

Original article

Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment

Background: Long-term treatment for atopic dermatitis (AD) using low dose, intermittent, topical anti-inflammatory agents may control acute disease and prevent relapses. This 12-month, European, multicentre, randomized study investigated whether the proactive use of 0.1% tacrolimus ointment applied twice weekly can keep AD in remission and reduce the incidence of disease exacerbations (DE).

Methods: During the initial open-label period, 257 adults with AD applied 0.1% tacrolimus ointment twice daily (b.i.d.) for up to 6 weeks to affected areas. When an Investigator Global Assessment (IGA) score of ≤ 2 was achieved, the patient entered the disease control period (DCP) and was randomized to either proactive tacrolimus ($n = 116$) or vehicle ointment ($n = 108$) twice weekly for 12 months. Exacerbations were treated with 0.1% tacrolimus ointment b.i.d. until an IGA ≤ 2 was regained, then randomized treatment was restarted. The primary endpoint was the number of DEs during the DCP that required a substantial therapeutic intervention.

Results: Proactive tacrolimus 0.1% ointment application significantly reduced the number of DEs requiring substantial therapeutic intervention (median difference 2; $P < 0.001$; Wilcoxon rank sum test), the percentage of DE treatment days (median difference: 15.2%; $P < 0.001$; Wilcoxon rank sum test) and increased the time to first DE (median 142 vs 15 days; $P < 0.001$; stratified log-rank test). The adverse event profile was similar for the two treatment approaches.

Conclusion: A 12-month, twice weekly proactive tacrolimus ointment application was an effective treatment in most study patients which prevented, delayed and reduced the occurrence of AD exacerbations.

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Atopic dermatitis (AD) is a common, inflammatory skin disease that typically runs a chronic course of flares and remissions. The underlying principle to effective treatment is to administer topical agents at sufficient dosage using the correct application procedure (1). Conventional long-term treatment for AD is based on the combination of daily emollient application to control disease and anti-inflammatory therapy, usually topical glucocorticoster-

oids or topical calcineurin inhibitors, applied reactively as dictated by the presence of visible skin lesions (1).

Conventional treatment approaches have been challenged by a newer treatment strategy which uses a *proactive* approach to treating AD on a long-term basis. This proactive approach uses intensive topical anti-inflammatory therapy until visible lesions have cleared followed by low dose intermittent application of

anti-inflammatory agents to previously affected skin areas to prevent disease exacerbation (DE). The immunobiological justification for a proactive approach to treatment is based on the fact that normal appearing skin of AD patients is not normal but rather has an impaired barrier function (2), a subclinical inflammatory infiltrate (3) and an elevated high affinity IgE-receptor expression of the Langerhans cells (4).

Using a proactive treatment approach, the results of one large randomized study which compared fluticasone propionate cream and fluticasone propionate ointment found that using either preparation twice weekly in combination with a daily emollient significantly reduced the risk of flares and extended the time of remission during the 16-week clinical trial (5). This was one of only a few published study reporting the results of proactive treatment for AD which could be found in the literature. Prolonged application of potent steroids to nonlesional skin, as used in the reported study, might lead to skin atrophy, striae and systemic side-effects (6). Furthermore, it is not known whether AD can be controlled when topical steroids are used for longer than 16 weeks due to possible treatment resistance.

The safety and efficacy of 0.1% tacrolimus ointment used as reactive treatment for AD for up to 12 months was demonstrated in children (7) and adults (8) and successful longer term treatment without an increased likelihood of infections or cumulative adverse events was shown up to 4 years in adults (9) and 29.5 months in children (10). Systemic absorption of tacrolimus through the skin is minimal (11, 12).

In this study, we examined whether 0.1% tacrolimus ointment administered proactively twice weekly would prevent or reduce the frequency of exacerbations of AD in adults, as compared with the conventional and licensed reactive approach. The results show that a proactive regimen significantly reduces the number of AD flares

and the potential of 0.1% tacrolimus ointment to improve control of AD.

Methods

Study design

This was a 12-month, multicentre, randomized, vehicle-controlled, phase III study conducted in 22 centres in 13 European countries. The study was implemented in accordance with the ethical principles described in the Declaration of Helsinki. The Ethics Committee of each centre reviewed the protocol and granted approval before the start of the study. The study design was explained to each patient and written informed consent was obtained before study enrolment. The timeframe for the study was March 2004 to November 2005.

The study consisted of a screening period of up to 1 week, an open-label period (OLP) of a minimum of 8 days to a maximum of 6 weeks and a subsequent randomized, double-blind, disease control period (DCP) of 12 months. If a patient experienced a DE [Investigator Global Assessment (IGA) score > 2], they entered the DE period whereby they applied 0.1% tacrolimus ointment for 1 to 6 weeks until the flare resolved before returning to their original blinded randomized treatment. The study design and timing of assessments are summarized in Fig. 1.

Participants

Male and female patients aged 16 years or older with a diagnosis of AD based on the criteria of Hanifin and Rajka (13) were enrolled in the study. The patients had mild (score at least 3.0) to severe AD as defined by the scoring system of Rajka and Langeland (14).

Method of assigning patients to the treatment group

A run-in number was allocated in chronological order to all patients who entered the OLP. If an IGA score of ≤ 2 was achieved, the patient was eligible for randomization; otherwise the patient was withdrawn from the study. Randomization was 1 : 1 stratified by centre and by disease severity (mild, moderate or severe). The

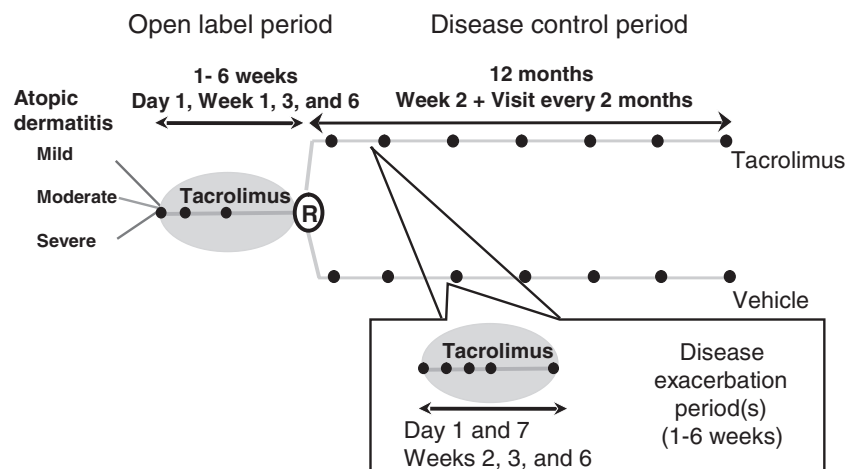


Figure 1. Design of the study.

randomization list and sealed emergency envelopes were generated by the study sponsor.

Blinding

During the OLP, 0.1% tacrolimus ointment was applied without blinding. The 12-month DCP was conducted as a double-blind study. The labels on the ointment tubes had identical lot numbers and expiry dates, and the ointment supply boxes bore no identifying information. Tacrolimus ointment was administered without blinding during the intermittent periods of DE treatment.

Treatment

During the OLP, patients applied a thin layer of 0.1% tacrolimus ointment twice daily for a minimum of 8 days and a maximum of 6 weeks to all affected body areas. Up to 100% of the body surface area could be treated. During the DCP, patients applied either 0.1% tacrolimus ointment or vehicle once daily twice per week to all affected areas. If in the opinion of the patient a DE had occurred, he or she was assessed by the physician at an unscheduled visit. Following confirmation of an exacerbation, the patient entered a DE period whereby the randomized treatment was stopped and the patient applied 0.1% tacrolimus ointment twice daily to all previously identified affected areas plus to any new skin areas where AD lesions had appeared. Treatment continued until an IGA of ≤ 2 was regained at which time the original blinded randomized treatment was reinitiated. All of the used and unused ointment tubes were weighed at the end of the study so that ointment usage could be calculated.

Patients were asked to make daily entries into a patient diary which was used for reporting the application and duration of treatment, as well as noting the appearance of any new lesions. During the study the investigator monitored compliance by reviewing the patient diary at each study visit.

Prohibited therapies

Therapies prohibited during the study included ultraviolet therapies, nonsteroidal immunosuppressive agents, medicated topical agents, other topical immunomodulators, coal tar, topical corticosteroids, systemic corticosteroids for the treatment of AD and other investigational drugs. The washout phase for these therapies ranged from a minimum of 3 days (for topical corticosteroids and topical immunomodulators) to a maximum of 6 weeks (for UV treatments). The washout period for systemic nonsteroidal immunosuppressants was 2 weeks and for systemic corticosteroids used to treat AD 5 days. Patients were permitted systemic antihistamines, leukotriene antagonists, antibiotics (including topical) and intranasal and/or inhaled corticosteroids regardless of the dose. In addition, patients could use bath oils and a nonmedicated emollient 2 h before and after ointment application.

Outcome measures

The primary endpoint was the number of DEs during the DCP that required a substantial therapeutic intervention which was defined as the use of 0.1% tacrolimus ointment for > 7 days to treat an IGA of 3–5 measured on day 1 of the DE treatment period. [IGA classification: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe disease (15)]. If a patient had two such DE periods with < 7 days separating them (with or without any type of treatment) then the episodes were combined and considered as one DE.

Secondary study endpoints included the total number of DEs during the DCP (including those that did not require a substantial therapeutic intervention), the percentage of days of DE treatment, the time to first DE, and the time to the first DE requiring a substantial therapeutic intervention. Clinical improvement was assessed using the IGA score, the Eczema Area and Severity Index (EASI) and the modified EASI (mEASI) (16), the patient's assessment of itch and global response and the Dermatology Life Quality Index (DLQI) (17).

Safety assessments during the study included the monitoring of adverse events and vital signs. Any clinically significant laboratory finding noted during the study visits was recorded as a secondary diagnosis or adverse event. An adverse event was defined as any untoward occurrence in a patient, regardless of whether it was related to the study treatment, which was reported by the patient or observed by the physician. Adverse events were coded using the Medical Dictionary for Regulatory Activities.

Statistical methodology

To calculate the sample size, it was first assumed that 30% of patients in the reactive treatment group would experience no flare throughout the DCP compared with 55% in the proactive treatment group. Secondly, it was assumed that, of the patients who experienced a flare, the proportions of patients experiencing 1, 2, 3 and ≥ 4 flares would be uniformly distributed. Under these assumptions, to power the study at 90%, to detect a difference between the treatment groups using a Wilcoxon rank sum test with a two-sided significance level of 5%, approximately 100 patients per arm were required.

The two treatment groups were compared using the Wilcoxon rank sum test stratified by disease severity. For the primary endpoint analysis, patients were ranked according to the number of DEs adjusted for length of time in the study; patients who prematurely discontinued the study for efficacy reasons were ranked below others. The treatment arms were compared using a two-sided Wilcoxon rank sum test stratified by randomization strata (mild, moderate, severe AD). The median difference in the number of DEs requiring a substantial therapeutic intervention adjusted for time at risk between the arms was estimated by Hodges–Lehmann method along with the 95% confidence interval (CI).

Populations for analysis

For the OLP, the patient population was described as the 'all patients enrolled set' (APS) and included all patients who were enrolled at the OLP screening visit and who applied study ointment at least once, or had any safety or efficacy data reported after day 1 of the OLP. The full analysis set (FAS) was the primary population for analysis and included all patients who were enrolled into the randomized DCP and who applied at least one application of study ointment or had any efficacy or safety data reported after baseline. The FAS was used for all of the statistical analyses unless stated otherwise.

Results

The OLP was designed to be a preparatory phase for the main randomized part of the study and therefore these data are summarized only briefly.

Open-label period

Patient demographics and baseline data. In total, 257 patients were enrolled into the OLP and according to the scoring of Rajka and Langeland, 74, 92 and 91 patients had mild, moderate or severe AD, respectively. The mean severity score on day 1 ranged from 3.7 to 8.4, respectively.

Patient withdrawals. Thirty-one patients (12.1%) discontinued the study prematurely during the OLP, of which 24 patients (77.4%) had severe AD. The most common reason for discontinuation was an IGA score > 2 at week 6 (20 patients, 7.8%) followed by withdrawal of consent (four patients, 1.6%), noncompliance, adverse event, lost to follow-up (each two patients, 0.8%) and lack of efficacy (one patient, 0.4%).

Ointment usage. The overall mean ($\pm$ SD) ointment usage during the 6-week OLP was 124.7 (164.6 g); total mean daily ointment usage was 4.7 g (4.4 g). As expected, patients with severe AD applied more ointment throughout the 6-week period (mean: 224.8 g) compared with 35.1 and 98.8 g for the patients with mild and moderate AD, respectively.

Efficacy outcomes. Most patients experienced improvement in their AD during the OLP. On day 1, 21.0% of patients had an IGA score of ≤ 2 which increased to 89.3% of patients at the end of the OLP. Similarly, 79.0% of patients had an IGA of > 2 on day 1 which decreased to 10.7% at the end of the OLP. Quality of life also improved with the overall mean DLQI score decreasing from 9.3 on day 1 to 4.8 at the end of the OLP.

Safety outcomes. A total of 136 patients (52.9%) experienced adverse events that were assessed by the study investigators to be related to the study ointment. Application site irritation (83 patients, 32.3%) and application site pruritus (46 patients, 17.9%) were the most common causally related adverse events (Table 1). Patients with severe AD had a higher incidence of application site irritation and pruritus (42.9% and 23.1%, respectively) compared with the patients with mild (24.3% and 13.5%) or moderate AD (28.3% and 16.3%). There were no serious adverse events (SAEs) reported during the OLP.

Disease control period

Patient demographics and baseline data. In total, 224 patients (87.2% of the patients who participated in the OLP) formed the FAS of the DCP: 116 patients in the proactive twice weekly tacrolimus ointment-based group and 108 patients in the reactive twice weekly vehicle ointment-based group. There was no difference between treatment groups in demographic and baseline characteristics (Table 2).

Table 1. Incidence of most common* causally related† adverse events during the OLP and DCP treatment periods – number of patients (%)

MedDRA preferred term	Tacrolimus ointment (n = 257)	
<i>OLP – all patients screened</i>		
Application site irritation	83 (32.3)	
Application site pruritus	46 (17.9)	
Application site warmth	18 (7.0)	
Application site folliculitis	11 (4.3)	
Pruritus	7 (2.7)	
Herpes simplex	5 (1.9)	
<i>DCP – FAS</i>		
	Proactive therapy (n = 116)	Reactive therapy (n = 108)
Application site pruritus	13 (11.2)	12 (11.1)
Application site folliculitis	6 (5.2)	8 (7.4)
Application site irritation	6 (5.2)	7 (6.5)
Pruritus	4 (3.4)	6 (5.6)
Herpes simplex	5 (4.3)	4 (3.7)
Application site infection	6 (5.2)	2 (1.9)
Impetigo	2 (1.7)	4 (3.7)

OLP, open-label period; DCP, disease control period; FAS, full analysis set.

*Reported in 3% of patients in either treatment group.

†Causally related defined as being assessed by the investigator as having a highly probable, probable, possible or nonassessable relationship to the study drug or missing assessment of relationship.

Patient withdrawals. Thirty-five (30.2%) patients in the proactively treated group and 53 (49.1%) patients in the reactively treated group discontinued during the DCP. The most common reasons for discontinuation in both groups were withdrawal of consent (nine patients, 7.8% and 14 patients, 13.0%, respectively) and an IGA > 2 at the DE period week 6 visit (eight patients, 6.9% and six patients, 5.6%, respectively). Most patients who discontinued from the study during the DCP did so within the first 3 months; patients treated reactively tended to withdraw earlier.

Study drug exposure. Regardless of severity strata, the patients applying tacrolimus ointment proactively twice weekly remained longer in the DCP compared with the patients applying vehicle reactively twice weekly (mean $\pm$ SD: 292.1 $\pm$ 122.9 vs 226.5 $\pm$ 149.8 days). Patients in the proactive group had fewer DE treatment days (mean $\pm$ sd: 30.5 $\pm$ 55.1 vs 61.5 $\pm$ 76.4 days), and the percentage of DE treatment days was significantly lower (mean: 12.3% vs 31.5%; median difference: 15.2%; $P < 0.001$, Wilcoxon rank sum test).

The mean per day tacrolimus ointment use during the DCP was similar in both groups: 1.38 g/day $\pm$ 1.59, tacrolimus, vs. 1.6 g/day $\pm$ 2.47, vehicle (Table 3): a comparison of ointment use is difficult due to the wide and treatment regimen-dependent distribution of the data (median, 0.98 vs 0.53 g/day; upper quartile, 1.82 vs 2.20 g/day; 90th percentile, 2.63 vs 4.37 g/day, respectively). (The protocol specified application of tacrolimus ointment for treatment of DEs.)

Table 2. Patient demographics and baseline characteristics on day 1 of the DCP – number of patients (%)

	Proactive therapy (n = 116)	Reactive therapy (n = 108)
Age (years), mean ± SD	31.0 ± 12.0	31.8 ± 11.7
Male : female (%)	42.2 : 57.8	36.1 : 63.9
Ethnic group		
Caucasian (%)	108 (93.1)	106 (98.1)
Black (%)	3 (2.6)	1 (0.9)
Oriental (%)	4 (3.4)	1 (0.9)
Other (%)	1 (0.9)	0 (0.0)
AD severity score, median (min–max)	6.0 (3.0–9.0)	6.0 (3.0–9.0)
Investigator's global assessment (IGA)*		
Clear (%)	13 (11.2)	11 (10.2)
Almost clear (%)	43 (37.1)	37 (34.3)
Mild disease (%)	60 (51.7)	60 (55.6)
Moderate disease (%)	0 (0.0)	0 (0.0)
Severe disease (%)	0 (0.0)	0 (0.0)
Very severe disease (%)	0 (0.0)	0 (0.0)
Total affected BSA (%), median (min–max)	3.5 (0–73.0)	3.6 (0–33.0)
EASI, median (min–max)	1.8 (0–22.2)	2.9 (3.0)
mEASI, median (min–max)	1.9 (0–22.2)	2.3 (0–13.4)
Patients assessment of itch median (min–max)	0.8 (0–8.5)	1.1 (0–8.9)
Original AD disease stratification – number of patients		
Mild	36	35
Moderate	45	42
Severe	35	31

*Scoring for IGA: 0, clear; 1, almost clear; 2, mild disease; 3, moderate disease; 4, severe disease; 5, very severe disease.

Efficacy outcomes. The primary endpoint analysis showed that twice weekly proactive tacrolimus ointment application significantly reduced the number of DEs requiring substantial therapeutic intervention (median difference 2; $P < 0.001$; Wilcoxon rank sum test). Sixty-six patients treated proactively (56.9%) had no DE that required substantial therapeutic intervention compared with only 32 patients (29.6%) in the reactive treatment group (Fig. 2). The patients in the proactive group experienced a median of two fewer DEs (when adjusting for the length of time in the study). And, the mean percentage of days of DE treatment during the DCP was much lower in the proactive group than in the reactive group: 12.4 days (SD ± 21.0) compared with 31.5 days (SD ± 27.6) (median difference: 15.2%; $P < 0.001$; Wilcoxon rank sum test).

Figure 3 shows that the time to first DE was significantly longer for the patients applying tacrolimus ointment proactively ($P < 0.001$, stratified log-rank test). The median (95% CI) time to first DE in the patients in the proactive group was 142 days (123, inestimable) compared with 15 days (13, 23) in the reactive group. Differences between treatment groups were observed consistently across the strata of patients with mild, moderate or severe AD at the start of the study.

Table 3. Cumulative tacrolimus ointment use, average ointment use per day during the DCP, and tacrolimus use for disease exacerbation (DE)

	Proactive therapy (n = 116)		Reactive therapy (n = 108)	
	n	Mean (SD) Median (range)	n	Mean (SD) Median (range)
<i>Cumulative tacrolimus ointment use (g)</i>				
All patients	112	385.8 (408.2) 272.5 (4.0–2353.4)	102	319.9 (585.9) 100.8 (0.0–3433.4)
<i>Average per day tacrolimus use (g/day)*</i>				
All patients	112	1.38 (1.59) 0.98 (0.05–9.72)	102	1.60 (2.47) 0.53 (0.00–11.0)
Mild	34	0.71 (0.79) 0.41 (0.05–3.28)	32	0.30 (0.69) 0.08 (0.0–3.69)
Moderate	44	1.62 (2.04) 1.10 (0.16–9.72)	39	1.71 (2.8) 0.7 (0.0–10.9)
Severe	34	1.75 (1.34) 1.68 (0.05–6.35)	31	2.81 (2.61) 2.27 (0.0–11.0)
<i>Tacrolimus use for DE (g)</i>				
All patients	115	117.1 (284.1) 1.1 (0.0–1825.3)	102	317.7 (580.2) 100.8 (0.0–3353.3)
Mild	36	41.9 (85.6) 0.0 (0.0–312.8)	32	61.4 (109.6) 5.3 (0.0–533.7)
Moderate	45	155.1 (333.5) 3.9 (0.0–1670.5)	39	328.0 (589.7) 119 (0.0–3149.6)
Severe	34	146.4 (337.3) 49.7 (0.0–1825.3)	31	569.4 (738.1) 215.1 (0.0–3353.3)

*In the proactive group, average tacrolimus ointment use per day was calculated as the ratio of the total tacrolimus used (total DE treatment + total blinded study medication) to the number of days in the DCP. In the reactive group, this was calculated as the ratio of the total DE treatment to the total number of days in the DCP.

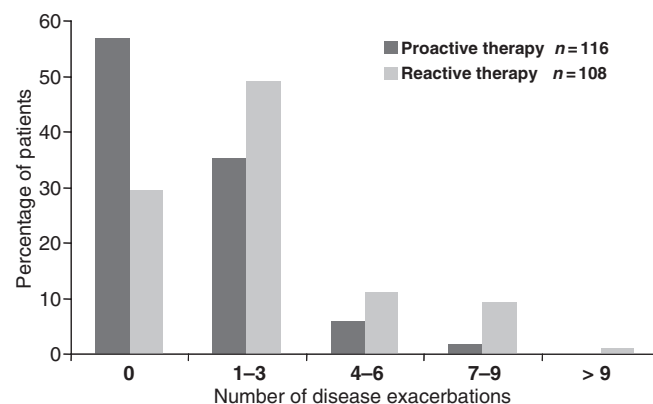


Figure 2. Number of disease exacerbations (DE) requiring substantial therapeutic intervention.

The maintenance of controlled disease was evident at conclusion of the DCP in the proactive group: For example, the median EASI score for the proactive group at study end compared with the score on day 1 indicates that disease was stable after 12 months: 1.6 (range: 0.0–33.7) and 1.8 (range: 0.0–22.2), respectively. In contrast, the median EASI score for the reactive group at study end compared with day 1 indicates a slight worsening of AD:

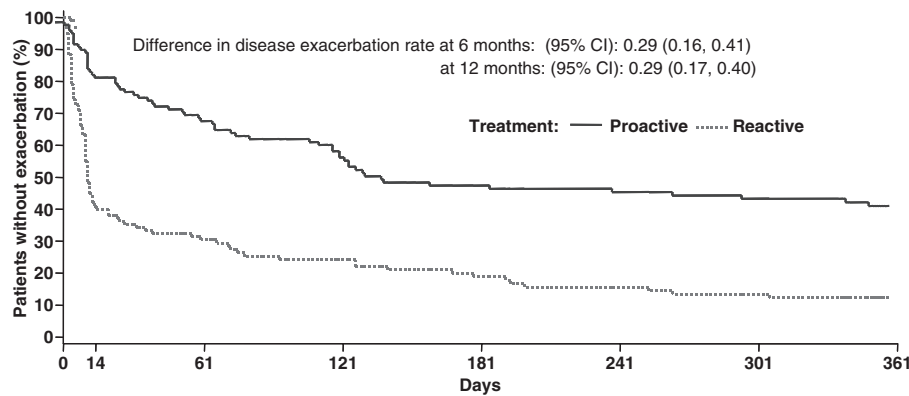


Figure 3. Time to first disease exacerbation (DE).

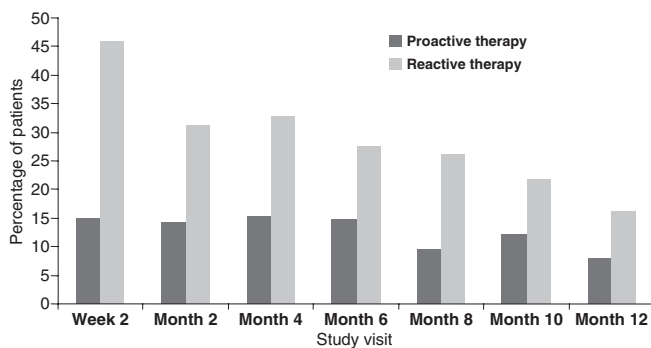


Figure 4. Clinical efficacy: percentage of patients with IGA > 2 during the disease control period (DCP).

3.2 (range: 0.0–53.7) and 2.0 (range: 0.0–12.8), respectively. mEASI scores for both groups at both measurement points showed similar results.

The percentage of patients with an IGA > 2 at each scheduled study visit was consistently lower in patients randomized to proactive tacrolimus treatment compared with patients randomized to reactive treatment (Fig. 4). Patients were pleased with the clinical efficacy of twice weekly tacrolimus as shown by the positive DLQI scores. At the DCP Month 12/end of study visit (LOCF), the mean total DLQI score was 3.6 for the proactive group and 6.8 for the patients in the reactive group (DLQI on day 1 of the OLP was 9.3).

Median scores for patient-assessed itch in the proactive group remained stable at the end of study compared with day 1: 1.2, range: 0.0–9.5 and 0.8 range: 0.0–8.6, respectively. Scores in the reactive group, however, were slightly worse at the end of study as compared with day 1: 2.3, range: 0.0–10.0 and 1.1, range: 0.0–8.9, respectively.

Safety outcomes. A total of 47 patients (40.5%) in the proactive group experienced adverse events during the DCP that were assessed by the study investigators to be related to the study ointment compared with 38 patients (35.2%) in the reactive group. Application site pruritus

(13 patients, 11.2%) and folliculitis (six patients, 5.2%) were the most common causally related adverse events in the proactive group with similar incidences observed in the reactive group (12 patients, 11.1% and eight patients, 7.4%, respectively) (Table 1).

There was a low incidence of SAEs in both groups during the DCP [five patients treated proactively (4.3%) and three patients in the reactive group (2.8%)]. Only two SAEs were considered to be related to the study treatment. One patient in the proactive group developed an application site infection (super-infection of dermatitis) on both hands on day 151 that was assessed as being highly probably related to the study medication. Tacrolimus ointment was permanently discontinued and the patient recovered. One patient in the reactive group reported Kaposi varicelliform eruption (eczema herpeticum) on day 181 that was assessed as probably related to study medication. The amount of vehicle ointment applied was reduced and the patient recovered. None of the patients in the proactive group discontinued the study because of an adverse event, three patients in the reactive group discontinued because of an adverse event.

Skin papillomas, manifested as verruca vulgaris and bilateral heel warts, were observed in three patients treated with proactive tacrolimus and were assessed as being unrelated to study medication. In the reactive group, one patient had viral warts that were assessed as being probably related to study medication. Two malignant neoplasms were reported in the proactive group, kidney cell carcinoma (one patient) and prostate cancer (one patient); both events were assessed as being unrelated to study medication.

Discussion

This is the first European, randomized, multicentre study of a 12-month duration that investigated a proactive disease management strategy using long-term intermittent 0.1% tacrolimus ointment against a reactive strategy based on placebo ointment. As flare treatment for both

groups consisted of open-label 0.1% tacrolimus ointment application twice daily, this is not a study of tacrolimus ointment against placebo, but instead a trial comparing two different ways of using tacrolimus ointment; a proactive approach with low dose, long-term intermittent application and a reactive approach which followed current tacrolimus ointment labeling. These study results demonstrated clearly that, regardless of the baseline severity of the patient's AD, twice weekly 0.1% tacrolimus ointment application was effective in preventing, delaying and reducing the occurrence of DEs in normal appearing skin.

A potential point of criticism of this study is that because of some dropouts during the OLP, our data is valid for a subgroup of AD patients and not necessarily relevant for all AD patients. The purpose of the OLP was to allow stabilization of disease so that patients entered the DCP in a relatively symptom-free condition. Twenty patients (7.8% of 257) did not attain an IGA of ≤ 2 after 6 weeks; the 6-week treatment period might have been too short for some patients with severe AD to attain the predetermined grade of disease severity.

During the DCP, the patients applying tacrolimus ointment proactively twice weekly had fewer DEs and the Kaplan–Meier estimate of median time to first DE was significantly longer. These observations indicate that twice weekly application of tacrolimus ointment was sufficient to effectively control AD in this study population.

The time to first DE in this study, 142 days, was comparable with that found in a 6-month clinical trial that investigated reducing the number of days of steroid treatment to treat flare (18). In that trial, 192 adults with moderate to severe AD applied either pimecrolimus cream or vehicle twice daily as needed and DEs were treated with a moderately potent corticosteroid. The median time to first flare was 144 days. However, a study which compared the time to DE using twice weekly application of fluticasone propionate cream or ointment in a proactive treatment approach (5) reported a median time to DE of 6 weeks (42 days) with fluticasone propionate cream, a time much shorter than the 142 days we report. We observed a 56.9% rate of flare prevention with twice weekly proactive application of 0.1% tacrolimus ointment. This is higher than the rate of 44.8% reported with application of pimecrolimus (18).

Because of the large SD in total daily and cumulative tacrolimus use, and the treatment regimen-dependent distribution of the data, it is difficult to draw conclusions with respect to total tacrolimus ointment use during the DCP.

We noted no unexpected adverse events of clinical significance during the study and the type and incidence of adverse events reported were as expected for patients with AD. Two patients discontinued the study (during the OLP) because of application site irritation and

pruritus. Warmth at the tacrolimus application site was experienced by patients during the OLP but the incidence of this adverse event decreased to $<3\%$ of patients during the DCP. We speculate that a twice weekly application of tacrolimus kept the patient's skin in a nonburning state. Other studies have found that the intensity and duration of warmth and burning decreases after 1 week of tacrolimus administration (7, 19).

The nature and incidence of infections observed during the study were consistent with previous reports (20). We saw no increase over time in the risk of cutaneous bacterial, viral or fungal infections, and the incidence of herpes simplex and other subcutaneous infections was low. One patient (0.9%) in the reactive group developed Kaposi's varicelliform eruption and recovered following reduction of the study medication. The overall incidence of herpes simplex during the 12-month DCP for patients in the proactive group was 5.2% which compares with reported incidence rates in AD patients of 6–10% (21, 22).

The purpose of this study was to evaluate the efficacy and safety of two different ways of using 0.1% tacrolimus ointment. The proactive treatment regimen was easy to follow and this could play an important role in its successful use in clinical practice. The patients using this treatment strategy expressed satisfaction with the regimen and assessed their quality of life to be considerably better. Having an effective and reliable treatment has a positive psychological effect on the patient and increases the likelihood that the patient will adhere to the regimen. Effective maintenance of an intact skin barrier over the long-term can lower the likelihood of skin infections and subsequently the cost burden of AD.

In conclusion, this study demonstrated that the twice weekly proactive application of 0.1% tacrolimus ointment is sufficient to control the occurrence of flares in a large number of patients. The disease management strategy was safe and did not lead to an increase in the incidence and number of adverse events during the 12-month treatment period. We believe that proactive application of 0.1% tacrolimus ointment has an invaluable role in the challenging management of AD and that these results are evidence of a novel and viable disease management option for AD patients.

Contributors

All named authors commented on the study design, took part in the study and reviewed and approved the final manuscript. Claire Foster and Carol Krcmar (Astellas Pharma GmbH) managed the publication process through to the final manuscript and Benoit Baron (Astellas Pharma GmbH) provided statistical advice. The preparation of this publication followed the Good Publication Practice guidelines for pharmaceutical companies.

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Conflict of interest statement

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Appendix

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