Preliminary Study of the Efficacy and Tolerability of Combination Therapy With Calcipotriene Ointment 0.005% and Tacrolimus Ointment 0.1% in the Treatment of Stable Plaque Psoriasis

Andrés Tirado-Sánchez, MD, MSc; Rosa María Ponce-Olivera, MD, MSc

*Calcipotriene ointment is widely used in the topical treatment of psoriasis, with tacrolimus ointment as an effective alternative in controlling stable plaque psoriasis. The efficacy of the combination of both products on stable plaque psoriasis has not been assessed in the literature consulted. We evaluated the efficacy of calcipotriene ointment 0.005% applied twice daily, tacrolimus ointment 0.1% applied twice daily, or a morning application of calcipotriene and an evening application of tacrolimus in 27 participants with stable plaque psoriasis over an 8-week treatment period. The mean reduction in the sum of the scores between baseline and week 8 was significant (*P=*.001) for calcipotriene alone (39.5%), tacrolimus alone (38.2%), and the combination of calcipotriene and tacrolimus (60.7%). Combination therapy was statistically more effective than tacrolimus alone (*P=*.043) but not statistically superior to calcipotriene alone (*P=*.056). Most adverse events (AEs) were related to skin irritation and pruritus; however, no AEs were evident in participants given the combination therapy.*

Cutis. 2012;90:140-144.

From the Department of Dermatology, Hospital General de México, Mexico City.

The authors report no conflict of interest.

Correspondence: Andrés Tirado-Sánchez, MD, MSc, Department of Dermatology, Hospital General de México, Dr. Balmis 148, Colonia Doctores, Delegación Cuauhtémoc, Distrito Federal, México C.P. 06726 (atsdermahgm@gmail.com).

Psoriasis is a chronic, relapsing, multifactorial, and inherited disease characterized by inflammation and hyperproliferation of the skin, which causes the development of erythematous plaques. However, the pathogenesis of the disease is not clear, and the underlying abnormality that produces the disease is unknown.[1] Many of the proposed mechanisms are related to abnormalities in the epidermis on dermal fibroblasts or the microvasculature and activated T cells in the dermis, though none of these mechanisms fully explain the pathogenesis of the disease.[2]

Treatment options for psoriasis are numerous and typically are accessible to the entire population. Although none of the treatments are curative, they still can effectively control the disease when applied alone or in combination. Topical treatment is the most preferred option by patients and is considered the first line of treatment for stable plaque psoriasis of limited extension.[3]

Combined topical treatment is widely used in the management of the disease, which reduces adverse side effects typically associated with the products when they are used separately and allows the clinician to use a lower dose. Among the most effective combinations are calcipotriene with betamethasone[4,5] and mometasone with salicylic acid.[6,7] Calcipotriene ointment 0.005% (50 μg/g) is one of the most effective topical treatments when used alone or in combination, and improvement in psoriasis plaques with calcipotriene ranges from 46% to 74%.[8,9]

Tacrolimus, a calcineurin selective inhibitor, has been used in the treatment of stable plaque psoriasis with reported efficacy of 61.9%.[10] However, the

efficacy and tolerability of the combination of calcipotriene and tacrolimus in the management of stable plaque psoriasis have not been assessed in the literature consulted; thus our study sought to determine the comparative efficacy and tolerability of these 2 agents in the treatment of stable plaque psoriasis.

Methods

Study Design and Treatment—Thirty adult patients (17 women; 13 men) with a mean age (standard deviation) of 42.07 (12.63) years (range, 18–68 years) who had stable plaque psoriasis on the limbs affecting a body surface area of 100 cm^2 or less were selected to participate in an 8-week, randomized, open-label, pilot study. The participants were given either calcipotriene ointment 0.005% (50 μg/g) applied twice daily, tacrolimus ointment 0.1% applied twice daily, or a morning application of calcipotriene and an evening application of tacrolimus. Participants were withdrawn from the study before the end of the 8-week treatment period if all lesions had cleared. Pregnant or breastfeeding patients were excluded, and patients who could potentially become pregnant during the trial were told to use 1 or 2 forms of contraception.

Assessments—The evaluation of treatment response was based on the sum of the score of erythema, scaling, and induration. The severity of each of these items was graded on a 5-point scale (0=none; 1=mild; 2=moderate; 3=severe; 4=very severe).[11] Efficacy measurements and skin safety evaluations (eg, skin irritation, pruritus, burning) were conducted at baseline and after 4 and 8 weeks of treatment. For each adverse event (AE), information such as onset, duration, severity, action taken, and outcome was reported.

Statistical Analysis—A nonparametric Mann-Whitney test was used to compare the response before and after each treatment, and a nonparametric Friedman test was used to evaluate differences between the treatment groups. A reduction less than 25% was judged as no response, 26% to 50% was considered minimal response, 51% to 75% was deemed moderate response, and more than 75% of the sum of the score was considered important.

Results

Twenty-seven participants (calcipotriene group, n=10; tacrolimus group, n=10; combined therapy group, n=7) completed the study. Results shown in Table 1 indicate that the mean reduction in the sum of the scores between baseline and week 8 was significant (P=.001) for calcipotriene alone (39.5%), tacrolimus alone (38.2%), and the combination of calcipotriene and tacrolimus (60.7%). Combination therapy was statistically more effective than tacrolimus alone (P=.043) but not statistically superior to calcipotriene alone (P=.056). The results of the sum of the scores for each treatment regimen are shown in the Figure. The reduction in erythema was higher in the calcipotriene group, though no statistically significant differences with the other 2 treatment groups were found. Additionally, all treatment groups showed similar efficacy in reducing scaling and induration. The rate of response was minimal or moderate in the 3 treatment groups, and thus none of the treatment options reached an important therapeutic response.

The description of AEs to calcipotriene and tacrolimus alone and in combination are shown in Table 2. Most AEs were related to skin irritation and pruritus. Skin irritation was reported in 40% (4/10) of participants administered tacrolimus alone and 20% (2/10) of participants administered calcipotriene alone. Pruritus occurred in 30% (3/10) of participants administered calcipotriene alone and 10% (1/10) of participants administered tacrolimus alone. No AEs were evident in participants given the combination therapy. The AEs did not require treatment or withdrawal from the study. No noncutaneous AEs were reported in any of the 3 groups.

Comment

Topical corticosteroids remain the most effective treatment in the management of psoriasis; however, they cannot be used for prolonged periods, which is an important aspect in the treatment of psoriasis, as it is a chronic and recurrent disease.[12] Among several options of topical treatment in psoriasis, the most effective are the analogues of vitamin D_3; however, none of these treatments are completely effective. Thus, investigating new treatment options is imperative. Calcipotriene is a vitamin D_3 analogue that acts in the psoriasis plaque by inhibiting keratinocyte proliferation, inducing cell differentiation, and generating an anti-inflammatory effect.

Vitamin D_3 derivatives currently are the main alternatives for the management of psoriasis, with calcipotriene as the most potent form. The effectiveness of vitamin D_3 derivatives ranges from 46% to 74% in plaque psoriasis.[8,9] Körver et al[8] conducted a double-blind, randomized study comparing calcipotriene and calcitriol as the most effective option in the normalization of epidermal proliferation with results in the induction of keratinocyte differentiation.

Tacrolimus is a selective calcineurin inhibitor that is widely used in the management of atopic dermatitis. It acts by blocking calcineurin, a cytosolic enzyme that leads to a reduction in inflammatory cytokine production by activated T cells.[13] Although the usefulness of oral tacrolimus in psoriasis has been reported,[14] topical tacrolimus also has shown an

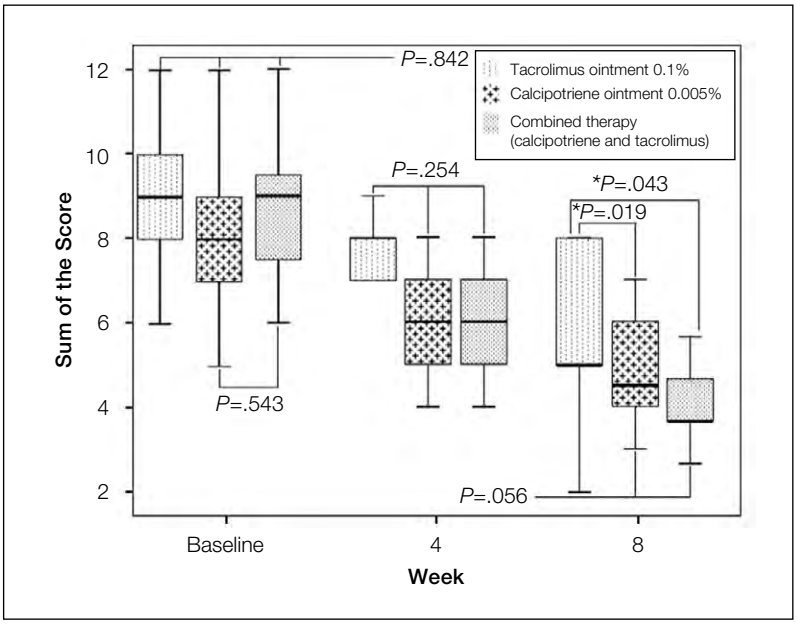
Table 1.

Treatment Response[a]

		Participants, n (%)								
		Calcipotriene Ointment 0.005% (n=10)			Tacrolimus Ointment 0.1% (n=10)			Combined Therapy (CP+TC)(n=7)		
Variable	Score	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
Erythema	0	0	0	0	0	0	0	0	0	0
	1	0	0	2	0	1	3	1	2	4
	2	3	7	8	2	4	5	1	2	3
	3	5	3	0	7	5	1	3	2	0
	4	2	0	0	1	0	1	2	1	0
Scaling	0	0	0	0	0	0	0	0	0	0
	1	0	0	1	0	1	2	0	0	3
	2	3	5	5	2	2	3	1	4	4
	3	3	4	4	2	4	4	4	3	0
	4	4	1	0	6	3	1	2	0	0
Induration	0	1	2	5	0	1	3	0	0	5
	1	2	5	2	1	3	4	1	5	1
	2	4	2	3	4	4	2	1	2	1
	3	1	1	0	3	2	1	4	0	0
	4	2	0	0	2	0	0	1	0	0

Abbreviation: CP+TC, combination of calcipotriene and tacrolimus.

[a]Graded on a 5-point scale (0=none; 1=mild; 2=moderate; 3=severe; 4=very severe).



Results of the sum of the scores for tacrolimus ointment 0.1%, calcipotriene ointment 0.005%, and combination therapy (calcipotriene and tacrolimus) at baseline, week 4, and week 8. Error bars indicate 95% confidence intervals ($P \leq .05$). Erythema, scaling, and induration were graded on a 5-point scale (0=none; 4=very severe); the scores were summed. Asterisk indicates statistically significant. The horizontal line in each bar represents the median.

Table 2.

Overview of Safety

	Participants		
Adverse Event	**Calcipotriene Ointment 0.005% (n=10)**	**Tacrolimus Ointment 0.1% (n=10)**	**Combined Therapy (CP+TC)(n=7)**
Total no. of adverse events	5	5	0
Skin irritation (dermatitis), n (%)	2 (20)	4 (40)	0 (0)
Pruritus, n (%)	3 (30)	1 (10)	0 (0)
Burning, n (%)	0 (0)	0 (0)	0 (0)
Noncutaneous adverse events, n (%)	0 (0)	0 (0)	0 (0)
No. of participants who reported adverse events	3 (30)	3 (30)	0 (0)

Abbreviation: CP+TC, combination of calcipotriene and tacrolimus.

adequate margin of efficacy in the control of stable plaque psoriasis with an improvement rate up to 61.9%.[10] Its effectiveness is influenced by the large molecular weight of tacrolimus, the vehicle (gel vehicle is more effective than cream,[10,11] and ointment also has been reported to be effective in the management of psoriasis), skin type, and occlusion.[15]

In a comparative study, Vissers et al[10] demonstrated the efficacy of topical tacrolimus in the management of plaque psoriasis with a response rate of 61.9%. Topical tacrolimus was as effective as calcipotriene in the control of epidermal proliferation and reduction of activated T cells, though calcipotriene was more potent in controlling keratinization.[10]

Given the effectiveness demonstrated for both products used separately, we conducted a study to compare the therapeutic efficacy of calcipotriene and tacrolimus as a combined therapy. The combined treatment regimen currently is one of the best options for the management of psoriasis, as it reduces AEs and in some cases synergizes. In the case of combined calcipotriene and steroid therapy, combination therapy demonstrated superior efficacy versus monotherapy with fewer AEs, especially those related to topical steroids.[15]

Topical calcipotriene and tacrolimus are effective agents for the control of stable plaque psoriasis, particularly for long-term use. The efficacy of combination therapy with topical calcipotriene and tacrolimus in stable plaque psoriasis has not been assessed. However, the combination of topical calcipotriene and tacrolimus has been used sequentially in the treatment of acrodermatitis continua of Hallopeau, a rare variety of pustular psoriasis, and led to improvement of disease with a remarkable difference in the effectiveness when compared with the products administered separately.[16]

Conclusion

The results of our study indicate that combination therapy for the treatment of stable plaque psoriasis is as effective as and possibly better tolerated than calcipotriene alone and more effective than tacrolimus alone. However, due to our small sample size, it is difficult to determine if the trend toward superiority (on safety and efficacy) with combination therapy is truly evident.

REFERENCES

1. Nograles KE, Davidovici B, Krueger JG. New insights in the immunologic basis of psoriasis. *Semin Cutan Med Surg*. 2010;29:3-9.
2. Dupont E, Savard PE, Jourdain C, et al. Antiangiogenic properties of a novel shark cartilage extract: potential role in the treatment of psoriasis. *J Cutan Med Surg*. 1998;2:146-152.
3. Housman TS, Mellen BG, Rapp SR, et al. Patients with psoriasis prefer solution and foam vehicles: a quantitative assessment of vehicle preference. *Cutis*. 2002;70:327-332.
4. Fleming C, Ganslandt C, Guenther L, et al. Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study [published online ahead of print April 23, 2010]. *Eur J Dermatol*. 2010;20:465-471.
5. van der Velden HM, Pasch MC, van Erp PE, et al. Treatment of plaque psoriasis with the two-compound product calcipotriol/betamethasone dipropionate versus both monotherapies: an immunohistochemical study. *J Dermatolog Treat*. 2010;21:13-22.
6. Tiplica GS, Salavastru CM. Mometasone furoate 0.1% and salicylic acid 5% vs. mometasone furoate 0.1% as sequential local therapy in psoriasis vulgaris [published online ahead of print March 11, 2009]. *J Eur Acad Dermatol Venereol*. 2009;23:905-912.
7. Koo J, Cuffie CA, Tanner DJ, et al. Mometasone furoate 0.1%-salicylic acid 5% ointment versus mometasone furoate 0.1% ointment in the treatment of moderate-to-severe psoriasis: a multicenter study. *Clin Ther*. 1998;20:283-291.
8. Körver JE, Vissers WH, van Rens DW, et al. A double-blind, randomized quantitative comparison of calcitriol ointment and calcipotriol ointment on epidermal cell populations, proliferation and differentiation. *Br J Dermatol*. 2007;156:130-137.
9. Franssen ME, de Jongh GJ, van Erp PE, et al. A left/right comparison of twice-daily calcipotriol ointment and calcitriol ointment in patients with psoriasis: the effect on keratinocyte subpopulations. *Acta Derm Venereol*. 2004;84:195-200.
10. Vissers WH, van Vlijmen I, van Erp PE, et al. Topical treatment of mild to moderate plaque psoriasis with 0.3% tacrolimus gel and 0.5% tacrolimus cream: the effect on SUM score, epidermal proliferation, keratinization, T-cell subsets and HLA-DR expression [published online ahead of print February 16, 2008]. *Br J Dermatol*. 2008;158:705-712.
11. Ortonne JP, van de Kerkhof PC, Prinz JC, et al. 0.3% tacrolimus gel and 0.5% tacrolimus cream show efficacy in mild to moderate plaque psoriasis: results of a randomized, open-label, observer-blinded study. *Acta Derm Venereol*. 2006;86:29-33.
12. Kalb RE, Bagel J, Korman NJ, et al. Treatment of intertriginous psoriasis: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2009;60:120-124.
13. Luger T, Paul C. Potential new indications of topical calcineurin inhibitors [published online ahead of print December 18, 2007]. *Dermatology*. 2007;215(suppl 1):S45-S54.
14. Remitz A, Reitamo S, Erkko P, et al. Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol*. 1999;141:103-107.
15. Kreuter A, Sommer A, Hyun J, et al. 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a double-blind, randomized controlled study. *Arch Dermatol*. 2006;142:1138-1143.
16. Brill TJ, Elshorst-Schmidt T, Valesky EM, et al. Successful treatment of acrodermatitis continua of Hallopeau with sequential combination of calcipotriol and tacrolimus ointments. *Dermatology*. 2005;211:351-355.