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Topical Pimecrolimus

A Review of its Clinical Potential in the Management of Atopic Dermatitis

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Data Selection

Data Selection Sources: Medical literature published in any language since 1980 on pimecrolimus, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'SDZ-ASM-981'. EMBASE search terms were 'ASM 981' or 'SDZ ASM 981'. AdisBase search terms were 'pimecrolimus' or 'ASM 981' or 'SDZ ASM 981'. Searches were last updated 12 Feb 2002.

Selection: Studies in patients with atopic dermatitis who received topical pimecrolimus. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Pimecrolimus, SDZ ASM 981, ASM 981, atopic dermatitis, atopic eczema, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Pimecrolimus (SDZ ASM 981), an ascomycin derivative, is a nonsteroid, has anti-inflammatory activity, and has demonstrated efficacy in reducing symptoms of atopic dermatitis in adult and paediatric patients when applied topically.

Compared with vehicle, topical pimecrolimus 1.0% cream was significantly more effective at reducing symptoms of atopic dermatitis, as measured by the Eczema Area and Severity Index (EASI), in infants aged 3 to 23 months, children aged 2 to 17 years and adults. The median reductions from baseline in the total EASI score in adults after treatment with pimecrolimus 1.0% or corresponding vehicle twice daily for 3 weeks were 47 and 0%, respectively. In infants and children, treatment with pimecrolimus 1.0% twice daily for 6 weeks resulted in significant decreases in mean EASI scores compared with vehicle.

The severity of pruritus was significantly reduced in patients of all age groups after topical treatment with pimecrolimus 1.0% cream. Compared with vehicle, the incidence of eczematous flares was also reduced by intermittent long-term use of topical pimecrolimus 1.0% in adults, children and infants. Sixty percent of children treated with pimecrolimus for 1 year completed the first 6 months of treatment without experiencing a flare, compared with 35% of patients who received vehicle. Furthermore, the use of topical corticosteroids for the treatment of uncontrolled flares in adults, children and infants was lower in the pimecrolimus groups than in the vehicle groups.

Topical pimecrolimus 1.0% cream is well tolerated in atopic dermatitis patients of all age groups. There were no clinically relevant systemic adverse events reported from any of the studies in patients with atopic dermatitis. The most frequently reported adverse events pertained to application site reactions, such as burning and a feeling of warmth.

In conclusion, topical pimecrolimus 1.0% cream has shown efficacy in the treatment of mild to moderate atopic dermatitis in infants, children and adults. Although tolerability data concerning infants and children have not yet been published in full, the drug appears to be well tolerated in all age groups, and there have been no reports of clinically relevant systemic adverse events. Furthermore, pimecrolimus 1.0% cream has shown no potential for skin atrophy, a problem commonly associated with treatment with topical corticosteroids. Pimecrolimus 1.0% cream provides a promising and well tolerated treatment option in the management of infants, children and adults with mild to moderate atopic dermatitis.

Pharmacodynamic Properties

Pimecrolimus binds to macrophilin-12 (FKBP12) at nanomolar concentrations (concentration required for 50% inhibition = 1.8 nmol/L), and the resulting complex inhibits calcineurin, causing a signal transduction blockade in target cells. As a consequence, the synthesis of inflammatory cytokines is blocked at the level of gene transcription. The release of T helper (T_h)-1 and T_h2 cytokines from a house dust mite-sensitive T_h cell clone was inhibited by pimecrolimus 0.2 to 0.42 nmol/L.

Pimecrolimus dose-dependently inhibited the anti-immunoglobulin E-induced release of the preformed pro-inflammatory mediators histamine and

tryptase from activated human dermal mast cells, and β-hexosaminidase, serotonin and tumour necrosis factor-α from activated rat basophilic leukaemia 2H3 cells. Furthermore, the up-regulation of co-receptors CD134 and CD137, which are implicated in the activation and expansion of inflammatory effector T cells, was dose-dependently inhibited by pimecrolimus (80% inhibition at 10 nmol/L in primary T cells).

Twice-daily topical pimecrolimus 1.0% showed no potential for skin atrophy when applied for 6 days/week to normal skin in a randomised, double-blind, vehicle-controlled 4-week study in 16 healthy volunteers. Conversely, betamethasone-17-valerate 0.1% and triamcinolone acetonide 0.1% creams significantly reduced skin thickness (by 7.9 and 12.2%, respectively) compared with baseline thickness.

Symptoms of nickel-induced allergic contact dermatitis in 66 healthy volunteers were significantly reduced by twice-daily topical pimecrolimus 0.6% for 12 days compared with vehicle. Furthermore, after 12 days, there was no significant between-group difference in mean reductions of the total symptom score for erythema, induration and vesiculation in patients treated twice daily with topical pimecrolimus 0.6% or betamethasone-17-valerate 0.1% (32% reduction for both).

Pharmacokinetic Profile

Systemic absorption of topically applied pimecrolimus 1.0% has been investigated in short-term (3 weeks) and long-term (up to 12 months) studies in a total of 52 adults and 58 children (aged ≥3 months) with moderate to severe atopic dermatitis. In all these studies, blood concentrations of pimecrolimus were consistently low, regardless of the extent of lesions treated (up to 92% body surface area involved) or duration of therapy. No systemic accumulation was observed over the treatment period.

In 12 adult patients with moderate to severe atopic dermatitis, blood concentrations of pimecrolimus during 3 weeks of twice daily treatment with topical pimecrolimus 1.0% were ≤1.4 μg/L [78% of the concentrations were below the assay limit of quantification (LoQ)]. The area under the whole-blood concentration-time curve from 0 to 12 hours ranged from <0.5 to 11.4 μg • h/L.

In 40 adult patients with extensive atopic dermatitis (up to 62% body surface area affected) treated with pimecrolimus cream 1.0% for 1 year, 98% of the blood samples collected provided concentrations below the assay LoQ; the maximum concentration measured was 0.8 μg/L.

In 58 patients aged 3 months to 14 years with moderate to severe atopic dermatitis (10 to 92% affected body surface area) treated with pimecrolimus 1.0% twice daily for 3 weeks, 93% of the blood concentrations of pimecrolimus were <2 μg/L. The concentrations were in a range similar to those measured in adult patients.

In a study examining the pharmacokinetics of single-dose oral pimecrolimus, healthy volunteers received 5, 15, 30 or 60mg under fasting conditions. The fall in concentrations after maximum plasma concentrations had been reached involved three disposition phases with an apparent terminal elimination half-life of 30 to 40 hours. The mean apparent systemic clearance among the pimecrolimus 30 and 60mg groups was 71 and 91 L/h, and the apparent volume of distribution was 3452 and 4830L, respectively. Proportionality between the dose of the drug and maximum concentrations of pimecrolimus was observed.

Pimecrolimus is stable in the skin but, when taken up into the circulation, it

is metabolised by the liver cytochrome P450 3A4 pathway and excreted in the faeces, as shown after oral administration.

Therapeutic Efficacy

Topical pimecrolimus 1.0% has been evaluated in randomised, double-blind, vehicle-controlled clinical trials in infants (aged 3 to 23 months), children (aged 2 to 17 years) and adults with mild to severe atopic dermatitis (the majority of patients had moderate disease). In clinical trials, the dosage of topical pimecrolimus was 1.0% administered twice daily as a cream unless otherwise stated.

In Adults: Twice daily administration of pimecrolimus 1.0% cream for 3 weeks was significantly more effective than once daily administration or vehicle at reducing symptoms of atopic dermatitis, as measured by the Atopic Dermatitis Severity Index (ADSI), in 34 patients with disease of mild to moderate severity. The group that received pimecrolimus twice daily showed a 71.9% mean reduction in the ADSI score at endpoint, compared with a mean reduction of 10.3% at the vehicle-treated sites. Furthermore, pimecrolimus demonstrated a significant therapeutic effect by day 2 compared with vehicle (a reduction in the ADSI score of 18.5% compared with a 1.5% increase, respectively). At sites treated with pimecrolimus once daily, the mean percentage reduction from baseline in the ADSI total score was 37.7%, compared with 6.2% at sites treated with vehicle.

In a dose-finding study involving 260 patients, pimecrolimus 0.2, 0.6 and 1.0% creams were significantly more effective than vehicle at reducing total Eczema Area and Severity Index (EASI) scores after 3 weeks of twice daily treatment. Among patients randomised to pimecrolimus 1.0%, the median reduction from baseline in EASI scores was 47%, compared with a 0% reduction among vehicle recipients. Pimecrolimus 0.6 and 1.0% were also associated with significant improvements in pruritus compared with vehicle; at endpoint, the proportion of patients with absent or mild pruritus increased to 52.4 from 11.9% at baseline and to 46.7 from 6.7% at baseline for pimecrolimus 0.6 and 1.0%, respectively. In comparison, absent or mild pruritus was present in 18.6 and 4.7% of vehicle recipients at endpoint and baseline, respectively.

In a study in 192 adults with mild to moderate atopic dermatitis, topical pimecrolimus 1.0% significantly reduced the incidence of eczematous flares and the need for rescue treatment with topical corticosteroids compared with vehicle. Among patients in the pimecrolimus group, 14.8% were treated with topical corticosteroids, compared with 37.3% of patients in the vehicle group. The mean number of disease flares in patients who received pimecrolimus was 1.2, compared with 2.6 in patients who received vehicle. Reductions in total EASI scores and the severity of pruritus were also significantly in favour of pimecrolimus.

In Infants aged 3 to 23 Months: In a study involving 186 infants with mild to moderate atopic dermatitis, treatment with pimecrolimus 1.0% cream for up to 6 weeks resulted in a significant reduction in EASI and Investigators Global Assessment (IGA) scores, as well as in the severity of pruritus.

Compared with a conventional therapy, pimecrolimus 1.0% cream significantly reduced the incidence of eczematous flares in the first 6 months of a 1-year study involving 251 infants with mild to very severe atopic dermatitis (the majority of patients had moderate disease). 70% of patients in the pimecrolimus group completed 6 months of treatment without experiencing a flare, compared with 33% of patients in the control group. The mean number of days that patients in the control group were treated with corticosteroids (all patients were able to receive emollients for skin care and medium potency corticosteroids for eczema-

tous flares not controlled by study medication) was approximately twice as high as that in the pimecrolimus group.

In children aged 2 to 17 years. Combined results from two studies showed that pimecrolimus 1.0% cream was significantly more effective than vehicle at reducing symptoms of the disease in 403 children with mild to moderate atopic dermatitis. After 6 weeks, the median reduction of the EASI total score was 59% in the pimecrolimus group, compared with 14% in the vehicle group. Treatment with pimecrolimus was also associated with a significant improvement in health-related quality-of-life scores based on a 28-point questionnaire filled out by the patients' parents.

Compared with a conventional therapy, pimecrolimus 1.0% cream significantly reduced the incidence of eczematous flares in the first 6 months of a year-long study involving 713 patients with predominantly moderate atopic dermatitis. At month 6, 60% of patients in the pimecrolimus group remained free of flares, compared with 35% in the conventional therapy control group. Over the course of the year, fewer patients in the pimecrolimus group than patients in the control group were treated with corticosteroids (57 *vs* 32).

Tolerability

Evidence to date indicates that topical pimecrolimus 1.0% is well tolerated in patients of all age groups (infants aged 3 to 23 months, children aged 2 to 17 years and adults) with atopic dermatitis.

The most frequently reported adverse events during treatment with pimecrolimus 1.0% cream were application site reactions, such as burning and a feeling of warmth, which occurred in approximately 10% of patients aged 2 to 17 years, and in about 26% of adults.

There were no significant between-group differences in the incidence of adverse events among 192 adult patients with moderate to severe atopic dermatitis who received pimecrolimus 1.0% or vehicle twice daily according to need for up to 1 year.

There are limited published data on the tolerability of pimecrolimus 1.0% in infants and children because the five clinical trials have, so far, been reported only as abstracts. However, there were no reports of clinically relevant systemic adverse events. The incidence of skin infections in 335 patients aged 2 to 17 years treated with pimecrolimus 1.0% cream was low (≈5%).

Dosage and Administration

Pimecrolimus 1.0% has been approved in the US for the short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥2 years who do not respond well to, or may have adverse effects with, conventional treatments.

Pimecrolimus 1.0% cream is applied twice daily to all affected skin areas as a thin layer and rubbed in gently and completely. The drug should be used as long as signs and symptoms persist. If disease resolution occurs, treatment should be stopped; if symptoms persist beyond 6 weeks, the patient should be re-evaluated.

A change in dosage is not required in patients with renal or hepatic insufficiency. Pimecrolimus should not be applied to areas of active cutaneous viral infection. Furthermore, because pimecrolimus may be associated with an increased risk of varicella zoster virus infection, herpes simplex virus infection or eczema herpeticum, the use of the drug in the presence of these infections is cautioned.

1. Introduction

Atopic dermatitis is a chronic inflammatory disease with a lifetime prevalence of between 15 and 20%, and usually manifests in early childhood.[1] Diagnosis of atopic dermatitis generally involves determining the presence of three of five major criteria: pruritus, characteristic eczematous changes (flexural lichenification or linearity in adults, and facial and extensor involvement in infants and children), history of atopy, early age of onset and chronic or chronically relapsing dermatitis.[2]

Although the pathogenic mechanism of inflammatory skin diseases such as atopic dermatitis, allergic contact dermatitis and psoriasis has not been fully determined, the activation of T cells seems to play a key role.[3-11] In patients with atopic dermatitis, a clinical response to common allergens results in an increase in specific immunoglobulin E (IgE), which is produced by B lymphocytes under the regulation of cytokines. These cytokines [e.g. interleukin (IL)-4, IL-10] are produced by a subpopulation of T lymphocytes, namely helper T lymphocytes (T_h) of the T_h2-subtype, in preference to those produced by the T_h1-subtype (e.g. IL-2, interferon-γ).[12,13] However, as reviewed by Boguniewicz and Leung,[3] acute and chronic atopic dermatitis lesions differ in their cytokine profile; acute lesions are characterised by T_h2 cytokines, whereas chronic lesions are characterised by both T_h2 and T_h1 cytokines. IgE, which mediates these clinical responses to systemic allergens, binds to tissue mast cells, Langerhans cells in the skin and airways, and circulating basophils through high affinity receptors such as FcεRI (high-affinity IgE receptor), thus stimulating the release of preformed or newly synthesised pro-inflammatory mediators.[4,12,13]

A recent study has demonstrated that the genetic loci for atopic dermatitis and psoriasis are closely positioned.[14] In children with atopic dermatitis and/or asthma, genetic linkage to atopic dermatitis was identified on chromosomes 1q21, 17q25 and 20p. These regions are closely coincident with three of the six known psoriasis loci: 1q21, 3q21, 4q, 6p (MHC), 17q25 and 20p. This result suggests that atopic dermatitis is influenced by genes that modulate dermal responses independently from atopic mechanisms.

Initial therapy for patients with atopic dermatitis involves bathing, application of emollients, use of antihistamines and minimisation of exacerbating factors. In patients refractory to these initial measures, the first line of pharmacological treatment is the application of a topical corticosteroid. However, prolonged use of corticosteroids is associated with a number of adverse effects, including skin atrophy and telangiectasia.[15] Thus, pimecrolimus was developed specifically for the topical treatment of inflammatory skin diseases.[16]

Pimecrolimus (32-epi-chloro-32-desoxyascomycin, SDZ ASM 981; figure 1) is a derivative of the macrolactam ascomycin; it is a nonsteroid, has anti-inflammatory activity, and has demonstrated efficacy in reducing symptoms of atopic dermatitis in both adult and paediatric patients.[17,18]

The use of pimecrolimus in the treatment of atopic dermatitis, allergic contact dermatitis, chronic irritant contact dermatitis and psoriasis has previously been briefly reviewed in *BioDrugs*.[17] This review examines the role of pimecrolimus in the management of atopic dermatitis in infants, children and adults.

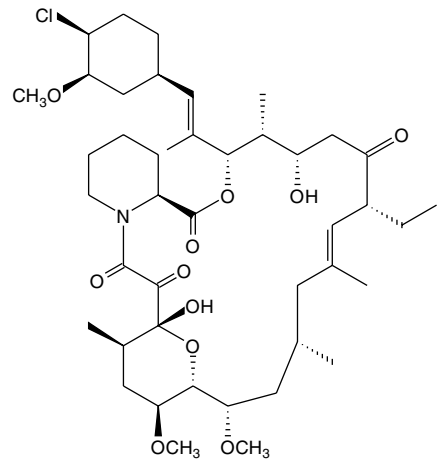

Fig. 1. Chemical structure of pimecrolimus (32-*epi*-chloro-32-desoxyascomycin).[17]

2. Pharmacodynamic Properties

The pharmacodynamic properties of pimecrolimus have mainly been examined in animal and *in vitro* studies, and have been recently comprehensively reviewed by Stuetz et al.[19] However, there have been two studies examining the anti-inflammatory activity and skin atrophogenic or phototoxic potential of topical pimecrolimus in healthy volunteers.[20,21] Table I overviews the results of *in vitro* and animal studies. Oral pimecrolimus has been evaluated in patients with psoriasis;[22] however, this is beyond the scope of the review and will not be discussed further.

2.1 Mechanism of Action

Pimecrolimus has been shown to bind to the cytosolic receptor macrophilin-12 (FKBP12) at nanomolar concentrations (table I). The resulting drug-protein complex inhibits the phosphatase calcineurin, resulting in the blockage of signal transduction in target cells.[4] As a consequence, the transcription of inflammatory cytokines, which is dependent on the dephosphorylated nuclear factor of activated T cells, is blocked.[4]

At nanomolar concentrations (0.2 to 0.42 nmol/L), pimecrolimus inhibited the release of both T_h1- and T_h2-type cytokines from a house dust mite (*Dermatophagoides pteronyssimus*)-sensitive T-helper cell clone (TCC) obtained from the skin of an allergic patient after epicutaneous challenge stimulated by allogenic monocyte-derived dendritic cells or autologous B cells loaded with extracts of *D. pteronyssimus* (table I). As a secondary effect, the drug also inhibited the proliferation of the TCC, probably because of the lower production of IL-2 and IL-4 which are autocrine and paracrine growth factors for stimulated T cells.[4]

Pimecrolimus was also shown to dose-dependently inhibit the anti-IgE-induced release of the preformed pro-inflammatory mediators histamine and tryptase from activated human dermal mast cells (table I),[23] and β-hexosaminidase, serotonin and tumour necrosis factor (TNF)-α from activated rat basophilic leukaemia 2H3 (RBL) cells.[4,5] Inhibition of the anti-IgE-induced secretion of histamine from human dermal mast cells preincubated with pimecrolimus was dose dependent and statistically significant when compared with controls.[23] Although significant inhibition ($p < 0.01$) was observed with pimecrolimus concentrations ≥10 nmol/L, maximum inhibition of histamine release (73%; $p < 0.01$ *vs* control) occurred with pimecrolimus 500 nmol/L. Anti-IgE-induced tryptase release was inhibited by pimecrolimus to a similar degree (75% at 500 nmol/L); however, statistical analysis was not reported.[23] Pimecrolimus also inhibited the FcεRI-mediated secretion of serotonin ($IC_{50} \approx 30$ nmol/L), β-hexosaminidase ($IC_{50} \approx 30$ nmol/L) and TNF-α ($IC_{50} \approx 100$ nmol/L) from RBL cells.[5]

Pimecrolimus dose-dependently inhibited the up-regulation of the co-receptors CD134 and CD137, as well as the high affinity IL-2 receptor CD25 and intercellular adhesion molecule-1 (ICAM-1, CD54) on purified $CD4^+$ T cells, in the allogenic mixed lymphocyte reaction using human monocyte-derived dendritic cells.[28] The co-receptors CD134 and CD137 are thought to play a role in the activation and expansion of inflammatory effector T cells, and may mediate preferential activation of $CD8^+$ T cells and T_h1 cells that produce inflammatory cytokines. At a concentration of 10 nmol/L, pimecrolimus showed 80% inhibition. Furthermore, pimecrolimus showed 10-fold more activity than cyclosporin in the same model, although quantitative data were not reported in the abstract.[28]

2.2 Anti-Inflammatory Studies in Animals

Topical pimecrolimus 0.1% cream was at least as effective as clobetasol-17-propionate 0.05%, betamethasone-17-valerate 0.1%, diflucortolone-21-valerate 0.1%, mometasone-17-(2-furoate) 0.1% and fluticasone propionate 0.05% creams, and significantly ($p < 0.001$) more effective than clobetasone-17-butyrate 0.05% and fluprednidene-21-acetate 0.1% at reducing gross lesions in pigs sensitised and topically challenged with 2,4-

Table I. Overview of the pharmacological activity of pimecrolimus

In vitro **anti-inflammatory activity**
Showed high affinity for human recombinant macrophilin-12 binding protein (IC_{50} = 1.8 nmol/L)[4]
Inhibited, as the pimecrolimus-macrophilin-12 complex, bovine brain calcineurin ($k_i \approx$ 100 nmol/L)[4]
Inhibited production of T_h1- (IL-2, interferon-γ) and T_h2- (IL-4, IL-10) type cytokines at nanomolar concentrations in a clone obtained from the skin of a patient with atopic dermatitis[4]
Suppressed the IgE/antigen-stimulated release of the preformed pro-inflammatory mediator hexosaminidase in the murine mast cell line CPII clone 12 (IC_{50} = 26.7 nmol/L)[4]
Dose-dependently inhibited anti-IgE-induced release of histamine and tryptase from human skin mast cells (maximum inhibition was 73 and 75%, respectively, at 500 nmol/L) and histamine from human skin basophils (maximum inhibition 82% at 500 nmol/L)[23]
Dose-dependently inhibited the calcium ionophore A23187- and PMA-induced release of human mast cell-derived TNF-α (maximum inhibition 90% at 100 nmol/L)[23]
Inhibited the PMA/PHA-induced transcription of a reporter gene (β-galactosidase) coupled to the human IL-2 promoter in the human T cell line Jurkat (IC_{50} = 0.4 nmol/L)[4]
Inhibited the FcεRI-induced expression of a reporter gene (luciferase) coupled to the human TNF-α in the murine mast cell line CPII clone 12 (IC_{50} = 100 nmol/L)[4]
In vivo **anti-inflammatory activity**
Oral pimecrolimus 12.5 and 25 mg/kg significantly ($p < 0.05$ and 0.01 *vs* vehicle, respectively) and dose-dependently inhibited DNFB-induced thickening of the skin in rats, whereas cyclosporin showed significant inhibition ($p < 0.05$ *vs* vehicle) only at a dose of 50 mg/kg (the drugs were administered 2 hours before and immediately after challenge).[24] In contrast, no significant effect was observed with tacrolimus at doses ≤25 mg/kg[25]
Oral pimecrolimus 90 mg/kg, administered 2 hours before and 4, 24 and 48 hours after the first antigen exposure in mice, did not inhibit sensitisation. Elicitation was dose-dependently inhibited by pimecrolimus 3 to 90 mg/kg administered 2 hours before and 4 hours after the second exposure (ED_{50} = 48 mg/kg). Tacrolimus 30 mg/kg and cyclosporin 60 mg/kg inhibited sensitisation by 71 and 60%, respectively. Pimecrolimus and tacrolimus exhibited equivalent potency in inhibiting elicitation; cyclosporin was less potent (ED_{50} >90 mg/kg)[26]
Subcutaneous pimecrolimus had no effect in rat models of localised graft-versus-host reaction at doses of 0.3 or 1.0 mg/kg, and showed only weak inhibition of lymph node weight increase at 3 and 9 mg/kg;[24] dose-dependent inhibition was observed with tacrolimus (ED_{50} = 0.3 mg/kg), cyclosporin (ED_{50} = 2.5 mg/kg) and pimecrolimus (ED_{50} = 20 mg/kg)[25]
Organ rejection in rats that had undergone orthotopic allogenic kidney transplantation was prevented for ≥100 days by oral pimecrolimus 15.6 mg/kg/day for 14 days. In comparison, cyclosporin and tacrolimus showed immunosuppressant activity at an oral dosage of 5 and 1 mg/kg/day, respectively[24,25]
Intravenous pimecrolimus alleviated the outcome of focal cerebral ischaemic/reperfusion injury in rats at a dosage of 1 mg/kg (37% reduction of the infarct volume induced by transient or permanent middle cerebral artery occlusion; $p < 0.01$ *vs* control animals)[27]
Inhibited the development of inflammatory ear edema in mice after oral or subcutaneous doses of ≥30 or ≥1.5 mg/kg, respectively ($p < 0.001$ *vs* control animals). Oral doses were given 2 hours before and immediately after challenge; subcutaneous injections were performed immediately after challenge[24]

DNFB = 2,4-dinitrofluorobenzene; **ED_{50}** = dose required for 50% of the maximal pharmacological effect ; **FcεRI** = high-affinity IgE receptor; **IC_{50}** = concentration required for 50% inhibition; **IgE** = immunoglobulin E; **IL** = interleukin; **k_i** = inhibition constant; **PHA** = phytohaemagglutinin; **PMA** = phorbol myristate acetate; **T_h** = helper T lymphocyte; **TNF-α** = tumour necrosis factor-α.

dinitrofluorobenzene (figure 2). Furthermore, topical pimecrolimus 0.04 and 0.4% solutions were as effective as clobetasol-17-propionate 0.04 and 0.4% solutions at reducing allergic contact dermatitis in the same pig model. Topical clobetasol-17-propionate 0.13% and fluticasone propionate 0.13 and 0.04% solutions were significantly ($p < 0.005$) more effective than pimecrolimus solutions at the same concentrations.[24]

In hypomagnesaemic hairless rats, the development of symptoms which mimic acute clinical features of atopic dermatitis, such as pruritic erythematous rash, were suppressed within 1 day of a 3-day regimen of orally (12.5 mg/kg once daily) or topically (0.4% solution twice daily) administered pimecrolimus.[29] Oral pimecrolimus almost completely relieved the animals of pruritus and rash from day 2 to day 4. Twice-daily topical treatment

on the ears significantly inhibited local erythematous swelling after 1 day and symptoms remained suppressed until 3 days after the last dose. Furthermore, histo- and immunopathological skin changes, as well as the numbers of degranulated mast cells in the dermis, were reversed towards normal. The same oral dosage given prophylactically almost completely suppressed the onset of erythematous and pruritic rash (one of seven rats developed a slight erythema on day 9).[29]

Topical application of an ethanolic solution of pimecrolimus 0.004% 30 minutes after challenge significantly ($p < 0.001$ *vs* control) inhibited oxazolone-induced ear edema formation in mice.[24] In comparison, SDZ 281 240 and dexamethasone 0.004% showed similar potency to pimecrolimus; cyclosporin was effective only at concentrations >0.01%.

2.3 Studies in Healthy Volunteers

Topical pimecrolimus showed no potential for skin atrophy when applied to normal skin in a randomised, double-blind, vehicle-controlled study.[20] Cream formulations of pimecrolimus 1.0%, betamethasone-17-valerate 0.1%, triamcinolone acetonide 0.1% and the vehicle for pimecrolimus were applied to the forearms of 16 healthy volunteers twice daily, 6 days per week, for 4 weeks. Skin and epidermal thickness were evaluated by ultrasound or histological examination, respectively, and clinical signs of skin atrophy were determined by stereomicroscopy.

After 4 weeks, there was no significant difference between the relative change in skin thickness at sites at which pimecrolimus or vehicle were applied (reductions from baseline skin thickness were not reported). Betamethasone-17-valerate and triamcinolone acetonide significantly reduced skin thickness (by 7.9 and 12.2%, respectively) compared with baseline thickness ($p < 0.001$); the reduction reached statistical significance after 8 days. Histological results from 12 of the 16 volunteers at day 29 showed that the mean epidermal thickness at sites treated with pimecrolimus or vehicle were not significantly different (57.8 *vs* 59.2μm). However, at sites treated with betamethasone-17-valerate or triamcinolone acetonide, the mean epidermal thickness was significantly lower than at pimecrolimus-treated sites (49.6 and 51.9μm, respectively, $p \leq 0.001$ *vs* pimecrolimus). Although more recipients of topical corticosteroids had evidence of telangiectasia manifest as hyperaemia and dilation of blood vessels, clinical evaluation did not show any significant changes in the clinical scores for skin atrophy parameters (atrophy and telangiectasia) in any of the four groups.[20]

Topical pimecrolimus 0.6% significantly reduced symptoms of nickel-induced allergic contact dermatitis in a randomised, nonblind, vehicle-controlled, multicentre, within-volunteer study ($p \leq 0.01$ *vs* vehicle).[30] Sixty six healthy volunteers challenged by a 48-hour application of a nickel sulphate solution received pimecrolimus 0.2 or 0.6% (both of which were evaluated using two different vehicle formulations of undisclosed composition), betamethasone-17-valerate 0.1% or vehicle twice

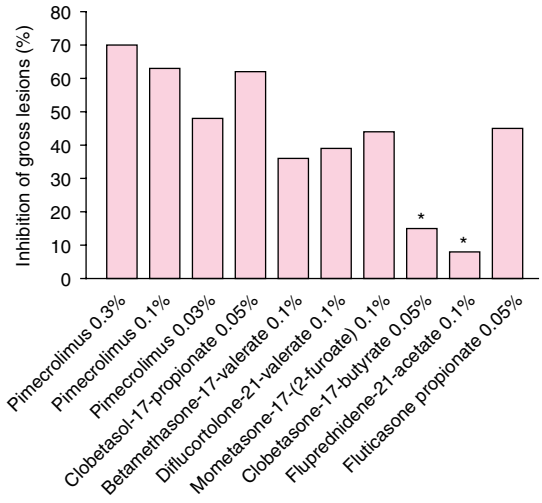

Fig. 2. A comparison of the percentage inhibition of allergic contact dermatitis by topical pimecrolimus creams and market formulation creams of topical corticosteroids in pigs sensitised and topically challenged with 2,4-dinitrofluorobenzene. The drugs were applied topically 30 minutes and 6 hours after challenge.[24] * $p < 0.001$ *vs* pimecrolimus 0.03, 0.1 and 0.3% creams.

daily for up to 12 days. Evaluation of erythema, induration and vesiculation was performed on a daily basis, with the sum of the individual scores (range 0 to 3, increasing in severity) making up the Total Symptom Score (TSS). Pimecrolimus 0.6% in both formulations was significantly more effective than vehicle ($p \leq 0.03$) in the time to partial clearance of dermatitis (a reduction of the TSS from ≥6 to ≤1); the median time to partial clearance was achieved one day earlier at pimecrolimus-treated sites than at sites applied with vehicle (actual data not reported). Pimecrolimus 0.2% was ineffective in this study; there was no significant difference between pimecrolimus 0.2% and vehicle. There was also no significant difference between pimecrolimus 0.6% or betamethasone-17-valerate 0.1%.[30]

Compared with both vehicle formulations, pimecrolimus 0.6% and betamethasone-17-valerate demonstrated the largest reductions in the TSS after 3 days. By day 12, the mean reductions in the TSS at pimecrolimus 0.6% and betamethasone-17-valerate sites were 32% compared with 21.5 and 18.5% at sites applied with the two vehicle formulations (statistical analysis not reported).[30]

No phototoxic potential was observed after application of pimecrolimus 1.0% under Finn chamber occlusion in 30 healthy volunteers. Phototoxicity was assessed, in comparison with vehicle or blank Finn chambers, after a single application for 24 hours followed by ultraviolet (UV) A and UVB irradiation. Further application of pimecrolimus also revealed no potential for photoallergy.[21]

3. Pharmacokinetic Profile

Systemic absorption of topically applied pimecrolimus has been investigated in short-term (3 weeks) and long-term (up to 12 months) studies in a total of 52 adults and 58 children (aged 3 months to 14 years) with moderate to severe atopic dermatitis.[31-34] All lesional areas, including the face and neck, were treated as necessary. The affected body surface area in these patients ranged from 14 to 62% in adults and 10 to 92% in children. Blood concentrations of pimecrolimus were determined by radioimmunoassay which had a limit of quantification (LoQ) of 0.5 μg/L, or by liquid chromatography in tandem with mass spectrometry (HPLC-MS) which had an LoQ of 0.1 μg/L.[31,33] In addition, the pharmacokinetics of pimecrolimus have been evaluated following single-dose oral administration in healthy subjects,[35] and after multiple-dose oral administration for 4 weeks in adult patients with psoriasis.[36]

3.1 Absorption and Distribution

In adults and children aged ≥3 months with atopic dermatitis who were treated with topical pimecrolimus cream 1.0%, blood concentrations of pimecrolimus were consistently low, regardless of the extent of lesions treated (up to 92% body surface area involved) or duration of therapy (3 weeks to 1 year).[31-34] No systemic accumulation was observed over the treatment period. In 12 adults treated topically for 3 weeks,[31,32] blood concentrations of pimecrolimus were measured at several time-points after the morning application on days 1 to 4, 6, 10 and 17 of treatment and 1 week after treatment had stopped. Blood concentrations of pimecrolimus in 443 of the 444 (99.98%; one sample was contaminated) samples were ≤1.4 μg/L, and 78% were below the assay LoQ (0.5 μg/L). The area under the whole blood concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) ranged from <0.5 to 11.4 μg • h/L.[31]

In 40 adult patients with extensive atopic dermatitis (up to 62% body surface area affected) treated with topical pimecrolimus 1.0% for up to 1 year,[31] blood concentrations of pimecrolimus in 98% of the samples (measured on day 1, weeks 1, 3, and 6, and then monthly up to study completion) were below the assay LoQ (0.5 μg/L). The maximum blood concentration (C_{max}) of pimecrolimus observed during the 1-year treatment period was 0.8 μg/L.

In a study involving 10 children aged 1 to 4 years who received pimecrolimus 1.0% cream twice daily for moderate to severe atopic dermatitis,[33] blood concentrations of pimecrolimus measured on day 4 and day 22 of a 3-week treatment

period ranged from <0.5 μg/L to 1.8 μg/L. More than half of the blood samples (63% of the 63 samples collected) provided pimecrolimus concentrations below the assay LoQ (0.5 μg/L). The average time to the C_{max} (t_{max}) of pimecrolimus was 3.2 hours. $AUC_{(0-12h)}$ values were determined from three patients who had at least three quantifiable concentrations; they ranged from 9.2 to 18.8 μg • h/L (mean = 13 μg • h/L).

In four noncomparative studies which were reported together in an abstract,[34] 58 patients aged 3 months to 14 years with moderate to severe atopic dermatitis (10 to 92% affected body surface area) were treated with pimecrolimus 1.0% cream twice daily for 3 weeks. Two of the studies included a year-long extension phase in which 11 patients continued to receive treatment. Blood samples were collected on day 1 or 4, 10 and 22, and at weeks 27 and 53. In 93% of the samples, the concentration of pimecrolimus was <2 μg/L and 60% were below the assay LoQ (0.5 μg/L); there was no evidence of systemic accumulation. Furthermore, the concentrations were in a range similar to those measured in adults.

The pharmacokinetics of single-dose oral pimecrolimus have been examined in a study presented as an abstract.[35] Healthy volunteers received pimecrolimus 5, 15, 30 or 60mg or placebo (six volunteers in each group received active drug and three received placebo) under fasting conditions. The mean t_{max} across all four treatment groups ranged from 0.7 to 1.4 hours. Proportionality between the dose and the C_{max} of pimecrolimus was observed.

In addition, a study, presented as an abstract and a poster,[36,37] evaluated the pharmacokinetics of multiple-dose oral pimecrolimus. Forty patients with psoriasis received pimecrolimus 5, 10, 20, 40 or 60 mg/day for 4 weeks (eight patients per group). At steady state, both the mean C_{max} and AUC were dose-proportional across the groups. Among patients who received pimecrolimus 60 mg/day, C_{max} and whole-blood $AUC_{(0-24h)}$ values were 54.5 μg/L and 589.8 μg • h/L, respectively.

3.2 Metabolism and Elimination

To date, there are no published data on the metabolism or route of elimination of topical pimecrolimus. However, according to the manufacturer, pimecrolimus is not metabolised or degraded during skin permeation after topical administration.[38] However, after it enters the circulation, it is metabolised via the liver cytochrome P450 3A4 pathway and excreted mainly in the faeces (as shown after oral administration).[39]

The fall in pimecrolimus concentrations after t_{max} was reported to involve three disposition phases with an apparent terminal elimination half-life of about 30 to 40 hours in healthy volunteers receiving 5 to 60mg single oral doses.[35] The mean apparent systemic clearance in the pimecrolimus 30 and 60mg groups was 71 and 91 L/h, respectively, and the apparent volume of distribution was 3452 and 4830L.

4. Therapeutic Efficacy

The therapeutic efficacy of topical pimecrolimus in the management of atopic dermatitis has been evaluated in adults,[40-42] children[43-47] and infants[48,49] in eight randomised, double-blind, vehicle-controlled studies. Two of the studies in children have been reported together in a series of abstracts,[45-47] and a further study in children has been presented in two abstracts.[43,44] The design and patient selection criteria used in these trials are presented in table II.

In a 3-week dose-finding study,[40] the efficacy of topical pimecrolimus 0.05, 0.2, 0.6, 1.0% and betamethasone-17-valerate 0.1% creams were compared, whereas in the seven other studies,[41-49] a treatment regimen based on topical pimecrolimus 1.0% cream was compared with a control treatment (e.g. vehicle or a conventional treatment) for 3 weeks to 1 year. In three studies,[42-44,48] patients in both treatment groups were able to receive emollients for skin care and treatment with medium potency corticosteroids for eczematous flares not controlled by study medication [i.e. an Investigator's Global Assessment (IGA) score of 4 (severe)

Table II. Study design and criteria for patient selection in studies of pimecrolimus in adults and children with atopic dermatitis

In adults
Study design
Randomised, double-blind, parallel group, vehicle-controlled, multicentre, dose-finding[40]
Randomised, double-blind, vehicle-controlled, right-and-left arm comparison, proof-of-concept[41]
Randomised, double-blind, parallel group, vehicle-controlled, multicentre (available as an abstract)[42]
Primary outcome measures
Eczema Area and Severity Index (EASI) total score and assessment of pruritus[40]
Patient assessment of improvement of atopic dermatitis[40]
Atopic Dermatitis Severity Index total score[41]
Percentage of days of topical corticosteroid use[42]
Inclusion criteria
Outpatients aged ≥18 years[40,41]
Atopic dermatitis affecting ≥1%[41] or between 5 and 30%[40] of body surface area
Patients with moderate to severe atopic dermatitis[42]
Exclusion criteria
Radiation therapy or systemic therapy with cytostatics or immunosuppressants within 24 weeks[41]
Phototherapy or systemic therapy for atopic dermatitis within 1 month[41]
Antibacterials or topical therapy for atopic dermatitis within 2 weeks[41]
Any treatment for atopic dermatitis or use of inhaled or oral corticosteroids during the study[40]
Not reported in abstract[42]
In infants and children (all studies were reported as abstracts)
Study design
Randomised, double-blind, parallel group, vehicle-controlled, multicentre[43-49]
Primary outcome measures
EASI total score and assessment of pruritus[45,49]
Investigator's Global Assessment[45,49]
Patient assessment of improvement of atopic dermatitis[45]
Incidence of flares observed over 6 months[43,44,48]
Inclusion criteria
Patients aged 2 to 17 years with mild to moderate atopic dermatitis[43-45]
Patients aged between 3 and 23 months with mild to moderate[49] or mild to very severe[48] atopic dermatitis
Exclusion criteria
Not reported in abstract[43-45,48,49]

or 5 (very severe)]. Following the use of corticosteroids, study medication was resumed. Application of the vehicle was used to maintain blinding.

The composition of the vehicle used in the trials was not reported; however, the cream base of the commercial preparation of pimecrolimus contains benzyl alcohol, cetyl alcohol, citric acid, mono-, di- and and triglycerides, oleyl alcohol, propylene glycol, sodium sulphate, sodium hydroxide, stearyl alcohol and water.[38]

Primary outcome measures included reductions from baseline on the Eczema Area and Severity Index (EASI, see table III for description),[50] the Atopic Dermatitis Severity Index (ADSI), an IGA [an evaluation of the extent of dermatitis utilising a 6-point scale ranging from 0 (clear) to 5 (very severe)], an assessment of the severity of pruritus, patient-assessment of improvement of dermatitis and the incidence of eczematous flares (table II). In the two fully published studies in adult patients, efficacy analysis was performed on an intention-to-treat basis.[40,41]

There have also been three preliminary studies evaluating the efficacy of oral and topical formulations of pimecrolimus in patients with chronic psoriasis,[51-53] and a further small trial with the

cream formulation in patients with chronic irritant hand dermatitis;[54] only one of these trials has been published in full.[51] However, it is beyond the scope of this review to discuss these studies further.

4.1 In Adults with Atopic Dermatitis

The efficacy of topical pimecrolimus in adult patients with atopic dermatitis has been evaluated in three randomised, double-blind, controlled trials.[40-42] Compared with vehicle or a conventional treatment, all studies demonstrated a significant improvement in symptoms of atopic dermatitis after the topical administration of pimecrolimus 1.0% cream.

Topical pimecrolimus 1.0% cream was more effective than vehicle in a double-blind, right-and-left arm comparison, proof-of-concept study.[41] 34 adult patients with atopic dermatitis (≥1% of body surface area affected on both arms), as defined by the criteria of Hanifin and Rajka,[55] were randomised to receive pimecrolimus 1.0% cream or vehicle once or twice daily for 3 weeks on two target areas. The severity of atopic dermatitis was assessed using the ADSI (score range 0-15, increasing in severity) which consists of the sum of the scores for pruritus, erythema, exudation, excoriation and lichenification (each scored on a 4-point scale from 0 to 3). Efficacy was evaluated three times per week.[41]

The group that received pimecrolimus twice daily (n = 16) showed a 71.9% mean reduction in the ADSI score at endpoint, compared with a mean reduction of 10.3% at vehicle-treated sites ($p < 0.001$).[41] Furthermore, pimecrolimus demonstrated a significant therapeutic effect by day 2 compared with vehicle (a reduction in the ADSI score of 18.5% compared with a 1.5% increase, respectively, $p = 0.008$). All the individual components of the ADSI were improved with pimecrolimus (exudation was minimal at baseline in all patients; see figure 3).

The drug showed considerably less efficacy in patients who were treated once daily (n = 18) than in those treated twice daily (figure 3, table IV).[41] At sites treated with pimecrolimus once daily, the mean percentage reduction from baseline to endpoint in the ADSI total score was 37.7%, compared with 6.2% at sites treated with vehicle once daily ($p = 0.002$).

In a multicentre, dose-finding study, a clear dose response was evident, with pimecrolimus 0.2, 0.6 and 1.0% creams being more effective than vehicle in reducing symptoms of atopic dermatitis (table V).[40] 260 patients aged between 18 and 71 years with mild to severe atopic dermatitis (i.e. 5 to 30% of body surface area affected), as defined by the criteria of Rajka and Langeland,[56] were randomised to receive pimecrolimus 0.05, 0.2, 0.6 or 1.0% cream, vehicle or betamethasone-17-

Table III. The Eczema Area and Severity Index (EASI)[50]

The EASI is calculated using regional body surface area tabulation. In patients ≥8 years of age, the head and neck, upper extremities, trunk and lower extremities are assigned proportionate body surface areas of 10, 20, 30 and 40%, respectively. In patients aged <8 years, the corresponding proportions are assigned 20, 20, 30 and 30%	
The affected area within each body region is estimated as a percentage of the total area of that particular body region, and is subsequently assigned a proportional score ranging from 0 to 6: 0 = no eruption, 1 = <10%, 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89%, 6 = 90-100%	
The key signs of inflammation are defined as erythema (E), induration/papulation (I), excoriation (Ex) and lichenification (L), and each are assigned a degree of severity ranging from 0 to 3 with half steps allowed (0 = none, 1 = mild, 2 = moderate and 3 = severe)	
In patients aged ≥8 years, the EASI is then calculated as below. For patients <8 years of age, the multiplication factor used is as described above	
Head/Neck	(E + I + Ex + L) x Area x 0.1
Upper extremities	(E + I + Ex + L) x Area x 0.2
Trunk	(E + I + Ex + L) x Area x 0.3
Lower extremities	(E + I + Ex + L) x Area x 0.4
EASI	Sum of the above scores (the EASI score can range from 0 to 72)

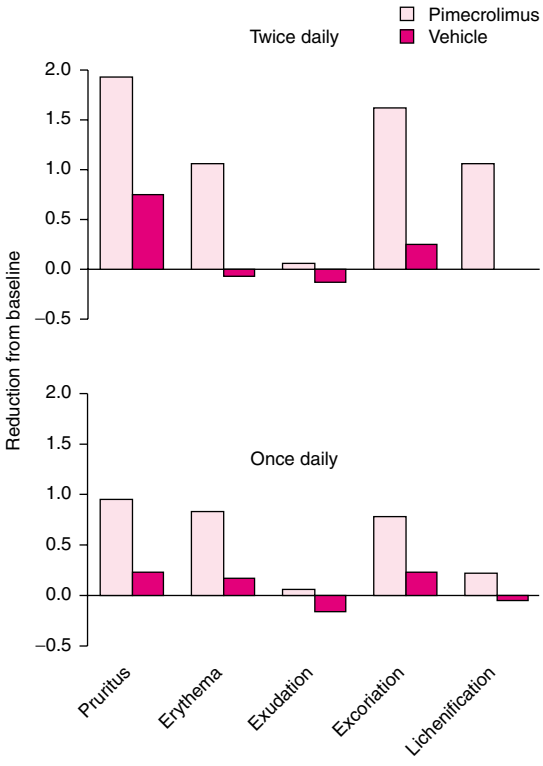

Fig. 3. Efficacy of topical pimecrolimus 1.0% cream in the treatment of mild to moderate atopic dermatitis. Reductions from baseline of the individual components of the Atopic Dermatitis Severity Index in 34 adult patients with mild to moderate atopic dermatitis receiving topical pimecrolimus 1.0% cream or vehicle applied once or twice daily for 3 weeks in a randomised, double-blind, vehicle-controlled right-and-left-arm comparison study. Exudation was minimal at baseline in all patients. Statistical analysis was not reported. [41]

valerate 0.1% cream for up to 3 weeks. Study medications were applied twice daily to all affected areas except the head and neck, and the extent of dermatitis was evaluated on days 1, 8, 15 and 22 using a modified EASI[57] (which took into account the head not being treated).

Whereas pimecrolimus 0.2, 0.6 and 1.0% creams were significantly ($p < 0.05$) more effective than vehicle at reducing total EASI scores (table V), pimecrolimus 0.05% did not demonstrate a significant therapeutic effect; efficacy was dose dependent. Pimecrolimus 1.0% cream showed the greatest efficacy among the pimecrolimus creams (median change from baseline of 47% on the EASI; table V). Figure 4 illustrates the effects of pimecrolimus 1.0%, betamethasone-17-valerate 0.1% or vehicle on EASI scores in patients with mild, moderate or severe atopic dermatitis, stratified by baseline EASI scores. Patients in the pimecrolimus 1.0% group with mild to moderate atopic dermatitis at baseline had an approximately 50% reduction in EASI scores, and pimecrolimus recipients with severe atopic dermatitis experienced a median 37.9% reduction (figure 4).[40]

Pimecrolimus 0.6 and 1.0% and betamethasone-17-valerate 0.1% creams were also associated with a significant improvement in pruritus compared with vehicle (table V).[40] Among the 45 patients randomised to pimecrolimus 1.0%, three (6.7%) had absent or mild pruritus (a score of 0 or 1, respectively, out of a possible score of 3) at baseline. By day 8, 18 (40%) patients had a score of 0 or 1 ($p = 0.008$ *vs* vehicle). At endpoint, 21 (46.7%) patients had mild or absent pruritus ($p = 0.007$ *vs* vehicle). Although the efficacy of pimecrolimus 0.6% was not significantly different to vehicle at day 8, 52.4% of patients had absent or mild pruritus at endpoint ($p = 0.001$ *vs* vehicle). Pimecrolimus 1.0% cream was subsequently further evaluated in adults, children and infants with atopic dermatitis.

Compared with vehicle, topical pimecrolimus 1.0% significantly ($p < 0.001$) reduced the incidence of eczematous flares and the need for rescue treatment with topical corticosteroids in a double-blind trial, presented as an abstract, in 192 adults with moderate to severe atopic dermatitis.[42] This 24-week study compared the efficacy of a treatment regimen based on pimecrolimus 1.0% cream with that of a conventional therapy (emollients plus reactive use of topical corticosteroids). Patients were randomised to receive pimecrolimus 1.0% cream or corresponding vehicle. Study medication (i.e. pimecrolimus or vehicle) was to be applied twice daily at the first signs or symptoms of atopic dermatitis and continued until clearance. All patients could use emollients for dry skin, and could receive rescue treatment with a medium potency topical corticosteroid (prednicarbate 0.25%) for

eczematous flares not controlled by study medication. If the use of prednicarbate was required, it was applied twice daily for 7 days and then once daily for a further 7 days. Following corticosteroid use, study medication was applied for 1 week for residual disease. Primary efficacy analysis involved the percentage of days that prednicarbate was used. Efficacy was also assessed at week 24 using the EASI instrument and an assessment of the severity of pruritus.

Among patients in the pimecrolimus group, 14.8% were treated with prednicarbate, compared with 37.3% of patients in the control group ($p < 0.001$).[42] This result was attributable to the significantly lower mean number of disease flares per patient in the pimecrolimus group (1.2 flares) compared with patients in the control group (2.6 flares, $p < 0.001$).

Reductions in both the total EASI scores and the severity of pruritus were significantly higher in the pimecrolimus group compared with the control group ($p < 0.001$ for both comparisons). At week 24, the mean decrease in the EASI score among patients in the pimecrolimus group was 5.5, compared with a decrease of 2.0 in patients in the control group (baseline scores were not reported). 58.3% of patients in the control group had mild or no pruritus at week 24, compared with 36.5% of patients in the control group.[42]

4.2 In Infants and Children with Atopic Dermatitis

Topical pimecrolimus was effective at treating predominantly moderate atopic dermatitis in children aged 3 months to 17 years in five randomised, double-blind, vehicle-controlled, multicentre trials, all of which have been presented as abstracts.[43-49] Two of the studies in children were reported together in a series of abstracts,[45-47] and a further study has been reported in two abstracts.[43,44]

4.2.1 In Infants Aged 3 to 23 Months

Pimecrolimus 1.0% cream was effective in treating mild to very severe atopic dermatitis (the majority of patients had moderate disease) in infants aged 3 to 23 months in two trials.[48,49] In both studies, patients were randomised to receive pimecrolimus or vehicle. In the 1-year study by Kapp et al,[48] all patients were able to use emollients for skin care and medium potency topical corticosteroids for eczematous flares not controlled by study medication (i.e. a conventional therapy for atopic dermatitis in the control group).

In the study by Ho et al,[49] 186 infants with mild to moderate atopic dermatitis were randomised 2:1 to receive pimecrolimus 1.0% (n = 123) or vehicle (n = 63) twice daily for up to 6 weeks. Primary efficacy analysis involved reductions in the total EASI and IGA scores at week 6, and an assessment of the severity of pruritus. Following this 6-week phase, all patients received pimecrolimus 1.0% twice daily for 20 weeks. In the other study,[48] 251 infants with mild to very severe atopic dermatitis (the majority of patients had mild to moderate disease) were randomised 4:1 to receive pimecrolimus 1.0% or vehicle. Study medication was applied twice daily for up to 1 year to treat the first signs or symptoms of atopic dermatitis and continued until clearance. The primary efficacy variable was the incidence of eczematous flares in the first 6 months of treatment.

Of the 186 patients enrolled in the 6-week study, 109 of 123 (89%) patients in the pimecrolimus group completed treatment, compared with 33 of

Table IV. Efficacy of pimecrolimus 1.0% cream (PIM) in 34 adult patients with atopic dermatitis; results of a 3-week randomised, double-blind, vehicle-controlled trial[41]

Treatment frequency	No. of patients	Mean baseline ADSI score		Results at endpoint (% reduction in mean ADSI scores)	
		area treated with PIM	area treated with VEH	area treated with PIM	area treated with VEH
Twice daily	16	8.06	8.13	71.9**	10.3
Once daily	18	7.72	7.78	37.7*	6.2

ADSI = Atopic Dermatitis Severity Index; **VEH** = vehicle; * $p = 0.002$, ** $p < 0.001$ *vs* vehicle.

Table V. Efficacy of pimecrolimus (PIM) creams in 260 adult patients with atopic dermatitis; results from a randomised, double-blind, vehicle-controlled, multicentre trial[40]

Treatment[a]	No. of patients	Mean baseline EASI score	Patients with absent or mild pruritus at baseline (%)	Results at endpoint		
				median reduction from baseline in EASI scores (%)[b]	patients with absent or mild pruritus (%)	patients who discontinued treatment because of lack of therapeutic efficacy (%)
PIM 0.05%	42	12.37	4.8	0	23.8	26.2
PIM 0.2%	46	11.16	8.7	16*	37.0	15.2
PIM 0.6%	42	11.49	11.9	35***	52.4***	9.5
PIM 1.0%	45	11.28	6.7	47**	46.7**	4.4
VEH	43	10.12	4.7	0	18.6	25.6
BMV 0.1%	42	10.28	11.9	79[c]	81.0***	0

a Treatment was given twice daily for up to 3 weeks.

b Values estimated from a graph.

c Statistical significance not reported

BMV = betamethasone-17-valerate cream; **EASI** = Eczema Area and Severity Index; **VEH** = vehicle; * $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ *vs* vehicle.

63 (52%) in the vehicle group.[49] Significantly more pimecrolimus-treated patients (54.5%) were clear or almost clear (IGA scores of 0 or 1, respectively) of atopic dermatitis at week 6 than vehicle recipients (23.8%, $p < 0.001$). Patients in the pimecrolimus group had a 61.8% mean reduction in the total EASI score at week 6, compared with an increase of 7.35% among patients in the vehicle group. Significantly more patients in the pimecrolimus group than the vehicle group had minimal or no pruritus after 6 weeks (72.4 *vs* 33.3%, $p < 0.001$). Although quantitative data were not presented in the abstract, it was reported that long-term control of atopic dermatitis was achieved during the 20-week extension phase and that continuous improvement was observed across all measures.[49]

Compared with patients in the vehicle group, the incidence of eczematous flares was significantly ($p < 0.001$) lower in the pimecrolimus group in the first 6 months of the 1-year study involving 251 infants.[48] 70% of patients in the pimecrolimus group completed 6 months of treatment without experiencing a flare, compared with 33% of the patients in the control group. Furthermore, the mean number of days that patients in the control group were treated with corticosteroids was approximately twice that in the pimecrolimus group ($p < 0.001$).[48]

4.2.2 In Children Aged 2 to 17 years

Pimecrolimus 1.0% cream was effective in treating mild to very severe atopic dermatitis (the majority of patients had moderate disease) in children aged 2 to 17 years in three randomised, double-blind, vehicle-controlled, multicentre studies,[43-47] two of which were reported together in a series of abstracts,[45-47] and one of which has been presented in two abstracts.[43,44] In all studies, patients were randomised to receive pimecrolimus 1.0% cream or vehicle. In the 1-year study by Wahn et al.,[43,44] as in the study in infants described in section 4.2.1,[48] all patients could use emollients for skin care and medium potency topical corticosteroids for eczematous flares not controlled by study medication (i.e. a conventional therapy for atopic dermatitis in the control group).[43]

In the large study by Wahn et al.,[43,44] 713 patients aged 2 to 17 years with mild to moderate atopic dermatitis were randomised 2:1 to receive pimecrolimus or vehicle. Twice-daily treatment was to commence at the first signs or symptoms of atopic dermatitis and to continue until clearance. The primary efficacy variable was the incidence of eczematous flares in the first 6 months, adjusted for discontinuations. In the two studies reported together in a series of abstracts,[45-47] 403 patients aged 2 to 17 years with mild to moderate atopic dermatitis (≥5% affected body surface area) re-

ceived pimecrolimus 1.0% cream (n = 267) or vehicle (n = 136) twice daily for 6 weeks. Following this 6-week double-blind phase, patients were enrolled in a 20-week open-label, noncomparative, extension phase.[47] Efficacy was assessed at week 6 using the EASI instrument, IGA, an assessment of pruritus, and self-assessment by the patient, all of which were carried out on days 1, 8, 15, 22, 27 and 43. The effect of treatment on the quality-of-life of the patients aged between 2 and 8 years was also determined at week 6 using a health-related quality-of-life index (the Parent's Index of Quality of Life-Atopic Dermatitis) score ranging from 0 to 28, with a high score indicating poor quality-of-life.[46] This index was designed to be completed by the parents of the patients and was performed on an intention-to-treat basis.

Of the 403 patients enrolled in the 26-week studies, 236 of 267 (88.4%) patients in the pimecrolimus group completed the 6-week double-blind treatment phase, compared with 102 of the 136 (75%) patients in the vehicle group.[45] Compared with the vehicle group, median reductions in the EASI total score were greater in the pimecrolimus group. After 6 weeks, the median reduction of the EASI total score was 59% in the pimecrolimus group, compared with 14% in the vehicle group. The proportion of patients with clear or almost clear (IGA = 0 or 1, respectively) dermatitis at endpoint was 35% in pimecrolimus recipients and 18% in patients who received vehicle ($p < 0.001$). Furthermore, significantly more patients in the pimecrolimus group had mild or no pruritus at endpoint and rated pimecrolimus better at disease control than vehicle ($p < 0.001$; actual values not reported). A therapeutic effect was observed at day 8 in all assessments and improved with further treatment. Although actual data were not reported, the treatment effect was maintained during the 20-week, open-label, noncomparative phase of the study, and patients who were switched to pimecrolimus from vehicle had a rapid treatment response similar to that of patients treated with pimecrolimus during the 6-week double-blind phase.[47]

After 6 weeks, quality-of-life scores were available for 193 of the 403 patients: 132 and 61 pimecrolimus and vehicle recipients, respectively.[46] Although quantitative data were not reported in the abstract, both groups experienced a significant improvement in quality-of-life ($p < 0.001$ and < 0.05 versus baseline for pimecrolimus and vehicle recipients, respectively); the combined-group mean baseline score of 9.2 was reduced to 6.6 at week 6. However, it was stated that there was a significantly greater improvement in the pimecrolimus group than in the vehicle group ($p < 0.05$).[46]

The incidence of eczematous flares was significantly ($p < 0.001$) lower in the pimecrolimus group than in the control group during the first 6 months of the 1-year study involving 713 children aged between 2 and 17 years with predominantly moderate atopic dermatitis.[43,44] At the sixth month, 60% of pimecrolimus-treated patients remained free of flares, compared with 35% of the control group ($p < 0.001$); corresponding values after 12

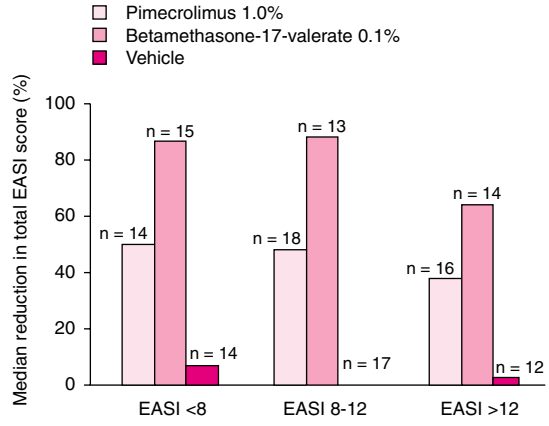

Fig. 4. Efficacy of topical pimecrolimus 1.0% and betamethasone-17-valerate 0.1% creams or vehicle in adult patients with mild to severe atopic dermatitis. Reductions from baseline in total Eczema Area and Severity Index (EASI) scores in patients with mild (EASI <8), moderate (8≤ EASI ≤12), or severe (EASI >12) atopic dermatitis. Patients were treated with topical pimecrolimus 1.0%, betamethasone-17-valerate 0.1% or vehicle twice daily for 6 weeks in a randomised, double-blind, multicentre, dose-finding study. Statistical analysis was not reported.[40]

months were 51 and 28%. Furthermore, 57 and 32% of patients in the pimecrolimus and control groups, respectively, completed the study without treatment with corticosteroids, and the time to first use of topical corticosteroids was significantly longer in the pimecrolimus group than in the control group ($p < 0.001$; quantitative data were not reported in the abstract).[43,44]

5. Tolerability

Evidence to date indicates that pimecrolimus is well tolerated in patients of all age groups (infants aged 3 to 23 months, children aged 2 to 17 years and adults) with atopic dermatitis, with no clinically relevant systemic adverse events reported from any of the efficacy studies.[40-49] However, all five of the clinical studies in infants or children with atopic dermatitis have so far been published only as abstracts, with limited tolerability data.

Among the most frequently reported adverse events during treatment with pimecrolimus 1.0% cream were application site reactions, such as burning and a feeling of warmth, which occurred in 8 to 26% of all patients.[38]

In a short-term study involving 34 adult patients with atopic dermatitis, there were no reports of skin irritation or other application site adverse events after application of pimecrolimus 1.0% cream or vehicle for 3 weeks.[41] Furthermore, there were no clinically significant treatment-related changes in patient laboratory values (haematological examination, clinical chemistry studies and urinalysis) in either trial.[40,41] However, according to the manufacturer,[38] the incidence of application site burning among 328 adults who received pimecrolimus 1.0% cream for 1 year was 25.9%.

There were no significant between-group differences in the incidence of adverse events among 192 adult patients with moderate to severe atopic dermatitis who received pimecrolimus 1.0% or vehicle twice daily according to need for up to 1 year.[42]

The incidence or description of adverse events were not reported in the two studies involving a total of 437 patients aged between 3 and 23 months with atopic dermatitis.[48,49] However, in the trial involving 251 infants randomised to topical pimecrolimus 1.0% cream or vehicle for 1 year, there was no significant between-group difference in the incidence of adverse events.[48]

In two studies involving 403 children aged between 2 and 17 years, 3.2% discontinued treatment prematurely because of adverse events (whether related to treatment or not).[47] 10.4 and 12.5% of pimecrolimus and vehicle recipients, respectively, reported application site burning;[38] there were no clinically relevant systemic adverse events.[45] Although the incidence was low (≈5%), there were reports of skin infection among the 335 patients who completed the 6-week study and entered the 20-week extension phase during which they were treated with pimecrolimus 1.0% cream. The following infections were observed: molluscum contagiosum (1.2%), herpes simplex (1.2%), varicella/chickenpox (0.9%), folliculitis (0.9%), skin papilloma (0.6%) and herpes simplex dermatitis/eczema herpeticum (0.3%).[38,47] Furthermore, among these patients, the incidence of application site burning was only 1.5%.[38]

Results from the 1-year study in 713 children (aged 2 to 17 years) with atopic dermatitis demonstrated no significant between-group differences at month 12 in the frequency of positive antigens in the recall-antigen test; 73% of patients in the pimecrolimus group had more than one positive antigen, compared with 67% of the control group.[44]

Because the majority of studies examining the efficacy and tolerability of pimecrolimus 1.0% cream have not yet been published in full detail, data concerning its long-term tolerability are lacking. However, figure 5 illustrates the incidence of adverse events (whether or not related to study medication) that occurred in ≥10% of 711 patients aged 2 to 17 years with mild to moderate atopic dermatitis who received a regimen based on topical pimecrolimus 1.0% or a conventional treatment for up to 1 year, according to the manufacturer.[39]

6. Dosage and Administration

Pimecrolimus 1.0% has been approved in the US for the short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥2 years who do not respond well to, or may have adverse effects with, conventional treatments. The following information has been taken from the US prescribing information.[38]

Pimecrolimus 1.0% cream is applied twice daily to affected skin as a thin layer and rubbed in gently and completely; it can be applied to all affected areas, including the head, neck and intertriginous areas. The drug should be used for as long as signs and symptoms persist. If disease resolution occurs, treatment should be stopped; if symptoms persist beyond 6 weeks, the patient should be re-evaluated. [38]

Although the effects of renal or hepatic insufficiency on the pharmacokinetics of topically administered pimecrolimus have not been evaluated, the manufacturer advises that a change in dosage is not required because of the low systemic exposure of the drug after topical administration.[38]

Pimecrolimus should not be applied to areas of active cutaneous viral infection. Furthermore, because pimecrolimus may be associated with an increased risk of varicella zoster virus infection, herpes simplex virus infection or eczema herpeticum, the use of the drug in the presence of these infections is cautioned.[38]

There are insufficient data concerning the use of topical pimecrolimus during pregnancy and,

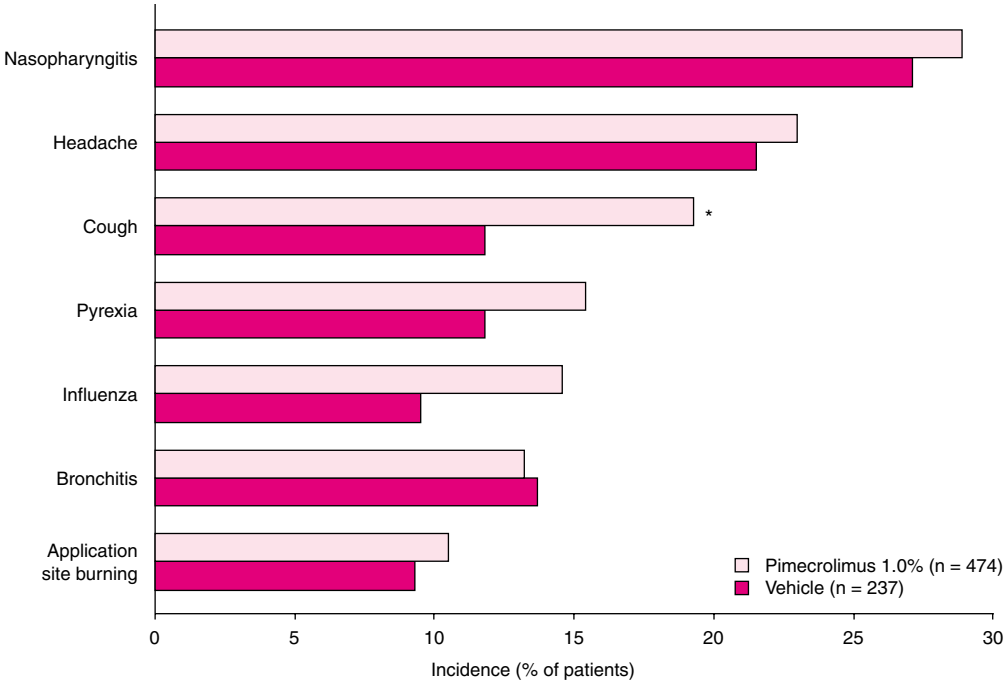

Fig. 5. Long-term tolerability of topical pimecrolimus 1.0% in children aged 2 to 17 years with mild to moderate atopic dermatitis. The incidence of adverse events in 711 paediatric patients who were randomised to receive pimecrolimus 1.0% cream or vehicle for up to 1 year. All patients could use emollients for skin care and medium potency topical corticosteroids for eczematous flares not controlled by study medication. Adverse events presented (whether related to treatment or not) occurred in ≥10% of pimecrolimus recipients. * p = 0.045 *vs* vehicle.[39]

therefore, it should only be used when the benefits to the mother outweigh the risks to the fetus. It is also not known if pimecrolimus is excreted in human milk; therefore, a decision should be made whether to discontinue nursing or to discontinue the drug.[38]

7. Place of Pimecrolimus in the Management of Atopic Dermatitis

Atopic dermatitis, a chronic or relapsing eczematous disease characterised by intense pruritus, is a common disease with a lifetime prevalence of about 15 to 20%,[1,58] a prevalence that has been increasing over the last half century.[59] Often referred to as atopic eczema, atopic dermatitis primarily manifests during early childhood, with between 10 and 15% of the world's children thought to be affected.[59,60] Although signs and symptoms of atopic dermatitis often clear during adolescence and early adulthood, they can persist throughout a patient's lifetime.[58] However, diagnosis of atopic dermatitis is difficult because symptoms are not always present and, when they are, their appearance varies. In 1980, Hanifin and Rajka defined the major and minor criteria for the diagnosis of atopic dermatitis in the general population;[55] since then, further refinements have been made to assist diagnoses in children and infants.[61,62]

The development of atopic dermatitis in an individual results from both inherited genetic susceptibility and exposure to environmental factors.[58,63] The recent increase in prevalence suggests that changes in our environment are a major factor in the manifestation of atopic dermatitis. Furthermore, there is a large worldwide variation in this prevalence, even among populations with a common genetic heritage.[64] Consequently, the role of environmental factors such as irritants, foods, aeroallergens and infection, especially with *Staphylococcus aureus*, has been receiving increasing interest.[63-67]

Atopic dermatitis can have a profoundly negative effect on the lives of affected infants, children and adults, and can have major secondary effects on the families of those with the disease.[68,69] The quality of life of a child with atopic dermatitis can be impaired because of disruption of family or social relationships and limited participation in play, sports and school. These factors can lead to environmental, social and emotional deprivation, and can cause delayed academic achievement.[69] Furthermore, the quality of life of the parents of affected infants and children can be impaired because of the stress involved in caring for the child. In addition to the emotional burden of caring for a child with atopic dermatitis, this stress has been attributed to the financial costs associated with care for the child, nightly sleep interruption, time missed from work for hospital visits or care at home and lost wages due to interruption of employment.[69]

The management of atopic dermatitis involves the minimisation of exacerbating factors as well as the use of therapeutic measures when necessary. Taking proper care of the skin can result in effective control of the disease in many patients. Frequent bathing in lukewarm water for at least 20 minutes to hydrate the skin, followed by the application of an emollient within 3 minutes of getting out of the bath to maintain hydration, is the standard initial therapy for atopic dermatitis.[2,70] Lesions develop when the skin is scratched,[71] therefore the avoidance of itch-inducing irritants is an essential part of the management of atopic dermatitis.[2] Furthermore, thermal, emotional and gustatory sweating can trigger itching.[70] Patient education concerning their damaging scratching behaviour, along with alternative methods of relieving itch (such as pinching the itch until the sensation goes away) can also produce positive results.[72]

Oral antihistamines are often used to relieve pruritus in patients with atopic dermatitis, and the anxiolytic effects of some antihistamines may offer symptomatic relief through their tranquilising and sedative effects.[73] However, histamine is only one of a number of mediators that can induce pruritus of the skin and, therefore, antihistamines are not always effective at relieving itch. The avoidance of allergens, emotional stressors and infectious agents

(particularly *S. aureus*[74]) is also important.[61] In patients refractory to first-line measures, treatment with anti-inflammatory or immunomodulatory agents is necessary.

Although there is currently no cure for atopic dermatitis, there are a number of options available for controlling the disease; topical corticosteroids are the most commonly used agents. The potency of these agents varies and, generally, a greater therapeutic efficacy is associated with an increased risk for adverse events. Furthermore, because atopic dermatitis is an aggressive inflammatory disease requiring an aggressive treatment regimen, the risk for systemic adverse events is increased with chronic corticosteroid use. However, corticosteroids remain the most effective form of treatment for atopic dermatitis, although a balance between efficacy and risk must be found. Adverse events associated with topical corticosteroid use include skin atrophy, depigmentation, steroid acne, telangiectasia and, rarely, suppression of the hypothalamic-pituitary-adrenal axis.[58,60] Because atopic dermatitis predominantly affects children, and symptoms often persist for an extended period of time, selection of corticosteroid therapy is more complicated than that for the treatment of some other dermatological diseases (e.g. psoriasis, pityriasis, neurodermatitis).[58] As such, topical corticosteroids of low potency (e.g. hydrocortisone cream) are usually used in infants and children; the more potent corticosteroids (e.g. betamethasone-17-valerate cream) are more often used for treating adults. The use of potent fluorinated corticosteroids should be avoided on the face, the genitalia and the intertriginous areas, and their use should be limited to short periods to avoid systemic absorption. According to US guidelines issued in 1997,[73] the use of emollients and low potency topical corticosteroids may be required to achieve the goals of treatment, which include enhancement of skin hydration and relief of symptoms of atopic dermatitis.

In a few patients with atopic dermatitis refractory to topical treatment, systemic treatments including oral corticosteroids and, rarely, systemic immunosuppressants (e.g. cyclosporin) may be required to manage the disease. Systemic treatment is associated with potentially severe adverse effects and is not recommended except as a last resort.[8,58,70,73] Topical immunomodulators have recently been developed for the treatment of atopic dermatitis.[75,76] Tacrolimus ointment has been approved in the US for the treatment of moderate to severe atopic dermatitis in patients aged ≥2 years.[77,78] However, the efficacy and tolerability of tacrolimus has not been established in patients aged <2 years.[79]

Topical pimecrolimus cream has proved effective in the treatment of atopic dermatitis in infants, children and adults in eight randomised, double-blind trials (section 4). Adult patients with mild to severe atopic dermatitis experienced a significant improvement in symptoms of the disease after treatment with pimecrolimus 1.0% cream for 3 weeks to 1 year in three studies. In a dose-finding study, pimecrolimus 1.0% cream applied twice daily was the most effective concentration at reducing total EASI scores (section 4.1), when compared with vehicle. Furthermore, compared with vehicle, long-term use (up to 1 year) of pimecrolimus 1.0% cream significantly reduced the incidence of eczematous flares and the need for rescue treatment with topical corticosteroids in a double-blind trial in 192 adults with moderate to severe atopic dermatitis.

Among patients aged 3 months to 17 years, treatment with topical pimecrolimus 1.0% cream (applied at the first signs or symptoms of disease until they cleared) for up to 1 year was effective at improving signs and symptoms of atopic dermatitis, as assessed by the EASI and IGA instruments (section 4.2). In two long-term studies (1 year) involving infants or children with predominantly moderate atopic dermatitis, topical corticosteroids were used to treat eczematous flares not controlled by study medication (pimecrolimus 1.0% cream or corresponding vehicle). In both studies, topical corticosteroids were used approximately twice as often in the control groups than in the pimecrolimus groups ($p < 0.001$ in both studies). Fur-

thermore, the severity of pruritus in infants and children was significantly reduced by pimecrolimus compared with vehicle or conventional therapy (section 4.2).

Pimecrolimus is well tolerated in patients with mild to very severe atopic dermatitis of all age groups (patients aged between 3 months and 62 years; section 5); however, six of the eight efficacy trials were reported as abstracts and, therefore, tolerability data are limited. The most frequently reported adverse events pertained to application site reactions, such as burning and a feeling of warmth; however, the majority of reactions were transient and of mild to moderate severity. There were no reports of clinically relevant systemic adverse events. In pharmacokinetic studies, blood concentrations of pimecrolimus in patients of all age groups were invariably <2 μg/L; the majority of blood concentrations of pimecrolimus were below the assay LoQ (section 3). About 3% of infants or children with atopic dermatitis treated with pimecrolimus 1.0% discontinued treatment prematurely because of adverse events (section 5).

Topical pimecrolimus has shown no potential for skin atrophy in any of the studies in patients with atopic dermatitis. Furthermore, a study in 16 healthy volunteers (with normal skin) demonstrated that 4 weeks of treatment with topical pimecrolimus 1.0% or vehicle resulted in no significant between-group differences in relative skin thickness (section 2.3). Conversely, treatment with the topical corticosteroids betamethasone-17-valerate 0.1% or triamcinolone acetonide 0.1% resulted in a significant reduction in skin thickness when compared with pimecrolimus.

Studies comparing tacrolimus ointment with pimecrolimus cream have not been conducted. Such studies would be beneficial in allowing the place of pimecrolimus to be more accurately determined.

In conclusion, topical pimecrolimus 1.0% cream has shown efficacy in the treatment of mild to moderate atopic dermatitis in infants, children and adults. Although tolerability data concerning infants and children have not yet been published in full, the drug appears to be well tolerated in all age groups, and there have been no reports of clinically relevant systemic adverse events. Furthermore, pimecrolimus 1.0% cream has shown no potential for skin atrophy, a problem commonly associated with treatment with topical corticosteroids. Pimecrolimus 1.0% cream provides a promising and well tolerated treatment option in the management of infants, children and adults with mild to moderate atopic dermatitis.

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