomized long term study on safety and efficacy of pimecrolimus in infants aged 3–23 months with atopic eczema ($n = 251$ patients). Pimecrolimus, used as an early intervention treatment, was compared with a group that received a current standard of care for atopic eczema, that is, a regimen of emollients, and corticosteroids. Vehicle cream was used instead of pimecrolimus in the control group in order to maintain the study blind. Medium to high potency corticosteroids were used to treat flares not controlled by pimecrolimus. Following the use of corticosteroids, pimecrolimus was resumed. The primary efficacy parameter was the incidence of flares during the 6 month study period.[12] It was found that pimecrolimus provided better control of atopic dermatitis than standard emollient treatment, with 70.1% of the pimecrolimus patients completing the treatment period without any flares compared with 32.6% in the control group. The mean number of days of corticosteroid use was about twice as great in the standard emollient treatment group than the pimecrolimus group. Therefore, pimecrolimus significantly reduced the incidence of flares and the dependence on corticosteroids in infants with atopic dermatitis as young as 3 months.

Harper *et al.*[13] performed short- and long-term pharmokinetic studies in children aged 3 months to 14 years with moderate to severe eczema ($n = 58$ patients). Initial treatment involved the application of pimecrolimus cream 1% twice daily for 3 weeks. Two studies followed 11 patients over 1 year who continued treatment on an 'as needed' basis. Blood samples were take throughout the studies. Patients as young as 3 months had blood levels, which were consistently low; 93% of pimecrolimus blood concentrations were lower than 2 ng/mL and 60% of samples were lower than 0.5 ng/mL. This pattern is similar to those found in adults.[13] The authors concluded that pimecrolimus was well tolerated in the treatment of pediatric patients, even as young as 3 months, regardless of extent of body surface involved, of lesions or of duration of treatment.[13]

Systemic absorption is very low and no accumulation is observed. A European study of 5–16-year-old children treated twice daily for 3 weeks with pimecrolimus 1% cream demonstrated a 70% mean reduction in dermatitis by the end of the treatment period.[14] The dermatitis recurred following the discontinuation of the pimecrolimus therapy. A pediatric study of ten patients, 1–14 years old, with moderate to severe atopic dermatitis on 23% to 69% of their body surface area, was performed for 3 weeks.[15] The patients were treated twice daily with pimecrolimus 1% cream for 3 weeks. By the end of the treatment period there was an improvement of Eczema Area and Severity Index (EASI) by 8% to 89% from the baseline score with the seven patients who completed the treatment.[15] No serious adverse events were reported and no clinically relevant adverse-effects were observed upon physical examination, vital signs or laboratory safety parameters. A total of 63 blood samples were taken throughout the treatment period; 63% of those samples had pimecrolimus concentrations less than 0.5 ng/mL, with the maximum concentration ranging from less than 0.5 to 1.8 ng/mL. The highest pimecrolimus blood levels were approximately 20 times lower than levels associated with no toxicity in animal toxicity studies and a human study where oral pimecrolimus was administered.[15] Blood samples drawn at the end of the study period demonstrated no accumulation of pimecrolimus after several weeks of treatment. While orally administered pimecrolimus may degrade into several minor metabolites, the metabolism of topically applied pimecrolimus is negligible through the skin;[15] therefore systemic exposure to pimecrolimus due to topical application is probably negligible.

Psoriasis

There has been one study of the treatment of psoriasis with pimecrolimus. Whereas the atopic dermatitis studies used a cream formulation of pimecrolimus, an oral formulation was used to treat psoriasis. Rappersberger *et al.*[16,17] evaluated the safety, tolerability and efficacy of treatment of patients with moderate to severe chronic plaque psoriasis by comparing five dose levels of oral pimecrolimus (5 mg o.d., 10 mg o.d., 20 mg o.d., 20 mg b.i.d. and 30 mg b.i.d.) to a placebo. Thirty-eight patients were treated with pimecrolimus and 10 patients treated with the placebo for 4 weeks. All five dose levels of pimecrolimus were well tolerated, with no serious adverse

effects; the only frequent adverse effect noted was a mild to moderate, transient feeling of warmth when the treatment was applied. As well, no clinical changes were noted with any of the physical and biochemical examinations. Pimecrolimus doses of 20 mg b.i.d and 30 mg b.i.d. were observed to have the greatest reduction in the Psoriasis Area and Severity Index (PASI) of 60% and 75%, respectively, compared to 4% for placebo.[16]

Topical treatment of psoriasis using pimecrolimus is usually restricted to mild disease because of its limited effectiveness,[18] due to the thick scaling and limited penetration into lesional psoriatic skin.[19] Pimecrolimus 0.3%, 1.0% ointment, ointment base and clobetasol-17-propionate were compared over 2 weeks in ten adult patients with stable chronic plaque-type psoriasis.[18] The treatments were applied daily for 2 weeks under occlusion using Finn chambers. Pimecrolimus 0.3% cream had only a mild effect on psoriatic lesions up to day 10, followed by little further resolution. Initially, 1% pimecrolimus provided a weaker response compared with clobetasol-17-propionate; however, by the end of the treatment period there was no significant difference between the two treatments in the ability to clear lesions. No adverse events were reported throughout the treatment period. Therefore, pimecrolimus, when applied under occlusion, was found to be effective in clearing psoriatic plaques in a dose dependent manner.

Mrowietz *et al.*[20] performed a study to evaluate the effectiveness of pimecrolimus without occlusion in 23 adults with plaque-like psoriasis. Pimecrolimus 1% cream was compared with vehicle, 0.005% calcipotriol ointment and 0.05% clobetasol-17-propionate ointment. The study medications were applied to the test sites twice daily for 21 days. Erythema, induration and scaling were evaluated for therapeutic effect. Pimecrolimus was significantly more effective than the vehicle, with improvement in scores of 50.0% and 28.6%, respectively in the two groups. However, both calcipotriol and clobetasol had a greater effectiveness than pimecrolimus, with improvements of 71.4% and 87.5%, respectively. This is the first study to report significant therapeutic effect by pimecrolimus in treating psoriasis without occlusion, where pimecrolimus had greater efficacy than the vehicle, although less efficacious than calcipotriol and clobetasol ointment.[20]

Allergic contact dermatitis

The effectiveness of topical anti-inflammatory drugs have often been tested on experimentally-established allergic contact dermatitis.[1] In a study by Queille-Roussel *et al.*[21] the effectiveness of two different formulations of pimecrolimus 0.2% and 0.6% cream, vehicle, and betamethasone-17-valerate 0.1% cream was compared in 66 adults with nickel contact dermatitis. The patients were treated twice daily for up to 12 days. Both formulations of the pimecrolimus were significantly more effective than the vehicle. As well, pimecrolimus 0.6% creams were comparable with betamethasone-17-valerate 0.1% cream. There were no serious side effects observed with pimecrolimus cream. This treatment of nickel allergic contact dermatitis with pimecrolimus is the first controlled trial where a topical non-corticosteroid has demonstrated efficacy.

Safety and tolerability of topically applied pimecrolimus

Topical application of pimecrolimus appears to be safe when used in both children and adults. The most common adverse events expected are application site reactions, for example, burning, feeling of warmth, smarting, pain, and soreness.[11] Most application site reactions have been found to be of mild to moderate severity. To some extent, subjects applying the vehicle have also reported these reactions. In patients applying pimecrolimus 1% cream the applications site reactions appear to be transient, usually beginning on the first day of treatment and resolving within the first 3 days of therapy.[11]

An important advantage of topical pimecrolimus over the topically applied corticosteroids is that the ascomycin derivative does not induce skin atrophy when applied to normal skin.[22] The traditional treatments of inflammatory skin diseases have been potent topical steroids. However, long term use of these treatments is limited due to several adverse events, including skin atrophy. Topical corticosteroids are known to inhibit collagen synthesis in the skin, leading to skin atrophy.[23,24] Queille-Roussel *et al.*[22] conducted a comparison study of pimecrolimus 1% cream, its vehicle, betamethasone-17-valerate 0.1% cream and triamcinolone acetonide 0.1% cream in 16 healthy adult volunteers. Each treatment was applied to the volar aspect of the forearms twice daily, 6 days a week, for 4 weeks. By using ultrasound it was determined that there was no relative change to the total skin thickness of the pimecrolimus treated sites compared with the vehicle, even by the last examination. However, application of topical corticosteroids resulted in significant reduction in skin thickness, which was apparent as early as day 8. None of the patients reported any adverse events at the application sites. This study demonstrated a clear lack of atrophogenic potential of pimecrolimus 1% cream.[22]

De Prost *et al.*[25] performed a study of 713 children, ages 2–17 years with atopic eczema, comparing the use of pimecrolimus 1% cream with a standard of care (SoC) regimen, which included the use of emollient creams and medium-high potency topical corticosteroids, for long term management of atopic eczema in children, each applied twice daily for up to 12 months. Topical corticosteroids were used only if flares occurred; following corticosteroid use, the assigned treatment was resumed. It was found that the pimecrolimus significantly reduced the use of corticosteroids; 57% of the pimecrolimus treated patients did not use corticosteroids within 12 months, while only 32% of the SoC group avoided corticosteroid use.[25] As well, pimecrolimus significantly reduced the incidence of flares over the 6 and 12 month periods. Within 6 months, 61% of pimecrolimus patients were without flares, however only

34% of the SoC group had none. At month 12, 51% of pimecrolimus patients had no flares while only 38% of emollient patients were free from flares.[25] Therefore, the use of pimecrolimus significantly reduced both the amount of time before flares first occur and the total number of flares, along with the frequency of topical corticosteroid use.[25–27] Use of pimecrolimus improves the quality of life of the patient.[28] Clinical trials by Whalley *et al.*[28] of 403 pediatric patients compared pimecrolimus 1% cream with its vehicle over 6 weeks. Significantly greater improvements were associated with the pimecrolimus treatment than the vehicle.[28]

Topically applied pimecrolimus has been associated with low systemic absorption. For example, in a study by Harper *et al.*[15] children aged 1–4 years with atopic dermatitis were treated twice daily for 3 weeks with pimecrolimus 1% cream. The blood concentrations of pimecrolimus were consistently low even in the patients with the most extensive surface areas treated (up to 69% body surface area). Furthermore, pimecrolimus did not accumulate over the treatment period and no systemic effects were detected. Similar findings have been reported by other investigators,[29,30] even with patients as young as 3 months,[31] and also in adult patients.[32,33]

Comparison with tacrolimus

Tacrolimus (FK 506) is also a newly developed immunomodulator that is being used for treatment of atopic dermatitis and several other inflammatory skin disorders. Tacrolimus was discovered from the fermentation broth of the soil microbe *Streptomyces tsukuba* found in Japan.[34] Initially, tacrolimus was used systemically to prevent the rejection of new grafts in patients who had undergone allograft transplants. The mechanism of action of tacrolimus and pimecrolimus is similar. Both tacrolimus and pimecrolimus bind specifically to the immunophilin macrophilin-12, which blocks the action of the phosphatase calcineurin. This ultimately results in the suppression of gene transcription and responsiveness of T cells.[35] Tacrolimus has a molecular weight of 822 daltons and is absorbed readily through damaged skin barrier. The patient's skin absorbs lower quantities of tacrolimus as lesions heal, which helps reduce adverse effects.[36]

While the structures of pimecrolimus and tacrolimus are similar, the structure of pimecrolimus possesses two different chemical group attachments; pimecrolimus is 20 times more lipophilic than tacrolimus.[37] A higher lipophilicity allows pimecrolimus to have a higher affinity to the skin; as a result, pimecrolimus has a lower permeation potential through the skin, with a skin-selective pharmacologic profile.[38] As well, although the mechanism of pimecrolimus and tacrolimus is similar, their selectivity is different. Meingassner *et al.*[39] compared pimecrolimus to both cyclosporine A and tacrolimus, demonstrating that pimecrolimus may have a weaker immunosuppressing capacity. Bochelen *et al.*[40] demonstrated that pimecrolimus has about a 3-fold lower inhibition potential of calcineurin than tacrolimus. This may result in pimecrolimus being less effective at lower doses but may be as effective as tacrolimus at higher doses.[40] In the United States, tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis in individuals aged 2 years and higher; pimecrolimus is indicated for treatment of mild to moderate disease in the same age group.

According to Stuetz *et al.*[38] pimecrolimus may need to be administered in significantly higher amounts than cyclosporine A or tacrolimus to prevent organ rejection in animal models. Meingassner *et al.*[42] support this statement with rat models of allogeneic kidney transplants. The lowest oral dose of pimecrolimus, which prolonged the survival of the animal to 100 days or longer, was 15 mg/kg. In comparison, 5 mg/kg of cyclosporine A and 1 mg/kg of tacrolimus were required to achieve the same long-term survival. Although pimecrolimus appears to have lower immunosuppressive properties, this may in turn allow pimecrolimus to have a more selective immunomodulatory activity than the other two treatments, as well as a lower potential for systemic immunosuppression when administered orally than tacrolimus.[42] Animal models have demonstrated that treatments of systemically applied pimecrolimus does not cause toxic adverse effects, like nephrotoxicity, hepatotoxicity or hypertension.[5]

Conclusion

Pimecrolimus has enormous potential as a topical treatment for inflammatory skin disease. It is highly efficient in blocking T cell activation and inhibiting the synthesis of inflammatory cytokines. Pimecrolimus is effective in dermatoses such as atopic dermatitis and allergic contact dermatitis, and is indicated in the United States for the short-term and intermittent long-term therapy of mild to moderate atopic dermatitis in non-immunocompromised patients aged 2 years and older where alternative conventional therapies are deemed inadvisable because of potential risks, or for patients who are not adequately responsive to, or are intolerant of conventional therapies. Adverse effects experienced with topical application have been transient events, generally of mild to moderate severity. Unlike topical corticosteroids, the ascomycin is not associated with the development of skin atrophy. This is an advantage compared to topical corticosteroids, particularly when considering long-term use and application at certain anatomic sites such as the face, neck and genital areas. Pimecrolimus has demonstrated a low blood level concentration, even over long term treatment periods with a low potential for affecting the systemic immune response when applied topically. The significant anti-inflammatory activity, immunomodulatory capabilities and highly favourable adverse effects profile of pimecrolimus make it an ideal treatment for several inflammatory skin diseases.

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