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CLINICAL REPORT

Safety and Efficacy of Tacrolimus Ointment Versus Pimecrolimus Cream in the Treatment of Patients with Atopic Dermatitis Previously Treated with Corticosteroids

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Adult and pediatric patients ($n=347$) with atopic dermatitis enrolled in three multicenter, randomized, 6-week studies who had previously used steroids were analyzed to examine the null hypothesis that improvement in atopic dermatitis initiated after prior treatment with steroids eliminates any subsequent treatment differences between tacrolimus ointment and pimecrolimus cream. Of these patients, 171 were randomized to tacrolimus ointment and 176 to pimecrolimus cream. Based on improvement in the Eczema Area and Severity Index at the end of study, tacrolimus ointment was significantly more effective than pimecrolimus cream ($p=0.0002$). Tacrolimus ointment was also significantly more effective than pimecrolimus cream at the end of study in all secondary end-points. Overall, the frequency of adverse events was comparable between treatment groups (24.0% for tacrolimus ointment vs. 25.6% for pimecrolimus cream). Tacrolimus ointment is more effective, with a similar safety profile, compared with pimecrolimus cream in patients with atopic dermatitis previously treated with topical corticosteroids. ***Key words: atopic dermatitis; tacrolimus; pimecrolimus; corticosteroids; efficacy.***

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by recurrent episodes of relapse (known as AD flares) and periods of remission. Management of this disorder involves the short-term control of AD flares in conjunction with long-term maintenance therapy that is designed to reduce the incidence and severity of flares, extend remission and improve patients' quality of life. Guideline recommendations include the intermittent use of topical corticosteroids as first-line therapy for AD flares and the frequent use of emollients as maintenance therapy during periods of remission (1, 2).

Topical corticosteroids have been the mainstay of conventional AD management for the past 50 years, as they are rapidly effective for the treatment of AD (3). However, their use in clinical practice must be weighed against the risk of side-effects such as skin atrophy, striae formation and glaucoma (4, 5), or rare systemic side-effects such as hypothalamic-pituitary-adrenal (HPA) axis suppression (6).

The non-steroidal topical calcineurin inhibitors (TCIs), tacrolimus ointment and pimecrolimus cream, are an important treatment option and are indicated in cases where the use of topical corticosteroids is unsuitable, or have failed to adequately control AD. Tacrolimus ointment and pimecrolimus cream are indicated for both short-term and intermittent long-term treatment of AD (7, 8). Both TCIs have shown substantial clinical benefit in short-term studies in adult and pediatric AD patients (9–12). In long-term studies, tacrolimus ointment has been shown to have an excellent safety profile when evaluated for periods of up to 4 years in more than 10,000 adult and pediatric patients (13–18). Long-term treatment with pimecrolimus cream 1% for up to 2 years resulted in a marked improvement in AD and was reported to be well tolerated (19–22). Research has shown that tacrolimus ointment is more effective than pimecrolimus cream in the treatment of AD, with a similar safety profile (23).

Very often, patients use topical corticosteroids as part of the routine treatment for AD. In this sub-analysis we examined the null hypothesis that improvement in AD initiated after prior treatment with topical corticosteroids eliminates any subsequent treatment differences between tacrolimus ointment and pimecrolimus cream. Administering topical corticosteroids before escalating to TCIs is a common treatment paradigm in clinical practice. This switch to TCIs may overcome some of the limitations associated with the long-term use of topical corticosteroids and may help to optimize the risk-benefit ratio in the therapeutic management of patients with AD. Thus, we were interested to determine if there was any evidence that patients with prior corticosteroid treatment would have a different result than the larger population when tacrolimus ointment was compared with pimecrolimus cream. The patients included in this sub-analysis were not topical corticosteroid refractory patients.

MATERIALS AND METHODS

Study overview

Three prospective, randomized, investigator-blinded, multicenter, 6-week studies evaluating the efficacy and safety of tacrolimus ointment and pimecrolimus cream in adult and pediatric patients with mild to very severe AD have been described in detail elsewhere and are summarized below (23). The subanalysis presented here was performed in patients treated with topical corticosteroids within the 30 days prior to enrolment.

Patients

Adult (≥ 16 years of age) and pediatric (2–15 years of age) patients were eligible for enrolment in the three original studies if they met the Hanifin & Rajka (24) clinical criteria for the diagnosis of AD, had at least 5% of their total body surface area (BSA) involved, and disease severity ranging from mild to very severe, according to the Investigator's Global Atopic Dermatitis Assessment (IGADA; a graded scale based on the signs and symptoms of AD that includes the following categories: clear, almost clear, mild, moderate, severe and very severe). Written informed consent was obtained from all patients or their parents/legal guardian. The institutional review board or ethics committee at each centre approved the protocols.

Study designs

In the original studies, patients were randomized (1:1) to receive either tacrolimus ointment or pimecrolimus cream. In one study, pediatric patients with mild AD were randomized to tacrolimus ointment 0.03% or pimecrolimus cream 1%; in the other two studies, adult patients with mild to very severe AD and pediatric patients with moderate to very severe AD were randomized to tacrolimus ointment 0.1% or pimecrolimus cream 1% (23). Patients treated with topical corticosteroids within the 30 days prior to enrolment were evaluated in this subanalysis to examine the null hypothesis that improvement in AD initiated after prior treatment with topical corticosteroids eliminates any subsequent treatment difference between tacrolimus ointment and pimecrolimus cream.

Following an initial washout period of 4 weeks for systemic treatments and a subsequent 4-day washout period for topical treatments (including topical steroids), patients applied a thin layer of the assigned study medication twice daily to all affected body areas for up to 6 weeks or until 1 week after the affected area(s) was completely cleared, whichever came first. Changes to therapy were permitted during the course of the studies following notification of the study investigators. Other medicated agents for the treatment of AD were not permitted during the studies. The use of non-medicated topical agents (e.g. emollients) was permitted only in areas not being treated during the studies.

Patients were assessed at baseline/Day 1, Day 8, Day 22 and Day 43/end of study (EOS) for efficacy and safety. For all patients who completed treatment early, the final visit was conducted before the scheduled Day 43 visit. The primary efficacy end-point in all three studies was the percent change in the Eczema Area Severity Index (EASI) score from baseline to Day 43/EOS. The EASI score is a validated composite score which ranges from 0 (clear) to 72 (very severe) and considers an assessment of disease severity (e.g. erythema, edema, excoriation and lichenification) and percentage of BSA involved in four body regions (head and neck, lower limbs, upper limbs and trunk) (25). Additional end-points included success of therapy based on the IGADA, where success equals "Clear" or "Almost Clear" and failure equals all other IGADA ratings; the percent change from baseline in the %BSA affected; and the patient's assessment of itch, based on a visual analogue scale (VAS) ranging from 0 cm (no itch) to 10 cm (worst itch imaginable). Safety end-points included the overall incidences of all cutaneous adverse events and all related adverse events, as well as the incidence of individual application-site adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

Statistical analysis

In all three studies, efficacy and safety analyses were performed on the cohort of randomized patients who applied study medication at least once during the study (intention-to-treat population). Analyses of EASI score, %BSA affected and patient's assessment of itch were performed using analysis of covariance, in which least square means calculated for each treatment group were adjusted for centre and baseline values. A last observation carried forward analysis was used to impute all missing efficacy data. Baseline values were carried forward as required. Treatment success (which was based on the IGADA score) was analyzed using the χ^2 test. All statistical tests were two-sided, with $\alpha = 0.05$.

Multiple linear regression analysis

In order to assess whether there was a significant treatment effect when additional factors known to influence the outcome of AD were considered, a multiple linear regression analysis (MRA) model was generated with the following set of factors: 1. "Head and Neck Affected at Baseline," 2. "Patient Age," 3. "Treatment Group (tacrolimus ointment vs. pimecrolimus cream)," 4."Baseline IGADA Score and the interactions between 1 and 3, 2 and 3, and 4 and 3.

RESULTS

Study patients

From the original three studies, we identified 347 of 1065 patients (32.6%) who were categorized as having prior steroid use within the 30 days prior to enrolment. Of these, 128 were from the study of adults with mild to very severe AD, 79 were from the study of pediatric patients with moderate to severe AD, and 140 were from the study of pediatric patients with mild AD (Fig. 1). Information on the type and strength of steroid were not recorded during the original studies. Of the 347 patients with prior topical steroid use in the antecedent studies, 171 patients had been randomized to tacrolimus ointment and 176 patients to pimecrolimus cream. Of these 347 patients, 78.9% of those who received tacrolimus ointment and 73.9% of those who received pimecrolimus cream completed the original studies. The most common reason for early study withdrawal was patients being lost to follow-up. Only four patients (2.3%) treated with tacrolimus ointment withdrew due to lack of efficacy, compared with 12 patients (6.8%) treated with pimecrolimus cream, although this difference was not statistically significant ($p < 0.08$). Similarly, only three patients treated with tacrolimus ointment withdrew due to adverse events, vs. 10 patients treated with pimecrolimus cream, but this difference was not statistically significant ($p < 0.09$; Fig. 1). Baseline patient demographics and disease characteristics were generally similar between the two

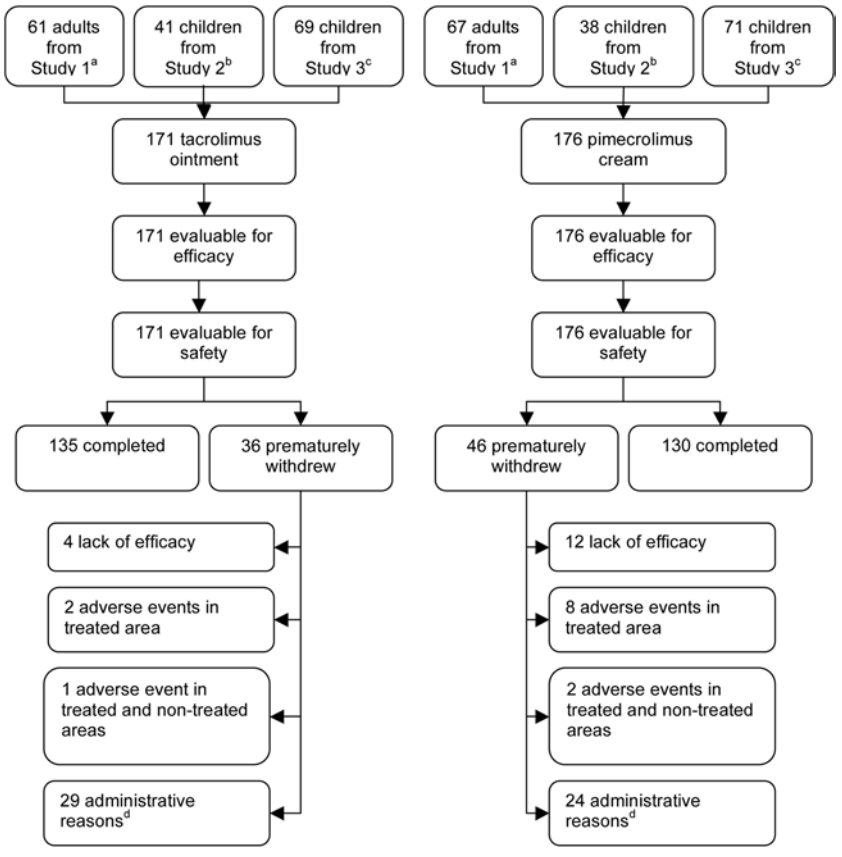

Fig. 1. Patient disposition (patients with prior steroid use ($n=347$)). [a]Study 1: adult patients with mild to very severe Atopic Dermatitis (AD), tacrolimus 0.1% vs. pimecrolimus 1%; [b]Study 2: pediatric patients with moderate to very severe AD, tacrolimus 0.1% vs. pimecrolimus 1%; [c]Study 3: pediatric patients with mild AD, tacrolimus 0.03% vs. pimecrolimus 1%; [d]administrative reasons include voluntary withdrawal, non-compliance, lost to follow-ups, sponsor discontinued patient and others.

treatment groups (see Table I). Although there were numerical differences between the treatment groups for some disease-related characteristics (i.e. head and neck involvement and IGADA), these differences were not statistically significant.

Efficacy

EASI score. At EOS, the percentage improvement in EASI score (by reduction from baseline) was significantly greater for patients treated with tacrolimus ointment compared with patients treated with pimecrolimus cream (mean percent improvement: 53.2% vs. 33.7%, respectively; $p=0.0002$; Fig. 2a). The improvement among patients treated with pimecrolimus cream was less at EOS (33.7%) than at Day 22 (39.8%).

Success of therapy. Significantly more patients treated with tacrolimus ointment achieved treatment success (defined as "Clear" or "Almost Clear" by IGADA score) at EOS than patients treated with pimecrolimus cream ($p=0.0007$; Fig. 3). Twenty-four percent of patients treated with tacrolimus ointment achieved this study end-point by Day 22 compared with 15.3% of patients treated with pimecrolimus cream ($p=0.04$). Overall, in a comparison of IGADA scores at baseline and EOS, significantly more of the patients (with mild, moderate or severe/very severe AD at baseline) treated with tacrolimus ointment than with pimecrolimus cream improved by one or more grades on the IGADA ($p=0.0006$; Fig. 4). In the subgroup of patients with moderate disease at baseline, 76.9% of patients treated with tacrolimus ointment improved by one or more

Table I. *Patient demographics and baseline disease characteristics*

	Tacrolimus ointment ($n=171$)	Pimecrolimus cream ($n=176$)	*p*-values
Age (years), mean (SD)	17.3 (17.7)	18.3 (18.1)	0.60
Gender, %			
Female	53.2	54.5	0.83
Male	46.8	45.5	
Race, %			
White	43.3	41.5	0.54
African-American	38.0	32.4	
Asian	6.4	8.0	
Hispanic	10.5	15.3	
Other race	1.8	2.8	
EASI score (LS mean)	10.0	10.7	0.50
Head and neck involvement, %	78.4	71.0	0.14
IGADA, %			
Mild	50.9	52.8	0.08
Moderate	38.0	29.0	
Severe/Very severe	11.1	18.2	
Total %BSA (LS mean)	20.3	19.9	0.83
Itch score, cm (LS mean)	5.9	6.2	0.43

BSA: body surface area; EASI: Eczema Area and Severity Index; IGADA: Investigator Global Atopic Dermatitis Assessment; LS: least square; SD: standard deviation.

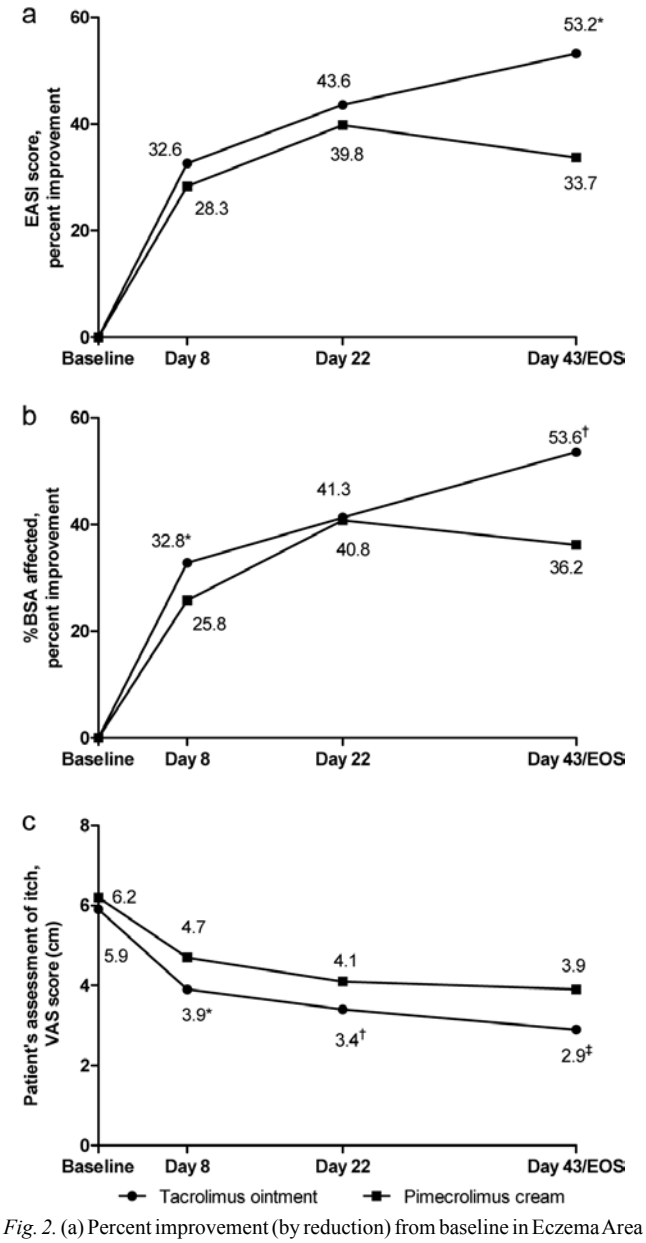

Fig. 2. (a) Percent improvement (by reduction) from baseline in Eczema Area and Severity Index (EASI) score. *$p=0.0002$ for tacrolimus ointment vs. pimecrolimus cream. (b) Percent improvement (by reduction) from baseline in percent body surface area (%BSA) affected. *$p=0.04$ and †$p=0.002$ for tacrolimus ointment vs. pimecrolimus cream. (c) Patient's assessment of itch, visual analogue scale (VAS) scores over time. *$p=0.008$, †$p=0.01$ and ‡$p=0.002$ for tacrolimus ointment vs. pimecrolimus cream. Values are least square means. EOS: end of study.

grades on the IGADA compared with 49.0% of patients treated with pimecrolimus cream ($p=0.002$).

Percent change in %BSA affected. Relative to baseline, the improvement in the %BSA affected was significantly greater with tacrolimus ointment than with pimecrolimus cream at EOS ($p=0.002$; Fig. 2b). Similarly, a statistically significant greater improvement in %BSA affected was observed as early as Day 8 with tacrolimus ointment vs. pimecrolimus cream ($p=0.04$; Fig. 2b).

Patient's assessment of itch. Itch (as measured by VAS score) was significantly improved among patients

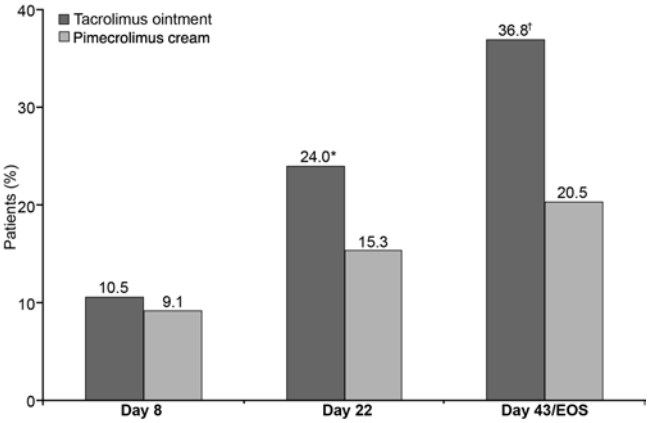

Fig. 3. Percentage of patients achieving success of therapy defined as "Clear" or "Almost Clear" by Investigator Global Atopic Dermatitis Assessment (IGADA) score. EOS: end of study; *$p=0.04$ and †$p=0.0007$ for tacrolimus ointment vs. pimecrolimus cream.

treated with tacrolimus ointment compared with those patients treated with pimecrolimus cream. In fact, a statistically significant difference in VAS score between tacrolimus ointment and pimecrolimus cream was observed as early as Day 8 ($p=0.008$; Fig. 2c) and was sustained until EOS ($p=0.002$; Fig. 2c).

Multiple linear regression analysis. The results of our MRA model (Table II), showed that there was no signi-

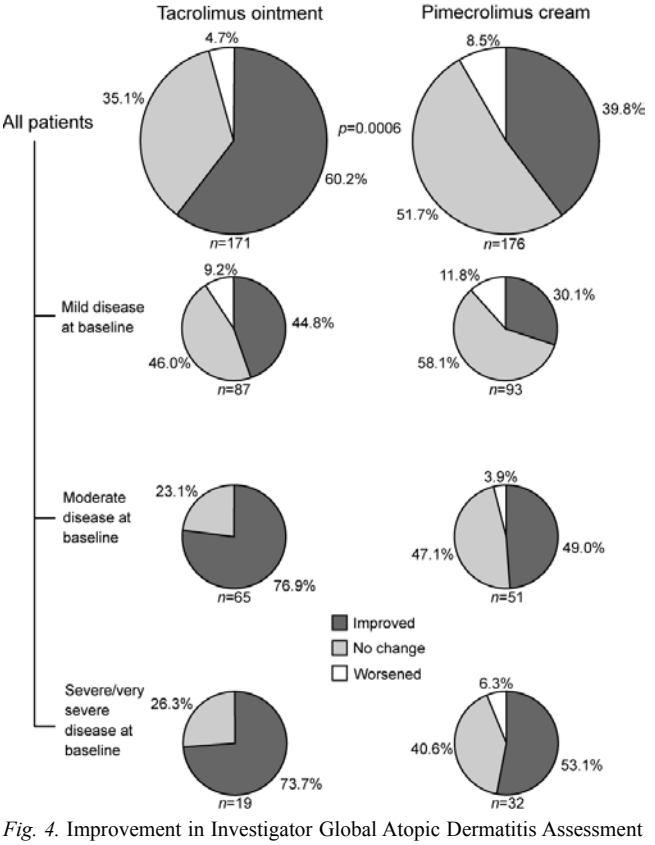

Fig. 4. Improvement in Investigator Global Atopic Dermatitis Assessment (IGADA) status at end of study for subgroups of patients with mild, moderate or severe/very severe disease at baseline (percentage who improved, had no change or worsened).

ficant interaction between treatment and head and neck involvement at baseline ($p = 0.1024$), between treatment and patient age ($p = 0.9609$) and between treatment and baseline IGADA ($p = 0.3892$). A significant treatment effect ($p = 0.0353$) remained when the head and neck affected at baseline, patient age and baseline IGADA and their interaction with treatment were included in the model. Thus, the observed treatment effect was not due to the potential confounding influences of head and neck involvement, age or baseline IGADA.

Safety

Overall, reported adverse events were similar and occurred at comparable frequencies with both treatments (24.0% for tacrolimus ointment vs. 25.6% for pimecrolimus cream; Table III). The most common adverse events were application-site burning (9.9% with tacrolimus ointment vs. 14.2% with pimecrolimus cream; $p = 0.3$) and application-site itching (7.0% with tacrolimus ointment vs. 10.2% with pimecrolimus cream; $p = 0.3$). In the tacrolimus ointment group, folliculitis and skin infection were each reported once. In the pimecrolimus cream group, there were four reports of skin infection and one report of infected dermatitis.

DISCUSSION

Topical corticosteroids are first-line therapy for treatment of patients with AD and their widespread use has continued for 50 years. While rapidly effective, the chronic use of topical corticosteroids, particularly to sensitive and widely extensive areas, is an important concern for patients and healthcare providers. Additionally, non-compliance or under-treatment issues may arise from patients' fears about the safety of topical corticosteroids ("steroid phobia") and can result in a reduction of disease control. Indeed, the results from the International Study of Life with Atopic Eczema (ISOLATE) reported that while the majority of patients with AD received topical corticosteroids, 49% of respondents were concerned about their use, 39% of respondents applied them less frequently or for shorter time periods than prescribed and 74% of respondents would prefer to apply a non-steroid treatment (26). Thus, treatment with TCIs, the recommended second-line therapy for the treatment of AD, may overcome some of the limitations associated with topical corticosteroid use, and may be used as part of an integrative or multi-therapy approach for improving the overall management of AD.

In this analysis of patients treated within the previous 30 days with topical corticosteroids – a common factor for many patients who receive TCIs in clinical practice – we explored the null hypothesis that improvement in AD initiated after prior treatment with steroids eliminates subsequent treatment differences between tacrolimus ointment and pimecrolimus cream. We found that tacrolimus ointment was the more effective TCI when compared with pimecrolimus cream in managing the signs and symptoms of AD. The percent improvements from baseline in EASI score and total %BSA affected were significantly greater with tacrolimus ointment than with pimecrolimus cream at EOS. For tacrolimus ointment, improvement in these parameters was incremental from Day 8 through EOS. For pimecrolimus cream, improvement in these parameters appeared to peak at Day 22. In the absence of compliance data, this anomaly remains unexplained. The percentage of patients with successful therapy, as well as the reduction in patient's assessment of itch, were also significantly greater with tacrolimus ointment than with pimecrolimus cream at EOS. Among patients with moderate disease at baseline – the indication shared by tacrolimus ointment and pimecrolimus cream – significantly more patients treated with tacrolimus ointment improved by one or more grades on the IGADA than patients with pimecrolimus cream. Clinical response tended to be faster in patients treated with tacrolimus ointment. For all parameters evaluated, numerically greater responses were observed by Day 8 (the first evaluation of efficacy) with tacrolimus ointment vs. pimecrolimus cream. Furthermore, at the first evaluation of efficacy, %BSA affected and patient's assessment of itch were significantly lower among patients treated with tacrolimus ointment than among those patients treated with

Table II. *Multiple regression analysis to determine impact of baseline factors on primary outcome*

Term	Factor	*p*-value
1	Head and neck involvement at baseline	0.0751
2	Patient age	0.0505
3	Treatment group (tacrolimus ointment vs. pimecrolimus cream)	0.0353
4	Baseline IGADA score	0.3734
5	Interaction between term 1 and term 3	0.1024
6	Interaction between term 2 and term 3	0.9609
7	Interaction between term 4 and term 3	0.3892

IGADA: Investigator Global Atopic Dermatitis Assessment.

Table III. *Adverse events. Data presented as number of patients (%)*

Adverse event	Tacrolimus ointment ($n = 171$)	Pimecrolimus cream ($n = 176$)
Any adverse event	41 (24.0)	45 (25.6)
Withdrawal due to adverse events	3 (1.8)	10 (5.7)
Application-site reactions		
Burning	17 (9.9)	25 (14.2)
Pruritus	12 (7.0)	18 (10.2)
Pain	7 (4.1)	3 (1.7)
Warmth	2 (1.2)	0 (0)
Erythema	3 (1.8)	6 (3.4)
Temperature intolerance	3 (1.8)	1 (0.6)
Alcohol intolerance[a]	2 (1.2)	0 (0)

[a]Localized facial flushing, erythema or heat sensation after ingestion of alcoholic beverages.

pimecrolimus cream. For patient's assessment of itch, the statistically significant difference in favor of tacrolimus ointment vs. pimecrolimus cream was maintained until EOS. Of course, it should be recognized that this is a retrospective analysis of data from three completed studies and was not specifically designed to detect statistical differences between the treatment arms.

Overall, the findings we present here for a subgroup of patients previously treated with topical corticosteroids are consistent with similar published studies (23, 27, 28). These studies support the evidence that tacrolimus ointment is more effective than pimecrolimus cream in patients with AD. In an analysis of three studies of adult and pediatric patients with mild, moderate and severe AD, tacrolimus ointment was found to be significantly more effective than pimecrolimus cream and had a faster onset of action (23). In a subanalysis of this trial data, tacrolimus ointment 0.1% was significantly more effective than pimecrolimus cream 1% with a similar safety profile in adult patients with moderate to very severe AD (27). In a 6-week study of pediatric patients with moderate AD, Kempers et al. (28) found that tacrolimus ointment 0.03% was associated with a higher success rate than pimecrolimus cream 1.0% (61% vs. 43%), although the sample size was not sufficient to detect a statistical difference between groups.

In the current study, tacrolimus ointment and pimecrolimus cream were found to be safe and well tolerated, consistent with previous studies (23, 27, 28). When compared with pimecrolimus cream, fewer tacrolimus ointment-treated patients withdrew due to adverse events and lack of efficacy, although statistical significance was not achieved in this small study population. More importantly, no unexpected adverse events were reported and the rates of adverse events, including local application-site reactions, were generally low in both treatment groups.

This sub-analysis was a *post-hoc* analysis of pooled data from three separate randomized controlled trials. The randomizations were not stratified by patient age or disease severity, so it was possible that any treatment differences were due to an imbalance in known prognostic factors. To assess this possibility a MRA model was generated with the percent change from baseline in EASI score (the primary end-point) as the dependent variable and the following as independent variables: head and neck involvement at baseline, age of patient, treatment (tacrolimus ointment vs. pimecrolimus cream), baseline IGADA score; the interaction between treatment and head and neck involvement at baseline; the interaction between treatment and age of patient; and the interaction between treatment and baseline IGADA score. The results showed that in the presence of these potentially confounding prognostic factors, treatment with a TCI following topical corticosteroid treatment remained a significant predictor for the primary end-point, percent change from baseline in the EASI score.

This subanalysis further supports the use of tacrolimus ointment in the effective short-term management of AD in both adult and pediatric patients, including those patients previously treated with topical corticosteroids.

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