

Safety and Tolerability of a Body Wash and Moisturizer When Applied to Infants and Toddlers with a History of Atopic Dermatitis: Results from an Open-Label Study

Eric Simpson, M.D., M.C.R.,* Nathan S. Trookman, M.D.,† Ronald L. Rizer, Ph.D.,‡
Norman Preston, Ph.D.,¶ Luz E. Colón, M.S.,¶ Lori A. Johnson, Ph.D.,¶
and Ronald W. Gottschalk, M.D.¶

**Department of Dermatology, Oregon Health and Science University, Portland, Oregon, †Penrose-St. Francis Health Services and Colorado Springs Dermatology Clinic, Colorado Springs, Colorado, ‡Thomas J. Stephens & Associates, Inc., Colorado Springs, Colorado, ¶Galderma Laboratories, L.P., Fort Worth, Texas*

Abstract: Improving skin barrier function and moisturizing without irritation are important components of managing patients with atopic dermatitis. This study evaluated the safety and tolerability of a body wash and moisturizer regimen for infants and toddlers with atopic dermatitis. This was an open-label study involving 56 children (3–36 months old) with a history of atopic dermatitis. The skin care regimen (Cetaphil Restoraderm Skin Restoring Body Wash and Cetaphil Restoraderm Skin Restoring Moisturizer; Galderma Laboratories, L.P.) was used at least once daily, but no more than twice daily, for 4 weeks. The primary variable of interest was the worst postbaseline scores for local tolerability (expressed as success or failure) using a 4-point scale for each component (erythema, edema, scaling and dryness, rash, and signs of discomfort upon application). Assessments of moisture content of the stratum corneum and transepidermal water loss were also performed. Fifty-three children completed the study. The percentage of subjects with no erythema increased from 33.9% to 50.0% by Week 4. The percentage of subjects with no scaling or dryness increased from 58.9% to 85.2% at Week 4. A statistically significant increase in corneometry from baseline ($p < 0.001$) and a statistically significant decrease in transepidermal water loss ($p = .009$) were observed. The body wash and moisturizer regimen was safe and well tolerated and improved hydration and skin barrier function in infants and toddlers as young as 3 months of age with a history of atopic dermatitis.

Address correspondence to Ronald Gottschalk, M.D., F.R.C.P.C., Medical Affairs, Galderma Laboratories, L.P., 14501 North Freeway, Fort Worth, TX 76177, or e-mail: ron.gottschalk@galderma.com.

Dr. Rizer has been a consultant for Johnson & Johnson.
This supplement was generously supported by Galderma.

DOI: 10.1111/j.1525-1470.2012.01809.x

Atopic dermatitis (AD), is a multifactorial dermatologic condition that is common in early childhood. Overall, AD affects approximately 14% of children younger than 4 years old (1), and disease onset occurs before 5 years of age in 90% of children with AD (60% begin experiencing symptoms in the first year of life) (2–4). The disease is characterized by extreme itching, with associated sleep loss, and may result in secondary infection. Caring for a young child with AD can have a considerable effect on the family (e.g., sleep disturbance, psychological pressure) and considerable use of health-care resources (5,6).

For children with AD, skin can be hydrated with regular bathing—once daily for several minutes using warm, not hot, water and a moisturizing cleanser (7). Liberal amounts of moisturizer should then be applied immediately after bathing, before the skin has completely dried, to prevent dryness and irritation (7,8). Understanding the safety and tolerability of products used in AD skin care is particularly important because infant skin is especially susceptible to irritation (9–11). Few studies have evaluated the tolerability and skin barrier effects of skin care products in this patient population.

The objective of the present study was to evaluate the safety and tolerability of a commercially available skin care regimen when applied to infants and toddlers with a history of AD over the course of 4 weeks. The regimen comprised Cetaphil Restoraderm Skin Restoring Body Wash and Cetaphil Restoraderm Skin Restoring Moisturizer (Galderma Laboratories, Fort Worth, TX), which was designed specifically for patients with sensitive skin, such as those with AD. The moisturizer is the only commercially available product that contains a combination of filaggrin breakdown products and ceramides, two important components that may play an important role in skin barrier function (12). Although the safety and tolerability of these products have recently been established in older populations (13), published reports on the safety and tolerability in infants and toddlers are limited.

METHODS

This was a single-center, open-label study conducted between February and April 2010 in Colorado Springs, Colorado. An Institutional Review Board reviewed and approved the study protocol, and the study was conducted under the guidelines described in the Declaration of Helsinki, Good Clinical Practice guidelines, the Code of Federal Regulations, and the Health Insurance Portability and Accountability Act. Written informed consent was obtained from the parent or legal guardian of each subject before enrollment in the study.

Subjects

Eligible subjects included boys and girls aged 3 to 36 months with AD meeting the Hanifin-Rajka criteria (N = 56 were screened; all were enrolled). The subjects' parents or legal guardians had to be able and willing to follow study instructions. Subjects were not excluded if they had active disease at screening, but subjects were excluded if they were using a topical steroid treatment other than a low-potency topical corticosteroid for their AD. Subjects who used a stronger topical steroid for rescue therapy but had not used it in a minimum of 30 days and whose AD had been stable for the last 30 days were allowed in the study. Subjects with known hypersensitivity to any topical body wash or moisturizer product were excluded from participation.

Product Description

The body wash and moisturizer in the test regimen include a variety of emollient, occlusive, humectant, barrier repair, antioxidant, and preservative ingredients. The moisturizer and body wash also contain the filaggrin breakdown products, arginine and sodium pyrrolidone carboxylic acid (PCA). The moisturizer also contains the ceramide precursor, hydroxypalmitoyl sphinganine.

Applications and Assessments

The parent or legal guardian of each eligible subject received up to two 10 fL oz (296 mL) units of test body wash and two 10 fL oz (296 mL) units of moisturizer at the first visit, based on parent or legal guardian estimated use and size of the subject. If additional product for the test regimen was needed during the study, the subject's parent or legal guardian was instructed to contact the clinic and request an additional unit, for up to a total of four units of test body wash and four units of test body moisturizer. Each subject's parents or legal guardians applied the test products at least once daily to the generalized skin surface and as often as needed for localized cleansing and skin moisturizing during the course of the 4-week study. The subjects' parents or legal guardians were instructed to cleanse and apply lotion approximately 2 hours before appointments on study visit days. Subjects' parents or legal guardians were counseled to not exceed two full body washes in a single day.

An application calendar (diary) was given to each subject's parent or legal guardian to record use of the test products. These diaries were collected at each study visit. At the final study visit (week 4 or early termination), parents or legal guardians completed an assessment

questionnaire (separate 25-question surveys for the body wash and moisturizer) regarding test product attributes.

At all study visits (baseline, week 2, and week 4), the clinical evaluator evaluated the scalp, body, and limbs for erythema, edema, scaling and dryness, rash, and signs of discomfort upon application. The clinical evaluator determined the score for each of these variables by direct evaluation (erythema, edema, dryness and scaling, rash) or through parent or legal guardian interview (signs of discomfort upon application). Table 1 defines the scoring system applied to evaluations of baseline skin irritation and inflammation and postbaseline local tolerability. For any subject who had a score of 3 (severe) for any of the local tolerability parameters, the parent or legal guardian was instructed to stop application of the test product(s) to the affected sites, but was allowed to continue applying both test products to unaffected body areas as appropriate at the discretion of the investigator. Any subject who had a score of 3 (severe) for any of the local tolerability assessments on multiple active eczema-

atous areas or on large areas of unaffected skin was discontinued from the study.

Corneometer CM 825 (Courage and Khazaka, Cologne, Germany) measurements were taken to measure the moisture content of the stratum corneum using an electrical capacitance method. The measurement has no units but is proportional to the dielectric constant of the surface layers of the skin and increases as the skin becomes more hydrated. The readings are directly related to the skin's electrical capacitance. Triplicate measurements were taken on one dorsal forearm and one lower leg (as selected by the clinician) of each cooperative subject at each study visit.

A single Tewameter TM300 (Courage and Khazaka) measurement was taken to measure transepidermal water loss (TEWL), which is water within the skin that is escaping through the stratum corneum. This measurement is based on the diffusion principle in an open chamber, and the density gradient is measured indirectly using two pairs of sensors located inside the hollow cylinder probe. Data were analyzed using a microprocessor and reported in gram per square meter per hour. A decrease in TEWL values reflects an improvement in the barrier properties of the skin (14). One measurement was taken from the leg at each study visit for all cooperative subjects. The decision was made to obtain only one TEWL measurement because of the amount of time required for the procedure. Because of the nature of TEWL measurements, every effort was made to generate good data for quiet, undistressed, cooperative subjects. The leg was chosen because subjects seem to be more cooperative when TEWL is measured on the leg than at other body sites. If a subject became distressed or behaved in a manner that would invalidate the TEWL measurements, the subject was allowed to calm down, if possible, and the measurement was retaken. If the subject did not calm down sufficiently, a note was made in the subject's source documents that the TEWL measurement was unattainable. At every study visit, subjects were acclimated for 20 minutes in the examination room before assessments. The temperature and humidity were captured hourly in every room in which the subjects were located during study visits. Throughout the study, temperature recordings ranged between 66°F and 75°F, and relative humidity recordings ranged between 18% and 28%.

TABLE 1. *Definitions of Terms Applied to the Local Tolerability Evaluations*

Erythema	Edema
0 None: no erythema	0 None: no swelling
1 Mild: slight pinkness present	1 Mild: slight swelling of skin, barely noticeable
2 Moderate: definite redness, easily recognized	2 Moderate: definite swelling, easily recognized
3 Severe: intense redness	3 Severe: intense swelling
Scaling and Dryness	Rash
0 None: no dryness	0 None: no rash
1 Mild: slight but definite roughness	1 Mild: slight rash characterized by mild/spotty erythema, minimal papulation
2 Moderate: moderate roughness	2 Moderate: moderate rash characterized by definite erythema, moderate papulation, may have mild edema
3 Severe: marked roughness	3 Severe: marked rash characterized by definite erythema, moderate-to-severe papulation, possible edema
Signs of discomfort (upon application)	
0 None: no signs of discomfort, application is well tolerated	
1 Mild: few signs of discomfort, subject rubs or holds test sites, occasionally pulls away, occasionally evidences desire to not have products applied	
2 Moderate: definite signs of discomfort, subjects pulls away, cries, evidences desire to not have products applied at least half of the time	
3 Severe: subject is distraught upon application, cries and screams, refuses to have products applied again	

Adverse Events

Adverse events were assessed from the time of study enrollment until exit from the study. The investigator-evaluator was responsible for documenting all reported

and observed adverse events during the study. The investigator made the determination as to the relation of the event to test product use.

Statistical Analysis

The data set analyzed was defined as the intention-to-treat (ITT) population, which included all subjects who were enrolled in the study, participated in at least one application of the test products, and had evaluable data. To evaluate the tolerability of the test products, the worst postbaseline local tolerability scores for each parameter (regardless of time point) were averaged, and standard deviations were calculated. The primary analysis for the worst postbaseline local tolerability scores consisted of dichotomizing each assessment as a success or failure. Success was defined as a score of 0, and failure was defined as a score of 1 or greater. A 95% confidence interval for the difference in success rates between the worst postbaseline local tolerability scores and baseline scores was calculated. For the TEWL measurements, a 95% confidence interval was calculated at baseline, week 2, and week 4 and for the change from baseline to weeks 2 and 4. The same assessments were performed for the average of the triplicate Corneometer measurements. For the parent or legal guardian assessment questionnaire, the frequency and percentage of responses were tabulated for each product, and a chi-square analysis was performed to test statistical independence of the responses. Descriptive statistics were used for recorded adverse events.

TABLE 2. Demographic Characteristics of the Study Population

	Study population (N = 56)
Age, months, mean $\pm$ standard deviation	21.8 $\pm$ 9.2
Male, n (%)	27 (48.2)
Race, n (%)	
Caucasian	40 (71.4)
African American	2 (3.6)
Hawaiian or Pacific Islander	1 (1.8)
Other or mixed	13 (23.2)
Hispanic or Latino ethnicity, n (%)	24 (42.9)
Fitzpatrick skin type classification, n (%)	
I	16 (28.6)
II	23 (41.1)
III	8 (14.3)
IV	5 (8.9)
V	4 (7.1)

RESULTS

Of the 56 subjects who were screened and enrolled, 53 (94.6%) completed the study. One subject withdrew, and the other two were withdrawn because of adverse events (1 subject for erythema and marked scaling on the face, worsening of AD, and impetigo; 1 subject for body rash). Demographic characteristics of the study population are shown in Table 2. Only one subject had active dermatitis during the study period.

Tolerability

The primary analysis for the worst postbaseline local tolerability scores consisted of dichotomizing each assessment as success or failure. Success was defined as a tolerability score of 0 and failure as a tolerability score of 1 or greater. As shown in Table 3, after application, the percentage of successes (tolerability score = 0) was higher after test product use than at baseline for erythema and scaling and dryness. There was little change in the percentage of successes for edema throughout the study.

The worst score exhibited by subjects (regardless of time point) was tabulated for each parameter that indicated scores > 0 . For erythema, 23 subjects had a score of 1 (mild), and four subjects had a score of 2 (moderate). One subject had an edema score of 1 (mild). Eight subjects exhibited scaling and dryness of 1 (mild). For rash, two subjects had a score of 1 (mild), and three had a score of 2 (moderate). All subjects reported a score of 0 for signs of discomfort upon application at all time points. Two subjects had evaluable data for the baseline and immediate time point measurements only, so their data are included in the worst postbaseline score assessments for signs of discomfort upon application but excluded from the other parameters.

Results for TEWL are shown in Fig. 1; an increase in TEWL indicates impairment to the skin barrier, whereas a decrease in TEWL means repair of the skin barrier. A statistically significant decrease in TEWL was noted as early as week 2 and continued through week 4.

Corneometry results indicate that application of the products resulted in increased hydration in the skin. Statistically significant increases in corneometry occurred on the dorsal forearm and the lower leg at weeks 2 and 4 (Fig. 2). The average values of triplicate measurements are shown.

At week 4 or early termination visit, the majority of parents and legal guardians who completed the assessment questionnaire (n = 55) rated the overall impression and particular product attributes of the body wash and moisturizer as pleasant or very pleasant (96.4% for the body wash and 100.0% for the moisturizer).

TABLE 3. Baseline and Postbaseline Severity of Cutaneous Irritation Tolerability Assessment

Parameter	Successes* at baseline	Successes* after application†	95% Confidence interval for the difference in successes between baseline and postapplication
Erythema	19/56 (33.93%)	27/54 (50.00%)	−2.14–34.28
Edema	55/56 (98.21%)	53/54 (98.15%)	−5.06–4.93
Scaling and dryness	33/56 (58.93%)	46/54 (85.19%)	10.26–42.25
Rash	47/56 (83.93%)	49/54 (90.74%)	−5.53–19.15

*Success defined as a tolerability score of 0.

†Of the 56 subjects enrolled, two had evaluable data for the baseline and 2 week visits only. Data for these two subjects were included in the worst postbaseline score assessments for signs of discomfort (upon application) but were excluded from other tolerability parameters. All subjects exhibited or reported a score of 0 for signs of discomfort at all evaluated time points.

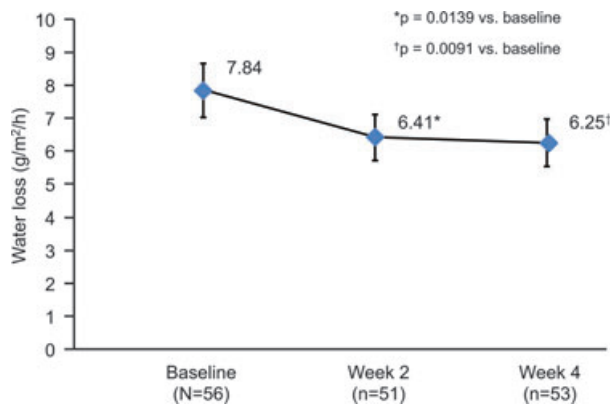


Figure 1. Transepidermal water loss measurements over the course of the study. Three subjects were unable to attend the week 2 visit so data were available for 51 subjects at this time point. Vertical bars represent 95% confidence intervals.

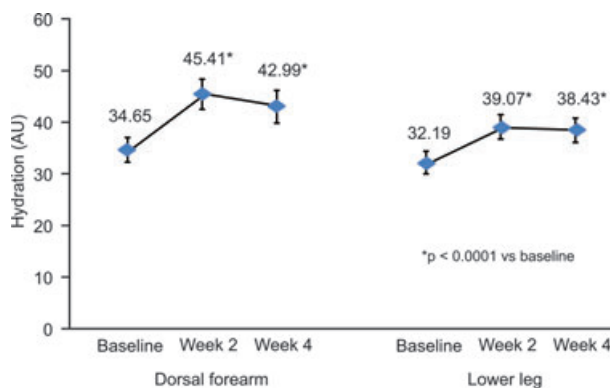


Figure 2. Corneometer measurements over the course of the study. Three subjects were unable to attend the week 2 visit, so data were available for 51 subjects at this time point. Vertical bars represent 95% confidence intervals.

(Table 4). In addition, 72.7% of parents indicated that the child's skin was better protected with the body wash than with the child's usual product, and 87.3% fully agreed or somewhat agreed that the cleanser fit the child's specific skin needs. Responses to the same questions for

the moisturizer were 76.4% and 83.6%, respectively. When asked about preference between the test products and the child's usual product, 65.5% and 72.7% of parents and legal guardians said they preferred the test body wash and moisturizer, respectively, and 78.2% and 81.8% indicated that they would like to continue using the body wash and moisturizer, respectively. Additional responses from the parent and legal guardian assessment questionnaire are shown in Table 5.

Safety

During the course of the study, 19 subjects experienced at least one adverse event; nine experienced one event, and 10 experienced more than one event. Of the 37 reported adverse events, 25 (67.6%) were determined to be definitely unrelated to study products, 5 (13.5%) were determined to be unlikely related, 3 (8.1%) possibly related, 2 (5.4%) probably related, and 2 (5.4%) definitely related. The adverse events that were determined to be definitely related to study products were stinging in the eyes with use of the test product, which was experienced twice (two episodes in the same subject). Two adverse events were considered probably related to study medication: burning in eyes with use and scalp itch. Adverse events that were possibly related to study products were application site reactions, which included a break out of the face, worsening of AD, and full body rash.

DISCUSSION

The results of this safety and tolerability study demonstrated that the test regimen was safe and generally well tolerated when used for infants and toddlers with a history of AD. All subjects reported a score of 0 (none) for signs of discomfort at all evaluated time points. Furthermore, skin inflammation scores measured at week 4 improved from baseline in three (erythema, scaling and dryness, and rash) of the four parameters evaluated, indicating that this skin care regimen is suit-

TABLE 4. *Tabulations for the Assessment Questionnaire*

	Very pleasant n (%)	Pleasant n (%)	Unpleasant n (%)	Very unpleasant n (%)
Body wash (n = 55)				
Overall impression of this product	27 (49.1)	26 (47.3)	1 (1.8)	1 (1.8)
Product attributes				
Texture	33 (60.0)	19 (34.5)	3 (5.4)	0
Color	28 (50.0)	27 (49.0)	0	0
Scent or smell	18 (32.7)	29 (52.7)	7 (12.7)	1 (1.8)
Foaming properties	18 (32.7)	29 (52.7)	6 (10.9)	2 (3.6)
Moisturizer (n = 55)				
Overall impression about this product	34 (61.8)	21 (38.2)	0	0
Product attributes				
Texture	38 (69.1)	17 (30.9)	0	0
Color	34 (61.8)	21 (38.2)	0	0
Scent or smell	28 (50.9)	20 (36.4)	7 (12.7)	0

TABLE 5. *Tabulations for the Assessment Questionnaire*

	Strongly agree n (%)	Somewhat agree n (%)	Somewhat disagree n (%)	Strongly disagree n (%)
Body wash (n = 55)				
Makes the skin soft and smooth	38 (69.1)	14 (25.5)	3 (5.5)	0 (0.0)
Is mild enough	38 (69.1)	11 (20.0)	6 (10.9)	0 (0.0)
Provides long-lasting hydration	32 (58.1)	12 (21.8)	9 (16.3)	2 (3.6)
Relieves dry skin	33 (60.0)	14 (25.5)	7 (12.7)	1 (1.8)
Relieves itchy skin	31 (56.3)	17 (30.9)	6 (10.9)	1 (1.8)
Is nonirritating	34 (61.8)	15 (27.2)	4 (7.2)	2 (3.6)
Moisturizer (n = 55)				
Makes the skin soft and smooth	40 (72.7)	15 (27.3)	0 (0.0)	0 (0.0)
Is mild enough	41 (74.5)	11 (20.0)	2 (3.6)	1 (1.8)
Provides long-lasting hydration	38 (69.1)	14 (25.5)	3 (5.5)	0 (0.0)
Relieves dry skin	38 (69.1)	15 (27.3)	2 (3.6)	0 (0.0)
Relieves itchy skin	39 (70.9)	11 (20.0)	4 (7.3)	1 (1.8)
Is nonirritating	40 (72.7)	12 (21.8)	2 (3.6)	1 (1.8)

able for infants and toddlers with the sensitive skin of AD. Although many infants included in the study had mild disease, global scores for the severity of AD were not determined. Some of the children had erythema scores of “severe” at baseline, suggesting that the results may apply to children with various degrees of severity. As such, it provides valuable information to clinicians, because few commercially available products have been evaluated in children with AD. Because clinical evaluation of the signs and symptoms of AD can be subjective, it is important to identify objective measures of disease severity and skin barrier function. Previous studies have shown good correlation between subjective evaluation of AD severity and corneometry and TEWL, which are objective measures of stratum corneum function (15,16). Atopic skin is characterized by impaired ability to bind and hold water, which is the result of a decrease in osmotically active amino acids in corneocytes and

abnormal stratum corneum lamellae that cannot hold water within the corneocytes (17–20). Corneometry is a good measure of atopic disease severity and response to treatment (15,16). In the present study, Corneometer bioinstrumentation results showed that the skin of the dorsal arm and lower leg was significantly more hydrated after 2 and 4 weeks of test product use than at baseline. TEWL is a direct assessment of the skin’s permeability barrier and has been used to examine normal skin and affected skin in patients with AD (15,16). In AD, an intrinsic or secondary decrease in ceramide content of the stratum corneum is thought to accompany the defect in barrier function (21–23). In this study, a significant decrease (improvement) in TEWL scores on the leg was observed after 2 and 4 weeks of test product use. These results suggest that the skin barrier of these children showed improvement during the study, which correlated with the subjective clinical assessments of erythema,

edema, scaling and dryness, and rash scores. The study design does not allow for separating the effects of the body wash from those of the moisturizer, but the advantage of the study design is that it represents a real-world situation, in which cleansing and moisturizing are usually performed in tandem. Although the results of the present study are intriguing, it is important to note that relative humidity, which was not actively controlled in this study, can influence TEWL measurements (24). Overall, these results warrant further research (e.g., randomized controlled trials) to evaluate the efficacy of the test products in children with AD.

The parent or legal guardian assessment questionnaire results were favorable for the body wash and the moisturizer for aesthetic properties, ability to help relieve dry skin and provide long-lasting hydration, and general opinion of the products. Additionally, the test body wash and test body moisturizer were perceived to have better skin protection properties than and were preferred overall over the child's usual body wash or moisturizer. Although these evaluations may not be scientifically rigorous, they are significant because any product used on infants must be acceptable to their parents and guardians who purchase and then must apply these products for extended periods. Furthermore, parents and guardians see the infants daily and have the greatest opportunity to assess changes in the status of their child's skin condition by interpreting the skin and behavioral reactions when products are applied.

Of the 37 adverse events reported during the study, only seven were either possibly, probably, or definitely related to the test products. Two definitely related and one probably related were described as stinging in the eyes upon application, which is a known side effect of the wash. It is now advised to avoid contact with eyes when using Cetaphil Restoraderm Skin Restoring Body Wash.

CONCLUSION

This study suggests that daily washing and moisturizing with the test regimen in this study is safe and well tolerated in infants and toddlers with AD. The skin care regimen demonstrated increases in hydration and improvements in the skin barrier function in children as young as 3 months old with AD defined by the Hanifin-Rajka criteria.

ACKNOWLEDGMENTS

Galderma Laboratories, L.P., Fort Worth, Texas, provided funding for these studies and for manuscript preparation. The authors acknowledge the role of Kevin Jarvis, PharmD, from BioCentric, Inc., in helping pre-

pare the manuscript (drafting an outline and manuscript first draft), compiling author comments, and styling and submitting the manuscript to the journal.

REFERENCES

1. Shaw TE, Currie GP, Koudelka CW et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131:67-73.
2. Williams HC, Wutherrich B. The natural history of atopic dermatitis. In: Williams HC, ed. *Atopic dermatitis*. Cambridge: Cambridge University Press, 2000:41-59.
3. Kay J, Gawkrödger DJ, Mortimer MJ et al. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35-39.
4. Rajka G. *Essential aspects of atopic dermatitis*. Berlin, Germany: Springer, 1989.
5. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;60:984-992.
6. Lapidus CS, Schwarz DF, Honig PJ. Atopic dermatitis in children: who cares? who pays? *J Am Acad Dermatol* 1993;28:699-703.
7. Eichenfield LF, Hanifin JM, Luger TA et al. Consensus conference on pediatric dermatitis. *J Am Acad Dermatol* 2003;349:1088-1095.
8. Simpson EL. Atopic dermatitis: a review of topical treatment options. *Curr Med Res Opin* 2010;26:633-640.
9. National Collaborating Centre for Women's and Children's Health. *Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years*. London, UK: RCOG Press at the Royal College of Obstetricians and Gynaecologists, 2007.
10. Pascher F. Systemic reactions to topically applied drugs. *Bull NY Acad Med* 1973;49:613-627.
11. Mancini AJ. *Skin*. *Pediatrics* 2004;113:1114-1119.
12. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2009;9:437-446.
13. Simpson E, Dutronc Y. A new body moisturizer increases skin hydration and improves atopic dermatitis symptoms among children and adults. *J Drugs Dermatol* 2011; 10:744-749.
14. Barel AO, Clarys P. Study of the stratum corneum barrier function by transepidermal water loss measurements: comparison between two commercial instruments: evaporimeter and Tewameter. *Skin Pharmacol* 1995;8: 186-195.
15. Sugarman HL, Fluhr JW, Fowler AJ et al. The objective severity assessment of atopic dermatitis score. *Arch Dermatol* 2003;139:1417-1422.
16. Chamlin SL, Kao J, Frieden IJ et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol* 2002;47:198-208.
17. Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. *Acta Derm Venereol* 1995;75:429-433.

18. Watanabe M, Tagami H, Horii I et al. Functional analyses of the superficial stratum corneum in atopic xerosis. *Arch Dermatol* 1991;127:1689–1692.
19. Tanaka M, Okada M, Zhen YX et al. Decreased hydration state of the stratum corneum and reduced amino acid content of the skin surface in patients with seasonal allergic rhinitis. *Br J Dermatol* 1998;139: 618–621.
20. Horii I, Nakayama Y, Obata M et al. Stratum corneum hydration and amino acid content in xerotic skin. *Br J Dermatol* 1989;121:587–592.
21. Di Nardo A, Wertz P, Giannetti A et al. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm Venereol* 1998;78:27–30.
22. Imokawa G, Abe A, Jin K et al. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol* 1991;96:523–526.
23. Yamamoto A, Serizawa S, Ito M et al. Stratum corneum lipid abnormalities in atopic dermatitis. *Arch Dermatol Res* 1991;283:219–223.
24. Rogiers V. EEMCO guidance for the assessment of transepidermal water loss in cosmetic sciences. *Skin Pharmacol Appl Skin Physiol* 2001;14:117–128.