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EXPERT OPINION

Pimecrolimus, a topical calcineurin inhibitor used in the treatment of atopic eczema

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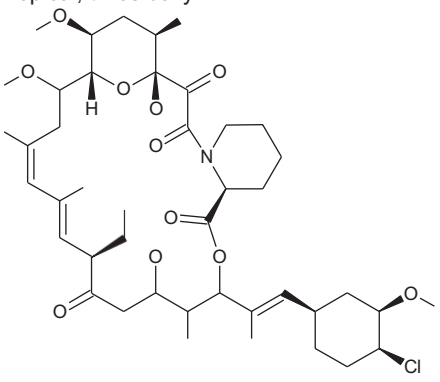
Introduction: Pimecrolimus, a calcineurin inhibitor, is a non-steroidal treatment option in patients aged ≠ 2 years with mild-to-moderate atopic eczema (AE). It was approved as a viable therapeutic option by the FDA in 2001 and in the European Union a year later in 2002. Calcineurin inhibitors inhibit the synthesis of inflammatory cytokines released from T cells and mast cells. In contrast to corticosteroids, calcineurin inhibitors act specifically on proinflammatory cells. Pimecrolimus shows comparative efficacy to mild topical corticosteroids and a special antipruritic effect. Furthermore, examinations of the systemic absorption of pimecrolimus implicated no systemic immunosuppression. In 2006, the FDA set a black box warning in the packaging materials of pimecrolimus alluding to the risk of skin malignancy or lymphomas due to theoretical consideration.
Areas covered: The authors provide a review of pimecrolimus as a treatment for AE. Specifically, the authors present the pharmacokinetic and pharmacodynamic information on pimecrolimus and also review its efficacy. The authors also discuss pimecrolimus' safety and tolerability profile.
Expert opinion: Pimecrolimus represents a valuable part of active and proactive therapy in AE. That being said, the long-term safety of topical calcineurin inhibitors remains to be investigated. Given the results from experimental photocarcinogenicity studies, effective sun protection should be employed during the therapy, although an increased risk for skin malignancies and lymphomas was not found in recent studies. Pimecrolimus should be considered as an alternative therapeutic approach in AE treatment management going along with a corticoid-sparing effect.

Keywords: ascomycin, atopic dermatitis, atopic eczema, pimecrolimus, topical calcineurin inhibitors

1. Introduction

For more than 10 years, pimecrolimus (formerly SDZ ASM 981), a topical calcineurin inhibitor (TCI), has been available for the treatment of atopic eczema (AE) and other inflammatory skin diseases as a nonsteroidal topical option [1-3]. Pimecrolimus 1% cream is approved in the United States and Europe for the topical treatment of mild-to-moderate AE patients aged > 2 years, while in some other countries, it is approved for the treatment of all severities of AE in patients ≠ 3 months of age. Moreover, pimecrolimus is indicated if topical glucocorticosteroids cannot be used or when a glucocorticoid-sparing AE management is desired. Especially in problem areas such as face, neck, intertriginous zones, it is advantageously used to reduce the symptoms of eczema and inflammation, according to the guidelines for treatment of atopic dermatitis published in 2012 [1,2,4].

Box 1. Drug summary.

Drug name	Pimecrolimus
Phase	Launched
Indication	Mild-to-moderate AE, not under age of 2
Pharmacology description	Immunosuppressant, anti-inflammatory
Route of administration	Topical, twice daily
Chemical structure	
Pivotal trial(s)	[64-67,63,68-70]

AE (synonymous with atopic dermatitis) is defined as a chronically relapsing, inflammatory, itching skin disease with a typical age-related distribution of lesions [5,6] and markedly impaired quality of life. AE is the result of complex interactions between individual genetic susceptibility, skin barrier dysfunction and environmental influence and leading to systemic or local immune deviation [7]. AE continues to attract growing attention because of its increasing prevalence in most countries of the world and the compromised quality of life of affected patients [8,9]. In the ISAAC study of 56 countries involving 458,623 children, a high worldwide variation of prevalence of the disease was confirmed, with an increasing prevalence, especially in industrialized countries, reaching 17% of children in Northern Europe [10]. The frequency in adults is lower, ranging from 1% at time of inspection to 5.1% for a lifetime prevalence [11].

Apart from AE, data are accumulating that TCIs are also effective in other inflammatory diseases such as allergic contact dermatitis and seborrhoeic dermatitis [12,13], cutaneous lupus erythematodes [14], vitiligo [15], alopecia areata [16], rosacea and perioral dermatitis [17,18].

2. Overview of the market

Currently available therapies of AE consist of adjuvant basic treatment of the impaired skin barrier with emollients, avoidance of individual trigger factors and anti-inflammatory treatment with glucocorticosteroids [19] or calcineurin inhibitors, which are mostly applied topically [20,21].

Clinical effectiveness and safety in the treatment of AE are scientifically proven for topical corticosteroids and TCIs such as tacrolimus and pimecrolimus. However, locally and systemically applied anti-inflammatory drugs do not completely cure the eczema but are highly effective in controlling or suppressing symptoms in most cases. Correct application, sufficient strength and dosage are essential principles of an effective topical therapy. It is important to make the appropriate choice of substance for the 'severity of eruption' without unnecessarily selecting strong topical corticosteroids. A stepwise approach -- taking into account the severity -- is essential in the management of AE. Owing to the increased potential for systemic absorption of topical drugs in infants, lower potency agents are recommended. Severe refractory cases can be treated by more potent topical steroids or phototherapy or systemic corticosteroids or immunosuppressives such as cyclo- sporine, methotrexate, mycophenolate mofetil [22]. In a holistic approach, the pharmacological treatment should be combined with individual recommendations regarding daily life and avoidance strategies, patient education and psychosomatic counseling [4,5,23-25].

Topical corticosteroids are mainly prescribed for short-term treatment of acute flares and are supplemented by emollients not just because of safety concerns associated with their use, especially when they are used over longer periods. Known side effects of topical steroids include skin atrophy, telangiec- tasia, hypopigmentation, steroid acne, increased hair growth and rosacea-like eruptions [5,25]. Rarely, systemic effects of topical corticosteroids have been reported such as suppression of the hypothalamic--pituitary--adrenal axis, growth retar- dation, glaucoma and Cushing syndrome [25]. However, the new generation of topical steroids is characterized by a low resorption profile and thus almost negligible systemic concentrations.

Other therapeutic options especially systemic treatments have a wide array of possible side effects. In summary, a satis- factory therapy of chronic inflammatory disease such as AE should reduce symptoms, prevent relapses/flares and provide long-term management with high safety also for children.

3. Introduction to the compound

SDZ ASM 981, an ascomycin derivate, is a compound in a novel class of anti-inflammatory macrolactams developed more than 20 years ago -- known today as pimecrolimus, a calcineurin inhibitor. Ascomycin was originally isolated in the early 1960s from the fermentation product of *Streptomyces hygroscopicus* var. ascomyceticus and had showed antifungal activity [26].

Pimecrolimus was especially developed for the treatment of chronic inflammatory diseases of the skin [27]. The drug inhib- its the synthesis of inflammatory cytokines released from T cells and mast cells [28]. In contrast to corticosteroids, which modify the growth and function of many other cell types, for example, fibroblasts or keratinocytes which cause the known side effects, SDZ ASM 981 acts specifically on inflammatory cells. Therefore, pimecrolimus is an established alternative to topical corticosteroids. Pimecrolimus binds to a cytosolic pro- tein, known as immunophilin (macrophilin) [29,30], forming inhibitory complexes that block calcineurin phosphatase activity, thus inhibiting initiation of cytokine transcription and activation of T-lymphocytes [31].

Two other calcineurin inhibitors cyclosporine and tacrolimus (topical macrolactam agent FK506) are well established over decades in transplantation medicine as systemic immunosuppressive treatments [32].

Oral cyclosporine has been intensively explored during the past decades and at present, cyclosporine shows the most con- vincing evidence as systemic treatment for severe, recalcitrant AE. However, concerns about renal toxicity and other sys- temic side effects limit the use of the drug. Topical treatment with cyclosporine, in AE and psoriasis, seemed to be ineffec- tive because of poor percutaneous penetration [33-35], whereas the use of tacrolimus is 10 -- 100 times more potent than cyclosporine in inhibiting T-cell activation [30,36].

4. Chemical structure

Pimecrolimus (Box 1), is a macrolide with a molecular mass of 810 Da.

Pimecrolimus has a very similar structure as tacrolimus. Both interact with macrophilin-12 (the cytosolic receptor FK506-binding protein) and inhibit the phosphatase calcineurin. Its effects resemble those of tacrolimus [37]. Both substances differ in their therapeutic effectiveness as well as in their structure-related limitations of formulation [38].

5. Pharmacodynamics

A major target of pimecrolimus is the nuclear factor of activated T cells (NFAT). This is a multiply phosphorylated transcription factor in the cytoplasm, which becomes activated by various stimuli and then results in calcineurin activation and modulation of gene expression in the nucleus. This is also a key pathway in AE.

Pimecrolimus acts by inhibiting the calcineurin/NFAT axis by inhibiting the NFAT nuclear translocation, thus suppressing the inflammatory pathway by inactivating T-cell response. It blocks both, the Th1-cytokines, such as IL-2 and IFN-γ, as well as the Th2-cytokines, such as IL-4, IL-13 and IL-10 [39,40]. It has a cell-selective mode of action. In mast cells, liberation of mediator substances such as hexosaminidase, histamine and tryptase are inhibited as well as *de novo* transcription of the late-phase cytokine TNF-α [28]. By inducing apoptosis, it inhibits accumulation of mast cells. Pimecrolimus has no effect on the differentiation and function of dendritic cells [28,41].

In the past years, there is accumulating evidence, that pimecrolimus can also target other cell types than lymphocytes, for example, mast cells [42,43], which are responsible for histamine liberation. Al-Daraji *et al.* have shown in a recent study of keratinocytes that the nuclear translocation of NFAT is also regulated by the enzyme calcineurin and influenced by its inhibitors [44]. Furthermore a role for calcineurin in the differentiation of keratinocytes has been described [45,46]. However, the effect of TCIs on T-lymphocytes seems to be most prominent mechanisms in anti-inflammatory treatment in acute eczematous lesions [47,48].

Because of the higher molecular mass and weaker lipophilicity, pimecrolimus penetrates much less through the skin than topical corticosteroids [13,37,43,49-53].

6. Pharmacokinetics and metabolism

In vitro and *in vivo* studies with TCIs show similar skin concentrations after local application, but the different products differ in their ability to pass through the skin. Pimecrolimus has a greater skin affinity than tacrolimus and permeates less through the skin by factors of 70 to 110 as compared to corticosteroids and factors 9 to 10 as compared with tacrolimus. This can be attributed to the high lipophilicity of pimecrolimus (in contrast to corticosteroids and tacrolimus) and its high molecular mass of 810 Da (in contrast to corticosteroids) [53]. In conclusion, systemic resorption is very low (typically < 1 ng/ml), even in patients with extensive skin lesions and impaired barrier function [3,27,54,55] independent from dosing regimens [56] and the area treated [55]. Staab *et al.* treated infants with AE with topical pimecrolimus and observed only a low systemic drug exposure, the drug concentrations remained < 2 ng/ml in 96% of the cases [57]. In a 2004 review of adult patients with moderate-to-severe AE who were treated with pimecrolimus cream 1% on all affected skin lesions for 3 weeks, the blood concentrations of pimecrolimus stayed below the level of detection in 78% of 444 samples evaluated. The highest concentration measured was 1.4 ng/ml, which was well below immunosuppressive activity [52,55].

Furthermore, it has been shown that pimecrolimus also has therapeutic potential after oral administration in patients with AE or psoriasis [58,59]. A study in healthy volunteers demonstrated, that a single oral dose of 15 mg pimecrolimus is absorbed rapidly in 1 -- 3 h [60]. Maximum blood concentrations were reached 1 h after dosing in three subjects and at 2 and 3 h when dosing in one subject with a rapid decrease, followed by a long termination phase. Small amounts of the drug, only 0.7 ± 0.9% of the administered dose, were detected in feces suggesting a nearly complete absorption or destruction in the intestine. The absolute bioavailability could not be determined in this study. The compound resided mainly within the blood cells, ~ 12% in plasma with a high distribution in the tissues. The metabolism seems to be very complex with many biotransformations; the oxidative steps are likely to be catalyzed by cytochrome P450 enzymes, CYP3A4 being mainly responsible for its metabolism. The elimination occurs almost exclusively by oxidative metabolism and the metabolites are excreted mainly via the feces [60]. In Europe, only cyclosporine as a drug in this category, is licensed for systemic treatment of skin diseases.

7. Clinical efficacy

In 1998, Van Leent *et al.* showed that pimecrolimus is effective in the treatment of AE patients in a randomized, double-blind, placebo-controlled, right-and-left comparison, proof-of-concept study [61]. A total of 34 adults with AE were treated with pimecrolimus 1% cream or vehicle in a very small area of 1 -- 2% of the body surface. A score measur- ing erythema, pruritus, excoriation, exudation and lichenifica- tion was used. After 3 weeks of twice daily treatment, a mean of 72% reduction of the score was observed in patients treated with pimecrolimus compared with a 10% reduction in patients treated with the vehicle. Within the first days of treat- ment with the compound, pruritus was relieved and other clinical signs of disease were improving. A cohort treated only once daily with pimecrolimus in AE, reached only a 38% improvement of the score. No side effects were observed and the systemic absorption was very low. In summary, these data show good effectiveness of pimecrolimus and tolerability with only minimal systemic absorption in AE patients.

In 2001, Harper *et al.* designed the first pediatric study using pimecrolimus cream 1% to evaluate the systemic exposure [62]. In these children aged 1 -- 4 years, there was no systemic accumulation of pimecrolimus after a period of 3 weeks topical treatment even in treatment up to 69% of the BSA. In 63% of patients, the blood concentrations were < 0.5 ng/ml (-1) and the maximum level reached was at 1.8 ng/ml (-1). The values were within the same range as in adults with the same therapy. No serious adverse event occurred, but two of ten infants experienced a flare of AE which was not controlled by the study medication.

In 2002, Kapp *et al.* [63] examined the efficacy of pimecrolimus in acute flares of AE in infants, in a double-blind, vehicle-controlled and randomized study. Fresh lesions of AE were treated with pimecrolimus cream to prevent an exacerbation. Indeed, pimecrolimus reduced AE flares in the pimecrolimus group and reduced the need for topical corticosteroids. Moreover, there were no clinical significant differences in incidence of side effects between the *verum* and placebo group.

Moreover, Luger *et al.*, Herbert *et al.* and Van Leent *et al.* performed long-term studies in adults and children [64-66] with good results; 17% of the pimecrolimus group patients in another study reported adverse events on the application area, such as burning and itching [56]. Pimecrolimus cream was also well tolerated in these long-term studies of 6 and 12 months. Significant improvement occurred versus conventional therapies. At 12 months, 57% of infants and 51% of children/adolescents had no flares. Long--term use of corticosteroids was significantly reduced during this phase [67,63].

Skin barrier disturbance represents a main feature in AE. Emollients are used as first-line therapy to restore the barrier deficiency. In context, comparative studies on the impact of locally applied anti-inflammatory drugs are of great importance. Jensen *et al.* compared topical steroids and pimecrolimus [68]. The gene expression data clearly show that even though corticosteroids exert more potent anti-inflammatory effects, skin barrier restoration is impaired in contrast to pimecrolimus, in which the expression of rate-limiting enzymes for lipid synthesis and the expression of involucrin and small proline-rich proteins are significantly reduced. Moreover, treatment for AE with corticosteroids in human skin and essential fatty acid-deficient mice (a model of chronic skin barrier disease with inflammation) caused a strong reduction in antimicrobial proteins. The reduction was less with pimecrolimus, which may explain the clinical observation that prolonged treatment with topical corticosteroids sometimes leads to bacterial infection [69]. This makes pimecrolimus a good candidate in long-term management of AE.

In 2003, Graham-Brown and Grassberger suggested the application of pimecrolimus at the first signs and symptoms of AE to prevent flare progression and to provide long-term control [51]. After 3 years, Weissenbacher *et al.* showed that pimecrolimus pretreatment has a potential to suppress the development of lesions induced by aeroallergens exposure in patients with AE [70]. Following these facts, Wollenberg *et al.* suggested the proactive therapy of AE, 'an emerging concept', by using topical TCIs several times a week resulting in less disease exacerbation and better quality of life [71].

In parallel, Rappersberger *et al.* examined the effectiveness of pimecrolimus in other inflammatory diseases, such as psoriasis, and obtained good results [72], but today pimecrolimus is only used in psoriasis patients for special lesions such as the face and intertriginous zones. One of the first studies in patients with severe psoriasis showed that after some days of therapy and semiocclusive conditions, psoriatic lesions cleared in a dose-dependent manner [73].

Pimecrolimus was used in allergic contact dermatitis with good results [74]. It was evaluated in a study of 66 patients with an established nickel contact dermatitis. The study compared pimecrolimus 0.2 and 0.6% with vehicle and betamethasone-17-valerate 0.1%. The therapeutic effect of pimecrolimus 0.6% was comparable to 0.1% betamethasone-17-valerate [12].

Furthermore, in recent years, there have been numerous reports about the off-label usage of pimecrolimus in a variety of diseases as mentioned before [75], for example, chronic hand eczema, perioral dermatitis, seborrhoeic dermatitis [76], Fox-Fordyce disease [76], orofacial Crohn's disease/granulomatosis [77], lichen sclerosus et atrophicus [78], Zoon's plasma cell balanitis [79], alopecia areata, Netherton syndrome, chronic actinic dermatitis, vitiligo, lupus erythematosus, dermatomyositis [80], sarcoidosis, rosacea, Darier's disease [81], graft versus host disease [82], Behcet's disease [83], mucosal lichen planus, cutaneous mastocytosis [84], uveitis, as well as bullous and erosive dermatoses.

8. Safety and tolerability

In clinical practice more than nine million patients have been treated since December 2001, and most of them were younger than 10 years of age.

8.1 Known side effects

8.1.1 Burning sensations

The most frequently reported side effect is a burning sensation at the site of application (1.3%) with erythema (0.3%) and pruritus (0.2%) within the first few days of therapy [67], thus sometimes leading to discontinuation of therapy. Some patients experience a general feeling of heat [77]. A possible explanation for these burning sensations may be neuropeptide release and mast cell degranulation in murine skin [78]. All these local reactions disappear by the second week of treatment. Furthermore, signs of alcohol intolerance, skin discoloration and hypersensitivity or allergic reactions were reported [79].

8.2 Side effects which cannot be ruled out

8.2.1 Infections

In a pooled analysis of many randomized studies, no increased risk for bacterial infections was shown, but there may be a trend for several viral skin infections with the use of pimecro- limus [67]. In this case, it is suggested to stop therapy with calcineurin inhibitors [13,67]. In other studies, there has been no significant difference in incidence of skin infections after topical pimecrolimus treatment compared to controls in infants and children [80,81].

8.2.2 Vaccination response

In a study with 70 children aged up to 23 months, the immune response to vaccination was not affected by topical therapy with pimecrolimus [81,82], when the antibody titers after vaccination were measured. No suppression of the immune system was observed [81].

8.2.3 Skin atrophy

In contrast to corticosteroids, pimecrolimus does not induce skin atrophy [83]. A placebo-controlled randomized study showed even a regression of skin atrophy in comparison to vehicle control [84] after long-term corticosteroid therapy.

8.3 Controversially discussed side effect

8.3.1 Photocarcinogenicity

Based on the current data, the cancer risk associated with the use of TCIs on sun-exposed areas appears to be minimal or nonexistent [85-87]. TCIs modify the immune regulatory function of the skin and may have the potential to enhance immunosuppressive ultraviolet (UV) effects. The information on UV protection in TCI patients is inconsistent. Following this problem, the European Dermatology Forum (EDF) published a position statement regarding this uncertainty after analyzing the data and found no conclusive evidence that long-term application of TCIs is photocarcinogenic. Moreover, this photoeffect could be a good approach in the therapy of other diseases, for example, vitiligo.

Photocarcinogenicity studies did not display a shortened time until the manifestation of skin tumors in the mouse model [88] and measurements of UV-induced dipyrimidine dimers gave no evidence of increased epidermal DNA damage [89]. In contrast, a study in hairless mice had shown an increased formation of skin papillomas after topical tacrolimus, but not after topical pimecrolimus; its relevance to humans remains unclear [87].

8.4 Ruled out side effect

8.4.1 Lymphoma risk

Arellano *et al.* examined in a recent study the association between TCIs and lymphoma in over 293,000 AE patients. No increased risk of cancer was established [90].

In summary, calcineurin inhibitors such as pimecrolimus are well tolerated after local application and exhibit less side effects than corticosteroids.

9. Black box warning

Since Spring 2006, the USA regulatory agency (Food and Drug Administration [FDA]) ordered a mandatory warning, a 'black box', in the packaging materials of pimecrolimus and tacrolimus alluding to a possibly increased risk of skin cancer or lymphomas due to theoretical consideration and in absence of ultra-long-term experience of 10 years or more. The recommendations were based on theoretical risk of malignancy derived from safety profiles after systemic application.

In January 2005, two malignancies were observed in an evaluation of over 19,000 patients treated with pimecrolimus 1% cream; neither case was considered to be treatment

related [91,92]. The two affected patients, a 74-year-old male and a 65-year-old female, experienced colon carcinoma and squamous cell carcinoma of the skin, whereas the 5 cases of malignancy occurred in the control group [91].

In March 2006, 50 malignancies have been reported in post-marketing surveillance including 16 cases of skin malignancies (e.g., squamous cell carcinomas in patients at high risk) and 27 lymphomas including 21 non-Hodgkin lymphomas. Also in this study and many other studies, no relationship could be demonstrated between these malignancies and the use of pimecrolimus cream 1%. Nevertheless, the necessity for further studies was pointed out by the European Medical Agency [79,93,94].

The German Federal Institute for Drugs and Medical Devices concluded the benefit:risk ratio as favorable. The FDA after reviewing evidence for this drug, determined in 2006, that no causal relationship has been established between the use of TCIs and cases of skin cancer and lymphomas [95].

According to the modified European Union license and the EDF guidelines, anti-inflammatory treatment based on topical glucocorticosteroids and calcineurin inhibitors is used in exacerbation management with the preferred use of calcineurin inhibitors in certain locations such as, for example, the face or intertriginous zones or as drug of first choice when corticosteroids are contraindicated or not tolerated [23].

Indeed, there is an increased risk of malignancy in patients with systemic immunosuppression. However, topically applied pimecrolimus does not lead to substantially elevated blood levels and thus does not cause systemic immunosuppression [55] and cancer [92].

The safety of pimecrolimus was examined in various short- and long-term studies with AE patients. Especially, children were treated with pimecrolimus and a significant reduction in AE flares and pruritus was observed, without any malignancies in children. Adverse events were rare and probably not related to the compound and not clinically relevant. However, in summary, there are only sparse data on specific malignancies among TCI-treated patients. Available data on lymphoma following TCI use are inconsistent and insufficient to draw a conclusion about the causal role of TCIs [96]. Among children enrolled in post-marketing pediatric registry studies for both tacrolimus and pimecrolimus, followed for up to 5.5 years (10,724 patient-years) or 6.5 years (16,219 patient-years), respectively, the observed number of malignancies and lymphomas is very low and similar to the number expected for a sample of similar size in the general population [97]. Until now, in United States and Europe, pimecrolimus 1% cream is not indicated for children aged under 2 years, but data so far suggest that an off-label use in this age group is safe [95].

10. Conclusion

TCIs, such as pimecrolimus and tacrolimus, represent an effective treatment for AE.

The current guidelines on AE state that pimecrolimus is indicated as first-line therapy when topical glucocorticoids are contraindicated or not well tolerated, especially in problem zones such as face and neck in adults and children aged > 2 years [23]. The effectiveness of pimecrolimus in contrast to vehicle and topical corticosteroids shows a favorable profile with the same efficacy as mild-to-moderate topical corticosteroids but with no risk of skin atrophy and only rare adverse events.

11. Expert opinion

Pimecrolimus 1% cream is an effective treatment for AE and safe alternative to topical corticosteroids.

Using pimecrolimus on a proactive or regular basis, while reserving potent topical corticosteroids for severe exacerbations, may help patients to take control of AE and thus have a better quality of life. TCIs are an alternative therapeutic approach, which has emerged in recent years, is immunobiologically founded and has been shown to be successful in numerous studies in the last years. Especially for young children and sensitive skin areas, calcineurin inhibitors are an appropriate therapy. A more proactive approach to disease control may better reflect patients' needs and improve prognosis.

The principle of proactive therapy is short-term induction therapy with classical topical anti-inflammatory therapy until most of the lesion are gone [71]. This should be followed by a long-term low-dose therapy, usually twice weekly, of previous affected areas of the body in combination with the long-term emollient therapy of the entire body as before. But till now, no studies about proactive therapy are available.

Furthermore a combination with avoidance of individual provocation factors and education is suggested. Most of the patients express concerns using topical steroids in the long term, especially for these patients, calcineurin inhibitors are an interesting corticoid sparing option without the typical side effects such as skin atrophy. Many patients even report that their skin was smoother, less dry and less sensitive after a therapy with pimecrolimus according, probably, to a positive pharmacological effect of pimecrolimus on the skin barrier function in AE patients.

Moreover, topical pimecrolimus appears to be an effective treatment for a variety of other disorders that seem to increase in the past years; further studies are awaited to show the effectiveness.

In general, ongoing epidemiological programs will provide further information, especially concerning the black box warning and the cancer risk which are raising confusion and concerns to many patients and parents.

Because of these concerns, prolonged ultra-long use of pimecrolimus 1% cream should be re-evaluated, especially in infants and under conditions, which could increase its systemic absorption such as an application to the whole

body surface area, large areas of ulcerated skin or in patients with immune system disorders. Because of unclear results from photocarcinogenicity studies, effective sun protection should be employed during the therapy with calcineurin inhibitors.

The risks and benefits in contrast to other available alternative therapies have to be considered. In summary, pimecrolimus is a very good option for short- and long-term treatment and proactive therapy management of AE patients and children with less side effects than topical corticosteroids.

Declaration of interest

Ring has been member in advisory boards and has received grants for clinical trials in cooperation with the following organizations: ALK-Abello´, Allergopharma, Almirall-Hermal GmbH, Astellas Pharma, Bencard Allergie, Biogen-Idec, Galderma, GlaxoSmithKline, Leo Pharma, Merck Sharp & Dohme, Novartis, Phadia, PLS-Design GmbH and Stallergenes. All other authors declare no conflict of interest and have received no payment in the preparation of their manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (.) or of considerable interest (..) to readers.

1. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol 2012;26:1045-60
2. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part II. J Eur Acad Dermatol Venereol 2012;26:1176-93
ŭ Guidelines for the treatment of atopic dermatitis.
3. Stuetz A, Baumann K, Grassberger M, et al. Discovery of topical calcineurin inhibitors and pharmacological profile of pimecrolimus. Int Arch Allergy Immunol 2006;141:199-212
4. Darsow U, Wollenberg A, Simon D, et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010;24:317-28
5. Ring J, Przybilla B, Ruzicka T. Handbook of atopic eczema. 2nd edition. Springer; 2006
6. Aoki T, Fukuzumi T, Adachi J, et al. Re-evaluation of skin lesion distribution in atopic dermatitis. Analysis of cases 0 to 9 years of age. Acta Derm Venereol Suppl (Stockh) 1992;176:19-23
7. Kjellman B, Hattevig G. Allergy in early and late onset of atopic dermatitis. Acta Paediatr 1994;83:229-31
8. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112:S118-27
9. Bjorksten B. The environment and sensitisation to allergens in early childhood. Pediatr Allergy Immunol 1997;8:32-9
10. Williams H, Robertson C, Stewart A, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. J Allergy Clin Immunol 1999;103:125-38
11. Wahn U, Wichmann H-E. Special report on allergies. Health monitoring of the federation. Metzler-Poeschel; Stuttgart: 2000
12. Queille-Roussel C, Graeber M, Thurston M, et al. SDZ ASM 981 is the first non-steroid that suppresses established nickel contact dermatitis elicited by allergen challenge. Contact Dermat 2000;42:349-50
13. Eichenfield LF, Beck L. Elidel (pimecrolimus) cream 1%: a nonsteroidal topical agent for the treatment of atopic dermatitis. J Allergy Clin Immunol 2003;111:1153-68
14. Avgerinou G, Papafragkaki DK, Nasiopoulou A, et al. Effectiveness of topical calcineurin inhibitors as monotherapy or in combination with hydroxychloroquine in cutaneous lupus erythematosus. J Eur Acad Dermatol Venereol 2012;26:762-7
15. Hui-Lan Y, Xiao-Yan H, Jian-Yong F, Zong-Rong L. Combination of 308-nm excimer laser with topical pimecrolimus for the treatment of childhood vitiligo. Pediatr Dermatol 2009;26:354-6
16. Ucak H, Kandi B, Cicek D, et al. The comparison of treatment with clobetasol propionate 0.05% and topical pimecrolimus 1% treatment in the treatment of alopecia areata. J Dermatolog Treat 2012;23(6):410-20
17. Schwarz T, Kreiselmaier I, Bieber T, et al. A randomized, double-blind, vehicle-controlled study of 1% pimecrolimus cream in adult patients with perioral dermatitis. J Am Acad Dermatol 2008;59:34-40
18. Kim MB, Kim GW, Park HJ, et al. Pimecrolimus 1% cream for the treatment of rosacea. J Dermatol 2011;38:1135-9
19. Leung DY, Hanifin JM, Charlesworth EN, et al. Disease management of atopic dermatitis: a practice parameter. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Work Group on Atopic Dermatitis. Ann Allergy Asthma Immunol 1997;79:197-211
20. Leung DY. Atopic dermatitis: immunobiology and treatment with immune modulators. Clin Exp Immunol 1997;1:25-30
21. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. Br J Dermatol 1998;139:73-6
22. Atakan N, Erdem C. The efficacy, tolerability and safety of a new oral formulation of sandimmun--sandimmun neoral in severe refractory atopic dermatitis. J Eur Acad Dermatol Venereol 1998;11:240-6
23. Ring J. Guidelines for treatment of atopic eczema (atopic dermatitis). JEADV 2012; In press
ŭ AE treatment guidelines.
24. Ellis C, Luger T. International consensus conference on atopic dermatitis II (ICCAD II): chairman's introduction and overview. Br J Dermatol 2003;148(Suppl 63):1-2

25. Ellis C, Luger T, Abeck D, et al. International consensus conference on atopic dermatitis II (ICCAD II): clinical update and current treatment strategies. Br J Dermatol 2003;148(Suppl 63):3-10

26. Arai T, Kouama Y, Suenaga T, Honda H. Ascomycin, an antifungal antibiotic. J Antibiot (Tokyo) 1962;15:231-2

27. Meingassner JG, Grassberger M, Fahrngruber H, et al. A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin diseases: in vivo pharmacology. Br J Dermatol 1997;137:568-76

28. Grassberger M, Baumruker T, Enz A, et al. A novel anti-inflammatory drug, SDZ ASM 981, for the treatment of skin diseases: in vitro pharmacology. Br J Dermatol 1999;141:264-73

29. Ho S, Clipstone N, Timmermann L, et al. The mechanism of action of cyclosporin A and FK506. Clin Immunol Immunopathol 1996;80:S40-5

30. Bieber T. Topical tacrolimus (FK 506): a new milestone in the management of atopic dermatitis. J Allergy Clin Immunol 1998;102:555-7

31. Hanifin JM, Chan S. Biochemical and immunologic mechanisms in atopic dermatitis: new targets for emerging therapies. J Am Acad Dermatol 1999;41:72-7

32. Bornhovd E, Burgdorf WH, Wollenberg A. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. J Am Acad Dermatol 2001;45:736-43

33. De Rie MA, Meinardi MM, Bos JD. Lack of efficacy of topical cyclosporin A in atopic dermatitis and allergic contact dermatitis. Acta Derm Venereol 1991;71:452-4

34. Hermann RC, Taylor RS, Ellis CN, et al. Topical ciclosporin for psoriasis: in vitro skin penetration and clinical study. Skin Pharmacol 1988;1:246-9

35. Reitamo S, Kayhko K, Lauerma AI, Mustakallio KK. Topical cyclosporine and contact dermatitis in guinea pig and man. Arch Dermatol 1989;125:568

36. Ruzicka T, Bieber T, Schopf E, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. N Engl J Med 1997;337:816-21

37. Wellington K, Jarvis B. Topical pimecrolimus: a review of its clinical potential in the management of atopic dermatitis. Drugs 2002;62:817-40

38. Bornhovd EC, Burgdorf WH, Wollenberg A. Immunomodulatory macrolactams for topical treatment of inflammatory skin diseases. Curr Opin Investig Drugs 2002;3:708-12

39. Hogan PG, Chen L, Nardone J, Rao A. Transcriptional regulation by calcium, calcineurin, and NFAT. Genes Dev 2003;17:2205-32

40. Macian F. NFAT proteins: key regulators of T-cell development and function. Nat Rev Immunol 2005;5:472-84

41. Kalthoff FS, Chung J, Musser P, Stuetz A. Pimecrolimus does not affect the differentiation, maturation and function of human monocyte-derived dendritic cells, in contrast to corticosteroids. Clin Exp Immunol 2003;133:350-9

42. Zuberbier T, Chong SU, Grunow K, et al. The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils. J Allergy Clin Immunol 2001;108:275-80

43. Grassberger M, Steinhoff M, Schneider D, Luger TA. Pimecrolimus -- an anti-inflammatory drug targeting the skin. Exp Dermatol 2004;13:721-30

44. Al-Daraji WI, Grant KR, Ryan K, et al. Localization of calcineurin/NFAT in human skin and psoriasis and inhibition of calcineurin/NFAT activation in human keratinocytes by cyclosporin A. J Invest Dermatol 2002;118:779-88

45. Buchau AS, Schauber J, Hultsch T, et al. Pimecrolimus enhances TLR2/6-induced expression of antimicrobial peptides in keratinocytes. J Invest Dermatol 2008;128:2646-54

46. Santini MP, Talora C, Seki T, et al. Cross talk among calcineurin, Sp1/Sp3, and NFAT in control of p21(WAF1/CIP1) expression in keratinocyte differentiation. Proc Natl Acad Sci USA 2001;98:9575-80

47. Ortiz De Frutos FJ. New horizons in the treatment of atopic dermatitis. Allergol Immunopathol (Madr) 2002;30:134-40

48. Novak N, Kwiek B, Bieber T. The mode of topical immunomodulators in the immunological network of atopic dermatitis. Clin Exp Dermatol 2005;30:160-4

49. Kapp A, Allen BR, Reitamo S. Atopic dermatitis management with tacrolimus ointment (Protopic). J Dermatol Treat 2003;14:5-16

50. Simpson D, Noble S. Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions. Drugs 2005;65:827-58

51. Graham-Brown RA, Grassberger M. Pimecrolimus: a review of pre-clinical and clinical data. Int J Clin Pract 2003;57:319-27

52. Wolff K, Stuetz A. Pimecrolimus for the treatment of inflammatory skin disease. Expert Opin Pharmacother 2004;5:643-55

53. Billich A, Aschauer H, Aszodi A, Stuetz A. Percutaneous absorption of drugs used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus. Int J Pharm 2004;269:29-35

54. Allen BR, Lakhanpaul M, Morris A, et al. Systemic exposure, tolerability, and efficacy of pimecrolimus cream 1% in atopic dermatitis patients. Arch Dis Child 2003;88:969-73

55. Van Leent EJ, Ebelin ME, Burtin P, et al. Low systemic exposure after repeated topical application of Pimecrolimus (Elidel), SD Z ASM 981 in patients with atopic dermatitis. Dermatology 2002;204:63-8

56. Ling M, Gottlieb A, Pariser D, et al. A randomized study of the safety, absorption and efficacy of pimecrolimus cream 1% applied twice or four times daily in patients with atopic dermatitis. J Dermatolog Treat 2005;16:142-8

57. Staab D, Pariser D, Gottlieb AB, et al. Low systemic absorption and good tolerability of pimecrolimus, administered as 1% cream (Elidel) in infants with atopic dermatitis--a multicenter, 3-week, open-label study. Pediatr Dermatol 2005;22:465-71

58. Rappersberger K, Komar M, Ebelin ME, et al. Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and

is well tolerated. J Invest Dermatol 2002;119:876-87

59. Gottlieb AB, Griffiths CE, Ho VC, et al. Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double-blind, multicentre, randomized, dose-finding trial. Br J Dermatol 2005;152:1219-27

60. Zollinger M, Waldmeier F, Hartmann S, et al. Pimecrolimus: absorption, distribution, metabolism, and excretion in healthy volunteers after a single oral dose and supplementary investigations in vitro. Drug Metab Dispos 2006;34:765-74

61. Van Leent EJ, Graber M, Thurston M, et al. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. Arch Dermatol 1998;134:805-9

62. Harper J, Green A, Scott G, et al. First experience of topical SDZ ASM 981 in children with atopic dermatitis. Br J Dermatol 2001;144:781-7

64. Luger T, Van Leent EJ, Graeber M, et al. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. Br J Dermatol 2001;144:788-94

.. Pivotal trial of pimecrolimus.

65. Hebert AA, Warken KA, Cherill R. Pimecrolimus cream 1%: a new development in nonsteroid topical treatment of inflammatory skin diseases. Semin Cutan Med Surg 2001;20:260-7

.. Pivotal trial of pimecrolimus.

66. Van Leent EJ, De Vries HJ, Ebelin ME, et al. Blood concentrations of pimecrolimus in adult patients with atopic dermatitis following intermittent administration of pimecrolimus cream 1% (Elidel) for up to 1 year. J Dermatolog Treat 2007;18:19-22

.. Pivotal trial of pimecrolimus.

67. Wahn U, Bos JD, Goodfield M, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics 2002;110:e2

.. Pivotal trial of pimecrolimus.

63. Kapp A, Papp K, Bingham A, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol 2002;110:277-84

.. Pivotal trial of pimecrolimus.

68. Jensen JM, Scherer A, Wanke C, et al. Gene expression is differently affected by pimecrolimus and betamethasone in lesional skin of atopic dermatitis. Allergy 2012;67:413-23

.. Pivotal trial of pimecrolimus.

69. Jensen JM, Ahrens K, Meingassner J, et al. Differential suppression of epidermal antimicrobial protein expression in atopic dermatitis and in EFAD mice by pimecrolimus compared to corticosteroids. Exp Dermatol 2011;20:783-8

.. Pivotal trial of pimecrolimus.

70. Weissenbacher S, Traidl-Hoffmann C, Eyerich K, et al. Modulation of atopy patch test and skin prick test by pretreatment with 1% pimecrolimus cream. Int Arch Allergy Immunol 2006;140:239-44

.. Pivotal trial of pimecrolimus.

71. Wollenberg A, Frank R, Kroth J, Ruzicka T. Proactive therapy of atopic eczema--an evidence-based concept with a behavioral background. J Dtsch Dermatol Ges 2009;7:117-21

72. Rappersberger K, Meingassner JG, Fialla R, et al. Clearing of psoriasis by a novel immunosuppressive macrolide. J Invest Dermatol 1996;106:701-10

73. Mrowietz U, Graeber M, Brautigam M, et al. The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. Br J Dermatol 1998;139:992-6

74. Paul C, Graeber M, Stuetz A. Ascomycins: promising agents for the treatment of inflammatory skin diseases. Expert Opin Investig Drugs 2000;9:69-77

75. Luger T, Paul C. Potential new indications of topical calcineurin inhibitors. Dermatology 2007;215:45-54

76. Kim GK, Rosso JD. Topical pimecrolimus 1% cream in the treatment of seborrheic dermatitis. J Clin Aesthet Dermatol 2013;6:29-35

77. Gollnick H, Luger T, Freytag S, Brautigam M. StabiEL: stabilization of skin condition with Elidel--a patients' satisfaction observational study addressing the treatment, with pimecrolimus cream, of atopic dermatitis pretreated with topical corticosteroid. J Eur Acad Dermatol Venereol 2008;22:1319-25

78. Stander S, Stander H, Seeliger S, et al. Topical pimecrolimus and tacrolimus transiently induce neuropeptide release and mast cell degranulation in murine skin. Br J Dermatol 2007;156:1020-6

79. Langley RG, Luger TA, Cork MJ, et al. An update on the safety and tolerability of pimecrolimus cream 1%: evidence from clinical trials and post-marketing surveillance. Dermatology 2007;215:27-44

80. Ho VC, Gupta A, Kaufmann R, et al. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. J Pediatr 2003;142:155-62

81. Paul C, Cork M, Rossi AB, et al. Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. Pediatrics 2006;117:e118-28

82. Papp KA, Breuer K, Meurer M, et al. Long-term treatment of atopic dermatitis with pimecrolimus cream 1% in infants does not interfere with the development of protective antibodies after vaccination. J Am Acad Dermatol 2005;52:247-53

83. Queille-Roussel C, Paul C, Duteil L, et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. Br J Dermatol 2001;144:507-13

84. Murrell DF, Calvieri S, Ortonne JP, et al. A randomized controlled trial of pimecrolimus cream 1% in adolescents and adults with head and neck atopic dermatitis and intolerant of, or dependent on, topical corticosteroids. Br J Dermatol 2007;157:954-9

85. Lerche C, Wulf HC. Photocarcinogenicity of selected topically applied dermatological drugs: calcineurin inhibitors, corticosteroids, and vitamin D analogs. Dermatol Rep 2010;2:e13

86. Margolis DJ, Hoffstad O, Bilker W. Lack of association between exposure to topical calcineurin inhibitors and skin cancer in adults. Dermatology 2007;214:289-95

87. Ring J, Barker J, Behrendt H, et al. Review of the potential photo-cocarcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. J Eur Acad Dermatol Venereol 2005;19:663-71

88. Shiga T, Yokogawa M, Nakajima K, et al. Topical tacrolimus treatment does not facilitate photocarcinogenesis in cancer-prone mice. J Dermatol Sci 2012;68:112-15

89. Doelker L, Tran C, Gkomouzas A, et al. Production and clearance of cyclobutane dipyrimidine dimers in UV-irradiated skin pretreated with 1% pimecrolimus or 0.1% triamcinolone acetonide creams in normal and atopic patients. Exp Dermatol 2006;15:342-6

90. Arellano FM, Wentworth CE, Arana A, et al. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol 2007;127:808-16

91. Hultsch T. Elidel (pimecrolimus) cream 1% safety update February 2005. Internet. 2005. Available from: http://www.fda.gov/ohrms/dockets/ac/05/ slides/2005--4089s2_02_02_Novartis%20Core%20Safety%20(CS).pdf
ü FDA update on the safety of pimecrolimus.

92. Hultsch T, Kapp A, Spergel J. Immunomodulation and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. Dermatology 2005;211:174-87

93. Ring J, Mohrenschlager M, Henkel V. The US FDA 'black box' warning for topical calcineurin inhibitors: an ongoing controversy. Drug Saf 2008;31:185-98

94. Orlow SJ. Topical calcineurin inhibitors in pediatric atopic dermatitis: a critical analysis of current issues. Paediatr Drugs 2007;9:289-99

95. Food and Drug Administration Pediatric Advisory Committee F. 2006

96. Tennis P, Gelfand JM, Rothman KJ. Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. Br J Dermatol 2011;165:465-73

97. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. Am J Clin Dermatol 2013;14:163-78

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