Pharmacokinetics of topical calcineurin inhibitors in adult atopic dermatitis: A randomized, investigator-blind comparison

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Objective: We sought to compare pharmacokinetics of pimecrolimus cream 1% and tacrolimus ointment 0.1% in adults with extensive, moderate to severe atopic dermatitis. Secondary end points included efficacy and safety.

Methods: Patients received twice-daily treatment for 13 days. Blood concentrations of pimecrolimus and tacrolimus were measured at days 1, 5, and 13. Treatment success was defined as an Investigators' Global Assessment score of 0 (clear) or 1 (almost clear).

Results: Tacrolimus was detectable in 36% of blood samples and pimecrolimus was detectable in 12%. In patients with measurable blood drug concentrations, systemic exposure to tacrolimus (mean area under the curve$_{0\text{-}10h}$ < 9.7 ng·h/mL; n = 7) was higher than to pimecrolimus (mean area under the curve$_{0\text{-}10h}$ < 2.5 ng·h/mL; n = 2). Whole-body treatment success (day 13) was achieved in 1 of 18 (5.6%) and 2 of 19 (10.5%) patients treated with pimecrolimus and tacrolimus, respectively, and face/neck treatment success in 5 of 18 (27.8%) and 5 of 19 (26.3%) patients, respectively. Patients included in the study were adult patients with severe atopic dermatitis. The results and conclusions drawn from this study population may not be applicable for the majority of patients with atopic dermatitis who have mild to moderate disease.

Conclusion: Pimecrolimus appears to be associated with lower systemic drug exposure than tacrolimus. (J Am Acad Dermatol 2005;53:602-9.)

Pimecrolimus cream 1% (Elidel) and tacrolimus ointment 0.1% (Protopic) are topical calcineurin inhibitors that have been shown to be safe and effective in the treatment of atopic dermatitis (AD).[1]

Pharmacokinetic studies have demonstrated that most patients with AD treated with topical calcineurin inhibitors experience negligible systemic absorption, resulting in low or undetectable blood concentrations of the active compound.[2-7] This is the first pharmacokinetic study to compare directly systemic exposure to pimecrolimus versus tacrolimus, after treatment with pimecrolimus cream 1% and tacrolimus ointment 0.1%, in adult patients with extensive, moderate to severe AD.

Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
IGA:	Investigators' Global Assessment
LOQ:	limit of quantification
TBSA:	total body surface area
TCS:	topical corticosteroids

METHODS

Study design

This was a randomized, investigator-blind, parallel-group, multicenter trial. Adult patients with moderate to severe AD (Investigators' Global Assessment[8] [IGA]

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Table I. Baseline patient characteristics

	Pimecrolimus n = 18, %	Tacrolimus n = 19, %
Age, y mean ± SD	40.9 ± 14.3	42.5 ± 15.1
Sex		
Male	33.3	10.5
Female	66.7	89.5
Race		
White	77.8	73.7
Black	11.1	15.8
Oriental	5.6	10.5
Other	5.6	0
Height, cm mean ± SD	165.9 ± 10.02	163.7 ± 11.38
Weight, kg mean ± SD	83.0 ± 19.5	71.9 ± 16.8
Fitzpatrick skin type		
I: Sensitive; always burns easily, never tans	5.6	15.8
II: Sensitive; always burns easily, tans minimally	33.3	31.6
III: Normal; burns moderately, tans gradually	33.3	26.3
IV: Normal; burns minimally, tans always	16.7	15.8
V: Insensitive; rarely burns, tans profusely	11.1	0
VI: Insensitive; never burns, deeply pigmented	0	10.5
Body surface area affected, % mean ± SD	56.1 ± 19.64	58.8 ± 17.75
Baseline overall IGA		
3: Moderate disease	55.6	42.1
4: Severe disease	33.3	57.9
5: Very severe disease	11.1	0
Baseline head/neck IGA		
2: Mild disease	16.7	10.5
3: Moderate disease	61.1	47.4
4: Severe disease	22.2	42.1
Baseline pruritus score		
1: Mild	16.7	10.5
2: Moderate	38.9	42.1
3: Severe	44.4	47.4
Age at onset, y mean ± SD	16.2 ± 19.76	14.2 ± 21.85
Duration of disease, y mean ± SD	25.3 ± 16.80	28.7 ± 16.88
Presence of disease		
Head/neck	100	100
Trunk	88.9	100
Upper limbs	100	94.7
Lower limbs	94.4	100

IGA, Investigators' Global Assessment.

score of 3-5) affecting at least 30% of the total body surface area (TBSA) received twice-daily treatment with either pimecrolimus or tacrolimus for 13 days. An investigator-blind design was used because the formulation differences between the two study treatments made it impossible to conduct the study in a double-blind manner.

Patients

Patients were eligible for inclusion if they had moderate to severe AD (the population specified by the tacrolimus ointment 0.1% label) and had a minimum TBSA affected of 40% (the first 12 patients enrolled) or 30% (the remaining patients enrolled). Patients who were pregnant, breast-feeding, or of childbearing potential and not using medically approved contraception, or who had any significant medical condition that might interfere with study evaluations, were excluded from the study. Patients were also excluded if they had used the following treatments known, or suggested, to have an effect on AD within the specified periods before the first use of study medication: phototherapy or systemic therapy within 1 month; pimecrolimus and/or topical tacrolimus within 2 weeks; other topical therapy within 7 days; systemic corticosteroids within 1 month;