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Original article

Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis

Background: Topical glucocorticosteroids are the gold standard in treatment of atopic dermatitis (AD). Recently, topical calcineurin inhibitors have been developed for treatment of this condition. This study compared efficacy and safety of 0.1% methylprednisolone aceponate (MPA) ointment with 0.03% tacrolimus ointment for 3 weeks, in children and adolescents with severe to very severe flare of AD.
Methods: The primary end point was treatment success, defined as a score of 'clear' or 'almost clear' in the static Investigator's Global Assessment (IGA) score. Secondary end points were the percentage change in the Eczema Area and Severity Index (EASI) and patients' assessment of itch and sleep, Children's Dermatology Life Quality Index, patient's assessment of global response, affected Body Surface Area and medication costs.
Results: 265 patients were randomized to either MPA ($n = 129$) or tacrolimus ($n = 136$) treatment, 257 patients completed the study. Methylprednisolone aceponate 0.1% ointment once daily provided rapid and relevant clinical benefit. Tacrolimus 0.03% ointment twice daily was equally effective with regard to success rate. Methylprednisolone aceponate was superior to tacrolimus for EASI, itch and sleep. Both treatments were well tolerated. Drug-related adverse events were only observed in the tacrolimus group. Medication costs were significantly lower for MPA.
Conclusions: While both treatment groups showed similar efficacy results regarding treatment success (IGA), significant advantages were observed for EASI, itch and sleep with MPA 0.1%. These advantages and the significantly lower treatment costs highlight the benefits of MPA treatment, underlining its first-line role in treatment of children and adolescents with severe AD.

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Key words: atopic dermatitis; children; clinical study; methylprednisolone aceponate; tacrolimus.

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Atopic dermatitis (AD) is a common chronic-relapsing skin disease, affecting on average 10–12% of the total population, with 80–90% of cases occurring in the under-5s, and the incidence is increasing. Atopic dermatitis significantly affects quality of life and productivity in both children and adults. Children and adolescents are the focus of this study. Patients in this age group are particularly affected by the disease, often with adverse effects on their schooling.

Topical glucocorticosteroids (TGCs) were developed in the early 1950s, and have since been established as the gold standard for anti-inflammatory therapy. Methylprednisolone aceponate (MPA; Advantan®) is a fourth-generation TGC, designed to combine potent but gentle therapy with high local efficacy and excellent tolerability in terms of systemic and local side effects (1, 2). Methylprednisolone aceponate has proven to be highly effective and very well tolerated in extensive clinical trials involving patients with differing forms of eczema and AD (3).

Recently, topical calcineurin inhibitors (TCIs) have been introduced for the treatment of AD. Topical calcineurin inhibitors form a new class of topical medications for the treatment of AD, and among these compounds, tacrolimus (Protopic®; Fujisawa, Munich, Germany) is considered to be the most efficient for dermatological indications (4).

There are few clinical comparisons of TCIs with more potent TGCs. In studies in children with AD in which tacrolimus was compared with less potent TGCs, tacrolimus proved to be superior (5, 6). When tacrolimus was compared with more potent TGCs in adults with AD, the TGC tested proved to be either superior to or nearly as effective as tacrolimus in populations with moderate to severe AD (7, 8). In the present study, we compared MPA with tacrolimus in patients with an acute flare assessed as severe to very severe at the time of enrolment. Both MPA and tacrolimus were applied according to the concentration currently licensed for use in children: MPA 0.1%

ointment once daily, tacrolimus 0.03% ointment twice daily. In order to maintain blinding the MPA patients were provided with the vehicle ointment, Neribas® (Schering, Berlin, Germany), for use in the morning. The maximum duration of treatment of 3 weeks was considered to be sufficient to treat an acute flare of AD [Investigator's Global Assessment (IGA) ≥ 4], and is in accordance with the prescribing information for tacrolimus.

Methods and patients

Study design

This randomized, double-blinded comparative study was conducted at 25 centres in Germany, Italy and Spain between February and August 2005. It was approved by the ethics committee of each centre and conducted according to the Declaration of Helsinki. Following written informed consent from the parents/guardians (and patients ≥14 years), eligible males and females aged 2–15 years experiencing an acute severe or very severe flare of the disease (IGA ≥ 4) were enrolled.

After initial screening, study evaluation visits were performed at baseline and on days 4 and 7, weeks 2 and 3 (end of treatment). At the week 2 visit, patients with cleared AD for at least 7 days discontinued treatment and terminated the study. Providing informed consent was in place and the patients met the washout criteria, the screening and baseline visit could take place on the same day.

Randomization and blinding

The randomization was done in blocks to achieve balanced randomization overall and within each centre. The study ointment was packed in identical tubes to ensure blinding. Two sets of tubes of ointment, one for use in the morning (blue labels) and another for the evening (red labels) were provided. The morning tube for the MPA group contained an emollient (Neribas® ointment) to maintain the blind.

Treatments

The patients applied a thin layer of either 0.03% tacrolimus ointment twice daily or 0.1% MPA ointment in the evening to all affected Body Surface Area (BSA). Those using MPA also applied Neribas® ointment in the morning, which has essentially the same composition as MPA but no active ingredient. Treatment was to continue for a minimum of 2 weeks and maximum of 3 weeks and cleared areas treated for an additional 7 days postclearance. Patients should not take a bath or shower for 2 h after application of study medication. If clinically necessary the patients could use nonmedicated topical emollients or bath oil. All of the used ointment tubes for each patient were weighed at the end of the study to calculate total ointment usage and treatment cost.

Inclusion and exclusion criteria

Inclusion criteria were: acute flare of AD according to the IGA (≥4: 'severe' or 'very severe'); history of moderate to severe AD for at least 1 year; age 2–15 years at baseline; affected BSA minimum of 5%; avoidance of excessive exposure to natural or artificial sunlight.

Exclusion criteria were: previous systemic therapy for AD or phototherapy (< 4 weeks); vaccination (< 4 weeks); antihistamine therapy (< 2 weeks); local therapy with tacrolimus, pimecrolimus or glucocorticosteroids (< 1 week); pregnancy or breast feeding; indication for systemic therapy; sensitivity to the test products or macrolides; lymphadenopathy; immune deficiency; hepatic or renal insufficiency; acute herpes simplex, mononucleosis or mollusca contagiosa infection; acute and severe impetigo contagiosa; severe other viral, bacterial or fungal skin infection; acute infestations; generalized erythroderma; Netherton's syndrome.

Study efficacy parameters

The primary study efficacy parameter was the static IGA score (9). All investigators were trained in the use of the IGA scoring system and provided with reference photographs.

Secondary efficacy parameters included the Eczema Area and Severity Index (EASI), the affected BSA, patient's assessment of itch, patient's assessment of quality of sleep and cost-effectiveness. Eczema Area and Severity Index is a validated tool to objectively assess dermatitis severity that incorporates surface area involvement (10).

Patients or parents assessed the intensity of itching during the previous 24 h and the quality of sleep using 100 mm Visual Analogue Scales (VAS), where 0 mm indicated 'no itch'/'slept well' and 100 mm represented 'worst itch imaginable'/'slept badly', respectively.

The study also included a modification of the EASI (mEASI), which integrates the patient's assessment of itch (6), the Children's Dermatology Life Quality Index (CDLQI; 11) and a scaled patient's assessment of the change of disease from baseline.

Safety assessments included physical examination, record of concomitant medications, pregnancy tests and medical history. Adverse events were monitored throughout the study.

Statistical analysis

The primary study efficacy parameter IGA was dichotomized into treatment success (IGA score clear or almost clear at the end of treatment) and no success (IGA score worse than almost clear or missing) and analysed using the extended Mantel-Haenszel test, controlled for centre. A one-sided 2.5% significance level was used. Results from centres, which recruited < 10 patients, were pooled for analysis. Change from baseline for secondary efficacy parameters 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 both the Full Analysis Set (FAS) patients and for the Per-Protocol (PP) patients. Safety was assessed for the FAS patients, including all randomized patients to whom medication was dispensed. The results from the FAS and PP groups were comparable. All statistical analyses were performed with SAS®, Version 8.2 (SAS Institute Inc., Cary, NC, USA) on a MS-Windows platform. Percentages were truncated to one decimal place.

Determination of sample size

The success rate of tacrolimus 0.03% ointment in children with moderate to severe AD was estimated to be between 35% and 40% (5, 6). Assuming a difference of 20% between treatments and taking a one-sided significance level of 2.5% with a power of 80%, it was calculated that at least 107 patients should be enrolled per treatment group. In order to allow for premature study terminations the sample size was increased to 125 patients per treatment group.

Results

Patient recruitment and numbers analysed

Figure 1 illustrates the screening, randomization and distribution of patients. A total of 266 patients were screened and only one failed to meet the inclusion criteria giving a total FAS population comprising 265 patients. Of these, 129 were randomized to MPA ointment and 136 to tacrolimus ointment. A total of 257 of 265 patients (96.9%) completed the study. All but two patients (1.6%) in the MPA group completed the study as planned (one patient was lost to follow up and one had a major protocol deviation). In the tacrolimus group, six patients (4.4%) failed to complete the study (four withdrew because of adverse events, one withdrew consent and one was lost to follow up). The PP population consisted of 101 patients.

Demographic features were comparable for the two treatment groups (Table 1). Analysis did not reveal effects that could be attributed to variation between centres or seasonal factors.

Efficacy

Primary end point. The assessment of the primary efficacy parameter IGA at the end of treatment is illustrated in Fig. 2. In both groups, the therapy was evaluated as being successful in the majority of patients (IGA score 'clear' or 'almost clear') by the end of treatment: MPA 86 of 129 (66.6%) and tacrolimus 91 of 136 (66.9%). The difference between treatment groups was 0.3% (95% confidence limits: −11.1 to 11.5%) and was not statistically significant ($P = 0.9314$). At day 14 the success rate was 50.3% (65 of 129) for MPA compared with 41.1% (56 of 136) for tacrolimus. The number of patients cleared at the end of treatment was 48 of 129 (37.2%) for MPA and 40 of 136 (29.4%) for tacrolimus. All patients in the MPA group and 132 of 136 (97.1%) in the tacrolimus group reported an improved IGA score at the end of treatment.

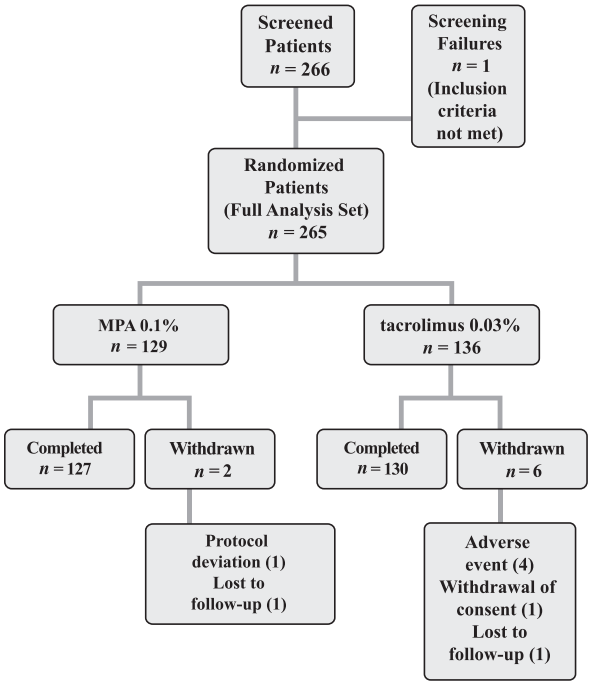

Figure 1. Screening, randomization and distribution of patients.

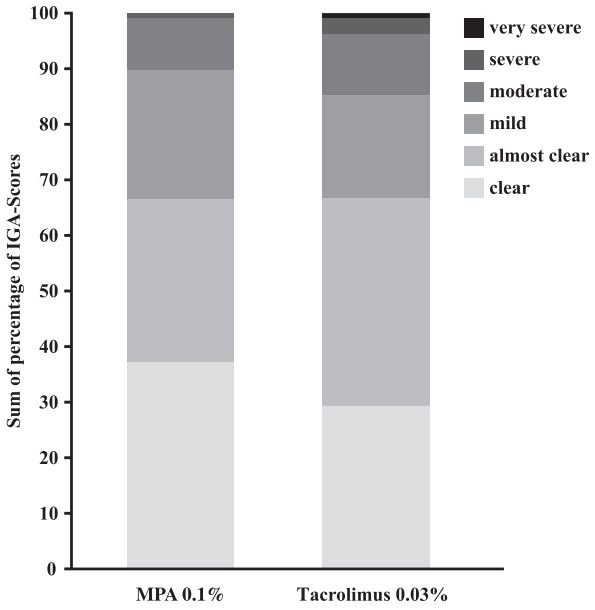

Figure 2. Investigator's Global Assessment scores at the end of the study.

Secondary end points

Eczema Area and Severity Index. Substantial improvement in EASI was noted at days 4 and 7 for both treatment groups. However, there was a greater mean percentage change from baseline for EASI with MPA compared with tacrolimus during the study (Fig. 3). At the end of treatment the mean percentage change from baseline for EASI was 89.7% in the MPA group compared with 85.3% in the tacrolimus group. The difference between the two groups was significant after 7 days of treatment ($P = 0.0352$) and after 14 days of treatment ($P = 0.0214$) but not at day 21 ($P = 0.0667$).

Body Surface Area affected. The percentage of affected BSA decreased from approximately 29% at baseline for both treatment groups to 6.8% in the MPA group compared with 7.7% in the tacrolimus group at the end of the study (Table 1).

Patients' assessment of itch. The mean intensity of itching declined substantially from baseline to end of treatment and was particularly pronounced in the MPA group. Figure 4A shows that with MPA the mean VAS decreased from 68.0 mm at baseline to 6.3 mm at the end of treatment compared with 63.6 mm at baseline and

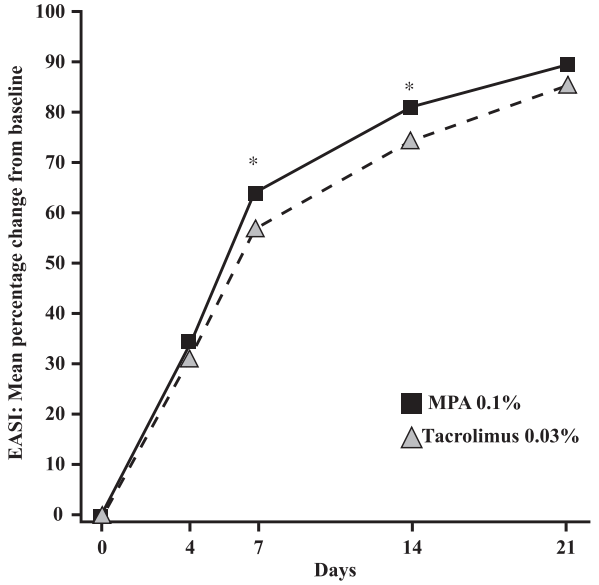

Figure 3. Mean percentage change from baseline in the Eczema Area and Severity Index (EASI; $*P \leq 0.05$).

13.8 mm at end of treatment with tacrolimus. The change in assessment of itch was already statistically significantly in favour of MPA by day 4 (day 4: $P = 0.026$; day 7: $P = 0.0006$; day 14: $P = 0.0007$; day 21: $P = 0.0004$).

Effect on quality of sleep. Starting from mean values of 54.6 mm (MPA) and 51.5 mm (tacrolimus) at baseline, the quality of sleep improved in both groups to 5.3 mm (MPA) and 11.0 mm (tacrolimus) at the end of treatment (Fig. 4B). The improvement in quality of sleep with MPA was significantly better than tacrolimus at day 14 ($P = 0.0409$), and at the end of treatment ($P = 0.0094$).

Medication costs. The mean amount of study medication needed for treatment in the MPA group was 53.7 g of MPA ointment compared with 89.3 g of tacrolimus ointment in the tacrolimus group. The mean cost of treatment in the MPA-treated group was 14.59 €, compared with 100.99 € in the tacrolimus group. Both findings were significantly in favour of MPA ($P = 0.0001$).

Additional analyses. The mEASI scales (data not shown) revealed similar results to EASI. Results for CDLQI in the categories 'symptoms and feelings' and 'sleep' reflected the more pronounced effect of MPA compared with tacrolimus on itch and quality of sleep detailed in the previous sections (data not shown). No patients in the MPA group but two patients in the tacrolimus group reported a worsening of the disease compared with baseline.

Safety

No patients in the MPA treatment group experienced adverse events attributed to treatment, while six patients (4.4%) in the tacrolimus treatment group did (Table 1). These patients reported pruritus, erythema, skin burning and hot flushes.

A total of four patients (all in the tacrolimus group) discontinued the study due to adverse events (one pruritus, one pruritus and skin burning, one pruritus and hot flushes, one scarlet fever). With the exception of the patient with scarlet fever, these were assessed by the investigator as being drug-related. The dose of study medication was reduced for one patient in the MPA group, who had varicella. This adverse event was not assessed as drug-related (Table 1).

Table 1. Demographic and baseline characteristics, reasons for withdrawal and adverse events

	MPA	Tacrolimus
n	129	136
Age (years; mean ± SD)		
All patients	7.8 ± 4.2	7.5 ± 4.2
2–6	56 (43.4%)	64 (47%)
7–11	40 (31.0%)	38 (27.9%)
12–15	33 (25.5%)	34 (25.0%)
Ethnic group, *n* (%)		
Caucasian	122 (94.5)	134 (98.5)
Black	3 (2.3)	1 (0.7)
Oriental	3 (2.3)	1 (0.7)
Other	1 (0.7)	–
Baseline values for secondary end points (mean)		
EASI (points)	18.7	18.7
Itch (VAS, mm)	68.0	63.6
Sleep (VAS, mm)	54.6	51.5
Percentage affected BSA		
Baseline	28.8	29.4
Day 4 of treatment	23.2	23.7
Day 7 of treatment	16.2	14.0
Day 14 of treatment	10.4	11.2
Day 21 of treatment	6.8	7.7
Reasons for treatment discontinuation		
Adverse events	–	4 (2.9%)
Protocol deviation	1 (0.7%)	–
Withdrawal of consent	–	1 (0.7%)
Lost to follow up	1 (0.7%)	1 (0.7%)
Total (8/3.0%)	2 (1.6%)	6 (4.4%)
Adverse events		
Number of patients reporting adverse events	16 (12.4%)	23 (16.9%)
Number of patients with adverse events related to study drug	–	6 (4.4%)
Number of patients reporting severe adverse events	–	6 (4.4%)

MPA, methylprednisolone aceponate; BSA, Body Surface Area; EASI, Eczema Area and Severity Index; VAS, Visual Analogue Scale.

Discussion

This study was conducted to investigate the treatment of children and adolescents with severe to very severe AD with once daily application of TGC, MPA (0.1%), in comparison with twice daily application of the TCI, tacrolimus (0.03%), with regard to efficacy and safety.

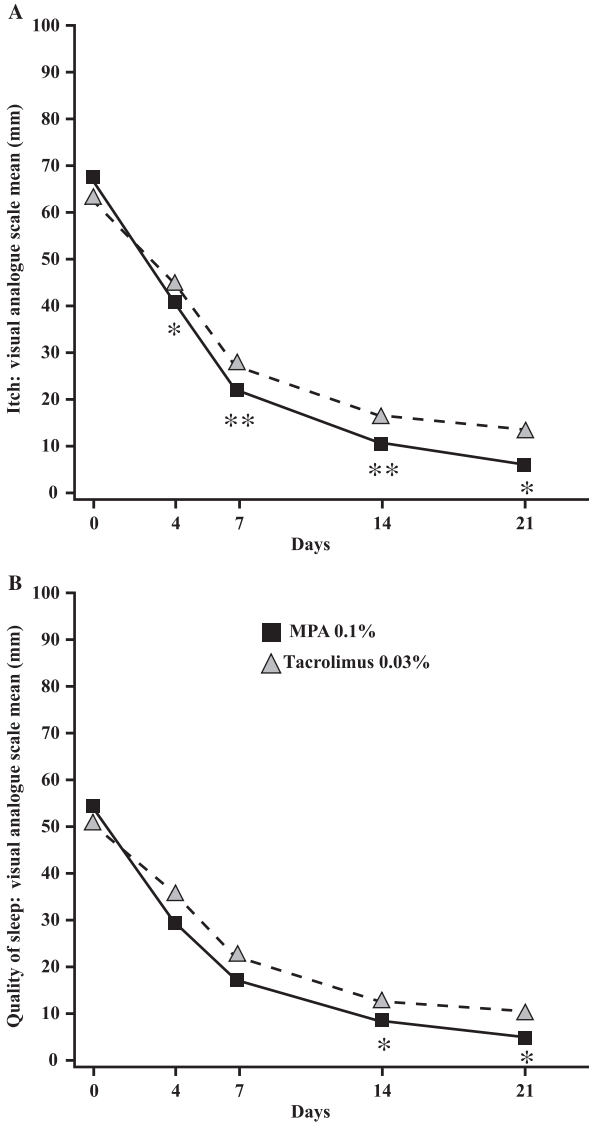

Figure 4. Effect on intensity of itch and quality of sleep. (A) Mean intensity of itch, (B) mean quality of sleep (*$P \leq 0.05$; **$P \leq 0.001$).

This was the first direct comparison of tacrolimus with MPA, and also differed from earlier studies in that the comparison was made in children and adolescents with severe or very severe episodes of AD (flares). As this was an acute study it was not designed to examine potential rebound effects post-treatment; however, this may be of interest for future studies.

The study design was limited by the formulation and licensed treatment duration for tacrolimus. An ointment would not be the formulation of choice for treating an acute flare of AD; however, tacrolimus is only available as an ointment and the ointment formulation of MPA was therefore used in order to blind the treatments appropriately. Tacrolimus is licensed for a maximum of 3 weeks continuous twice daily application, which determined the treatment duration in this study. Consequently, the results presented here may not reflect the outcome of long-term treatment.

Topical glucocorticosteroids remain the gold standard of therapy. The results of this study show that treatment with MPA leads to rapid relief of symptoms in patients with severe and very severe AD. Complete or near complete clearing of AD lesions occurred in two-thirds of patients. While both treatments were efficacious, more patients treated with MPA had completely cleared symptoms by the end of treatment (37.2% MPA *vs* 29.4% in the tacrolimus group) and experienced a significantly more rapid decrease in the EASI score than those patients treated with tacrolimus.

The goal of therapy in AD is to relieve symptoms and improve the quality of life in those who suffer from this condition. This is especially true in children and adolescents, who need fast, reliable and, above all, safe treatment. Lost sleep or sleep of poor quality and itching impact negatively on school and leisure time activities. In the present study, patients treated with MPA experienced significant improvement in quality of sleep, probably related to the decrease in the intensity of itching.

The results of a meta-analysis of randomized-controlled trials examining the efficacy and tolerance of two TCIs (pimecrolimus and tacrolimus) in the treatment of AD were published in 2005 (12). It reported 25 trials in which pimecrolimus and tacrolimus were compared with either vehicle, each other, or with TGCs (longer term treatment was applied in one of the studies). Two of these studies compared tacrolimus with hydrocortisone acetate treatment in children with moderate to severe AD over 3 weeks, which was the maximum treatment period of the study reported here. As expected, tacrolimus proved to be superior in efficacy to the weak TGC.

The study reported here confirmed several of the findings in the earlier meta-analysis (12). When tacrolimus was compared with more potent TGCs (hydrocortisone butyrate 0.1%) in adults with moderate to severe AD according to the criteria of Rajka and Langeland (13), tacrolimus 0.03% was significantly less effective. Comparing higher-strength tacrolimus (0.1%) to hydrocortisone butyrate 0.1% and betamethasone valerate 0.1% in adults with AD, tacrolimus 0.1% was shown to be as effective as the two TGCs. In the study reported here, while both treatment groups showed similar efficacy results regarding the treatment success (IGA), significant advantages following once daily administration of MPA 0.1% ointment compared with twice daily application of tacrolimus 0.03% ointment were observed for the EASI, itch and sleep. The differences between MPA and tacrolimus were small but statistically significant and consistently in favour of MPA and taken together the results should translate into a real clinical benefit of MPA treatment.

The results of the present study confirmed the excellent safety profile of MPA and the findings in the meta-analysis mentioned above. Trials examined in the meta-analysis showed no significant differences between TCIs

and TGCs with regard to rates of withdrawal from treatment. In the study reported here, four patients in the tacrolimus group withdrew due to adverse events, while no patients withdrew from the MPA group.

The trials included in the meta-analysis showed that tacrolimus was significantly more likely to cause sensations of skin burning than the TGCs. We did not note increased frequency of this adverse event in our study. This may have been due to methodological reasons. First, some patients included in the study had previously used tacrolimus and were thus used to this problem. Secondly, the patients in the study were informed about possible side effects before beginning treatment and might not have reported them because they were anticipated. Finally, we did not ask specifically about any one adverse event.

The cost of therapy in today's environment of dwindling resources on the part of both government and private health insurers is increasingly a major concern, especially in management of chronic conditions. National Health Service annual costs for the treatment of AD were reported to be in excess of 189 Mio Euros in a recent report, and this figure did not include costs to individuals and society at large (14). Costs alone cannot, and should not, be the only factor in deciding which therapy to offer. However, this study demonstrated that MPA ointment, with its rapid onset of action, reliable efficacy and an excellent safety profile, could be an affordable option.

Although we did not address the issue in this study, compliance can be improved when treatment is applied once daily, rather than twice daily. This can especially be true in a population that, because of the nature of their disease, has to apply skin care products (emollients, oils, moisturizers) on a regular basis. The rapid onset of action, short treatment duration, excellent therapeutic results and good tolerability confirmed that, in this study, MPA was the best option for treatment of children and adolescents with AD. Together with its significantly lower treatment costs than tacrolimus, the study highlights the first-line role for MPA in treating children and adolescents with AD.

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