

CLINICAL REPORT

Proactive Treatment of Adult Facial Seborrhoeic Dermatitis with 0.1% Tacrolimus Ointment: Randomized, Double-blind, Vehicle-controlled, Multi-centre Trial

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The effectiveness of intermittent topical tacrolimus to prevent relapse in patients with stabilized facial seborrhoeic dermatitis has not been evaluated. The aim of this study was to determine whether proactive use of 0.1% tacrolimus ointment can keep adult facial seborrhoeic dermatitis in remission. A total of 75 patients who had stabilized facial seborrhoeic dermatitis after 2 weeks' (open-label induction) treatment with 0.1% tacrolimus were randomized in a double-blind fashion to treatment with 0.1% tacrolimus once a week, twice a week, or vehicle twice a week, for 10 weeks (maintenance). Significant improvement in erythema, scaling and pruritus compared with baseline was maintained during the maintenance phase in both tacrolimus groups, but not in the vehicle group. The mean recurrence rate according to global assessment was significantly higher in the tacrolimus once-weekly group than in the twice-weekly group. In conclusion, twice-weekly treatment with 0.1% tacrolimus ointment had superior effects in keeping facial seborrhoeic dermatitis in remission. Key words: seborrhoeic dermatitis; tacrolimus; maintenance therapy.

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Seborrhoeic dermatitis (SD) is a common chronic papulo-squamous dermatosis, which affects 2–10% of the adult population. It mainly occurs in men between the ages of 20 and 50 years. The affected skin appears erythematous and oedematous, covered with yellow-brown scales, and it is often accompanied by pruritus. It typically affects areas containing sebaceous glands, particularly the scalp, ears, face, chest and the intertriginous areas (1).

SD has a chronic course and relapse is common. Therefore, therapy is directed toward reducing the symptoms or aggravating factors of SD, such as loo-

sening and removal of scales and crusts, inhibition of yeast colonization, control of secondary infection, and reduction in erythema and pruritus (1). Standard topical treatments for SD include corticosteroids and anti-mycotic medications (2). However, the chronic use of topical corticosteroids, particularly on the face, can result in undesirable outcomes, such as telangiectasia, atrophy, striae, peri-oral dermatitis, or tachyphylaxis, and early relapse after discontinuation of treatment (3).

Topical calcineurin inhibitors have been found to be safe and effective alternatives for the treatment of facial SD in many clinical trials (4–6). We previously treated 20 patients with adult facial SD with 1% pimecrolimus cream, and observed significant improvement after 1–4 weeks of treatment (7). After completion of the study, 12 patients were available for follow-up telephone surveys 4–8 weeks later. Patients who continued application of pimecrolimus had no recurrence of SD; however, patients who discontinued the treatment had disease relapse after 3–8 weeks. Intermittent application of tacrolimus ointment for atopic dermatitis has been reported to be effective for flare-up prevention and long-term disease control (8, 9).

Therefore, we hypothesized that intermittent use of tacrolimus ointment could also be effective in preventing relapse of SD. This study was designed to compare the efficacy of once- and twice-weekly application of 0.1% tacrolimus ointment with that of a vehicle control in maintaining adult facial SD remission and in reducing the incidence of disease exacerbation.

MATERIALS AND METHODS

Study design

The study had an open-label induction phase (phase I) and a maintenance phase (phase II) (Fig. 1). The trial was conducted according to the ethical guidelines of the Declaration of Helsinki and performed according to Good Clinical Practice guidelines (10). The study protocol was approved by the Institutional Review Board of each hospital, and all patients gave written informed consent.

The open-label induction phase was a preparatory period for the selection of eligible patients for the maintenance phase. All patients involved in the open-label induction phase were instructed to apply 0.1% tacrolimus ointment to the entire face,

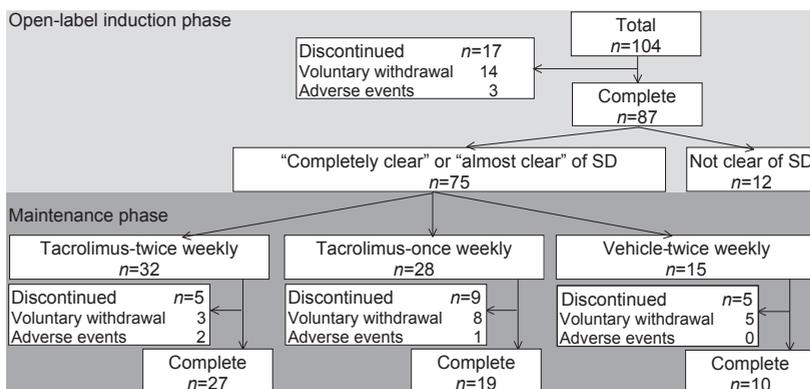


Fig. 1. Study design. SD: seborrhoeic dermatitis.

including the forehead, eyebrows, peri-nasal area, cheeks, chin, and post-auricular area, twice daily for 2 weeks. Patients were provided information on possible adverse events, such as mild tingling and burning sensation.

The maintenance phase of the study was a randomized, parallel-group, double-blind, vehicle-controlled 10-week trial. Patients were divided into the following 3 groups across all centres in a 5:5:3 ratio: once-weekly application of 0.1% tacrolimus ointment; twice-weekly application of 0.1% tacrolimus ointment; and twice-weekly application of vehicle ointment. Tacrolimus ointment were applied once or twice per day and vehicle ointment were applied twice per day in control group.

During the study (phases I and II), no other medications were permitted, except for the study medication. Sunscreen and makeup were permitted 30 min after application of the study medication.

Patients

Eligible patients for the open-label induction phase of the study (phase I) were those who were at least 18 years of age with a diagnosis of facial SD. Patients who met any of the following conditions were excluded: taking other systemic or topical treatments for facial SD within the previous 4 weeks; a known allergy to the components of tacrolimus ointment; malignant neoplasm; immunological abnormality; active infection; and other definitive cutaneous findings, such as erythroderma, acne and psoriasis.

Patients eligible for the maintenance phase of the study (phase II) were required to have an Investigator's Global Assessment (IGA) and Patient's Global Assessment (PGA) score of 0 (completely clear) or 1 (almost clear) after study phase I.

Study assessment

Patients were assessed at baseline and every 2 weeks during phases I and II. Clinical assessments of erythema, scaling and pruritus were made by 4 dermatologists using the following 4-point scale: 0 (absent), 1 (mild), 2 (moderate) or 3 (severe). Erythema and scaling were scored by comparison with standardized severity photographs. The assessment was performed by dividing the face into 6 sections: forehead, eyebrows, peri-nasal area, cheeks, peri-oral area, and post-auricular area, and then by totalling the score for each area.

The IGA and PGA for the evaluation of disease recurrence were scored using the following 5-point scale: 0 (completely clear, no evidence of SD), 1 (almost clear, <10% recurrence compared with baseline), 2 (slight recurrence, 10–25% recurrence compared with baseline), 3 (moderate recurrence, 25–50% recurrence compared with baseline), 4 (marked recurrence, 50–100% recurrence compared with baseline), and 5 (worse, compared with baseline). We defined stabilization of facial SD as completely clear and almost clear.

Adverse events, including burning sensation, tingling sensation, pain, and infection, were checked at every visit. The severity of the adverse events was also monitored.

Sample size estimation

A sample size of 20 patients in the tacrolimus once- and twice-weekly groups, and 10 patients in the vehicle group was calculated to give each comparison between the tacrolimus and vehicle 80% power to detect a difference of 20% in the change in the mean clinical assessment of erythema, scaling and pruritus. This assumes a common standard deviation of 30, and uses a 2-group *t*-test with a 0.05 two-sided significance level.

Randomization and blinding

Patients were randomized in a 5:5:3 ratio, to 1 of the 3 treatment groups (tacrolimus twice weekly, tacrolimus once weekly, or vehicle twice weekly). A randomization code list was generated (Clin-Pro/LBL version 8.0; Clinical Systems, Inc., Garden City, NY, USA) and a unique randomization number was assigned to each patient at the day 0 visit according to the order of entry into the study. Randomization occurred in the order that patients met selection criteria at each centre.

All study medications were labelled "for investigational use only". To preserve blinding during the phase II double-blind period, the products were over-labelled with non-removable labels, and the tubes of ointment were packaged in identical boxes that were sealed with tamper-proof seals. Neither the patients nor the study personnel (with the exception of the pharmacist at the site) knew the nature of the study ointment being applied by each patient. The principal investigator was not involved in the distribution or the assignment of the study ointments and did not come into contact with the study ointment.

Statistical analysis

The efficacy analysis for phase II was performed on the intent-to-treat (ITT) population, including all randomized patients who met the phase II entry criterion of being completely clear or almost clear of facial SD according to the IGA and PGA scores at the end of phase I, and who had taken at least one application of study ointment during phase II. The missing values due to drop-out were replaced using the last observation carried forward (LOCF) method. The safety population was defined as all patients who used at least one application of the study treatment.

Baseline categorical data were summarized for all the patients, and the differences were analysed using Fisher's exact test or the χ^2 test, when appropriate, and continuous data were analysed using analysis of variance.

The target variables were tested using analysis of variance for repeated measures, with the baseline value as covariate. Maintenance of stabilized facial SD during phase II was defined as significant improvement of clinical assessment in erythema, scaling and pruritus compared with the baseline values. In statistical analysis, the limit for rejection of the null hypothesis was set for each procedure used at the two-tailed value of 5%. This trial was registered with the ClinicalTrials.gov (number NCT01591070).

RESULTS

Study patients

In this multicentre study conducted at 4 investigational centres in Busan, Korea between November 2010 and May 2011, 104 patients were enrolled in phase I. Of these, 87 patients completed phase I (application

of 0.1% tacrolimus ointment twice daily), while 17 patients withdrew (14 subjects voluntarily withdrew and 3 subjects withdrew because of adverse events). Of the 87 patients who completed phase I, 75 patients were completely clear or almost clear of disease, and they were randomly assigned to phase II as follows: 32 patients to the tacrolimus twice-weekly group, 28 to the tacrolimus once-weekly group, and 15 to the vehicle twice-weekly group (Fig. 1). As shown in Table I, there were no significant differences among the groups in the mean scores of erythema, scaling and pruritus. Of the 75 patients who began phase II (the 10-week application of study treatments), 56 patients completed phase II, while 19 patients did not; 16 patients voluntarily withdrew, and 3 withdrew because of adverse events.

Open-label induction phase (phase I)

At baseline, 87 (100%) patients had erythema with a mean score of 7.3; 79 (91%) patients had scaling with a mean score of 4.0; and 74 (85%) patients had pruritus with a mean score of 4.7. Compared with the baseline, the mean score of erythema, scaling and pruritus at 2 weeks showed significant improvements ($p < 0.001$). For most patients, both investigators and the patients themselves noticed significant improvement after 2 weeks of treatment. Seven patients (8%) reported that they were completely clear, and 68 (78%) reported that they were almost clear according to PGA; 5 patients (6%) were assessed as completely clear, and 70 (80%) were assessed as almost clear according to IGA.

Maintenance phase (phase II)

A total of 56 patients completed phase II (10-week application of study treatments). Erythema, scaling and pruritus in facial SD improved significantly compared with baseline, and was maintained during the 10 weeks in both tacrolimus groups ($p < 0.001$ for both, ITT analyses). However, clinical improvement was not significantly different from the assessment in the vehicle group throughout the study ($p > 0.05$, ITT analyses) (Fig. 2).

The mean recurrence rate during phase II according to PGA and IGA in the vehicle group was significantly higher than that in both tacrolimus groups ($p < 0.005$). Furthermore, the mean recurrence rate in the tacrolimus

once-weekly group was significantly higher than that in tacrolimus twice-weekly group ($p < 0.005$) (Fig. 3). In addition, the mean PGA and IGA scores during phase II in the vehicle group were significantly higher than those in both tacrolimus groups, and the tacrolimus twice-weekly group had significantly lower mean PGA and IGA scores than the once-weekly group (data not shown).

Adverse events (Table II)

During phase I, 22 patients (21.2%) reported at least one local adverse event. Most of these were burning or tingling sensations. Three patients withdrew from the study because of severe burning sensation.

During phase II, although the overall incidence of application-site adverse events in the tacrolimus group was higher than in the vehicle group, there was no significant difference between the study groups. Three patients (2 in the tacrolimus twice-weekly group and 1 in the tacrolimus once-weekly group) withdrew from the study because of severe burning and tingling sensation. Most adverse events did not last more than 1 h, and the severity of adverse events tended to decrease over time. There were no other local or serious adverse reactions associated with 0.1% tacrolimus ointment use throughout the study.

DISCUSSION

This study fulfilled its objective of comparing the efficacy of 0.1% tacrolimus ointment application once and twice weekly for the prevention of adult facial SD that was in remission and for reducing the incidence of disease exacerbation. After phase I, the therapeutic efficacy rate for the ITT population was 72%. Statistically significant improvements relative to baseline were observed in the mean scores of erythema, scaling and pruritus in both tacrolimus treatment groups during phase II. Meanwhile, improvement in facial SD in the vehicle group was not significant compared with baseline. During phase II, the mean recurrence rates and mean PGA and IGA scores of the ITT population in both tacrolimus groups were significantly lower than those in the vehicle group, indicating the superiority of tacrolimus over vehicle for the prevention of SD exacerbation.

Although other studies have shown the efficacy of topical calcineurin inhibitors for the short-term treatment

Table I. Baseline characteristics of patients. There were no significant differences in the mean scores of erythema, scaling and pruritus

	Open-label induction phase (n = 104)	Maintenance phase (n = 75)		
		Tacrolimus twice weekly (n = 32)	Tacrolimus once weekly (n = 28)	Vehicle twice weekly (n = 15)
Age, years, mean (SD)	46.0 (17.6)	40.4 (15.6)	50.7 (19.7)	43.2 (13.5)
Sex, n (%)				
Female	38 (36.5)	17 (53.1)	6 (21.4)	6 (40.0)
Male	66 (63.5)	15 (46.9)	22 (78.6)	9 (60.0)
Duration, years, mean (SD)	8.0 (10.4)	9.6 (12.2)	8.4 (9.2)	6.0 (10.3)
Erythema score, mean	7.3	7.2	7.1	7.2
Scaling score, mean	4.2	4.1	3.8	4.0
Pruritus score, mean	4.6	4.5	5.4	4.0

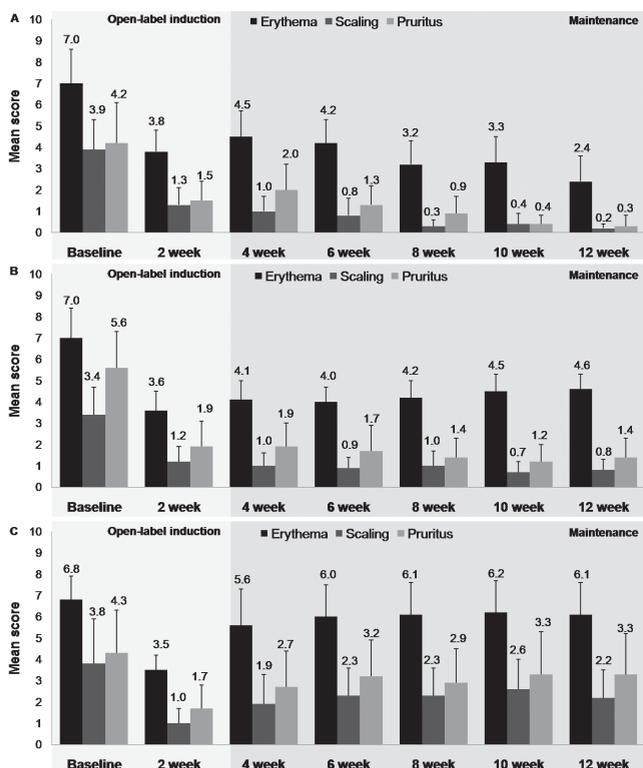


Fig. 2. Clinical assessment of erythema, scaling, and pruritus; (A) tacrolimus twice-weekly group, (B) tacrolimus once-weekly group, and (C) vehicle group ($p < 0.001$ for the tacrolimus twice-weekly group, $p < 0.001$ for the tacrolimus once-weekly group, and $p > 0.05$ for the vehicle group during maintenance phase compared with baseline).

of facial SD, this study was the first clinical trial to clarify the efficacy of long-term treatment for the prevention of exacerbation in stabilized facial SD. Our findings in phase I support the results of previous studies evaluating the efficacy of tacrolimus ointment for the treatment of SD (11, 12). Meshkinpour et al. (12) evaluated the therapeutic efficacy of tacrolimus ointment in 18 patients with SD for 12 weeks. Tacrolimus application resulted in complete clearance in 61% of the patients, while the remaining patients showed a marked improvement at the end of the treatment. Another study compared the efficacy and safety of tacrolimus with those of standard

corticosteroid treatments for adult facial SD and showed that significantly fewer applications of 0.1% tacrolimus ointment were required compared with 1% hydrocortisone ointment to achieve a comparable clinical response in adult facial SD (13). Although prevention strategies of relapse of SD have not yet been established, there have been some reports on the use of anti-Pityrosporum (anti-dandruff) shampoo prophylaxis for SD of the scalp (14–16). Shuster et al. (15) reported that SD of the scalp responded well to 1% ciclopirox shampoo once or twice weekly for 4 weeks, and a low relapse rate was maintained by shampooing once weekly or once every 2 weeks. Topical tacrolimus was directly compared with topical betamethasone lotion or zinc pyrithione shampoo for the treatment of scalp SD in an open-label trial of 83 subjects (16). Tacrolimus was found to be as effective as betamethasone or zinc pyrithione; moreover, tacrolimus offered more prolonged remission than topical betamethasone. However, to the best of our knowledge, no clinical trials of maintenance therapy or long-term control of facial SD have been published. The aforementioned study of pimecrolimus cream for the treatment of SD speculated that intermittent application of topical calcineurin inhibitors might be effective in preventing relapse of SD (7).

Unlike topical corticosteroids, tacrolimus ointment is not associated with skin atrophy, striae, or skin thinning, and can be safely used on the face, neck and intertriginous regions (17–19). The adverse events related to tacrolimus use in our study were mostly burning and tingling sensations at the application site. In phase I, 21% of the patients reported burning or tingling sensations after application of 0.1% tacrolimus ointment, and 23% of the patients reported these sensations during phase II. These adverse events were mostly tolerable; however, 6 patients withdrew from the study because of these adverse events. These symptoms are well-documented adverse events associated with the use of tacrolimus ointment, which were reported at a rate of approximately 25% in a large-scale study (19). Typically, these symptoms occur on the first few days of application and decrease in severity over time. Subjects using tacrolimus ointment may be at increased risk for other adverse events, such as folliculitis, alcohol intolerance, hyperaesthesia and cutaneous infection (19). However, none of our subjects experienced these adverse events.

The limitations of this study include a small sample size and the large number of drop-outs. The eligibility criteria for patients of phase II could have resulted in selection bias by selecting a group of people who were more likely to respond to the treatment, thereby making the results seem more favourable for the active treatment. Therefore, large-scale clinical trials with controlled,

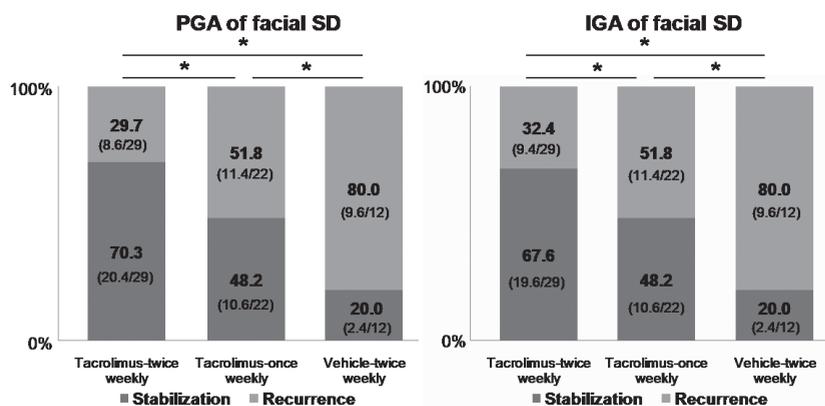


Fig. 3. Mean recurrence rates according to Patient's Global Assessment (PGA) and Investigator's Global Assessment (IGA). * $p < 0.05$.

Table II. Number of patients (%) showing adverse events during open-label induction phase and maintenance phase

Adverse events	Open-label induction phase (n = 104)	Maintenance phase		
		Tacrolimus twice weekly (n = 32)	Tacrolimus once weekly (n = 28)	Vehicle twice weekly (n = 15)
Burning sensation	12 (11.5)	6 (18.8)	4 (14.3)	1 (6.6)
Mild	6 (5.8)	4 (12.5)	2 (7.1)	1 (6.6)
Moderate	3 (2.9)	1 (3.1)	1 (3.6)	0 (0.0)
Severe	3 (2.9)	1 (3.1)	1 (3.6)	0 (0.0)
Tingling sensation	10 (9.6)	2 (6.3)	2 (7.1)	1 (6.6)
Mild	6 (5.8)	1 (3.1)	2 (7.1)	1 (6.6)
Moderate	4 (3.8)	1 (3.1)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	22 (21.2)	8 (25.0)	6 (21.4)	2 (13.3)

long-term follow-up protocols may be warranted to determine the precise efficacy and preventative action of tacrolimus in the management of facial SD.

In conclusion, our results contribute to the understanding of the use of intermittent 0.1% tacrolimus ointment for maintenance of stabilized facial SD. We found that once- and twice-weekly tacrolimus ointment therapy in patients with stabilized facial SD maintains remission of clinical symptoms and improvements in global assessments compared with vehicle control. Although twice-weekly treatment was the most effective, once-weekly treatment may also be an effective and well-tolerated option for reducing the exacerbation of adult facial SD.

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The authors declare no conflicts of interest.

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