



Pimecrolimus for the treatment of atopic dermatitis

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Atopic dermatitis is a chronic inflammatory skin disease which runs periods of exacerbations and remissions. The calcineurin inhibitor pimecrolimus – an immunomodulatory macrolactam – is a cell-selective inhibitor of inflammatory cytokines specifically developed to treat inflammatory skin diseases. In this article the currently available data on pharmacology, clinical efficacy and safety are reviewed. In several short and long-term studies on children and adults with AD, most patients showed an improvement of their eczema, paralleled by a rapid relief of pruritus. Moreover, pimecrolimus reduced the incidence of flares and the need for corticosteroids in children and adults. Pimecrolimus has a favourable safety profile. In several pharmacokinetic studies, the topical application of pimecrolimus did not lead to significant blood levels in children and adults. Symptoms of irritation such as burning, erythema and pruritus may occur in the first days. A significant increase of skin infections or systemic infections was not observed, though the incidence of viral skin infections tended to increase slightly. Thus, pimecrolimus may represent an alternative compound to the topical corticosteroids for the treatment of atopic dermatitis.

Atopic dermatitis (AD) is a chronic inflammatory skin disease which often begins in infancy and runs a course of remissions and exacerbations. Eczematous skin lesions, dry skin, pruritus and sleeplessness are characteristics of AD [1], thus leading to a restriction in daily activities and influencing achievements at school and professional life. AD is a disease occurring predominantly in childhood with 85% of affected children presenting the first lesions by the age of 5 years [2]. Besides the social burden, the economical burden is of considerable importance for the community [3].

In atopic dermatitis, eczematous patch test lesions and spontaneous lesions are dominated by CD4⁺ T-helper cells. Mononuclear cells and eosinophil granulocytes can be found mainly in the dermis [4,5], Langerhans' cells (LCs) with specific immunoglobulin (Ig)E bound to Fcε-RI on their surface in the epidermis [6,7]. It is now widely accepted that the T-helper (Th)2-like cytokine interleukin (IL)-4 plays a role in the initial phase of cutaneous inflammation, whereas the Th1-like cytokine interferon (IFN)-γ predominates in chronic lesions in AD [8,9].

An abundance of trigger factors have been identified for AD over the last decades. Whereas food allergens are major provocation factors for the flares of AD in infancy, inhalant allergens are of greater importance in adults [10–12].

Cutaneous infections are frequent complications in patients with AD. In a prospective study

of 190 children with the disease studied over a period of 2 and a half years, 40% had episodes of bacterial infection [13]. Over the last few years, *Staphylococcus aureus* has been identified as an important trigger factor of AD, and staphylococcal exotoxins with both superantigenic and allergenic properties have been shown to influence cutaneous inflammation via activation of different cell types, such as T-cells, and professional and non-professional antigen-presenting cells (APCs) [14,15]. The increased susceptibility to *S. aureus* colonization and infection may be explained by a decreased expression of human defensins on keratinocytes of patients with AD [16,17].

Avoidance of trigger factors and regular application of emollients are recommended for all patients with AD. Further therapeutic approaches have to consider the severity of AD [18]. For the last decades topical glucocorticosteroids have been the first choice therapy for the treatment of flares. Potential side effects of topical corticosteroids such as skin atrophy, acneiform eruption, hypertrichosis and teleangiectasia may occur particularly when applied on facial lesions or after long-term use [19]. Infants are particularly sensitive to systemic side effects after topical corticosteroids because of the greater surface area:weight ratio [20], with patients who have extensive AD being most at risk. A suppression of the hypothalamic–pituitary–adrenal axis was observed in some infants after application

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of strong corticosteroids such as clobetasol propionate [21]. Bearing these facts in mind, short courses of steroids are commonly used to treat acute flares. Reports of potential side effects have led to a corticosteroid phobia, although modern corticosteroids have been proven to be safer. Besides topical treatment, systemic drugs and ultraviolet (UV) therapy may be considered in more severe cases [18]. UVA/B therapy is a widely accepted treatment regimen for the therapy of mild-to-moderate AD. Patients with severe AD may also be treated with moderate or high-dose UVA1 therapy. Oral antihistamines are often helpful in treating pruritus, and symptomatic relief may be caused by their sedative effect. However, there are still conflicting results concerning the role of histamine as a mediator of itch in AD and concerning the efficacy of antihistamines in the relief of pruritus in AD [22]. Patients who suffer from recalcitrant AD may be treated with oral immunosuppressants such as cyclosporine, mycophenolate mofetil and azathioprine – drugs that may induce systemic side effects.

Due to potential side effects of topical corticosteroids, the development of new compounds for the treatment of inflammatory skin diseases was needed. The immunosuppressive polypeptide cyclosporine is a potent inhibitor of T-cell activation. It exerts its effects by inhibition of the phosphatase calcineurin and has proven to be an effective drug for the systemic treatment of severe AD and psoriasis. However, it does not penetrate the epidermis when applied topically. Due to the potential toxic side effects that may occur upon systemic application such as nephrotoxicity and hypertension, it is only used in severe cases of AD. Therefore, the development of new compounds with a similar efficacy for the treatment of inflammatory skin conditions but a different chemical structure and pharmacokinetic profile was enforced.

Topical calcineurin inhibitors have a complex macrocyclic structure, but are molecules small enough to penetrate lesional skin, thereby exhibiting effects on the cells of the cutaneous immune system without inducing systemic side effects. The calcineurin inhibitor ascomycin is a natural product from *S. hygroscopus var. ascomyceticus*. SDZ 281–240 was the first ascomycin derivative which showed clinical efficacy in the treatment of psoriasis [27]. Due to its skin selectivity and safety profile, SDZ ASM 981 (pimecrolimus) was finally chosen for further development. Pimecrolimus has a molecular weight of 810Da [23]. The anti-inflammatory

potency of pimecrolimus was first evaluated in mouse, rat and pig models of allergic contact dermatitis, localized graft versus host reaction, allogeneic kidney transplantation and *in vitro*, before the first clinical studies were performed in 1996 [24,25]. Tacrolimus, also known as FK506, was isolated from the culture of *S. tsukubaensis* and was first used to prevent the rejection of transplanted organs [26]. It was shown to penetrate the epidermis of inflamed skin in significant amounts due to a relatively small molecular weight of 822 Da. Besides pimecrolimus and tacrolimus, other calcineurin inhibitors are currently under development for the treatment of inflammatory skin diseases such as ascrolimus (ABT-281) and ISA TX 247 [28,29].

T-cells are activated via calcium-dependent pathways in which calcineurin dephosphorylates the nuclear factor of activated T-cells (NF-AT). Once dephosphorylated, NF-AT translocates to the nucleus and leads to the transcription of various cytokines [30].

Pimecrolimus has a high affinity to macrophilin-12 (FKBP12), a cyclophilin-like cytoplasmic protein, and this complex inhibits the ability of calcineurin to dephosphorylate the transcription factor NF-AT [31]. Since only dephosphorylated NF-AT is able to translocate into the nucleus, the transcription of various pro-inflammatory cytokines and other mediators of the allergic inflammatory reaction is inhibited [30] (Figure 1).

Pimecrolimus is able to inhibit the early activation and proliferation of human T-cells by downregulation of IL-2 at nanomolar concentrations. The production of Th1 and 2 type cytokines was downregulated in human T-cells derived from the skin of a patient with AD [31]. Furthermore, the expression of costimulatory molecules on T-cells is decreased [32].

In addition to their impact on T-cells, the immunomodulatory macrolactams have been shown to influence mast cells. SDZ ASM inhibits the FcεRI-mediated activation of human mast cells *in vitro* through a mechanism that involves binding to the FKBP12. The production of tumor necrosis factor (TNF)-α and the secretion of inflammatory mediators such as histamine and tryptase was decreased in human dermal mast cells [33–36]. These effects might explain the fast relief of pruritus and erythema which occurs shortly after initiation of the treatment. Pimecrolimus does not influence the growth of keratinocytes, endothelial cells and fibroblasts [31].

Table 1. Efficacy of topical pimecrolimus in adult patients with atopic dermatitis. Results of short and long term studies (cont.)

					- Median percentage EASI change significantly different between pimecrolimus (-48.3%) and vehicle (-15.9%) - Significantly greater improvement of quality of life in the pimecrolimus group as compared with vehicle group	[54]
Meurer <i>Dermatology</i> (2004)	Double-blind Vehicle controlled Long-term (6 months)	130 1:1 (62/68)	Moderate AD (at least 5% of the total body surface area) Adults	1% pimecrolimus/vehicle Twice daily All affected areas Second line medication): moderately potent corticosteroids (prednicarbate 0.25% cream)	- Significant reduction of steroid use (pimecrolimus: 9.7%, vehicle: 37.8% of days during study period) - Significantly more patients who did not use steroids in the study period (pimecrolimus 59.7%, vehicle 25%) - Significant difference in the incidence of flares (pimecrolimus 1.0, vehicle 2.3) - Patients with treatment success (IGA 0–2): pimecrolimus 80.6%, vehicle 36.8% - Median percentage EASI change significantly different between pimecrolimus (-71.1%) and vehicle (-11.6%) - Significantly greater improvement of quality of life in the pimecrolimus group as compared with vehicle group	[55]
Luger <i>J. Dermatol. Treat.</i> (2004)	Double-blind Comparative Long-term (1 year)	658 1:1 (328/330)	Moderate-to-severe AD. (At least 5% total body surface area) Adults	1% pimecrolimus/topical corticosteroid (0.1% triamcinolone acetonide and 1% hydrocortisone acetate for face, neck, intertriginous areas) All affected areas	- Efficacy better in patients treated with corticosteroids (median EASI scores lower in the corticosteroid group as compared to the pimecrolimus group) - Proportion of patients moderately clear or better significantly greater in corticosteroid group as compared to pimecrolimus group at day 8, 22, month 7, but not at the end of the study - 42% of patients in the pimecrolimus group needed no corticosteroids - More than 50% of the patients in the corticosteroid group used these drugs almost continuously for 1 year	[62]

likely as a result of contamination [46]. In a further study by van Leent and colleagues, the pimecrolimus blood concentration was under the detection limit (0.5ng/ml) in 78% of 444 blood samples derived from 12 adult patients with AD [47]. No relationship between body surface area affected and blood concentration was observed. During a 3-week treatment with 1%

Table 2. Efficacy of topical pimecrolimus in children with atopic dermatitis. Results of short and long term studies

Author	Study design	N	Patients	Treatment	Efficacy	Refs
Harper <i>Br. J. Dermatol.</i> (2001)	- Open - Noncomparative - Short-term (3 weeks) Pharmacokinetic study	10	- 23–69% of the total body surface area affected - Children (1–4 years)	- 1% pimecrolimus - Twice daily - All affected areas	- Improvement in 8 children, 2 children discontinuation due to flare not controlled by pimecrolimus - Improvement of EASI 8–89% after 3 weeks	[44]
Kapp <i>J. Allergy Clin. Immunol.</i> (2002)	- Double-blind - Vehicle controlled - Long-term (1 year)	251 4:1 (204 /47)	- Mild-severe AD (at least 5% of the total body surface area) - Children (3–23 months)	- 1% pimecrolimus/vehicle - Twice daily - All affected areas - Flares not controlled by study medication (second line medication): moderately potent corticosteroids	- Significantly lower incidence of AD flares in pimecrolimus group at 12 months, significantly longer flare-free period in the pimecrolimus group - Significant difference in the proportion of patients without flares at 12 months (pimecrolimus 56.9%, vehicle 28.3%) - Reduction of steroid use (pimecrolimus: 3.2%, vehicle: 6.2% of days in the study period) - Significantly more patients who did not use steroid during study period (pimecrolimus 63.7%, vehicle 34.8%) - Significantly higher numbers of patients with IGA 0–1 up to 6 months (3 weeks 54.9% vs. 39.1%), at month 12 not significant (53.9% vs. 47.8%)	[59]
Wahn <i>Pediatrics</i> (2002)	- Double-blind - Vehicle controlled - Long-term (1 year)	713 2:1 (476/237)	- Mild-severe AD (at least 5% of the total body surface area) - Children (2–17 years)	- 1% pimecrolimus/vehicle - Twice daily - All affected areas - Flares not controlled by study medication (second line medication): moderately potent corticosteroids	- Significantly lower incidence of AD flares in pimecrolimus group regardless of disease severity at 12 months, significantly longer flare-free period in the pimecrolimus group - Significant difference in the proportion of patients without flares at 12 months (pimecrolimus 50.8%, vehicle 28.3%) - Significant reduction of steroid use (pimecrolimus: 4.1%, vehicle: 9.1% of days in the study period) - Significantly fewer patients who needed steroid within 12 months (pimecrolimus 42.6%, vehicle 68.4%) - Significantly greater reduction in median EASI and IGA scores in the pimecrolimus group	[58]

Table 2. Efficacy of topical pimecrolimus in children with atopic dermatitis. Results of short and long term studies (cont.)

					- Sustained efficacy over 1 year	
Eichenfield <i>J. Am. Acad. Dermatol.</i> (2002)	- Double-blind - Vehicle controlled - Short-term (6 weeks)	403 2:1 (267/136)	- Mild- moderate AD (at least 5% of the total body surface area) - Children (1-17 years)	- 1% pimecrolimus/vehicle - Twice daily - All affected areas	- Significantly more patients with treatment success in pimecrolimus group (IGA 0–1) at day 43 (pimecrolimus 34.8%/vehicle 18.4%) - Mean percentage EASI change significantly different, greatest at day 29 (pimecrolimus -47%, vehicle +1%)	[52]
Ho <i>J. Pediatr.</i> (2003)	- Double-blind/open - Vehicle controlled - Long-term (6 weeks double-blind, 20 weeks open)	186 2:1 (123/63)	- Mild-to-moderate AD (at least 5% of the total body surface area) - Children (3-23 months)	- 1% pimecrolimus/vehicle - Twice daily - All affected areas	- Significantly more patients with ‘treatment success’ in pimecrolimus group (IGA 0–1) at day 43 (pimecrolimus group 54,5%, vehicle 23,8%), greater improvement in children <1 year of age - Median percentage EASI change significantly different (pimecrolimus 81.6%, vehicle 25%) - Sustained improvement during open label phase	[57]
Allen <i>Arch. Dis. Child.</i> (2003)	Open Non-controlled Short-term Pharmacokinetic study	26	- At least 10% of body surface area affected - Children (4 months-4 years)	- 1% pimecrolimus - Twice daily - All affected areas	- Significant change of EASI on days 4, 10, 22	[43]
Kaufmann <i>J. Allergy Clin. Immunol.</i> (2004)	Double-blind/open Vehicle controlled Long-term (4 weeks double-blind, 12 weeks open, 4 weeks follow-up)	2:1 (130/66)	- Mild to very severe AD (at least 5% of the body surface area, affecting the face) - Children (3-23 months)	- 1% pimecrolimus/vehicle - Twice daily - All affected areas	- Mean percentage EASI change significantly different after 4 weeks (pimecrolimus 71.5%, vehicle +19.4%) - Mean percentage EASI change in patients with severe AD 74.7%, moderate-to-moderate AD 70% after 4 weeks - Mean percentage IGA change significantly different after 4 weeks (pimecrolimus 50.7%, vehicle 5.5%) Significant differences in single key signs of eczema after 4 weeks Infiltration: pimecrolimus 61.5%, vehicle 4.3%, excoriations: pimecrolimus 60.3%, vehicle +24.1%, erythema: pimecrolimus -54.0%, vehicle +7.4%, lichenification: pimecrolimus 37.1%, vehicle +10.5% edema: pimecrolimus -48.7%, vehicle +13.1%	[61]
Breuer <i>Dermatology</i> (2004)						

Table 2. Efficacy of topical pimecrolimus in children with atopic dermatitis. Results of short and long term studies (cont.)

					<ul style="list-style-type: none"> - Significant differences in the proportion of patients with 'treatment success' (IGA 0–1) after 4 weeks (pimecrolimus 53.5%, vehicle 10.6%) - Significant differences in proportion of children with dry skin after 4 weeks (pimecrolimus 26.5%, vehicle -5.3%) - Mean percentage EASI change, key signs of eczema significantly different already by day 4 - Sustained efficacy in open label phase, only slight increase in severity after 4 weeks follow-up 	
Papp <i>J. Am. Acad. Dermatol.</i> (2004)	<ul style="list-style-type: none"> - Open - Non-comparative - Long-term (1 year) - Extension study to [59] 	91	<ul style="list-style-type: none"> - Mild-severe AD (at least 5% of the total body surface area) - Children (3-23 months) 	<ul style="list-style-type: none"> - 1% pimecrolimus - Twice daily - All affected areas - Second line medication: moderately potent corticosteroids 	<ul style="list-style-type: none"> - 76.9% of the patients had no flares, 8.8% of the patients with one flare - Proportion of patients with IGA 0–1 increased from 36.3% to 71.4% in the study period, the mean EASI decreased from 5.8 to 2.9 - 27.5% of all patients used corticosteroids during the study period - Mean days of steroid use 7.5 	[60]

pimecrolimus ointment in children with AD, blood levels were below the detection limit of 0.5ng/ml in 63% of samples, irrespective of the body surface area affected, the other samples exhibited maximum concentrations of up to 1.8ng/ml [44]. 81% of all samples were lower than 1ng/ml in a study in 26 infants and children who applied 1% pimecrolimus to all affected areas [43]. The highest concentration observed was 2.6 ng/ml. In this study, a significant increase in blood concentration with increasing body surface area was observed, and a small but not significant decrease of the concentration with increasing age was seen. The values were in the same range as those observed after topical treatment of adult patients with AD [46,47]. Moreover, no systemic accumulation was observed. Very low blood concentrations or concentrations below the limit of detection were also found during the treatment of 58 infants aged 3 to 23 months who had an affected body surface area between 10 and 92% [45]. The low level of systemic absorption of pimecrolimus might be explained by the lipophilicity of the molecule. In

a recent *in vitro* study, percutaneous absorption and penetration of pimecrolimus was investigated and compared with tacrolimus and different topical corticosteroids [48]. The cutaneous drug concentrations of pimecrolimus, tacrolimus and topical corticosteroids were about the same, whereas the permeation of pimecrolimus through the skin was lower by a factor of 70 to 110 compared with corticosteroids. Permeation of pimecrolimus was also lower than that of tacrolimus by a factor of 9 to 10 when measured in human, pig and rat skin. Lipophilicity of pimecrolimus was higher compared with topical corticosteroids and tacrolimus.

Since significant plasma levels were not detected in clinical studies, it is unlikely that a topical treatment can cause systemic side effects. Toxicology studies which were performed in the animal model with rats and minipigs point to the kidney, the pancreas and the lymphoid tissue as target organs for toxic side effects of pimecrolimus. No toxic side effects occurred after long-term topical application for up to 24 months, and neither changes of the

appropriate laboratory parameters nor clinical symptoms pointing to systemic toxicity were observed in children and adults in any clinical study. In a study performed in adult patients with psoriasis, 60mg pimecrolimus was administered orally per day for 4 weeks [49]. No toxic side effects were observed, though the mean peak level was 54.5ng/ml. The highest blood concentration after a 3 week topical treatment in a pharmacokinetic study performed in children with AD was 2.6ng/ml [43]. Thus, levels were lower than those observed following oral administration without any toxic side effects.

Since patients with Netherton syndrome may be at high risk of systemic absorption of drugs due to the highly impaired skin barrier [50], topical calcineurin inhibitors such as pimecrolimus are contraindicated for the treatment of cutaneous lesions in patients with Netherton syndrome.

Pimecrolimus is able to inhibit the liver enzyme CYP3A4 and oral administration of topical immunomodulators may thus reduce the clearance of co-administered drugs which are predominantly metabolized by CYP3A4. Since significant plasma levels are not observed after the topical use of topical immunomodulators in patients with AD, co-administration of drugs such as itraconazole or macrolactams is permitted.

Clinical efficacy (Tables 1 & 2)

In most clinical studies on pimecrolimus cream, efficacy was assessed using the Eczema Area and Severity Index (EASI) [51] and the Investigator’s Global Assessment (IGA) [52] (Tables 3&4).

Studies in adults

The efficacy and safety of 1% pimecrolimus cream was first assessed in a double-blind placebo-controlled study performed in 34 adults with moderate AD [46]. A significant improvement in AD with a mean reduction of nearly 72% in the local eczema score was observed within 3 weeks. AD improved as early as after 2 days of treatment. Both pruritus and excoriations improved significantly. A twice-daily application was found to be superior to once-daily treatment. In a dose finding study, 260 adult patients were treated twice daily with either 0.05, 0.2, 0.6 or 0.1% pimecrolimus cream, vehicle or 0.1% betamethasone-17-valerate cream for up to 3 weeks [53]. A clear dose-response relationship became evident when the EASI and pruritus scores were taken into account. 1% pimecrolimus cream was demonstrated to be significantly more effective than a 0.6 or 0.2% formulation, whereas 0.05% cream failed to exert therapeutic effects. 1, 0.6 and 0.2% pimecrolimus creams were more effective than vehicle but less effective than the potent corticosteroid betamethasone valerate. All concentrations were less effective in severely affected patients. In a long-term study by Meurer and colleagues, the potential of pimecrolimus to prevent flares of AD was investigated for a 6-month period. 192 adults with moderate-to-severe AD were randomized to receive either pimecrolimus 1% cream or vehicle cream for 6 months [54]. In the event of flares which could not be controlled with pimecrolimus, a moderately potent corticosteroid was applied as a rescue medication. Treatment

Table 3. Eczema Area and Severity Index (EASI).

Area involvement of each body region						
0	1	2	3	4	5	6
0%	<10%	10–29%	30–49%	50–69%	79–89%	80–100%
Severity of key signs						
0	None	Erythema	Infiltration	Excoriation	Lichenification	
1	Mild					
2	Moderate					
3	Severe					
Body regions						
Upper limbs	(E + I + Ex + L) x Area involvement x 0.2*					
Lower limbs	(E + I + Ex + L) x Area involvement x 0.4*					
Trunk	(E + I + Ex + L) x Area involvement x 0.3*					
Head and neck	(E + I + Ex + L) x Area involvement x 0.1*					

*Coefficient depending on age of evaluated subject
EASI: sum of the above four body areas*

Table 4. Investigator’s Global Assessment (IGA).

Assessment		
0	Clear	No inflammatory signs of AD
1	Almost clear	Just perceptible erythema and just perceptible papulation/infiltration
2	Mild disease	Mild erythema and mild papulation/infiltration
3	Moderate disease	Moderate erythema and moderate papulation/infiltration
4	Severe disease	Severe erythema and severe papulation/infiltration
5	Very severe disease	Severe erythema and severe papulation/infiltration with oozing/crusting

with pimecrolimus significantly reduced the need for corticosteroids compared with vehicle. Moreover, significantly fewer patients in the pimecrolimus group experienced flares compared with the control group and the median time to the first flare was significantly longer. In all studies performed in adults, a significant reduction of the EASI score was observed.

Patients with moderate-to-severe AD showed a median percentage EASI reduction between 38% in a short-term study [53] and 48% in a long-term study [54]. The efficacy of pimecrolimus in patients with moderate AD was better than in patients severely affected by their AD. The mean EASI reduction was 71% in the 6-month study by Meurer and colleagues, when only patients with moderate AD were taken into account [55]. Treatment success as defined as an IGA between 0 and 2 was achieved in 71% of patients with moderate-to-severe AD, when only patients with moderate AD were analyzed, treatment success was 81% [54,55].

Studies in children

The first study exploring primarily the safety and pharmacokinetic profile of pimecrolimus 1% in children with AD was performed by Harper and colleagues in 1998 [44]. An improvement of the skin condition was seen in eight children, while two children were excluded due to a flare which could not be controlled with pimecrolimus. Topical application was found to be effective and safe when applied for 6 weeks [52]. In a recent double-blind vehicle controlled study, a significant difference in the key signs of AD (i.e., infiltration, excoriation, erythema, lichenification and edema) between the pimecrolimus and the vehicle group was seen as early as after 4 days (Figure 2) [56]. Pruritus and sleep loss were significantly reduced after 2 resp. 3 days of treatment. A significant reduction in the proportion of children with dry skin as compared with vehicle was observed.

In a study performed by Ho and colleagues, the treatment was extended to 26 weeks [57]. At the end of the 6-week blinded phase there was a significant difference in improvement of AD between the pimecrolimus and vehicle group. A significant difference in pruritus and clinical score was reached after 8 days of treatment. These beneficial effects of pimecrolimus remained stable during the 20-week open-label phase.

The efficacy and safety of a long-term treatment with 1% pimecrolimus versus vehicle over 1 year was studied in a large multicenter trial performed in 713 children and adolescents aged between 2 and 17 years [58]. In this double-blind randomized controlled study, the treatment of early AD signs resulted in a significantly reduced incidence of flares compared with the control group, regardless of disease severity. Furthermore significantly fewer patients in the pimecrolimus group compared with vehicle needed steroid treatment, which was given

Figure 2. Improvement of different morphological key signs of eczema in children treated with pimecrolimus 1% cream compared with vehicle.

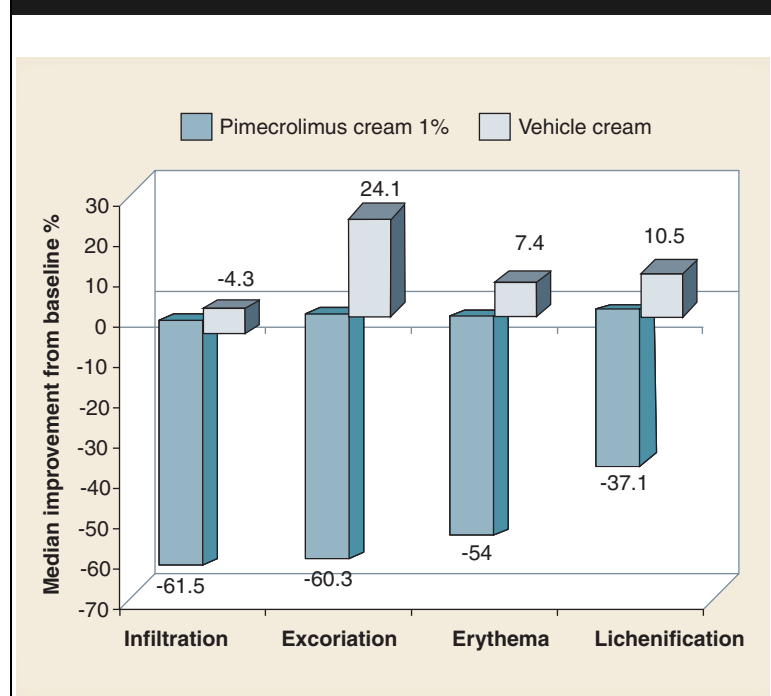


Figure adapted from: Breuer, Brautigam, Kapp, Werfel. Influence of Pimecrolimus cream 1% on different morphological signs of eczema in infants with atopic dermatitis. *Dermatology* (2004). (In Press). Reprinted with kind permission from Karger publishers, S. Karger AG, Basel, Switzerland.

as a second line medication for flares not controlled by study medication. The described effects were sustained for the duration of the study. There were neither significant differences in the overall incidence of adverse events, nor of application site reactions. The rate of overall skin infections was not significantly different between the groups. The authors conclude that a long-term treatment with pimecrolimus leads to better control of AD, reserving topical steroids for flares which cannot be controlled by pimecrolimus.

Similar results were obtained when infants aged 3–23 months were investigated using the same treatment regimen in a study with a similar design [59]. The clinical effect as measured by the IGA was better in the pimecrolimus group, although not being statistically significant at month 12. The maximum benefit was seen after 3 weeks. The lack of significance between the treatment groups at month 12 was explained by the premature discontinuation in the control group as a result of unsatisfactory therapeutic effect. However, treatment with pimecrolimus was associated with a significantly longer flare-free period. This study was extended to a further 1 year open label treatment [60]. The clinical efficacy became even more pronounced over the second year of pimecrolimus use, while local adverse events such as irritation and skin infections did not occur more frequently than in the first year. However, the possibility of spontaneous remission of AD in children of this age group must be taken into account.

In children, the mean EASI reduction ranged between 47% in short-term studies and 82% in long-term studies [57]. The number of patients who experienced ‘treatment success’ (IGA 0–1) ranged between 35% in short-term studies and 71% in long-term studies [52,60]. While most of these studies were performed in children with mild-to-moderate AD, a recent study also investigated the efficacy of pimecrolimus in children with severe AD. Patients with severe AD experienced a mean EASI reduction of 74.7%, whereas the EASI reduction was 70% in patients with mild-to-moderate AD. The head and neck region responded equally well [61].

Efficacy compared with topical corticosteroids & tacrolimus

1, 0.6 and 0.2% pimecrolimus cream were more effective than vehicle but less effective than 0.1% betamethason-17-valerate in a 3 week study performed in adults [53]. A better efficacy of topical corticosteroids compared with pimecrolimus was also seen in a recent long-term study performed

by Luger and colleagues [62], where 1% pimecrolimus was compared to 0.1% triamcinolone acetonide/1% hydrocortisone acetate. The median EASI scores were lower in patients on therapy with topical corticosteroids. 42% of the pimecrolimus-treated patients could be maintained for 1 year without topical corticosteroids whereas more than 50% of the patients in the corticosteroid group used these drugs almost continuously for the 1-year study period. No comparative studies with topical corticosteroids have been performed with pimecrolimus in children so far. The efficacy of tacrolimus was compared with that of corticosteroids in each one study in children and adults [63,64]. The median percent improvement of the clinical score in these studies was more pronounced in patients treated with tacrolimus as compared with pimecrolimus, and treatment with tacrolimus was associated with a higher incidence of local side effects such as burning and irritation.

It is difficult to compare the clinical efficacy of pimecrolimus and tacrolimus since the published studies differ in their study designs and outcome variables, and there is only one study performed in children which compared the effect of tacrolimus and pimecrolimus directly. In this trial, 141 patients with moderate AD aged between 2 and 17 years received either pimecrolimus 1% cream or tacrolimus 0.03% ointment [65]. The percentage of patients achieving IGA scores of 0 or 1 increased over the course of the study, with no significant differences between the two treatment groups at any time. However, there was a statistically non-significant trend towards lower IGA scores in the tacrolimus group. No significant differences were seen when pruritus and affected body surface area were compared between both groups. The formulation attributes of pimecrolimus cream were rated significantly better than those of tacrolimus for four out of five investigated features, including suitability for use on sensitive areas, non-sticky feel, ease of application and ease of rub-in. No significant differences in the number of adverse events, specifically of skin infections were reported. Erythema/irritation and itching was significantly more frequently reported in the tacrolimus group as compared with the vehicle group at day 4, whereas no differences in the feeling of warmth/stinging/burning were reported.

Taken together, these results suggest that the efficacy of pimecrolimus is comparable to that of mild corticosteroids with a slightly higher efficacy of tacrolimus compared with pimecrolimus.

Quality of life data

Quality of life (QoL) data are available from a 6 months double-blind study on adults with moderate-to-severe AD [54,55]. The QoL was assessed using the the Dermatology Life Quality Index (DLQI) and the Quality of Life Index-Atopic Dermatitis (QoLIAD). These scores assess symptoms and perception of the disease, daily activities, personal relationships, leisure and consequences of treatment. The improvement in quality of life was significantly greater in the pimecrolimus group compared with the vehicle group; improvement in the DLQI and QoLIAD were 22.0 versus 6.7% and 25.6 versus 7.4%, respectively.

In two long-term studies performed in children aged between 2 and 17 years, the parents' QoL data improved significantly, independently of the age of their child [66].

Efficacy in other inflammatory skin diseases than AD

Besides AD, a variety of other inflammatory skin diseases have successfully been treated by topical application of pimecrolimus. Nickel-induced patch test reactions were shown to clear upon application of pimecrolimus [67]. Other diseases such as chronic hand dermatitis (under occlusion) have been reported to respond to pimecrolimus, whereas no efficacy as compared to vehicle was observed in poison ivy contact dermatitis [68,69]. In a double-blind study in patients with chronic plaque psoriasis, an experimental

1% pimecrolimus ointment formulation was applied without occlusion [70]. Pimecrolimus demonstrated a greater efficacy than the vehicle, but a lower efficacy than calcipotriol and clobetasol-17-propionate. Repigmentation of vitiligo was observed in a young female patient after 5 months of treatment [71]. Significant regression of cutaneous lupus erythematosus was observed in 11 patients receiving pimecrolimus cream for 3 weeks [72]. Also mucosal inflammatory diseases may respond to pimecrolimus: Oral lichen planus was found to resolve after the application of pimecrolimus as an adhesive denture paste or adhesive gel [73,74]. Furthermore, pimecrolimus may be beneficial in the treatment of steroid-induced rosacea [Own unpublished observations].

Safety & tolerability (Table 5)

Intolerance

The most common side effects after application of topical calcineurin inhibitors are symptoms of

local intolerance such as skin burning, stinging, pruritus and erythema at the application site. These symptoms may be caused by an initial release of neuropeptides from sensory nerves and subsequent mast cell degranulation [75].

Most of these side effects are only mild-to-moderate and decrease over time, likely due to healing of the skin. Signs of intolerance may occur during the first 30 to 90 min upon application of 1% pimecrolimus cream. In studies performed in children there was no significant difference in the incidence of these effects between pimecrolimus (up to 10%) and vehicle groups [52,57,58].

In adult studies, local intolerance was more frequently reported by patients treated with pimecrolimus than in patients treated with vehicle or topical corticosteroids. The proportion of patients who reported intolerance was up to 49% of all patients treated with 1% pimecrolimus cream. The majority of these reactions resolved within 3 days of treatment [53–55,62].

Infections

Skin infections are common complications of AD. The mechanism of action of the topical calcineurin inhibitors led to the hypothesis that cutaneous infections may be more frequent or severe in patients treated with pimecrolimus. Therefore several comparative studies have addressed this question.

The occurrence of skin infections in children and adolescents with AD treated with pimecrolimus 1% was assessed in several short and long-term trials. No significant differences in skin infections between the pimecrolimus and the vehicle group were observed in most short [44,52] and long-term studies [57–59,61]. However, in some studies a slight but not significant increase in the incidence of viral infections was observed. All patients improved without further complications after antiviral drugs had been administered. In the study by Wahn and colleagues, a significantly higher incidence of grouped viral infections (i.e., different viral skin diseases that were evaluated together) was seen in the pimecrolimus group, while there was no significance when the occurrence of individual viral skin infections was compared between the groups [58]. In this study, bacterial infections were more common in patients who received vehicle. Infants aged 3 to 23 months were investigated using the same treatment regimen in a study with a similar design [59]. In this trial, viral infections and viral rash were more common in the control group than in the pimecrolimus

group. This study was extended to a further 1 year study with open design [60]. Skin infections were not more common in the second year than in the first year of pimecrolimus use. In the study by Ho and colleagues, the incidence of bacterial infections was slightly higher in patients who received vehicle as compared with patients in the pimecrolimus group

Table 5. Safety and tolerability of topical pimecrolimus in children and adults with atopic dermatitis. Results of short and long term studies

Author	Safety	Refs
Van Leent <i>Arch. Dermatol.</i> (1998)	- No skin intolerance or other local adverse events - Pimecrolimus concentrations in 2/121 samples from patients treated twice daily above the detection limit (0.1 ng/ml) (2.39 ng/ml, 0.22 ng/ml).	[46]
Van Leent <i>Dermatology</i> (2001)	- 78% of 444 samples below the detection limit (0.5 ng/ml), blood concentration in the other samples between 0.5–1.4 ng/ml - No significant relationship between body surface area and the individual maximum AUC _{0–12h} over the treatment period - No systemic accumulation	[47]
Luger <i>Br. J. Dermatol.</i> (2001)	- Skin local intolerance more frequent in pimecrolimus groups (pimecrolimus 1%: 48.9%, pimecrolimus 0.6%: 42.9%, vehicle: 34.9%), resolving within the first 3 days	[53]
Meurer <i>Dermatology</i> (2002)	- Skin intolerance: 10 patients in the pimecrolimus group, 3 patients in the vehicle group - No significant difference in overall skin infections (pimecrolimus 18.8%, vehicle 9.4%) - No significant difference in viral skin infections (Herpes infections: pimecrolimus group 10 patients, vehicle group 5 cases, eczema herpeticum: 2 patients of the vehicle group) - No significant difference in bacterial and fungal infections	[54]
Meurer <i>Dermatology</i> (2004)	- Local intolerance: 14.5% of the patients in the pimecrolimus group, 8.8% of the patients in the vehicle group - Overall skin infections: pimecrolimus group (21.0%) and vehicle group (11.8%). - Herpes labialis: pimecrolimus group 4 patients, vehicle group 1 patient, eczema herpeticum: 1 patient of the vehicle group - No difference in bacterial and fungal infections	[55]
Luger <i>J. Dermatol. Treat.</i> (2004)	- Local intolerance: 25.9% of patients in the pimecrolimus group, 10.9% in the corticosteroid group - No significant difference in overall skin infections between pimecrolimus and corticosteroid group, 2 cases of eczema herpeticum in pimecrolimus group, no case in the vehicle group; 7 cases of skin papilloma in corticosteroid group, no case in pimecrolimus group - Significantly lower incidence of skin infections in pimecrolimus group than in corticosteroid group in patients with >30% body surface area affected	[62]
Harper <i>Br. J. Dermatol.</i> (2001)	- Pimecrolimus blood concentrations in 63% of 63 blood samples below detection limit (0.5 ng/ml); 37% of samples range from 0.5–1.8 ng/ml - No correlation between pimecrolimus concentration and BSA - No systemic accumulation of pimecrolimus	[44]
Kapp <i>J. Allergy Clin. Immunol.</i> (2002)	- No significant difference in the incidence of overall skin infections - Bacterial skin infections: pimecrolimus group 12.7%, vehicle group 9.1% - Viral skin infections: pimecrolimus group 3.3%, vehicle group 6.9%, eczema herpeticum: pimecrolimus group 0.5%, vehicle group 0%	[59]

Table 5. Safety and tolerability of topical pimecrolimus in children and adults with atopic dermatitis. Results of short and long term studies (cont.)

Wahn <i>Pediatrics</i> (2002)	- Most common application site reaction burning, no significant differences between pimecrolimus and vehicle group (10.5% vs. 9.3%) - Slightly higher incidence of 'grouped viral skin infections' in the pimecrolimus group (not significant for individual infections): pimecrolimus group 12.4%, vehicle group 6.3% Eczema herpeticum: Pimecrolimus group 2.1%, vehicle group 0.8% - No significant differences in bacterial skin infections: pimecrolimus group 14.2%, vehicle group 30.9% - No differences in the response to recall antigens	[58]
Eichenfield <i>J. Am. Acad. Dermatol.</i> (2002)	- No significant difference in the incidence of skin burning (pimecrolimus 10.4%, vehicle 12.5%)	[52]
Ho <i>J. Pediatr.</i> (2003)	- No significant difference in 'application site reactions' - No significant difference in overall skin infections, bacterial skin infections 6.3% in vehicle group, 0.8% in pimecrolimus group	[57]
Allen <i>Arch. Dis. Child.</i> (2003)	- Pimecrolimus blood concentration in 81% of all samples below 1 ng/ml, highest blood concentration 2.6 ng/ml on day 4, two hours after application of cream - Significant increase of blood concentration with increasing body surface area affected and treated, slight but not significant decrease of blood concentration with increasing age - No systemic accumulation	[43]
Kaufmann <i>J. Allergy Clin. Immunol.</i> (2004)	- No significant difference in local adverse events - Double-blind phase: Bacterial superinfection: pimecrolimus group 1 case, vehicle group 1 case, eczema herpeticum: pimecrolimus group 1 case, vehicle group no case, irritation: pimecrolimus group 1 case, vehicle group 1 case - Open label phase: Impetigo: 2 cases, herpes simplex: 1 case, varicella: 1 case, burning: 1 case	[61]
Papp <i>Arch. Dermatol.</i> (2004)	- No local intolerance was reported - Skin infections not more frequent than in first year of pimecrolimus use, impetigo: 7 cases, eczema herpeticum: 2 cases (one case serious adverse event), herpes zoster: 2 cases	[60]

[57]. There are no reports that varicella infections in children take a severe course when occurring under therapy with topical calcineurin inhibitors. Thus a negative varicella immunization status is not a contraindication for use of topical immunomodulators.

As in children, there was no increase in the frequency of skin infections in adult patients with AD. In a 6 months study in adults with moderate-to-severe AD, more patients in the pimecrolimus group than in the vehicle group experienced skin infections, but the difference was not statistically significant [54]. A higher number of herpes infections were seen in patients receiving pimecrolimus, while the incidences of bacterial and fungal infections were similar.

In a recent 1 year long-term study on 658 adults with moderate-to-severe AD, the incidence of skin infections in the pimecrolimus group was similar to that observed in the control group which was treated with topical corticosteroids [62]. When only patients with more than 30% of the body surface area affected by AD were taken into account, the incidence of skin infections was significantly higher in the pimecrolimus group compared with the corticosteroid group.

In a recent case report, a 43-year-old woman with AD developed rosaceiform dermatitis with detection of demodex mites after a few weeks of pimecrolimus use [76]. A similar case of a patient who was treated with tacrolimus has been

reported by Antille and colleagues [77]. Recently, the development of eczema molluscatum in an adult patient with AD who used tacrolimus 0.1% for 3 months was reported [78]. This complication has not been observed with pimecrolimus so far.

No decrease in recall antigen reactions was observed after long-term use of pimecrolimus in children with AD [58]. Treatment of infants with 1% pimecrolimus cream did not interfere with the development of a normal immune response to vaccinations. 79 patients treated with pimecrolimus for 1 to 2 years showed a high seropositivity to tetanus, diphtheria, measles and rubella [79]. The overall seropositivity was comparable to that of an age-matched general pediatric population, and there were no significant differences in seropositivity when vaccinated patients who received pimecrolimus at the time of vaccination and patients who did not were compared. However, it is generally recommended to avoid pimecrolimus at least 14 days prior to immunization.

Taken together, recent studies do not suggest a significantly higher incidence of local infections during short-term and long-term application of pimecrolimus in children and adults, and there was no indication for an increased risk of infections with cumulative use. A tendency towards a higher incidence of viral infections was observed. However, from the published studies it is difficult to obtain the information whether cutaneous infections might take a more severe course in patients treated with topical calcineurin inhibitors. For safety reasons, pimecrolimus should not be applied to active cutaneous infection, specifically viral infection. It has to be kept in mind that at the moment, there is no experience with topical immunomodulators for extensive treatment periods and that side effects might become evident after a longer period.

Photocarcinogenesis

In a 52-week photocarcinogenicity study in hairless mice, the median time to tumor onset was decreased from 42 weeks in the control group to a range of 34 to 35 weeks in mice treated with vehicle, 0.03 and 0.1% tacrolimus. So there was no difference between vehicle and tacrolimus ointment. A study using a similar design was also performed with pimecrolimus. In this study, the period of spontaneous tumor onset was found to be comparable in mice treated with vehicle and active formulation [M. Bräutigam, Novartis, Pers. Comm.].

The understanding of this model is limited and the predictivity for the situation in humans is at present unclear. The effect seen with both vehicle and active compound may be explained by the increased moisture of the stratum corneum which leads to an increase in light transmission in the skin. However, for safety reasons, sun protection should be recommended to any patient treated with topical calcineurin inhibitors, and studies evaluating the long term safety are necessary.

Moreover, no experience with a simultaneous treatment with pimecrolimus and immunosuppressant therapeutics such as cyclosporine, azathioprine or UV therapy exists.

Skin atrophy

Corticosteroids exhibit an atrophogenic potential by modifying the growth and function of fibroblasts and keratinocytes [80], particularly when applied topically. In a double-blind study the application of 1% pimecrolimus over a period of 4 weeks did not lead to skin atrophy in normal healthy subjects, whereas an 8 day treatment with moderately and highly potential corticosteroids exhibited an atrophogenic potential as measured by ultrasound and stereomicroscopy. Furthermore, the epidermal thickness, which was determined by image analysis in punch biopsies was not altered in patients treated with pimecrolimus [81]. Moreover, pimecrolimus did not induce skin atrophy as assessed clinically in several short and long-term trials in adults and children.

Application in pregnant & lactating women

There are no data available about potential risks of pimecrolimus use in pregnant women with AD. Studies performed in the animal system do not point to a possible teratogenic potential of pimecrolimus and the resorption after topical application is marginal. However, due to the limited experience, pimecrolimus should be avoided during pregnancy. Similarly, no data about a potential secretion of pimecrolimus into the breast milk are available. Therefore, pimecrolimus should also not be applied by lactating women.

Pharmacoeconomics

Economic aspects have to be considered when new therapeutic compounds are assessed. Due to the high costs for the development of new therapeutics, these are mostly very expensive when newly approved on the market. In a recent analysis, a therapy of moderate-to-severe AD in adults

Highlights

Mechanism of action

- Pimecrolimus binds to macrophilin-12 (FKBP12). The FKBP12-pimecrolimus complex inhibits the ability of calcineurin to dephosphorylate the transcription factor NF-AT. As a result, the transcription of various pro-inflammatory cytokines and other mediators of the allergic inflammatory reaction is inhibited.
- The activation of T-cells is inhibited.
- The release of histamine and tryptase from mast cells is inhibited.
- Pimecrolimus does not influence dendritic cells, keratinocytes, endothelial cells and fibroblasts.

Pharmacokinetic properties

- Pimecrolimus has a molecular weight of 810 Da and a high lipophilicity.
- Permeation of pimecrolimus through the skin is lower by the factor 70–110 as compared to the corticosteroids. Permeation of pimecrolimus is lower than that of tacrolimus by the factor of 9–10.
- The topical application of pimecrolimus does not result in a significant absorption through the skin.
- The highest blood concentration observed in children was 2.6 ng/ml after topical application of 1% pimecrolimus cream.
- No systemic accumulation of pimecrolimus was observed in clinical studies.
- Pimecrolimus is able to inhibit the liver enzyme CYP3A4. Since significant plasma levels are not observed after topical use of topical immunomodulators in patients with AD, co-administration of drugs metabolized by CYP3A4 is permitted.

Clinical efficacy

- A twice-daily application is superior to once-daily treatment.
- 1% pimecrolimus cream is significantly more effective than a 0.6% or 0.2% formulation, whereas 0.05% cream has no therapeutic effects.
- Key signs of AD (i.e., infiltration, excoriation, erythema, lichenification and edema) are significantly reduced after 4 days in children. Pruritus and sleep loss are significantly reduced after 2 resp. 3 days of treatment.
- Treatment with pimecrolimus significantly reduces the need for corticosteroids in adults and children.
- Pimecrolimus reduces the incidence of flares in adults and children.
- Adults with moderate-to-severe AD showed a median percentage EASI reduction between 38 and 71%.
- In children, the mean EASI reduction ranged between 47% and 82%.

Safety and tolerability

- Signs of intolerance may occur during the first 30–90 min upon application of 1% pimecrolimus cream.
- No significant increase of skin infections was observed in most clinical studies. In some studies a slight increase in the incidence of viral infections was observed.
- No decrease in recall antigen reactions was observed after long-term use of pimecrolimus in children with AD.
- Treatment of infants with 1% pimecrolimus cream does not interfere with the development of a normal immune response to vaccinations.
- Pimecrolimus does not induce skin atrophy.

Drug interactions

- No drug interactions are known.
- No experience for a simultaneous treatment with immunosuppressants exists.

with the topical calcineurin inhibitor tacrolimus was calculated to be as expensive as a standard therapy with high-potency corticosteroids when assessed for a longer period [82].

Status of marketing

Pimecrolimus was approved as a 1% cream in the USA in 2001, it has also been available on the European market since 2002 where it is approved for short-term use for the treatment of signs and symptoms of AD and intermittent long-term use for the prevention of flares in children under 2 years of age and adults with moderate-to-moderate AD. Pimecrolimus should be prescribed by physicians who are experienced in the treatment of AD. In some other countries such as New Zealand or some South American Countries, pimecrolimus has already been approved for use in children under the age of 2 years.

Expert opinion

Over the last years the topical calcineurin inhibitors have become effective and safe alternatives to topical corticosteroids for short-term and long-term use in patients with AD. Pimecrolimus is approved for the treatment of mild-to-severe AD in children over 2 years of age and adults. The treatment with topical immunomodulators may be beneficial particularly in patients with facial lesions who are prone to skin atrophy or in patients with severe, longstanding disease. Due to its safety profile, pimecrolimus may be favored for use in children. For safety reasons, pimecrolimus should not be applied under occlusion.

The results of several long-term and short-term studies suggest that pimecrolimus may reduce the incidence of eczematous flares when applied upon early signs and symptoms of AD, thus having a steroid sparing effect particularly in patients with longstanding AD who experience frequent flares. Moreover, a substantial improvement of the QoL was reported by patients treated with pimecrolimus. However, topical corticosteroids still have their place in the treatment of AD. Eczematous flares are an indication for treatment with corticosteroids. Patients with a large body surface area affected by severe eczematous lesions may also be treated with systemic immunosuppressants or UV therapy.

No severe side effects were observed with pimecrolimus in several clinical trials in children aged 3 months to 17 years and adults, whereas subjective and objective clinical signs of AD were found to improve after a few days of treatment. Pimecrolimus is not approved for children under 2 years on the European market yet. Since no experience with a continuous ultra-long treatment with topical calcineurin inhibitors exists,

the indication for long-term use should be considered carefully. Moreover sun protection should be advised during treatment.

Outlook

Currently, topical calcineurin inhibitors are widely accepted compounds for the treatment of AD in childhood and adult age. A few thousand patients have been treated with pimecrolimus and tacrolimus in various short and long-term studies which have focused particularly on safety and efficacy of these compounds. In some of these trials, the beneficial effect of calcineurin inhibitors has also been shown in children aged 3 to 23 months. Pimecrolimus is only available as a cream preparation, tacrolimus as an ointment. Further galenic preparations may be developed in order to influence the penetration but also to offer patients the most appropriate preparation for their skin condition. Liposomal preparations may improve the penetration of topical immunomodulators also in skin conditions which are associated with hyperkeratosis such as psoriasis.

A total of 40 years experience exists with the topical corticosteroids, whereas the first studies

with pimecrolimus in humans have been performed in 1996. Therefore, no long-term experience exists for topical calcineurin inhibitors. Future long-term observations have to address this aspect. A photocarcinogenesis study performed in the animal model suggests that topical calcineurin inhibitors may have the potential to increase the incidence of skin cancer. Further studies in the animal model, but also long-term observations are needed to investigate this topic. In addition, long-term studies have to clarify whether skin infections are increased or take a more severe course in patients who use topical calcineurin inhibitors on a long-term basis.

Apart from one study in children, studies comparing the efficacy and safety of pimecrolimus and tacrolimus directly are still outstanding. Such studies could help to identify subgroups of patients who profit from the one or the other drug. In the near future, larger studies which investigate the efficacy of calcineurin inhibitors for the treatment of other inflammatory skin conditions than AD are desirable, since smaller studies and case reports suggest a beneficial effect of these compounds also in other skin diseases.

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