DOI 10.1111/j.1365-2133.2008.08436.x

Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study

A. Peserico, G. Städtler,* M. Sebastian,† R. Suarez Fernandez,‡ K. Vick* and T. Bieber§

Department of Dermatology, University of Padua, Padua, Italy
**Global Clinical Development, Intendis GmbH, Berlin, Germany*
†*Group Practice, Mahlow, Germany*
‡*Servicio de Dermatologia, Hospital Gregorio Marañón, Madrid, Spain*
§*Department of Dermatology and Allergy, University Hospital, Sigmund-Freud-Straße 25, D-53105 Bonn, Germany*

Correspondence
Thomas Bieber.
E-mail: thomas.bieber@ukb.uni-bonn.de

Accepted for publication
12 November 2007

Key words
atopic dermatitis, corticosteroid, maintenance treatment, methylprednisolone aceponate, relapse

Conflicts of interest
None declared.

Summary

Background The relapsing nature of atopic dermatitis (AD) presents a challenge for its long-term treatment. Efficacy and safety of corticosteroids have been proven in the acute treatment of active AD, but their long-term efficacy and potential to reduce or prevent relapses have only partially been addressed.

Objectives To investigate long-term management (16 weeks) of AD with methylprednisolone aceponate (MPA) 0·1% cream twice weekly in addition to an emollient (Advabase®) after stabilization of an acute severe or very severe flare of AD with MPA cream.

Methods Patients ≥ 12 years of age with a ≥ 2-year history of moderate to severe AD were eligible for this multicentre, randomized, double-blind, controlled study if they presented with an acute flare of severe or very severe AD [Investigator's Global Assessment (IGA) score ≥ 4]. After successful treatment of the flare in an acute phase (AP), patients received either MPA twice weekly plus emollient or emollient alone over a 16-week maintenance phase (MP). The primary study endpoint was time to relapse of AD. Secondary endpoints included relapse rate and disease status, the patient's assessment of intensity of itch, the Eczema Area and Severity Index, the IGA score, affected body surface area, Dermatology Life Quality Index (DLQI) and children's DLQI (CDLQI), patient's and investigator's global assessment of response and patient's assessment of quality of sleep.

Results Two hundred and forty-nine patients entered the AP and 221 continued into the MP. Time to relapse was longer in the MPA group than in the emollient group. The probability of remaining free from relapse after 16 weeks was 87·1% in the MPA group compared with 65·8% for the emollient. Patients treated with MPA twice weekly had a 3·5-fold lower risk of experiencing a relapse than patients treated with emollient alone (hazard ratio 3·5, 95% confidence interval 1·9–6·4; $P < 0·0001$). MPA was also superior to emollient for all other efficacy endpoints. Therapy with both treatments was well tolerated.

Conclusions MPA twice weekly plus an emollient provides an effective maintenance treatment regimen to control AD. Once stabilized, treatment with MPA significantly reduces the risk of relapse and the intensity of itching, and improves the overall patient status.

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Atopic dermatitis (AD) is a chronic, relapsing disease predominantly affecting infants, children and adolescents aged ≤ 16 years.[1,2] However, the disease often has a more severe and persistent character in adults than in children.

AD is usually managed by avoidance of triggering factors and treatment with corticosteroids while the disease is active, and intensive skin care including emollients on an ongoing basis. The efficacy and safety of topical corticosteroids have been proven in the acute treatment of active AD;[3,4] however, their long-term potential to prevent relapses is not well known. Although very potent, these drugs can exhibit serious side-effects, especially when applied over a long time and at high doses. Currently, there is no consensus as to the best course of long-term management and optimal control of AD.[5,6]

Several treatment regimens with corticosteroids are used.[7] Options include intermittent use of corticosteroids or initial therapy with a highly potent corticosteroid followed by a time-dependent dose reduction or change to a less potent preparation.[4,7]

Methylprednisolone aceponate (MPA) is a corticosteroid with strong vasoconstrictive and potent glucocorticoid receptor-binding properties and rapid metabolic clearance. Topical MPA demonstrates a low rate of percutaneous penetration and an associated low incidence of local and systemic side-effects.[8] Applied once daily to affected skin, topical MPA is rapidly effective and safe in the treatment of acute moderate to severe AD.[9,10]

The present study was designed to investigate a long-term therapeutic strategy for managing recurring AD using MPA 0·1% cream. Because of its placebo-controlled and long-term character the study included only adolescents and adults.

Methods

Study design

This multicentre, double-blind, placebo-controlled, randomized, parallel-group study consisted of two phases: the acute treatment phase (AP) and the maintenance phase (MP). The study was approved by the study centres' Independent Ethics Committees and conducted according to Good Clinical Practice guidelines.

Study population

Patients were recruited at 20 centres in Germany, Italy and Spain. Patients ≥ 12 years of age with a history of moderate to severe AD for ≥ 2 years were eligible if they had an acute flare of AD according to the Investigator's Global Assessment (IGA) scores of 'severe' or 'very severe' (IGA score ≥ 4) at baseline. Other inclusion criteria were: washout periods for systemic AD therapy, vaccination, local therapy with tacrolimus, and pimecrolimus (≥ 4 weeks) or glucocorticoids (≥ 1 week) and antihistamine therapy (≥ 2 weeks). Exclusion criteria included pregnancy and lactation, indications for systemic AD therapy, known sensitivity to MPA, emollient and/or to any content of the respective formulations, known immune, hepatic, or renal insufficiency, and acute infections and infestations.

Procedures

After screening, patients entered the AP, during which they received open-label MPA cream once a day to stabilize their flare as well as open-label emollient once a day for a maximum of 4 weeks.

Patients whose flares stabilized during the AP (i.e. IGA score ≤ 1) were eligible to enter the double-blind MP. Randomization at the end of the AP was carried out in blocks according to the patients' arrival at the study centre and aimed to achieve a 1 : 1 randomization ratio overall and within each centre. MP medication was packed in identical tubes to ensure blinding.

Patients either applied MPA once daily plus emollient (Advabase®; Intendis GmbH, Berlin, Germany) once daily for two consecutive days a week (weekends) and emollient twice daily for 5 days a week, or emollient twice daily for 7 days a week. They were advised to apply the study medication once in the morning and once in the evening to the affected skin, including predilection areas that had healed during the AP and newly occurring lesions. Patients were evaluated at weeks 2, 6, 10 and 16 of the MP, or at relapse, in which case they were withdrawn from the study.

Compliance was monitored throughout the study by weighing the used and unused medication that was to be returned by the patients.

Efficacy variables

The primary efficacy variable was the time to relapse, defined as the number of days from start of the MP until AD relapsed. A relapse was defined as the need to intensify MP treatment from the patient's perspective and the patient requested more intense treatment. In order to distinguish precisely the preventive action of maintenance therapy from early treatment of new lesions, new lesions were reported separately. Secondary efficacy variables included the relapse rate, the Eczema Area and Severity Index (EASI),[11] the assessment of target lesions, and intensity of itching on a 100-mm visual analogue scale (VAS). Further efficacy variables were the IGA score,[12] affected body surface area (BSA), Dermatology Life Quality Index (DLQI) and children's DLQI (CDLQI),[13,14] patient's and investigator's global assessment of response, and patient's assessment of quality of sleep. All assessments were performed under double-blind conditions.

Safety variables

Adverse events (AEs) were documented at all study visits. Signs of skin atrophy, striae formation and telangiectasia were monitored. The number of local bacterial, viral and fungal

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infections, and the degree of treatment-related pruritus, irritation and burning, were also documented as AEs.

Analyses

Time to relapse was compared between treatment groups using a Cox proportional hazards model with centre included as covariate. Results from centres that recruited fewer than 10 patients were pooled for analysis. Kaplan–Meier estimates were calculated to describe the time to relapse distribution. The relapse rate at the end of the MP was analysed using the extended Mantel–Haenszel test, controlled for centre. Patients who withdrew prematurely were considered to have relapsed for this analysis. Both hypotheses were tested at a one-sided 2·5% significance level. Hierarchical testing was applied to account for multiplicity. Change during the MP for all other efficacy variables was compared using the Student's t-test. The last-observation-carried-forward principle was applied to impute missing values in secondary analyses. Explorative tests were two-tailed and a 5% significance level was applied.

Efficacy was assessed for the full analysis set (FAS), including all patients who entered the MP, and for the per protocol set (PPS), which excluded patients with major protocol violations. Safety was assessed for all patients to whom AP medication was dispensed and for the FAS. The efficacy results from the FAS and PPS groups were comparable. Analysis by centre did not reveal differences. All statistical analyses were performed with SAS®, version 9.1.3 on a MS-Windows platform.

Determination of sample size

A hazard ratio of 1·9 for the time to relapse was observed in a previous trial with a corticosteroid.[15] A total of 76 relapses needed to be observed to detect this hazard ratio with a log-rank test at a one-sided 2·5% significance level and a power of 80%. Thus, 250 patients were to be enrolled in the AP to account for (i) not all patients being eligible for the MP and (ii) an estimated relapse rate for emollient treatment of 55–65%.

Results

Patient recruitment and numbers analysed

A total of 252 patients were screened between August 2005 and January 2006, of whom only three did not comply with the inclusion/exclusion criteria (Fig. 1). Thus, 249 patients entered the AP, the majority of whom (221 patients) were eligible for the MP. These 221 patients, who represented the

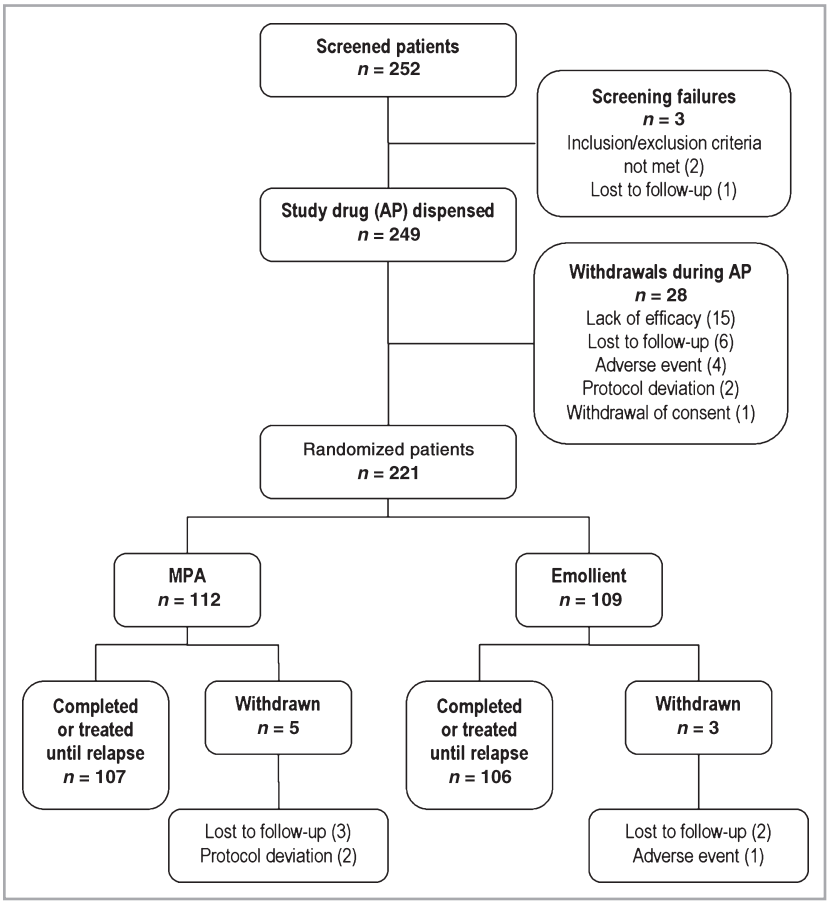

Fig 1. Subject flow chart. AP, acute phase; MPA, methylprednisolone aceponate.

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Table 1 Demographic and disease characteristics at screening, reasons for withdrawal and adverse events

Variable	MPA (n = 112)	Emollient (n = 109)
Age (years), mean ± SD	31·1 ± 14·7	30·6 ± 14·7
Female, n (%)	66 (58·9)	76 (69·7)
Male, n (%)	46 (41·1)	33 (30·3)
Caucasian, n	112	108
Asian, n	0	1
EASI (points), mean		
Screening	17·2	15·3
End of the AP	1·9	1·4
Itching (VAS, mm), mean		
Screening	67·5	67·7
End of the AP	10·1	8·7
Affected BSA (%), mean		
Screening	24·2	22·9
End of the AP	6·2	5·1
Adverse events		
Number of patients reporting adverse events (MP)	17	26
Number of patients with adverse events related to study drug	0	0
Number of patients with severe adverse events	0	2

MPA, methylprednisolone aceponate; SD, standard deviation; EASI, Eczema Area and Severity Index; AP, acute phase; VAS, visual analogue scale; BSA, body surface area; MP, maintenance phase.

FAS, were randomized to MPA (112 patients) or emollient (109 patients), and 213 completed 16 weeks of treatment or were treated until relapse (107/112 in the MPA group and 106/109 in the emollient group). Eight patients withdrew from the study (five in the MPA group and three in the emollient group), but only one patient (emollient group) withdrew due to an AE (worsening of itching) during the MP. The PPS consisted of 186 patients (97 in the MPA group and 89 in the emollient group).

The treatment groups were balanced with regard to demographic and disease characteristics at screening (Table 1).

Efficacy results

Primary efficacy variable

Treatment with MPA plus emollient more effectively prevented a relapse than emollient alone. The probability of not having experienced a relapse after 16 weeks was 87·1% (MPA group) compared with 65·8% (emollient group) (Fig. 2).

The difference between treatments for the time to relapse was statistically significant ($P < 0·0001$) in favour of MPA, with a hazard ratio of 3·5 (95% confidence interval 1·9–6·4). Due to the low number of relapses, the median time to relapse could not be calculated in either group.

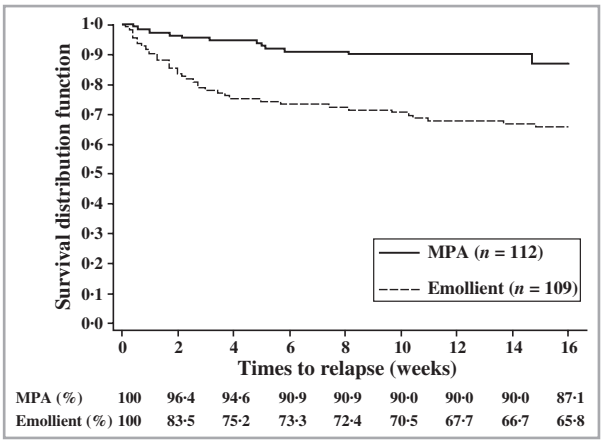

Fig 2. Kaplan–Meier plot for time to relapse. The function shows the proportion of patients without a relapse at the given time point. Kaplan–Meier estimates for the probability of not experiencing a relapse are given below the *x*-axis of the graph for both treatment groups. MPA, methylprednisolone aceponate.

Secondary efficacy variables

The relapse rate at the end of the study was significantly lower in the MPA group (16·1%) than in the emollient group (36·7%; $P = 0·0003$, confirmatory testing). Of the 51 patients who had a relapse, new lesions occurred in three MPA patients, compared with 12 emollient patients.

Changes in the EASI also demonstrated a better treatment effect with MPA compared with emollient alone (Fig. 3). During the MP, the mean EASI remained relatively stable in the MPA group, (mean increase of 0·50 points relative to the end of the AP), whereas it increased by 2·97 points in the emollient group. The difference between treatment groups was statistically significant at all visits during the MP ($P < 0·001$).

Intensity of itching declined substantially compared with baseline in both treatment groups. However, during the MP,

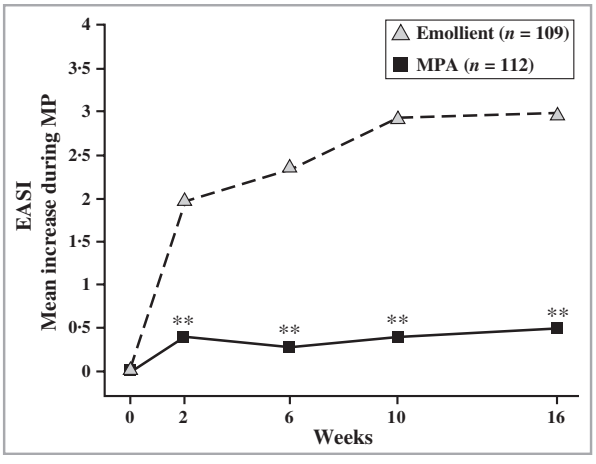

Fig 3. Mean increase in the Eczema Area and Severity Index (EASI) during the maintenance phase (MP), relative to the end of the acute phase. MPA, methylprednisolone aceponate; **$P < 0·001$.

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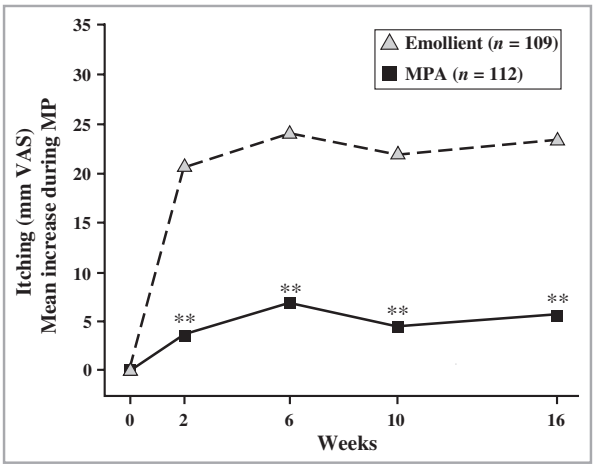

Fig 4. Mean increase in the intensity of itching during the maintenance phase (MP), relative to the end of the acute phase. VAS, visual analogue scale; MPA, methylprednisolone aceponate; **P < 0·001.

Table 2 Intensity of itching in patients with or without a relapse

	Mean intensity of itching (VAS) (mm)			
	Patients with relapse		Patients without relapse	
Time point	MPA	Emollient	MPA	Emollient
Start of the MP	10·1	12·2	10·1	6·6
End of the MP	42·7	57·1	10·5	17·5

VAS, visual analogue scale; MPA, methylprednisolone aceponate; MP, maintenance phase.

success was considerably better in the MPA group than in the emollient group (Fig. 4). The mean intensity of itching increased during the MP by only 5·5 mm on the VAS in the MPA group, compared with 23·3 mm in the emollient group. Interestingly, in the MPA patients who did not relapse, the intensity of itching remained completely stable over the course of the MP (Table 2). The difference between the treatments was statistically significant at each visit (P < 0·0001).

Further efficacy variables

Analysis of all further efficacy variables, especially quality of sleep and global assessment of response, confirmed the superior maintenance effect of MPA over emollient alone (data not shown). The mean quality of sleep worsened only slightly under MPA treatment, whereas it clearly deteriorated in patients using emollient alone. The change in disease during the MP was not assessed as 'much worse' for any patient in the MPA group, compared with 11 out of 96 (patient's assessment) or 4 out of 107 (investigator's assessment) patients in the emollient group. During the MP, the IGA score remained grade 0 or 1 for 72% of MPA patients (emollient 45%). Only one MPA patient had an IGA score grade 4 (emollient 10 patients with grade 4, one patient with grade 5). The DLQI total score improved under MPA treatment by 0·6 points, mainly due to improvements in the categories 'leisure' (1·6 points) and 'personal relationships' (1·2 points) but worsened in all categories (by 4·4 to 13·8 points) in the emollient group. Similarly, the CDLQI had better results in the MPA group in all categories assessed (data not shown). The percentage of affected BSA decreased by 0·6 points in the MPA group, compared with an increase of 3·5 points in the emollient group.

Safety results

During the entire study, 61 of 249 patients (24%) reported at least one AE, of which only one (skin burning) was related to the study drug. During the MP (221 patients), 43 (20%) reported at least one AE, with 17 (15%) in the MPA group and 26 (24%) in the emollient group. No AEs during the MP were considered related to the study drug and no serious AEs were reported.

A worsening of AD was reported for six MPA patients (three with new lesions) and 15 emollient patients (12 with new lesions). No new visual signs of atrophy were reported during the study.

Discussion

Topical corticosteroids are currently a standard treatment option for acute AD.[3,4] However, as these drugs can exhibit serious side-effects, there is no standard treatment strategy for long-term management of the disease.[5,6] As there is no cure for AD, more data are needed on the long-term use of corticosteroids in order to understand the best course of long-term management and optimal control of AD.[6]

AD is a chronic inflammatory disease and characterized by dry skin, even involving nonlesional skin, and an increased transepidermal water loss. Among other factors, a reduced content of ceramides and overexpression of stratum corneum chymotryptic enzyme are known to contribute to the disturbed epidermal barrier of AD patients.[7] As a consequence of the barrier dysfunction and the chronic inflammation of the skin, most AD patients become sensitized to food and/or aeroallergens, which can develop into a sensitization to self-proteins.[16]

Recently, mutations in the gene encoding the epidermal protein filaggrin have been found to be strongly associated with a disturbed epidermal barrier and, consequently, with a predisposition to AD.[17–20] Repeated barrier disruptions are thought to induce an inflammatory reaction causing acute AD flares.[16] As the use of emollients helps to restore the protective function that is partially lost by skin barrier disruptions, treatment with emollient alone can already be an effective AD maintenance therapy.[21,22] However, skin inflammation during acute flares requires treatment with anti-inflammatory agents such as topical steroids.

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Due to the chronic nature of AD, inhibition of flare development by early intervention with anti-inflammatory therapies is also an important therapeutic target.[23] Intermittent use of the corticosteroid fluticasone propionate in combination with daily emollient following stabilization of acute AD flares has been shown to provide efficient and safe maintenance therapy.[15,21,22] The findings of the present study confirm the appropriateness of this therapeutic design with another corticosteroid, MPA.

The use of MPA during the AP effectively stabilized severe or very severe flares of AD in 89% of all patients. As other studies have shown, this is a critical factor in a regimen of intermittent long-term therapy to ensure long-term maintenance.[21–25]

During the MP, MPA proved to be superior to the emollient control in all efficacy variables assessed. After 16 weeks of treatment, the probability of not having a relapse was 87·1% in the MPA group, compared with 65·8% in the emollient group (Kaplan–Meier estimates). The risk of having a relapse was reduced 3·5-fold with MPA compared with emollient. The overall relapse rate was also lower with MPA (16·1%) compared with emollient treatment (36·7%). The relapses included new lesions in three MPA and 12 emollient patients, indicating that treatment with MPA hinders the occurrence of new lesions and therefore controls the spreading of the existing AD.

In agreement with a recently published study,[10] MPA effectively reduced the intensity of itching. During the MP, the mean intensity of itching increased slightly in the MPA group (from 10·1 mm to 15·7 mm) whereas it increased considerably in the emollient group (from 8·7 mm to 32·0 mm). Itching, the key symptom for evaluating the treatment response,[4] is a major triggering factor of AD and usually precedes other skin symptoms, as the provoked scratching worsens the present inflammation and makes the skin prone to infections. By reducing the intensity of itching, MPA may improve control of the disease and thereby contribute to the reduction in relapses.

Despite the known importance of itching as a trigger factor, the pathogenetic role of pruritus in atopic individuals remains elusive. Different peripheral itching mediators and receptors may be involved, each impacting the disease differently.[26] Acute lesions are characterized by high concentrations of interleukin (IL)-4 and/or IL-13 within the affected skin, whereas in chronic lesions IL-12 accumulates.[27,28] Recently, a new pruritus- and AD-inducing cytokine, IL-31, has been described.[29] Glucocorticoids exert their effects by interfering with inflammatory pathways. It would be of interest to explore further whether or not topical glucocorticoids such as MPA contribute to the stabilization of AD by interfering with itching mediators.

The superiority of MPA over emollient alone was supported by the analyses of all further efficacy variables, particularly quality of sleep and global assessment of response. In addition, a significantly higher proportion of MPA patients completed the study with an IGA score grade 0 or 1, and fewer reported severe or very severe disease. Significantly superior results were also obtained for DLQI, CDLQI, target lesion score and affected BSA. These findings underline the clinical advantages for MPA treatment in maintenance therapy of AD, particularly for relieving symptoms and improving the quality of life.

The safety results showed that after 20 weeks the use of MPA cream for maintenance treatment was well tolerated and not associated with an increased risk compared with use of emollient alone. The frequency of patients reporting AEs was not higher with MPA (15·2%) than with emollient alone (23·9%). No AEs during the MP were considered related to the study drug and no serious AEs were reported.

The findings of this study thus show that the combination of MPA with emollient provides an effective and safe maintenance treatment regimen to control AD in patients ≥ 12 years of age. In particular, the reduced risk of relapse and the improvement in itching may have important implications for physicians when considering strategy options for patients who need long-term treatment.

Acknowledgments

We thank the additional investigators involved in this study: S. Fischer MD (Leipzig, Germany); H. Franz MD (Berlin, Germany); H. Friedrich MD (Oranienburg, Germany); C. Guillén MD (Valencia, Spain); M. Lochno MD (Löbau, Germany); M. Lübke MD (Berlin, Germany); K.-G. Meyer MD (Berlin, Germany); A. Patrizi MD (Bologna, Italy); K. Peris MD (L'Aquila, Italy); J. Peyri MD (Esplugues de Llobregat, Spain); T. Rieken MD (Berlin, Germany); M. Schröder MD (Berlin, Germany); J. Sánchez del Rio MD (Oviedo, Spain); S. Seidenari MD (Modena, Italy); M. Simon MD (Berlin, Germany); K. Weis MD (Reichenbach, Germany); and D. Wilsmann-Theis (Bonn, Germany). This study was sponsored by Intendis GmbH, Berlin.

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