

# Clocortolone Pivalate Cream 0.1% Used Concomitantly With Tacrolimus Ointment 0.1% in Atopic Dermatitis

Helen M. Torok, MD; Rainer Maas-Irslinger, MD; Rossi M. Slayton, BS

*This study was designed to evaluate the safety and efficacy of concomitant therapy with the corticosteroid clocortolone pivalate cream 0.1% (Cloderm® Cream 0.1%) and the topical immunosuppressive agent tacrolimus ointment 0.1% (Protopic® Ointment 0.1%) and to compare each drug alone for the treatment of atopic dermatitis in adolescents and adults. Concomitant therapy may minimize the potential adverse effects of both treatments taken alone and may potentially improve overall response. In this 21-day study with 57 patients with atopic dermatitis, groups of 19 patients were randomized to 1 of 3 treatments: concomitant treatment with clocortolone pivalate cream 0.1% and tacrolimus ointment 0.1% (CPC+TO), monotherapy with clocortolone pivalate cream 0.1% (CPC), or monotherapy with tacrolimus ointment 0.1% (TO). CPC+TO was statistically superior to TO alone in the percentage change for dermatologic sum score at days 14 (P=.024) and 21 (P=.033), excoriation at day 21 (P=.028), induration at day 21 (P=.033), and erythema at day 14 (P=.048). The dual therapy was also superior to CPC alone in excoriation at days 7 (P=.045) and 14 (P=.037), oozing or crusting at days 3 (P=.034) and 7 (P=.012), and lichenification at day 3 (P=.031). In addition,*

*unlike the 2 single-therapy treatment groups, percentage reductions from baseline in scores for the sensation of transient pruritus and burning or stinging were statistically significant for the concomitant treatment at days 14 (P=.016) and 21 (P=.016).*

*Cutis.* 2003;72:161-166.

**N**o single treatment is perfect for treating atopic dermatitis. The profile of common side effects associated with topical tacrolimus (eg, pruritus, stinging or burning sensation on application, potential increase in UV damage to the skin) and the moderate effectiveness of treatment suggest that trials of other approaches to treatment are warranted.<sup>1-4</sup> Therapy combining drugs with 2 different mechanisms of action (the standard topical corticosteroid and the novel drug tacrolimus) may enhance the effectiveness of both and reduce the frequency of unwanted side effects.

## METHODS

### Patients

Male and female patients with a history of atopic dermatitis, ranging in age from 16 to 65 years, were enrolled in this investigator-blinded, controlled, parallel study and randomized to receive 1 of 3 treatments: concomitant therapy with clocortolone pivalate cream 0.1% (Cloderm® Cream 0.1%) and tacrolimus ointment 0.1% (Protopic® Ointment 0.1%)(CPC+TO), clocortolone pivalate cream 0.1% (CPC) alone, or tacrolimus ointment 0.1% (TO) alone. A person other than the investigator was responsible for dispensing drugs to the patient and instructing patients on proper use. All patients

Accepted for publication March 27, 2003.

Dr. Torok is from HMT Dermatology, Inc, Medina, Ohio.

Dr. Maas-Irslinger is from Healthpoint, San Antonio, Texas.

Ms. Slayton is from Topical Solutions, Ltd, North Richland Hills, Texas.

Dr. Torok and Ms. Slayton are paid consultants for and

Dr. Maas-Irslinger is an employee of Healthpoint.

Reprints: Helen M. Torok, MD, HMT Dermatology Associates, Inc, 780 E Smith, Medina, OH 44256 (e-mail: helenmtorok@aol.com).

had a history of atopic dermatitis for at least 6 months, affecting between 5% and 20% of the body (excluding the face), and a baseline dermatologic sum score (DSS) of at least 5 for the target area to be evaluated (approximately 30–50 cm<sup>2</sup>, excluding the face).

Patients were not eligible for the study if they had underlying disease or other dermatologic conditions that required systemic therapy or use of a topical agent. All patients, legal guardians, or both, signed the Institutional Review Board–approved informed consent form.

### Treatment Regimen

Treatment products were applied twice a day for 21 days. Patients were instructed in the daily use of a mild cleanser (Cetaphil® Gentle Skin Cleanser) and moisturizer (Cetaphil Moisturizing Lotion). Patients were not permitted to treat the skin of the face, scalp, or groin. Those patients randomized to a treatment regimen of CPC alone or TO alone were treated according to the approved labeling for each product. Patients randomized to the CPC+TO treatment group applied both products twice a day, with at least one application after bathing. CPC was applied first, and TO was applied 15 minutes later. Additional applications of CPC (more than twice a day) were allowed if the cleanser or lotion did not reduce skin irritation adequately at the site of TO treatment.

### Evaluation

Patients were evaluated at baseline (day 0) and at days 3, 7, 14, and 21. Physicians and patients evaluated a variety of signs and symptoms using quantitative scales. Physicians evaluated disease signs or symptoms (excoriation, oozing or crusting, induration, lichenification, dryness or scaling, erythema, and transient pruritus and burning or stinging) and global improvement. Patient self-assessment measures were obtained for treatment-related pruritus and burning or stinging and overall improvement at the end of treatment. Patients also completed a questionnaire concerning the products' attributes.

The 3 treatment regimens were evaluated for clinical effectiveness by investigator assessments of the target treatment area, global improvement, and summary of the DSS.

### Statistical Analysis

Descriptive statistics (mean±SD, median, and range) were prepared for all clinical scores. Within-day clinical scores were evaluated by the Kruskal-Wallis test, and separate pairwise comparisons of group responses were tested by the Wilcoxon rank

Table 1.

### Patient Characteristics (N=57)

	No. of Patients (%)
<b>Sex</b>	
Male	22 (38.6)
Female	35 (61.4)
<b>Race</b>	
White	54 (94.7)
Black	2 (3.5)
Other	1 (1.8)
<b>Skin phototypes</b>	
I	11 (19.3)
II	29 (50.9)
III	14 (24.6)
IV	1 (1.8)
V	2 (3.5)

sum test. All statistical tests were 2 tailed, and  $\alpha=.05$  was used to determine the statistical significance of observed differences.

## RESULTS

### Patient Demographics

A total of 57 patients were enrolled and completed various phases of the study. Patient characteristics are summarized in Table 1. Females outnumbered males in an approximately 2:1 ratio. Equivalent numbers of patients were enrolled in each 10-year age cohort; 88% of patients were younger than 50 years and 60% were younger than 40 years. Almost all patients (94.7%) were white. Most patients were of skin phototype II (50.9%), but a significant number of patients were types I (19.3%) and III (24.6%). The 3 treatment groups were equal in number of patients (n=19) and had an affected skin surface area of approximately 10 cm<sup>2</sup>.

### Assessment of Clinical Effectiveness

**Dermatologic Sum Score**—The DSS is the sum of scores for excoriation, induration, and erythema. DSSs were significantly lower than baseline at days 3, 7, 14, and 21 for each of the 3 treatment groups (Table 2). The mean DSS for the CPC+TO group was much lower than for the group receiving TO

Table 2.

### Percentage Change From Baseline in Dermatologic Sum Scores by Treatment Group and Observation Day\*†

Observation Day	Treatment Group, mean±SD		
	CPC+TO (n=19)	CPC (n=19)	TO (n=19)
3	-26±22	-13±12	-22±20
7	-53±25	-41±24	-40±24
14	-71±23‡	-54±29	-53±28
21	-79±25§	-69±32	-57±31

\*CPC+TO indicates clocortolone pivalate cream 0.1% and tacrolimus ointment 0.1%; CPC, clocortolone pivalate cream 0.1%; and TO, tacrolimus ointment 0.1%.

† $P < .001$  for all treatment groups at all observation days vs baseline.

‡ $P < .024$  for CPC+TO change from baseline vs TO change from baseline.

§ $P < .033$  for CPC+TO change from baseline vs TO change from baseline.

alone. Reduction in the mean DSS from baseline (computed as actual change from day 21) was statistically significant ( $P < .001$ ) for each treatment group (CPC+TO,  $-1.53$ ; CPC,  $-0.76$ ; and TO,  $-1.42$ ). Percentage change in DSS comparing days 14 and 21 with baseline was statistically significant for the dual therapy versus TO alone ( $P = .024$  and  $P = .033$ , respectively) but not when compared with CPC versus TO ( $P = .240$  at day 21) or CPC versus CPC+TO ( $P = .272$  at day 21).

**Global Severity**—Investigators' assessment of percentage change in global severity was a reduction of  $-58\% \pm 36$  in patients receiving the concomitant treatment of CPC+TO,  $-48\% \pm 37$  in patients receiving CPC alone, and  $-44\% \pm 31$  in patients receiving TO alone. Although investigators found the greatest improvement in global severity in patients receiving the concomitant treatment, differences in percentage change among the 3 treatment groups for global severity were not significant (CPC+TO vs CPC,  $P = .412$ ; CPC+TO vs TO,  $P = .194$ ; and CPC vs TO,  $P = .698$ ).

**Global Improvement**—Likewise, although scores of global improvement (Figure 1) showed the effectiveness of the 3 treatments, the CPC+TO and CPC groups did not differ ( $P = .450$ ). CPC and TO administered alone did not differ from each other ( $P = .232$ ), but there is a suggestion that the concomitant treatment of CPC+TO would have been statistically favored if more patients were in the groups ( $P = .063$ ). By the end of treatment, percent-

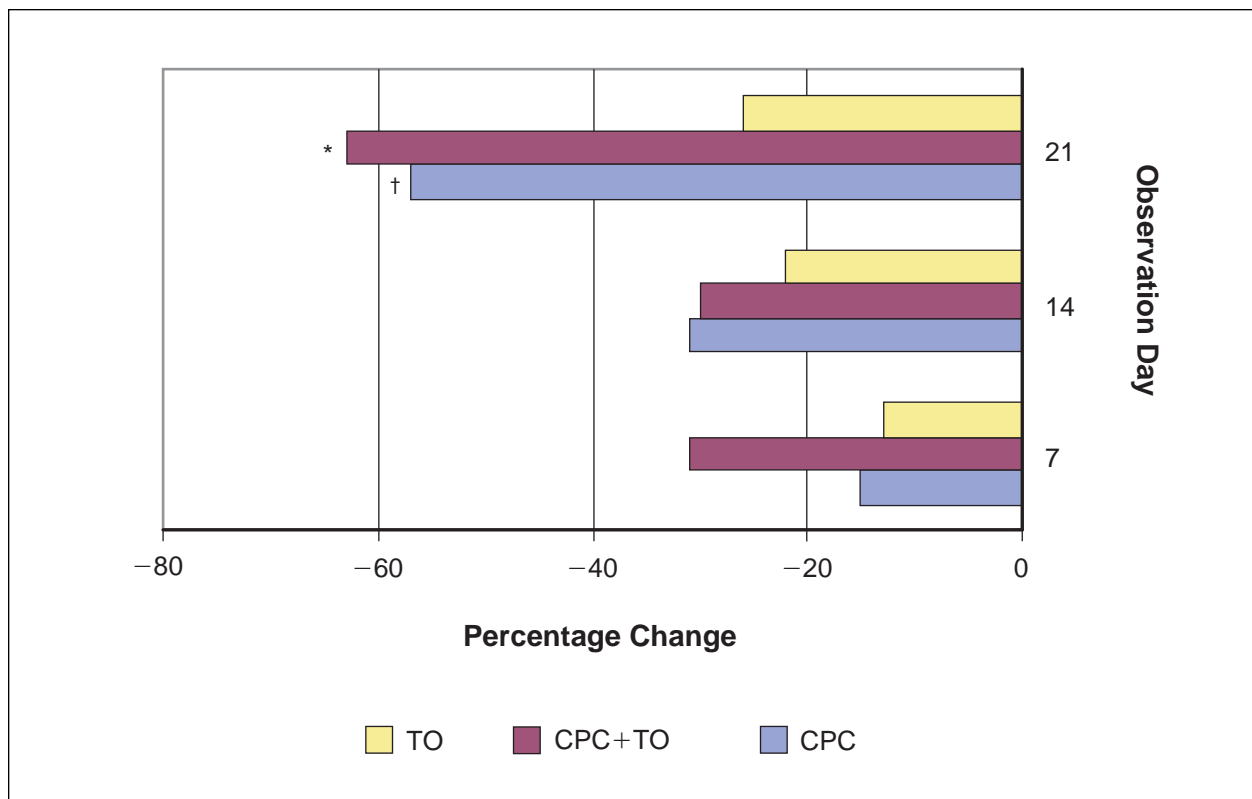
age global improvements at day 21 were as follows: CPC+TO, 63%; CPC, 57%; and TO, 26%. Further clinical evidence of global improvements in patients randomized to the concomitant treatment of CPC+TO after 21 days is shown in the pretreatment and posttreatment photographs (Figure 2).

### Evaluation of Clinical Features

Results of the secondary efficacy parameters also favored treatment with the concomitant regimen of CPC+TO over TO alone.

**Excoriation**—Observed scores were reduced in the CPC+TO group from a baseline mean of  $1.55 \pm 0.62$  to  $0.26 \pm 0.56$  by day 21, compared with  $1.79 \pm 0.61$  to  $0.47 \pm 0.59$  in the CPC group and  $1.87 \pm 0.74$  to  $0.71 \pm 0.71$  in the TO group. The percentage changes were significant at day 21 ( $P = .028$ ) in favor of CPC+TO versus TO. For the CPC+TO versus CPC groups, significant percentage changes were noted on days 7 ( $P = .045$ ) and 14 ( $P = .037$ ). The median scores for excoriation in both the CPC+TO group and the CPC group were reduced to zero by day 21. The median for the TO group, however, remained greater than zero at the end of treatment.

**Oozing or Crusting**—Observed scores were reduced in the CPC+TO group from a baseline mean of  $1.84 \pm 0.82$  to  $0.45 \pm 0.71$  by day 21, compared with  $1.66 \pm 0.62$  to  $0.58 \pm 0.82$  in the CPC group and  $2.11 \pm 0.39$  to  $0.84 \pm 0.85$  in the TO group. Differences in percentage change scores



**Figure 1.** Percentage change in global improvement from baseline. TO indicates tacrolimus ointment 0.1%; CPC+TO, clocortolone pivalate cream 0.1% and tacrolimus ointment 0.1%; CPC, clocortolone pivalate cream 0.1%. Asterisk indicates not statistically significant ( $P=.45$ ) vs CPC monotherapy; dagger, not statistically significant ( $P=.232$ ) vs TO monotherapy.

avored CPC+TO compared with CPC at days 3 ( $P=.034$ ) and 7 ( $P=.012$ ). The median score for the CPC+TO group for oozing or crusting was reduced from 2 (definite oozing or crusting on 26% to 50% of the lesions) to 0 (clear). The median score for the TO group, in contrast, was reduced from 2 to 1. Signs of oozing or crusting were still visible on 25% or less of lesions in the TO treatment group by day 21.

**Induration**—Observed scores were reduced in the CPC+TO group from a baseline mean of  $2.39 \pm 0.52$  to  $0.55 \pm 0.81$  by day 21, compared with  $2.26 \pm 0.42$  to  $0.68 \pm 0.84$  in the CPC group and  $2.55 \pm 0.40$  to  $1.13 \pm 0.83$  in the TO group. Patients treated with CPC+TO had significant differences ( $P=.033$ ) in the percentage change from baseline by day 21 versus patients treated with TO alone. There were no significant differences between CPC+TO and CPC.

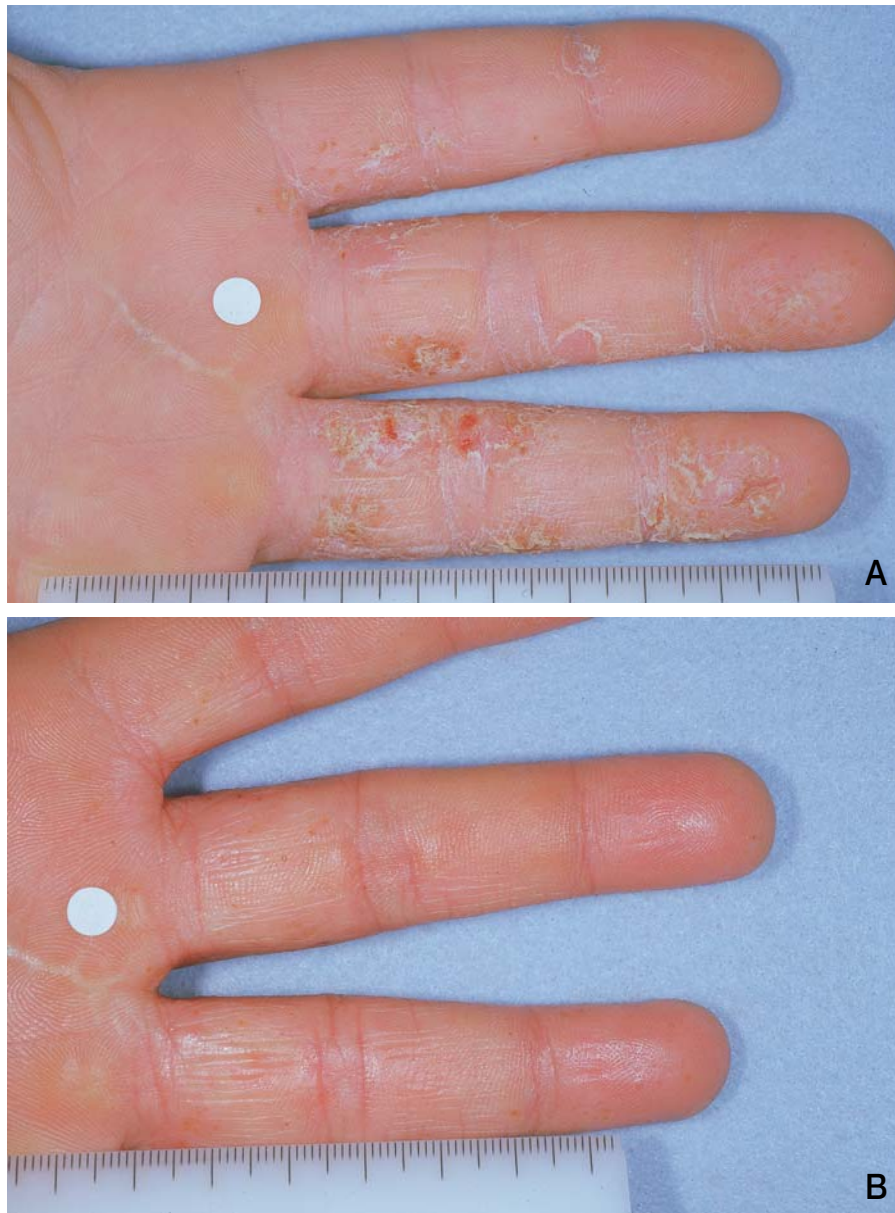
**Lichenification**—Observed scores were reduced in the CPC+TO group from a baseline mean of  $2.32 \pm 0.58$  to  $0.66 \pm 0.80$  by day 21, compared with  $2.16 \pm 0.55$  to  $1.00 \pm 0.93$  in the CPC group and  $2.50 \pm 0.44$  to  $1.21 \pm 0.79$  in the TO group. The

difference in observed scores between the CPC+TO group and the TO group was statistically significant by day 21 ( $P=.046$ ) in favor of the concomitant treatment. The CPC+TO group also showed statistically significant percentage changes in lichenification at day 3 compared with the CPC group ( $P=.031$ ).

**Dryness or Scaling**—The 3 treatment groups improved similarly from baseline to day 21 in skin dryness or scaling; the treatment groups did not differ from each other.

### Evaluation of Potential Drug-Related Adverse Effects

**Erythema**—Observed scores were reduced in the CPC+TO group from a baseline mean of  $2.13 \pm 0.37$  to  $0.58 \pm 0.56$  by day 21, compared with  $2.08 \pm 0.56$  to  $0.82 \pm 0.82$  in the CPC group and  $2.32 \pm 0.51$  to  $1.08 \pm 0.89$  in the TO group. Differences in observed scores between CPC+TO and TO were statistically significant at day 14 ( $P=.044$ ) and suggestive at days 7 ( $P=.054$ ) and 21 ( $P=.083$ ) in favor of the concomitant treatment. Patients treated with CPC+TO also had significant



**Figure 2.** Clinical improvement of a sample patient before (A) and after (B) 21 days of concomitant treatment with clocortolone pivalate cream 0.1% and tacrolimus ointment 0.1%.

differences ( $P=.048$ ) in the percentage change from baseline by day 14 compared with patients treated with TO alone. The level of erythema by day 14 was similar in the CPC+TO and CPC groups.

*Transient Pruritus and Burning or Stinging*—Comparisons of the 3 treatment groups showed no statistically significant differences. However, results for the significant side effect associated with TO (ie, transient burning or stinging on application) were suggestive. Observed scores at day 21 for the group receiving CPC alone or TO alone were the same ( $0.05 \pm 0.16$ ). For the concomitant treatment, the score for transient burning or stinging at day 21 was zero. It is worth noting that the range of values

for transient burning or stinging for CPC patients at days 14 and 21 were 0 to 2 and 0 to 0.5, respectively, and for TO patients, the ranges were 0 to 1 and 0 to 0.5 at days 14 and 21, respectively; however, in patients treated concomitantly with CPC+TO, the range for those 2 observation periods was never greater than zero. If there had been a larger number of patients in the 3 treatment groups, the differences among the groups probably would have been statistically significant at each visit. There were, however, significant differences from baseline in patients treated with the dual therapy at days 14 ( $P=.016$ ) and 21 ( $P=.016$ ). The percentage changes were suggestive at day 7 ( $P=.063$ ) in

patients treated with CPC+TO. Suggestive differences from baseline in transient pruritus also were shown in patients treated concomitantly with CPC+TO by day 21 ( $P=.063$ ). Neither monotherapy alone had statistically significant changes from baseline in transient pruritus and burning or stinging.

## COMMENT

The discomfort, cosmetic alterations, and impaired quality of life associated with atopic dermatitis are troublesome for patients. One study of 366 patients in a Swedish dermatology clinic found, for example, that patients would pay the US equivalent of \$116 to \$131 per month for a cure of their atopic dermatitis.<sup>5</sup> For physicians, too, treating atopic dermatitis is a challenge that often ends in frustration for both the physician and the patient.<sup>6</sup>

Because atopic dermatitis is a chronic condition with multiple underlying pathophysiologic mechanisms (immune cellular dysregulation, inflammatory cytokine dysregulation, genetic factors, chronic *Staphylococcus aureus* infection, and sensitivity to environmental allergens and autoallergens),<sup>7</sup> it is best managed with multifactorial therapy. Topical corticosteroids have been the mainstay of treatment. Today, a topical immunosuppressive drug is also available. This study shows that dual therapy, which is based on the entirely different mechanisms of action of these 2 drug classes, may be better than either drug taken alone.

Scores for pruritus were captured by questioning the patient. These *subjective* scores are often the source of statistical variance and, in fact, did not show a significant difference among treatment groups in this study. Excoriation, on the other hand, is an *objective* score made by the investigator. Excoriation associated with target lesions was reduced more effectively early in the treatment cycle in patients receiving CPC+TO, strongly suggesting that the pruritus associated with atopic dermatitis also was reduced. In addition, the oozing or crusting associated with the excoriated lesions was reduced more in the CPC+TO group than in either the CPC or TO groups. Although significant differences were shown in both treatments alone at

various time points, the clinical effectiveness of the concomitant treatment was superior to either therapy alone.

Unlike the monotherapy groups, the CPC+TO group had statistically significant differences from baseline in scores for the sensation of burning or stinging at days 14 ( $P=.016$ ) and 21 ( $P=.016$ ). Moreover, the scores for these observation periods were never greater than zero for any patient in the group receiving the concomitant regimen. The effectiveness of using CPC+TO rather than TO alone is an important finding of this study because the burning or stinging sensation is the most commonly reported adverse event associated with TO. If the concomitant use of CPC+TO ameliorates this undesirable side effect and is more effective than either treatment alone, atopic dermatitis will be improved, and the likelihood of patient compliance will be increased.

*Acknowledgment*—The authors acknowledge the editorial assistance provided by Robert N. Ross, PhD.

## REFERENCES

1. Frankel SJ, Kerdel FA. Topical tacrolimus 0.1%. *Skin Therapy Lett.* 2001;6:1-2, 5.
2. Bergman J, Rico MJ. Tacrolimus 0.1% clinical studies for atopic dermatitis and other conditions. *Semin Cutan Med Surg.* 2001;20:250-259.
3. Gianni LM, Sulli MM. Topical tacrolimus 0.1% in the treatment of atopic dermatitis. *Ann Pharmacother.* 2001;35:943-946.
4. Cheer SM, Plosker GL. Tacrolimus 0.1% ointment: a review of its therapeutic potential as a topical therapy in atopic dermatitis. *Am J Clin Dermatol.* 2001;2:389-406.
5. Lundberg L, Johannesson M, Silverdahl M, et al. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. *Br J Dermatol.* 1999;141:1067-1075.
6. Rudikoff D, Lebwohl M. Atopic dermatitis. *Lancet.* 1998;351:1715-1721.
7. Boguniewicz M, Leung DY. Pathophysiologic mechanisms in atopic dermatitis. *Semin Cutan Med Surg.* 2001;20:217-225.