STUDY

Topical Tacrolimus Ointment Combined With 6% Salicylic Acid Gel for Plaque Psoriasis Treatment

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Background: While oral tacrolimus is effective for the treatment of psoriasis, tacrolimus ointment has shown only spotty efficacy in the treatment of plaque psoriasis. The efficacy of tacrolimus ointment for the treatment of facial and intertriginous psoriasis suggests that if tacrolimus penetration can be increased, the ointment could be used for effective treatment of plaque psoriasis.

Objective: To assess whether tacrolimus ointment is an effective psoriasis treatment when used in a combination regimen with the penetration-enhancer salicylic acid.

Methods: A total of 30 adult subjects with generally symmetrical plaque-type psoriasis were randomized to treatment with 6% salicylic acid gel plus vehicle or 6% salicylic acid gel plus 0.1% tacrolimus ointment in a 12-week left-right comparison study. The primary outcome was the difference between tacrolimus- and vehicle-treated target lesions in the change in the sum of erythema, scale, and thickness scores from baseline to end of treatment.

Results: A total of 24 subjects completed the trial. Combination treatment with tacrolimus ointment or vehicle plus salicylic acid gel was well tolerated. There was greater improvement of the sum score in the tacrolimus plus salicylic acid–treated target plaques than in the vehicle plus salicylic acid–treated plaques at weeks 1, 2, and 8 ($P<.05$). The efficacy of this regimen was confirmed by investigator and subject global assessments of plaque severity.

Conclusions: The combination of 0.1% tacrolimus ointment and 6% salicylic acid gel is an effective treatment for psoriasis. Although the results reported herein are from a small exploratory study, the magnitude of the effect was sufficiently large as to be detectable with statistical significance ($P<.05$).

Arch Dermatol. 2005;141:43-46

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Financial Disclosure: None.

PATIENTS WITH RELATIVELY localized psoriasis are generally treated with topical therapies, including corticosteroids, vitamin D and A derivatives, and tar products. Patients with more severe, extensive disease may be treated with phototherapy and/or systemic therapies.[1,2] Oral tacrolimus is an effective systemic therapy for psoriasis.[3] The efficacy of oral tacrolimus therapy for psoriasis, along with the efficacy of topical tacrolimus ointment for the treatment of another inflammatory skin disease, atopic dermatitis, raises the question of whether topical tacrolimus therapy is effective for psoriasis.

While topical tacrolimus is an effective anti-inflammatory agent in atopic dermatitis, it appears less effective when used on thick, scaly psoriasis lesions. Zonneveld et al[4] found that 0.3% tacrolimus ointment applied once daily (n=24) was no more effective than placebo (n=23). Remitz et al,[5] however, found that, compared with placebo, the use of 0.3% tacrolimus ointment in conjunction with other topical agents resulted in less erythema and thickness. Tacrolimus ointment at a concentration of 0.1% has been shown to be quite effective for the treatment of facial and inverse psoriasis, with 81% of patients (n=21) reporting complete clearing by day 57.[6] Topical therapies generally penetrate facial and intertriginous skin more easily, and the effectiveness of topical tacrolimus therapy for psoriasis in these areas suggests that efficacy may be improved if penetration can be increased.

See also pages 19, 31, and 80

Salicylic acid has been used alone as a treatment for psoriasis, but is most commonly used to increase the penetration of other topical preparations, primarily cor-

Table 1. Symptom Scores at Baseline and End of Treatment (Week 8)

	Mean (SD), %					
	Baseline*		Week 8		Paired *t* Test†	
Symptom	Tacrolimus+Salicylic Acid	Vehicle+Salicylic Acid	Tacrolimus+Salicylic Acid	Vehicle+Salicylic Acid	*t* Value	*P* Value
Pruritus	34.9 (23.7)	32.2 (23.7)	13.2 (17.0)	18.8 (22.8)	2.49	.02
Erythema	1.67 (0.61)	1.70 (0.60)	1.04 (0.75)	1.42 (0.65)	2.14	.04
Scaling	2.34 (0.89)	2.30 (0.79)	1.00 (0.78)	1.29 (0.69)	2.20	.04
Thickness	1.79 (0.78)	1.80 (0.76)	0.79 (0.66)	1.21 (0.58)	1.89	.07

*The difference between the treatment and placebo score for each patient was compared using a *t* test of means at $\alpha = .05$. None of the symptoms were significantly different at baseline (all *P* values $>.40$).

†For comparison in change from baseline between tacrolimus ointment– and vehicle-treated plaques.

ticosteroids.[7] The purpose of the present study was to assess whether 0.1% tacrolimus ointment is an effective treatment for plaque psoriasis when used in combination with 6% salicylic acid.

METHODS

An investigator-initiated, phase 4 clinical trial was completed at Wake Forest University, Winston-Salem, NC. Human subjects' approval was obtained from the institutional review board. Adult subjects, aged 18 years or older, with generally symmetrical plaque-type psoriasis were randomized to treatment with 6% salicylic acid plus vehicle or 6% salicylic acid plus 0.1% tacrolimus ointment in a left-right comparison study. Women of child-bearing age were required to have negative urine pregnancy test results and to agree to use adequate birth control before enrolling in the study. Subjects stopped using any topical therapy 2 weeks before the study began and discontinued phototherapy or systemic therapy 4 weeks before. No other therapies for psoriasis were allowed during the study. Subjects had to have 10% or less involvement of body surface area, with a target plaque of at least 1 cm^2 in area on each side of the body in the same body region, each with a score of at least 1 for erythema, thickness, and scale.

Treatment was given for 8 weeks. The subjects were instructed to apply 6% salicylic acid gel (Keralyt; Summers Laboratories Inc, Collegeville, Pa) to all psoriasis lesions twice a day and to let it dry. They then were to apply either 0.1% tacrolimus ointment (Protopic, 0.1% ointment; Fujisawa Healthcare Inc, Deerfield, Ill) or its vehicle to the lesions on each half of their body. Subjects were seen at baseline and weeks 1, 2, 4, 8, and 12 (follow-up). At each visit, the erythema, scale, and thickness of a designated target lesion were measured (on a scale of 0-3, with 0 indicating no symptom) on each half of the body. The subjects completed visual analog scales to quantify pruritus on each side of the body. At weeks 8 and 12, both the investigators and the subjects completed global assessments for response to treatment. The investigators' global assessments included both a static (on a scale of 0-5, with 0 indicating no disease) and a dynamic component. The dynamic component was scored on a scale of 0 to 6 as follows: 0, complete clearing; 1, almost clear (90% clearing); 2, marked improvement (75% clearing); 3, moderate improvement (50% clearing); 4, slight improvement (25% clearing); 5, no change; and 6, worse.

The primary outcome was the difference in the sum of the erythema, scale, and thickness scores (static assessments) from baseline to end of treatment between the tacrolimus- and the vehicle-treated target lesions. The results of evaluation of each clinical sign, erythema, scale, and thickness were also compared from baseline to end of treatment. In addition, the global assessments and pruritus were compared between both sides of the body. The subjects were monitored for adverse events throughout the study.

All data were entered into a database program, and SAS software (SAS Institute Inc, Cary, NC) was used to analyze the data. The differences in the symptom scores for the tacrolimus- and the vehicle-treated sides between baseline and week 8 were then compared using *t* tests accounting for unequal variances between the 2 groups using the Satterthwaite correction. Pruritus was compared the same way after the visual analog score was converted into a percentage figure. Paired *t* tests were used to analyze differences in total severity (the sum of pruritus, erythema, thickness, and scaling scores) between treatment and placebo; global assessment scores were also evaluated for all periods for which scores were available. Treatment success was defined as a score of 0, 1, or 2 on the Investigator's Dynamic Global Assessment at week 8. Finally, the McNemar test, a comparison of dependent proportions, was used to compare the treatment and placebo groups.

RESULTS

A total of 30 subjects were enrolled in our study, and 24 of them completed the full 12-week protocol. Of the 30 subjects, 15 were male and 15 were female, 26 (87%) were white, 3 (10%) were black, and 1 (3%) was American Indian. The average age was 43.6 years (age range, 18-70 years). Target lesions were located on the upper extremities, predominantly the elbows, in 21 subjects (70%) and on the lower extremities in 9 subjects (30%). The average involvement of body surface area was 3% (range, 0.25%-6.5%). The target lesion scores for erythema, scale, thickness, and pruritus were not significantly different at baseline (**Table 1**).

Treatment with 6% salicylic acid gel and 0.1% tacrolimus ointment was well tolerated. Some minor stinging was noted by 4 subjects, who could not attribute it to more to one side than the other. Some subjects noted peeling of normal skin around the plaques. Six of the original 30 subjects did not complete the study. One subject noted tinnitus for approximately 12 hours on day 6, but it had resolved before presentation to the clinic and did not recur. Less than 2.5 mg of salicylic acid gel had been applied over those 6 days to 2.5% of the subject's body surface area. The investigators thought that this occurrence was unrelated to the use of the salicylic acid, but the subject wished to discontinue the study regardless. Two subjects were disqualified from the study for starting pred-

nisone therapy for nonrelated health conditions. One subject was incarcerated, and 2 subjects discontinued because of regimen factors (messiness and twice-daily dosing) that were unrelated to treatment outcomes.

There were significant differences between the 2 treatment groups at weeks 1, 2, and 8, with the tacrolimus plus salicylic acid–treated side of the body showing greater improvement in the target lesions than the vehicle plus salicylic acid–treated side (**Figure**). At week 8, there was greater improvement on the tacrolimus-treated side than on the placebo-treated side in erythema, scaling, and pruritus. Also, thickness improved more on the tacrolimus plus salicylic acid–treated side, but the difference was not significant (Table 1) ($P=.07$).

The tacrolimus plus salicylic acid treatment also resulted in greater improvement according to the investigators' global evaluation (**Table 2**). The subjects' global evaluations showed a trend toward decreased severity of disease on the tacrolimus-treated side of the body, but the differences were not significant ($P=.19$). If successful treatment was defined as a score of 0 to 2 on the Investigator's Global Dynamic Assessment (representing >75% improvement in disease) at the end of treatment, 11 (46%) of the 24 subjects had success on the tacrolimus plus salicylic acid–treated side compared with only 4 (17%) of the 24 subjects on the vehicle plus salicylic acid–treated side ($P=.39$).

COMMENT

The results of previous studies of tacrolimus ointment as a treatment for plaque psoriasis have been equivocal. In our small study, the use of 6% salicylic acid gel in conjunction with tacrolimus ointment showed statistically significant improvement for the treatment of plaque psoriasis compared with the use of salicylic acid alone. Despite the small size of this exploratory study, tacrolimus treatment resulted in greater improvement than vehicle treatment in erythema, scale pruritus, and global assessments. The efficacy of the tacrolimus plus salicylic acid combination was clinically significant as evidenced by the frequency of treatment success (defined as >75% disease clearing) on the salicylic acid plus tacrolimus–treated side.

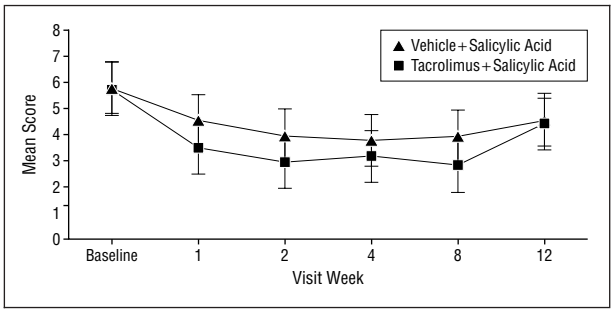

Figure. Disease severity was assessed as the sum of the erythema, scale, and thickness scores for each visit. Significant differences were detected at 1, 2, and 8 weeks ($P<.05$).

The adverse events in this study were minor, and because the burning could not be localized to one side or the other, we are left to guess whether the burning was caused by the use of salicylic acid or tacrolimus. In atopic dermatitis studies, mild burning or stinging has been reported as the most common adverse effect of tacrolimus therapy.[8,9] We do know that neither of these symptoms nor the peeling (which likely due to the use of the salicylic acid) caused the subjects to stop treatment. Nevertheless, irritation may be better tolerated in the generally highly motivated clinical trial population and less so in clinical practice.

While a significant limitation of our study was its small sample size, the magnitude of the tacrolimus effect was sufficient to be detectable. The use of patients as their own controls helps to reduce interindividual variation, thereby increasing the power of the study. However, some subjects may have applied agents to the wrong side. Also, we have not performed pharmacologic studies to determine if there is increased penetration of tacrolimus when it is used in conjunction with salicylic acid, and we are assuming a penetration-based causal mechanism for the improvement of disease with the combination therapy.[10]

There have been important advances in new biologic treatments of psoriasis; however, these therapies are only appropriate for individuals with severe psoriasis. The National Psoriasis Foundation reports that 65% of individuals with psoriasis, or 2.9 million persons, have localized psoriasis. For patients with localized psoriasis, and for many of those with moderate psoriasis as well, the mainstay of treatment is still topical therapy. The quality of life is still greatly affected in such patients, and they often express high levels of dissatisfaction with current treatment options. Safe, convenient, and effective topical regimens, such as combination therapy with topical tacrolimus and salicylic acid, can be of great benefit in this large population. Future studies of a single product that can pro-

Table 2. Investigator Global Assessment Scores*

Global Assessment (Week 8)	Mean (SD)		*t* Value	*P* Value
	Tacrolimus+Salicylic Acid	Vehicle+Salicylic Acid		
Dynamic	2.38 (1.46)	3.29 (1.19)	–2.70	.01
Static	1.00 (0.66)	1.42 (0.65)	–2.85	.009
Scaling	1.04 (0.86)	1.50 (0.78)	–2.70	.01
Thickness	0.83 (0.64)	1.25 (0.61)	–2.46	.02
Erythema	1.00 (0.72)	1.91 (2.10)	–1.97	.06

*The investigator global assessments included both a static (0-5 scale, with 0 being no disease) and a dynamic component. The dynamic component was scored on a scale of 0 to 6 as follows: 0 (complete clearing); 1 (almost clear, 90% clearing); 2 (marked improvement, 75% clearing); 3 (moderate improvement, 50% clearing); 4 (slight improvement, 25% clearing); 5 (no change); and 6 (worse).

vide better penetration of topical tacrolimus would be of further help in simplifying the treatment regimen.

Accepted for Publication: May 7, 2004.
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Funding/Support: This study was supported by a grant from Fujisawa Healthcare Inc.
Additional Information: Dr Feldman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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