Tacrolimus 0.1% versus ciclopiroxolamine 1% for maintenance therapy in patients with severe facial seborrheic dermatitis: A multicenter, double-blind, randomized controlled study

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Background: No long-term maintenance therapy has been tested in patients with seborrheic dermatitis (SD).

Objective: We sought to compare the efficacy and tolerance of tacrolimus 0.1% ointment versus ciclopiroxolamine 1% cream as maintenance therapy for severe SD.

Methods: This double-blind randomized controlled study was conducted from 2014 to 2017 in 5 Dermatology Departments and 15 dermatology practices in France. Consecutive patients with severe and chronic facial SD were included. Patients were initially treated with desonide 0.05% cream twice daily for 7 days. Patients cleared after this open phase were randomized to receive tacrolimus 0.1% or ciclopiroxolamine 1% cream 2 times a week 24 weeks. The primary endpoint was disease-free-duration, defined as the time from randomization to first relapse.

Results: One hundred fourteen patients were randomized (tacrolimus, n = 57; ciclopiroxolamine, n = 57). Twelve patients relapsed in the tacrolimus group after a median delay of 91.5 days (range 15-195 days) versus 23 patients in the ciclopiroxolamine group (median delay, 27 days [range 13-201 days]). Comparison of disease-free duration curves showed that patients in the tacrolimus group had a longer duration of complete remission than those in the ciclopiroxolamine group (P = .018), corresponding to a hazard ratio of relapse of 0.44 (95% confidence interval 0.22-0.89; P = .022).

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Conflicts of interest: None declared.

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Limitations: The theoretical sample size was not reached.

Conclusion: Tacrolimus 0.1% is more effective than ciclopiroxolamine 1% as maintenance therapy for patients with facial SD. (J Am Acad Dermatol 2021;84:1278-84.)

Key words: ciclopiroxolamine; maintenance therapy; seborrheic dermatitis; tacrolimus.

Seborrheic dermatitis (SD) is a skin disorder with an estimated prevalence in the general population ranging from 2.5% to 3%.[1-6] The role of Malassezia and an inflammatory reaction characterized by an increase in proinflammatory cytokines such as interleukin-2 has been suggested.[7-9]

Some types of SD are considered severe because of their highly recurrent and sometimes chronic course. These severe types of SD have a major impact on patients' quality of life.[10] Patients affected by severe SD often chronically use large quantities of topical corticosteroids (CSs), leading to CS-dependent lesions and CS side effects.

The efficacy of topical antifungal drugs has mainly been assessed during the acute phase of SD.[11-14] Although these drugs are widely used as maintenance treatment of SD in clinical practice, their efficacy has only been assessed over short periods of time (ie, 4 weeks). Moreover, when tested versus placebo in randomized controlled studies, the efficacy of topical antifungal drugs was limited, even in moderate types of SD.[13,15]

Tacrolimus, a calcineurin inhibitor, is a local immunosuppressant that is mainly used in the treatment of atopic dermatitis. Tacrolimus ointment has been shown to be effective in the prevention of flares in patients with atopic dermatitis.[16] The efficacy of topical calcineurin inhibitors tacrolimus and pimecrolimus in the treatment of SD has been suggested in few studies, most of them having included a limited number of patients.[17-24]

The objective of this study was to compare the efficacy and tolerance of tacrolimus 0.1% ointment versus ciclopiroxolamine 1% as maintenance therapy in patients with severe facial SD, after the clearance of SD lesions with an initial topical CS treatment, in order to reduce initial skin inflammation and improve local tolerance. We chose tacrolimus in this study because pimecrolimus is not available in France.

METHODS

Participants

Inclusion criteria in the initial open-label phase were the following: 1) adult patients ≥18 years of age with 2) a diagnosis of severe facial SD. The diagnosis of SD was made clinically on the presence of erythema or squamous lesions located on the seborrheic areas of the face.[1] Scalp and other extrafacial localizations were not taken into account. Severe SD was defined as: 1) a clinical severity score ≥4 on a scale ranging from 0 to 8 and 2) a chronic or recurrent course characterized by the onset of ≥3 recurrences during the last 6-month period, or a continuous or intermittent course of SD with skin lesions that were present for >15 days during the last 2-month period. SD severity was evaluated according to an 8-point scale detailed in the Supplemental Appendix (available via Mendeley at https://doi.org/10.17632/y3hmp9nbty.1).

Inclusion criteria in the double-blind maintenance phase was achievement of complete remission (disappearance of erythema and desquamation corresponding to a total score of 0), or almost complete remission (persistence of mild erythema or mild desquamation corresponding to a total score of 1 of 8), 7 days after the start of treatment with topical desonide.

The main exclusion criteria are detailed in the Supplemental Appendix.

Procedures

This academic, double-blind, randomized controlled trial was conducted from January 2014 to April 2017 in 5 dermatology departments and by 15 office-based dermatologists from 5 regions in France. The study included 2 treatment phases. Patients in the initial open-label phase were treated with desonide 0.05% cream, which was applied twice a day for 7 days. Patients whose lesions were cleared or almost cleared after this initial treatment were included in the double-blind phase and randomly assigned in a 1:1 ratio to receive twice weekly applications of tacrolimus 0.1% ointment, or twice weekly applications of ciclopiroxolamine 1% cream until their first relapse or for ≤24 weeks in patients who did not relapse. Treatment was assigned through central computer-generated randomization. All participants remained unaware of group assignments once the decision was made to stop enrollment.

Study assessments and treatment of relapses

The total duration of the study was 25 weeks. Four visits were planned: 1) an inclusion visit at day 1; 2) a randomization visit scheduled at day 7 (ie, the end of the open-label phase of the study; patients who were in complete or almost complete remission were given the study products for the maintenance phase [tacrolimus or ciclopiroxolamine] at the end of this visit); 3) patients who relapsed during the double-blind maintenance phase had to call investigators to plan an additional visit within 2 days after the phone call for assessment of the primary endpoint; and 4) an end of study visit at day 180. In addition, 3 phone call assessments were performed at days 30, 90, and 120 to evaluate treatment tolerance and compliance.

Treatment of the relapsing patients is detailed in the Supplemental Appendix.

Outcome measures

The primary endpoint was disease-free duration (DFD), defined as the time from randomization to first relapse, ie, the duration during which patients remained completely cleared (disappearance of erythema and desquamation corresponding to a total score of 0) or almost completely cleared (persistence of mild erythema or mild desquamation, corresponding to a total score of 1 of 8).

The first relapse had to be confirmed by the investigator during an additional visit, which was performed within 48 hours after the telephone call of patients who suspected a relapse. Relapse was defined as the recurrence of erythema or desquamation on the seborrheic areas of the face with a total score ≥3.

Secondary endpoints were: 1) number of relapses during the double-blind phase of the study; 2) cumulative number of days with SD lesions according to patients' evaluation; 3) cumulative number of days during which patients had to apply desonide cream to treat relapsing SD lesions during the double-blind phase of the study; 4) evolution of the quality of life and stress level during the study, as evaluated by the French version of Skindex and Dermatology Life Quality Index (DLQI) questionnaires[25-27] and the 14-item Cohen Perceived Stress Scale (PSS),[28,29] respectively; 5) safety evaluated by severe and nonsevere treatment-related side effects; and 6) patients' global assessment of drug efficacy and tolerance.

Compliance was evaluated according to forms filled in by the patients during the study and the number of tubes of study products used.

Statistical analysis

We hypothesized that the median DFD of patients would increase from 8 weeks in patients treated with ciclopiroxolamine to 12 weeks in those treated with tacrolimus (150% increase in DFD).[17,18] To achieve 80% power relative to this difference at the 2-sided 0.05 level and allowing for 10% dropouts, 240 patients (2 × 120) were required for enrollment in the initial open phase. Expecting that 90% of patients would be cleared or almost cleared after the initial CS treatment, 260 patients (2 × 130) had to be randomized in the double-blind phase of the study. Analyses were based on the intention-to-treat principle.

The distribution of the primary endpoint (DFD, or the number of days without lesions from the start of the double-blind phase of the study to the visit at which the first relapse was confirmed by the investigator) was estimated using the Kaplan–Meier method, and comparisons between the 2 treatment groups relied on the log rank test.

Multivariate Cox regression analysis was performed to control for several potential baseline prognostic factors on DFD (ie, gender, baseline severity of lesions, inflammatory or squamous type of SD, stress level assessed by the Cohen PSS [0-20, 21-26, and ≥27]) and the DLQI and Skindex scores. We estimated hazard ratios (HR) and corresponding 95% confidence intervals (CIs) from Cox regression.

Statistical analyses used for secondary endpoints, study oversight, and the role of the funding source are detailed in the Supplemental Appendix (available via Mendeley at https://doi.org/10.17632/y3hmp9nbty.1).

RESULTS

Study population

Between January 2014, and April 2017, 114 patients with a mean ± SD age of 46.2 ± 15 years were included. Baseline characteristics of patients recruited in dermatology departments and by office-based dermatologists are shown in the Supplemental Appendix. All 114 patients were cleared or almost cleared after the open phase of CS treatment and were randomly assigned to receive either tacrolimus (n = 57) or ciclopiroxolamine (n = 57) in the double-blind phase of the trial. Because of slow patient accrual, enrollment was stopped before the target sample size was reached.

Fifteen patients did not complete the study (6 in the tacrolimus group and 9 in the ciclopiroxolamine group). Reasons for dropout are detailed in Fig 1. The 2 groups were well-balanced for main baseline characteristics, except DLQI and Skindex scores, which were higher in patients from the tacrolimus group (Table I).

Primary outcome

Twelve of 57 patients (21.1%) had ≥1 relapse in the tacrolimus group versus 23 patients (40.4%) in

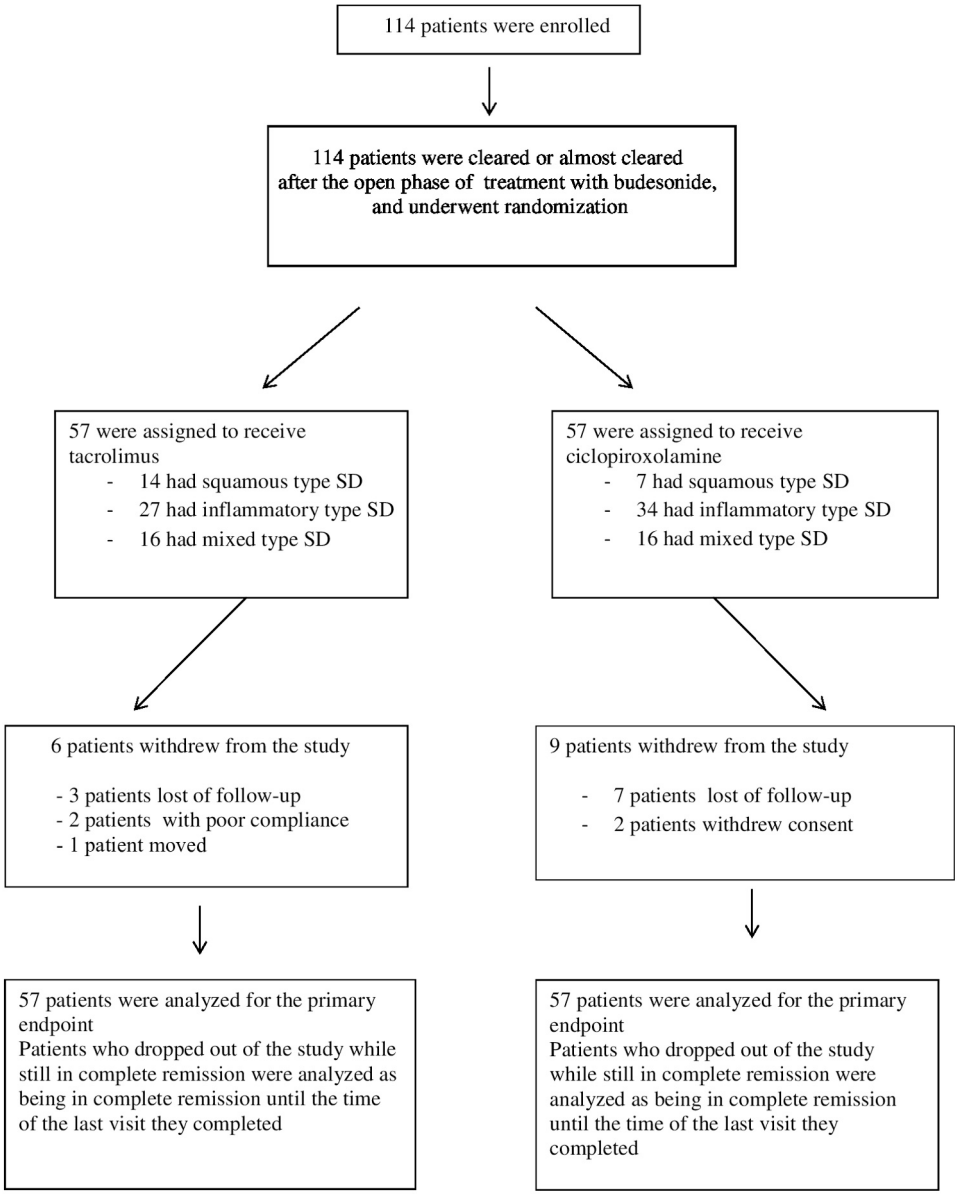

Fig 1. Flow chart of the study. *SD*, Seborrheic dermatitis.

the ciclopiroxolamine group. The median delay to first relapse was 91.5 days (range 15-195 days) in the tacrolimus group versus 27 days (range 13-201 days) in the ciclopiroxolamine group.

Patients in the tacrolimus group had longer DFD than patients in the ciclopiroxolamine group (P = .018; Fig 2). This difference corresponded to a HR of relapse of 0.44 (95% CI 0.22-0.89; P = .022 from the Cox proportional hazard model). After adjusting for gender, SD type (squamous vs inflammatory or mixed), baseline severity, Cohen PSS, DLQI, and Skindex scores, the beneficial effect of tacrolimus was still evidenced with a HR of relapse of 0.32 (95% CI 0.13-0.80; P = .015).

We then performed a sensitivity analysis in which all patients who prematurely withdrew from the study (patients who were lost to follow-up, moved, experienced a treatment adverse event, or withdrew their consent) were considered as treatment failure for the primary endpoint from the time of their last visit. Patients in the tacrolimus group still had longer DFD than patients in the ciclopiroxolamine group (P = .008), corresponding to a HR of relapse of 0.47 (95% CI 0.26-0.83; P = .010).

Secondary outcomes

A total of 36 relapses were observed in patients from the tacrolimus group and 47 relapses occurred

Table I. Baseline characteristics of study patients according to treatment groups

	Ciclopiroxolamine (n = 57)	Tacrolimus (n = 57)	*P* value
Age, y, mean ± SD	47.9 ± 14.7	44.6 ± 15.3	.2425
Gender, n (%)			
Female	12 (21.1)	10 (17.5)	.635
Male	45 (78.9)	47 (82.5)	
Severity score, mean ± SD	5.3 ± 0.9	5.7 ± 1.3	.0907
Type of seborrheic dermatitis, n (%)			
Inflammatory	34 (60)	27 (47)	.02084
Squamous	7 (12)	14 (25)	
Mixed	16 (28)	16 (28)	
Duration of lesions before inclusion, months, median (range)	86.2 (0-185.3)	49.7 (0-368.7)	.5073
Cohen Perceived Stress Scale score, mean (SD)	31.1 (6.1)	30.9 (8.3)	.08674
Skindex score, mean (SD)	60.4 (21.4)*	71.1 (24.4)*	.0101
Dermatology Life Quality Index score, mean (SD)	3.77 (3.6)†	6.3 (5.7)†	.0089

SD, Standard deviation.
*In 55 patients.
†In 56 patients.

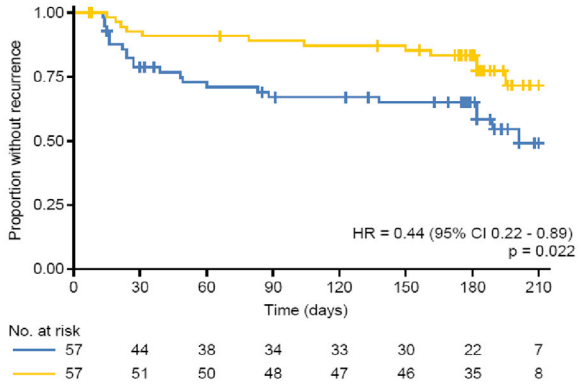

Fig 2. Kaplan-Meier disease-free duration curves of patients treated with tacrolimus (yellow) and ciclopiroxolamine (blue).

in patients from the ciclopiroxolamine group. In order to assess if seasonality could be a confounding factor of relapse, we analyzed the number of patients included or who relapsed according to seasons (Table II). No difference in the rate of inclusions or relapses was evidenced between the 2 treatment groups.

According to the patients' evaluation, the mean cumulative number of days with SD lesions in the ciclopiroxolamine group was 31.6 ± 45.8 days versus 24.4 ± 37.4 days in the tacrolimus group (*P* = .74). The mean cumulative number of days during which patients had to apply desonide cream to treat relapsing SD lesions during the double-blind phase of the study was 15.9 ± 13.0 days in the ciclopiroxolamine group versus 16.8 ± 14.5 days in the tacrolimus group (*P* = .77).

Two severe adverse events unrelated to study treatments were observed (infectious colitis and a flare of Crohn disease). Thirty-seven treatment-related adverse events were observed in 21 patients from the ciclopiroxolamine group and 62 adverse events in 33 patients from the tacrolimus group, corresponding to a mean number of 0.6 ± 0.9 treatment-related adverse events per patient in the ciclopiroxolamine group and 1.1 ± 1.1 in the tacrolimus group (*P* = .027). The most frequent adverse events were burning sensation, pruritus, and erythema (Table III). Forty-seven of the 62 (76%) tacrolimus-related adverse events and 37 of 37 (100%) ciclopiroxolamine-related adverse events were observed in patients with inflammatory/mixed type SD. No cutaneous carcinoma or lymphoma was observed during the study.

Patients' reported outcomes

The mean improvement in quality of life scores from baseline to the end of the study was −1.4 ± 3.7 points in the ciclopiroxolamine group versus −4.2 ± 4.6 points in the tacrolimus group for the DLQI score (*P* = .11) and −12.1 ± 18.3 points in the ciclopiroxolamine group versus −22.5 ± 22.9 points in the tacrolimus group for the Skindex score (*P* = .22).

The mean baseline PSS scores of patients in the ciclopiroxolamine and tacrolimus groups were 31.1 ± 6.1 points and 30.9 ± 8.3 out of 50 points, respectively, indicating a high level of stress. No significant evolution of this score was observed during the study in either treatment group.

Patients' global assessment of the efficacy and tolerance of the study drug was available in 89 cases. Tacrolimus and ciclopiroxolamine were evaluated highly effective by 32 (66.7%) and 20 (48.8%) patients, rather effective by 12 (25.0%) and 11 (26.8%) patients, and poorly effective/ineffective

Table II. Inclusions and relapses in patients according to the seasons

	Ciclopiroxolamine (n = 57)	Tacrolimus (n = 57)	Total (n = 114)	*P* value*
Inclusions, n (%)†				.7931
Winter	22 (39)	24 (42)	46 (40)	
Spring	15 (26)	12 (21)	27 (24)	
Summer	10 (17.5)	8 (14)	18 (16)	
Autumn	10 (17.5)	13 (23)	23 (20)	
First relapses, n (%)†	n = 23	n = 12	n = 35	.9577
Winter	5 (22)	2 (16.5)	7 (20)	
Spring	11 (48)	5 (42)	16 (46)	
Summer	4 (17)	3 (25)	7 (20)	
Autumn	3 (13)	2 (16.5)	5 (14)	

*The χ^2 test was used for the comparison of inclusions and the Fisher exact test was used for the comparison of relapses.
†Seasons were determined according to the dates of the solstices (winter, December 21-March 19; spring, March 20-June 19; summer, June 21-September 20; and autumn, September 21-December 20).

Table III. Treatment-related adverse events

	Ciclopiroxolamine	Tacrolimus
Nature of treatment-related adverse events	n = 37	n = 62
Pruritus	18	23
Burning sensation	17	29*
Erythema	0	3
Others	2†	7‡

*Including 1 patient with rosacea.
†Folliculitis (n = 1) and herpes (n = 1).
‡Folliculitis (n = 4), herpes (n = 2), and conjunctivitis (n = 1).

by 4 (8.3%) and 10 (24.4%) patients, respectively. Tacrolimus and ciclopiroxolamine were evaluated well tolerated by 28 (58.3%) and 35 (85.4%) patients, rather well tolerated by 14 (29.2%) and 4 (9.7%) patients, and poorly tolerated by 6 (12.5%) and 2 (4.9%) patients.

DISCUSSION

This clinical trial showed that tacrolimus 0.1% ointment applied twice weekly is more effective than ciclopiroxolamine 1% cream for maintenance therapy in patients with severe facial SD. Ciclopiroxolamine was preferred over vehicle as the comparator in this randomized controlled trial, and although ciclopiroxolamine has been tested as maintenance therapy only on short duration periods there is extensive clinical experience from practicing dermatologists suggesting its efficacy in chronic types of SD.[11,12]

Patients assigned to the tacrolimus group had almost half of the relapses compared with those in the ciclopiroxolamine group (12 vs 23 relapses). In addition, the median delay to first relapse was 3-fold longer (91.5 days) in the tacrolimus group than in the ciclopiroxolamine group (27 days), resulting in a highly significant difference in DFD between the 2 drugs ($P = .018$). The therapeutic effect of tacrolimus was major because it corresponded to a HR of relapse of 0.44 relative to ciclopiroxolamine ($P = .022$). In addition, the beneficial effect of tacrolimus was still evident and even slightly enhanced after adjusting for gender, baseline severity, inflammatory versus squamous type of SD, Cohen PSS, and quality of life scores (HR of relapse = 0.32; $P = .015$), the last 3 variables showing some imbalance between the 2 groups.

No severe drug-related adverse events were observed in this study, in particular no cases of cutaneous lymphoma.[30,31] As expected, the most frequent side effects were pruritus, burning sensation, and erythema, which were more frequently observed in patients with inflammatory/mixed type SD than in patients with squamous type SD. Despite initial applications of desonide cream for 7 days to clear inflammatory lesions, local adverse reactions were quite frequently observed, in particular in patients from the tacrolimus group (1.1 ± 1.1 treatment-related adverse event per patient vs 0.6 ± 0.9 in the ciclopiroxolamine group). Accordingly, patients reported that ciclopiroxolamine tolerance was better than that of tacrolimus.

The main limitation of our study is that because of slow patient accrual, enrollment was stopped before the sample size was reached. The final sample of 114 patients was sufficient to provide 80% power to detect a between-group 50% increase of the DFD if the median DFD in the ciclopiroxolamine group was 50% shorter than the hypothesized 8 weeks. Accordingly, a statistically significant difference was obtained for assessment of the primary endpoint (delay to first relapse), since the observed delay to first relapse in patients from the ciclopiroxolamine group (27 days) was in fact 50% shorter than planned in our study hypothesis (8 weeks). Since sunlight has

a notable beneficial effect on SD activity, we assessed whether seasonality of inclusion or relapses might be a confounding factor. No difference in that rate of inclusions or relapses was evidenced between the 2 treatment groups.

Overall, this academic, double-blind, randomized controlled trial has shown that tacrolimus applied twice a week as maintenance therapy after an initial CS treatment with desonide cream is more effective than ciclopiroxolamine to prevent the occurrence of relapse in patients with severe SD.

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