A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

The Role of a Novel Daily Cleansing and Moisturizing Regimen in the Management of Atopic Dermatitis: A Clinical Review

ISSN: 1545 9616

July 2013 • Volume 12 • Issue 7 (Supplement)

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Disclosure of Commercial Support

Editorial support and funding for this supplement to the *Journal of Drugs in Dermatology* is provided by Galderma Laboratories, L.P.

EDITORIAL

ORIGINAL ARTICLE

Over-the-Counter Product Role in the Daily Management of Atopic Dermatitis: Achieving Success With Advanced Technology

Leon H. Kircik MD

As understanding of the structure and function of the epidermal barrier has improved over the past several years, treatment strategies for various dermatologic conditions have changed to incorporate barrier support and repair. Barrier support is now commonly used for atopic dermatitis,[1,2] as well as for other inflammatory diseases of the skin such as psoriasis, acne, and rosacea. The market for epidermal barrier repair formulations is large, and it includes both prescription and over-the-counter (OTC) options. The cost of these formulations varies widely and, because of their approval status as a medical device rather than a drug, some third-party payers unfortunately may not cover prescription barrier therapies, thus limiting their use.

Cetaphil® Restoraderm® Moisturizer (Galderma Laboratories, L.P.; Fort Worth, TX) and its associated Body Wash from Galderma are a welcome OTC option for atopic dermatitis patients. Restoraderm Body Wash and Moisturizer are specifically created to address the needs of atopic dermatitis patients, both adult and pediatric. Of note, the Restoraderm product line is formulated with advanced ceramide technology and filaggrin breakdown products to support the natural components of the epidermal barrier.

Cetaphil Restoraderm products are widely available and competitively priced, making them accessible to a large majority of the patient population.

The emerging and available data on epidermal barrier function and its repair confirm that barrier support is a crucial element in treating patients with atopic dermatitis and several other common dermatoses. As discussed in the pages ahead, the Restoraderm Body Wash and Moisturizer product line has extensive clinical data to support its positive effect on the epidermal barrier system in atopic patients.

Leon H. Kircik MD
Mount Sinai Medical Center, New York, NY
Indiana University School of Medicine, Indianapolis, IN
Physicians Skin Care, PLLC, Louisville, KY

Disclosures

Dr. Kircik has received compensation from the *Journal of Drugs in Dermatology* for his editorial support.

References

1. Wollenberg A, Schnopp C. Evolution of conventional therapy in atopic dermatitis. *Immunol Allergy Clin North Am.* 2010;30(3):351-368.
2. Elias PM, Wakefield JS. Therapeutic implications of a barrier-based pathogenesis of atopic dermatitis. *Clin Rev Allergy Immunol.* 2011;41(3):282-295.

Copyright © 2013 ORIGINAL ARTICLE Journal of Drugs in Dermatology

The Integration of Physiologically-Targeted Skin Care in the Management of Atopic Dermatitis: Focus on the Use of a Cleanser and Moisturizer System Incorporating a Ceramide Precursor, Filaggrin Degradation Products, and Specific "Skin-Barrier–Friendly" Excipients

James Q. Del Rosso DO FAOCD[a] and Leon H. Kircik MD[b]

[a]Valley Hospital Medical Center, Las Vegas, NV; Las Vegas Skin and Cancer Clinics, JDRx Dermatology LLC, Henderson, NV; Touro University College of Osteopathic Medicine, Henderson, NV

[b]Mount Sinai Medical Center, New York, NY; Indiana University School of Medicine, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY

ABSTRACT

Atopic dermatitis (AD) may be considered the "poster disease" for exemplifying the significance of abnormalities of the epidermal barrier that occur predominantly within the stratum corneum (SC) and upper epidermis. Specifically, impairments of the SC permeability barrier, antimicrobial barrier, and immunologic barrier contribute markedly to the fundamental pathophysiology of AD. The multiple clinical sequelae associated with epidermal barrier impairments inherent to AD include dry skin, pruritus, increased skin sensitivity to irritants and allergens, eczematous skin changes, staphylococcal skin and anterior nares colonization, and increase in some cutaneous infections (ie, molluscum contagiosum). This article addresses the pathophysiology of AD with clinically relevant correlations, and discusses the scientific basis of a specially designed cleanser and moisturizer system that incorporates ceramide technology and filaggrin degradation products along with other "barrier-friendly" excipients.

J Drugs Dermatol. 2013;12(7 suppl 1):s85-s91

INTRODUCTION

Atopic dermatitis (AD) is one of the most common dermatologic disorders encountered in both pediatric and general dermatologic practices in the United States and globally, especially in well-developed countries with multiple urban areas.[1-3] The complexity of AD is typified by multiple pathogenic associations, including genetic factors, environmental influences, lifestyle, dietary exposures, innate abnormalities of multiple epidermal barrier functions, hyper-responsiveness to both cutaneous allergens and irritants, impact from increased bacterial colonization with *Staphylococcus aureus,* and neurogenic/neuroimmunological factors.[1-33] Importantly, these pathogenic factors do not operate in a vacuum, with supporting evidence from the observation that filaggrin (FLG) null mutations alone do not appear to cause AD.[33] Rather, the pathogenic factors of AD interact to produce a varied spectrum of phenotypes that present every day in clinical practice to dermatologists, allergists, and primary care physicians.[1-3,20] Independently and collectively, these pathogenic factors may also correlate directly to AD severity, persistence and/or frequency of recurrence, and response to therapy.[5-7,13,14,21-26] Further details on these pathogenic associations are outlined in Table 1, which depict important pathophysiologic reference points that relate to the common clinical features of AD.[1-45]

Clinical Overview of Atopic Dermatitis

Atopic dermatitis is one of the most common dermatoses encountered in pediatric and general dermatology practice, and most commonly presents initially in infancy or early childhood. It has been estimated that 45% of patients with AD present within the first 6 months of life, 60% within the first 12 months of life, and 85% before 5 years of age.[1] The association of polyvalent immunoglobulin E sensitization to inhalant and/or food allergens characterizes extrinsic AD and explains the subsequent development of asthma, seasonal rhinitis, and sometimes food hypersensitivity in many patients with AD, as extrinsic AD accounts for 60% to 90% of AD cases.[1,46] The clinical presentations and associated manifestations of AD, as well as its range of severity and the course of the disease over time, are well covered in virtually all major general and pediatric dermatology textbooks for the interested reader who is less familiar with AD.

The heavy educational and research emphasis on pediatric and adolescent AD often results in adult AD being overlooked as a diagnostic consideration, especially as the eczematous presentations of AD in adults are often localized. Although AD is most predominant during childhood and adolescence and may "burn out" after the teenage years in some cases, persistence into adulthood is still common. Many cases of AD in adults present as various recurrent forms of eczema and pruritus, often with associated allergic sinusitis (and sometimes adult asthma) noted in the medical history.[47-50] Some of the localized eczematous presentations commonly affecting adults with AD include lichen simplex, chronic/recurrent hand eczema, eyelid dermatitis, genital pruritus (including vulvar pruritus, vulvar hyperplastic dystrophy [lichen simplex], and scrotal pruritus often with lichen

TABLE 1.

Pathogenic Associations in Atopic Dermatitis With Clinical Correlations[1-45]

Pathogenic Associations	Specific Factors/Consequences	Clinical Correlations
Genetic	Parental history of AD of major importance	Strongest risk factor for AD – Risk doubled if 1 parent – Risk tripled if both parents
Environmental /Lifestyle	Urban vs rural living influences risk and prevalence of AD	Urban with higher prevalence – House dust mite antigen exposure – Air pollutant exposures
	Pet exposures may be significant in some cases	Pet-related antigens can exacerbate AD and may lead to inadequate response to therapy/more frequent exacerbations
Dietary	Overall attempts to reduce risk without consistent benefit	– Breast feeding not protective against AD – Delaying introduction of solid foods not protective against AD
	Individual food allergies may be significant in some cases	May be problematic in some cases that are poorly responsive, more severe, and/or with frequent exacerbations of AD
Epidermal/ Stratum Corneum Barrier Impairments	**Permeability Barrier** – Reduced ceramide (cer) subfractions (total reduced; reduced cer-1>cer 2-6) in lesional[a] and nonlesional skin[b] (reductions greater in lesional skin) – Increased sphingomyelin deacylase (lesional and nonlesional skin) causing decreased ceramide precursor – Loss of function FLGm in some patients	Factors collectively cause increased TEWL with predisposition to xerosis/pruritus/eczema – Decreased ceramides impair intercellular lipid membrane (physiologically controls TEWL) – FLGm cause decrease in NMF, causing less ability to sustain SC hydration – AD with FLGm in the United States with greater persistence causing less ability to sustain SC hydration and lower likelihood of symptom-free periods – Ultimate outcome of persistent impairment of SC permeability barrier is xerotic, poorly resilient scaly skin; depending on severity, skin is microfissured, macrofissured, inelastic, scaly and hyperkeratotic (the latter especially on hands and feet), palmar and plantar keratotic changes often without visible inflammation – Xerotic changes can be accompanied by or progress to subacute and chronic eczematous dermatitis with visible inflammation (ie, erythema, scaling, crusting, lichenification) – Flaking, scaling, and hyperkeratosis due to impaired desquamation (proteolytic enzymes function poorly without adequate SC water content and gradient) – Atopic skin less capable of using self-repair mechanisms (ie, increase epidermal ceramide/lipid synthesis, increase FLG production to increase NMF in SC) due to inherent SC barrier deficiencies; vicious persistent cycle ensues if not corrected by proper exogenous barrier repair – Acute allergic contact dermatitis in AD often presents as acute eczematous dermatitis; some cases may appear urticarial with lesser eczematous change clinically
	Antimicrobial Barrier – Multiple AMPs (cathelidins, defensins, dermicidins) decreased in AD skin – Reduced hBD2 and LL-37 (cathelicidin) in acute and chronic lesional AD – Up to 90% of AD patients with *S aureus* colonization (lesional and nonlesional vs 5% in healthy control skin); up to 60% with toxin-producing strains (superantigens) – Specific superantigen toxins (eg, enterotoxins A and B, TSST-1) expand skin-homing T cell populations – Superantigens may activate infiltrating mononuclear cells and Th2 cells, mast cell degranulation, and skin-homing receptors on T cells – *Staphylococci* can produce proinflammatory non toxins (ie, protein A, lipoteichoic acid)	Increased susceptibility to bacterial and viral infections (ie, eczema herpeticum, molluscum contagiosum) – LL-37 exhibits broad range of antimicrobial activity including *Staphylococcus aureus* and HSV – *S aureus* colonization may trigger and/or prolong an AD flare (toxins, other compounds)

continued on next page

Pathogenic Associations in Atopic Dermatitis With Clinical Correlations,[1-45] *continued*

Epidermal/ Stratum Corneum Barrier Impairments, continued	**Immune Response Barrier** – Innate and acquired response dysregulation with Th2 imbalance; Th2-Th1 shift – Skin hyper-responsiveness to irritants and allergens – Impaired microbial recognition (innate immune detection) and response impaired – Multiple defects in pattern recognition receptors (TLRs) in AD skin that are present normally to detect various microbes and protect against skin invasion/infection –TLR genetic polymorphisms in AD alter innate immune detection and response –TLR2 mutation increased R753Q in AD – Low levels of CD14 receptor that detects bacterial cell wall components in AD (ie, lipopolysaccharides) – Permeability barrier impairment (increased TEWL, decreased hydration) induces "jump start" cytokine release (IL-1, IL-6, TNF-α) as response to initiate repair and nonspecific inflammation; SC IL-1 levels increased in AD with FLGm (consistent with murine data) – Increased IgE and eosinophilia systemic association in many cases (identifies extrinsic AD noted in 60%-90% of patients)	Immune aberrations of AD lead to multiple clinical sequelae including xerosis, pruritus, eczematous dermatitis, lichenification, "impetiginization," and cutaneous infections – Predisposes to chronic eczematous skin changes (ie, lichefication, dyspigmentation) – Predisposes to irritant and allergic contact dermatitis (ie, chronic hand eczema, periumbilical pruritic papules [nickel allergy]) – Predisposition to *S aureus* colonization, impetiginization, and infection –TLR2 mutation associated with greater AD severity, increased staphylococcal colonization, and higher serum IgE levels – Cytokine release from keratinocytes secondary
Neurogenic/ Neuroimmunologic Factors	Neuropeptides and neurotropins in epidermal nerve fibers (proximity to mast cells and Langerhans cells) Increased serum levels of nerve growth factor (correlation with AD disease activity) Substance P containing nerves increased in lesional skin in AD; levels also increased (correlation with AD severity) – Neurotransmitter and neuromodulatory functions involved in nocioception of pain and pruritus, vasodilation, and cytokine release from keratinocytes (negligible impact on Th1 and Th2 cytokine profiles) – Receptors for substance P on mast cells, cutaneous vasculature, lymphocytes, leukocytes, and macrophages – Substance P involved in vasodilation and wheal and flare reaction; release of mast cell mediators (ie, histamine) and messengers from macrophages (ie, thromboxane B2, prostaglandin E2)	Associated with cardinal symptom (pruritus) and signs (edema) of AD – Substance P correlation with pruritus in AD – Other neurogenic mediators appear to be operative – Role of histamine in pruritus of AD does not alone but may contribute; selected response to non-sedating antihistamines in some AD patients (may need high doses) – Urticarial component (wheal/flare) observed in some AD flares in addition to eczematous dermatitis (more consistent feature)

[a]Lesional skin refers to sites of active eczematous dermatitis in a patient with AD.
[b]Nonlesional skin refers to clinically normal-appearing skin in a patient with AD; may sometimes include xerotic skin with no visible evidence of skin inflammation or active eczematous dermatitis.
AD, atopic dermatitis; AMP, antimicrobial peptide; FLG, filaggrin; FLGm, filaggrin null mutation; hBD2, human β-defensin 2; HSV, herpes simplex virus; IL, interleukin; NMF, natural moisturizing factor; SC, stratum corneum; TEWL, transepidermal water loss; TLR, toll-like receptor; TNF, tumor necrosis factor; TSST-1, toxic shock syndrome toxin-1.

simplex), and asteatotic dermatitis often affecting the legs.[20,21] Diffuse forms of adult AD also occur and can present as xerotic/pruritic skin without visible eczematous changes, nummular eczema, and "winter itch," the latter a form of asteatotic eczema.[20,21]

Clinical Manifestations of Epidermal Permeability Barrier Impairment

Table 1 describes pathophysiologic features related to epidermal permeability barrier impairment along with other pathogenic components of AD, and other relevant clinical sequelae. The following discussion focuses on epidermal barrier dysfunctions inherent to AD, especially the permeability barrier that predominantly involves the stratum corneum (SC). The normal SC is dynamic in its ability to adapt to a wide variety of exogenous insults to its functional and structural integrity, such as climatic changes, ambient humidity, use of poorly formulated and/or irritant skin care products, overwashing, or exfoliating skin procedures.[1,4-9,20,21,51,52] Physiologic repair mechanisms incorporated by a fully functional SC include its "biosensor detection" of increased transepidermal water loss (TEWL), loss of SC water content, and disruption of the physiologic SC water gradient. The SC "biosensor detection" initiates self-repair via immediate deposition from the granular layer of stored precursors of primary lipids into the SC to be integrated into the intercellular lipid membrane (bilayer), and upregulates FLG production, to increase the production of natural moisturizing factor (NMF).[4-9,14,15,20,21,51] An intact intercellular lipid membrane functions to physiologically modulate and control TEWL in order to maintain the optimal SC hydration that allows for normal functioning of epidermal enzyme systems.[1,4-9,14,15,20,21,51,53-56] NMF, which is a collection of small molecules mostly derived from FLG degradation, functions as "nature's humectant" as it holds within SC corneocytes water that flows into the epidermis from the dermis by upward diffusion and from humid ambient air by downward diffusion, rather than allowing excessive evaporative loss through the skin surface (ie, TEWL).[1,4-10,12,20,21,51,53-55,57-59]

Unfortunately, multiple epidermal barrier dysfunctions, including those directly affecting the SC permeability barrier (ie, decrease in multiple ceramide subfractions and total SC ceramide content; FLG loss-of-function [null] gene mutations) compromise self-repair in atopic skin, leading to xerotic and eczematous skin changes and pruritus.[1,4-11,13-15,17,19-21,23,43,51,60] In fact, the decrease of ceramides in atopic skin, which is most profound with ceramide-1 and ceramide-3, contributes to the inherent propensity for increased TEWL observed in lesional and nonlesional skin of people with AD, and a direct correlation exists between reduction in CER-3 and an increase in TEWL.[4,5,15,20,51]

Stratum corneum permeability barrier impairment is an integral component of the pathophysiology of AD, and self-repair of atopic skin is compromised by epidermal barrier dysfunctions innate to AD. Therefore, consistent attention to avoiding practices that damage the SC, along with regular use of skin care/barrier repair products that provide for SC permeability barrier maintenance and repair, are very important both in the daily management of atopic skin and during flares of AD.[4-8,15,20,21,51,59,61] This is further supported by evidence that topical corticosteroids (TCs), although highly effective in rapidly controlling the cutaneous inflammation, clinical signs, and symptoms of AD, may induce some adverse SC permeability barrier changes.[62-64] There is widespread consensus in the literature that proper adjunctive therapy through skin care directed at barrier maintenance and repair in AD is an important complement to medical therapies, and may augment the therapeutic benefit of the treatment regimen. It may also afford a more favorable long-term therapeutic outcome, may be steroid-sparing in milder cases of AD or in certain body locations where TC use is more of a concern (especially if prolonged), and has the potential to lengthen flare-free intervals by working to reverse the adverse effects of SC permeability barrier impairment associated with atopic skin and AD flares.[15,20,21,24-26,51,59,61,65,66]

"The heavy educational and research emphasis on pediatric and adolescent atopic dermatitis often results in adult atopic dermatitis being overlooked as a diagnostic consideration."

A Cleanser and Moisturizer System Designed for Use in Atopic Skin

Many proprietary products helpful for the management of xerosis in patients with AD are available in the marketplace. A specific product line marketed for use in atopic skin is discussed here. The components of this skin care system, consisting of a cleanser (Cetaphil® Restoraderm® Body Wash, Galderma Laboratories, L.P.; Fort Worth, TX) and moisturizer (Cetaphil® Restoraderm® Moisturizing Lotion) designed specifically for use by individuals with atopic skin and AD, have been reviewed elsewhere.[20] This treatment contains proprietary information, images and/or links to unlicensed drugs (Table 2).[68]

TABLE 2.

Ingredients Used in Specific Cleanser and Moisturizer Skin Care Products Designed for Atopic Skin, With Rationale for Inclusion

Ingredient	Product(s)[a]	Rationale for Inclusion[20,59,67-75]
Pseudoceramide-5	Moisturizer	Exogenous ceramide precursor; increased ceramides 1, 2, and 3 in reconstructed human skin model; transformation to endogenous ceramides suggested; marked ceramide depositon in SC confirmed by Raman spectroscopy at 2 depths (5 µm, 10 µm) after 28 days of moisturizer application BID (human leg skin); TEWL decreased, and hydration (by corneometry) increased - all 3 results statistically superior to untreated leg ($P<.05$, $P=.002$, $P<.001$; day 28)
Sunflower Seed Oil *(Helianthus annuus)*	Body wash, moisturizer	Contains lipids similar to SC composition May increase SC ceramide and cholesterol synthesis
Shea Butter *(Butyrospermum parkii)*	Body wash, moisturizer	Contains stearic acid, linoleic acid (SC essential fatty acid), and catechin antioxidants
Panthenol	Moisturizer	Shown to assist in reducing TEWL and increasing SC hydration
Filaggrin Degradation Products	Body wash, moisturizer	Arginine and PCA both major components of NMF
Niacinamide	Body wash, moisturizer	Marked increases in ceramide precursors (sphingomyelin, glucosylceramides), free fatty acids, cholesterol (in vitro) Increase in ceramides and decreased TEWL after use on xerotic skin
Glycerin	Body wash, moisturizer	Commonly used humectant

[a]Cetaphil® Restoraderm® Body Wash (cleanser) and Cetaphil® Restoraderm® Lotion (moisturizer)
BID, twice daily; NMF, natural moisturizing factor; PCA, pyrrolidone carboxylic acid; SC, stratum corneum; TEWL, transepidermal water loss.

The scientific rationale behind the specific designated ingredients is summarized in Table 2.[20,59,67-75] Importantly, recent data not included in the previous article show that the ceramide precursor used in the moisturizer (pseudoceramide-5) deposits ceramides into the SC at 2 depths after 28 days of twice-daily application to the leg, with markedly higher levels than in the SC of the untreated leg ($P<.05$) (Table 2).[68]

TABLE 3.

Results of Clinical Studies With a Cleanser[a] and a Moisturizer[a] Designed for Use in Patients With Atopic Skin/Atopic Dermatitis

Study	Characteristics	Outcomes
Studies with Moisturizer[76]		
Single-center, evaluator-blinded study; history of AD and at least mild xerosis; adults (N=30); intra-individual comparison; single application of moisturizer	Mean age 39.5 years 83% females 3 distinct products[b] used on defined forearm non-lesional skin; 1 site untreated (control)	– Corneometry testing at baseline, 2, 4, 6, 8, and 24 hours – Increased hydration all time points vs control site (P<.001) with moisturizer 1 containing ceramide precursor and filaggrin degradation products[b] – Superior to moisturizer 2 at all time points (P<.05)[b] – Superior to moisturizer 3 at 2 hours and 4 hours (P<.05)[b]
Single-center, evaluator blinded study; history of inactive or active AD; adults (N=29); intra-individual comparison post-skin insult; repeated application of moisturizer TID x 5 days	Mean age 43.9 years 93% females SDS patch x 24 hours to 4 defined forearm sites; 3 distinct products[b] to designated sites; 1 untreated site after SDS patch (control)	–TEWL and hydration (corneometry) measured at day 2 and day 5 – Superior barrier repair with moisturizer 1 containing ceramide precursor and filaggrin degradation products[b] vs control (P<.05); other 2 products P=NS with TEWL – Superior numerical trend compared to moisturizer 2 and moisturizer 3 with reduction in TEWL – All 3 test products prevented further loss of hydration
Open-label, 4-week trial; inactive AD at enrollment; children and adults (N=60) repeated application of moisturizer BID x 4 weeks	DLQI evaluation of 3 subset groups (age 3-4 years n=4, age 5-16 years n=24, age >17 years n=32)	– Improved DLQI indices observed – Marked reduction in pruritus (P=.001) and stinging (P=.028) from baseline to week 4 – Highly favorable tolerability ratings
Multicenter, evaluator-blinded, randomized, intra-individual comparison (split-body) study (N=123; n=42 corneometry tested BID x 28 days; assessments at baseline and days 7, 14, 21, and 28 (end of study)	Subjects >3 years of age mild-moderate AD treated with TCS + moisturizer 1 on 1 side only with 23.8% given Class I-III TCS; opposite side no moisturizer used (control comparator)	– Skin hydration improved in both groups; TCS + moisturizer 1 side with superior skin hydration (P<.05) – mEASI results improved in both groups with more rapid improvement with TCS + moisturizer 1 – Greater magnitude of skin hydration with TCS + moisturizer 1
Randomized, intra-individual comparison, investigator-blinded study; adults with controlled AD with very dry skin; moisturizer applied BID to 1 leg for 28 days, other leg used as a control[68]	Mean age 40.9 years 80% female TEWL, corneometry, and Raman spectroscopy taken 10 to 16 hours after application at baseline and day 28	–TEWL significantly decreased at day 28 on treated leg (P=.002) –Skin hydration significantly increased on the treated leg after 28 days (P<.001) – Ceramide levels, as measured by Raman spectroscopy significantly increased at depths of 5 µm and 10 µm on the treated leg (P<.05)
Studies With Cleanser (Body Wash) and Moisturizer (Lotion)[77]		
Single center, open-label, 4-weeks; infants/toddlers (age 3-36 months) with history of AD (N=56), bathed/moisturized at least once daily; TEWL/corneometry at baseline, week 2, and week 4 (end of study)	Skin barrier function assessments at least 2.5 hours after moisturizer application; corneometry tested at 2 skin sites (forearm, leg)	– Well tolerated with few tolerability reactions – Maintained permeability barrier function with reduced TEWL and increased hydration – Scaling/dryness resolved in 85.2% of subjects at week 4 – Erythema resolved in 51.8% of subjects at week 4 – Very high parent satisfaction ratings with products

[a]Cetaphil® Restoraderm® Body Wash (cleanser) and Cetaphil® Restoraderm® Lotion (moisturizer)
[b]Moisturizer 1 (Cetaphil® Restoraderm® Lotion); moisturizer 2 (MimyX® Cream); moisturizer 3 (Eucerin® Skin Calming Creme)
AD, atopic dermatitis; BID, twice daily; DLQI, Dermatology Life Quality Index; mEASI, modified Eczema Area Severity Index; NS, insignificant; SDS, sodium dodecyl sulfate (used to induce epidermal [stratum corneum] permeability barrier dysfunction); TEWL, transepidermal water loss; TCS, topical corticosteroid.

Clinical Data with Specific Cleanser and Moisturizer for Atopic Skin/Atopic Dermatitis

Multiple studies have been completed of the individual products and of both used together in subjects with atopic skin/AD, with clinically relevant results obtained.[76] The results of these studies are tabulated in Table 3, and demonstrate outcomes achieved with the designated cleanser and moisturizer products and the combined system designed for use in atopic skin and AD.

CONCLUSION

As atopic skin inherently exhibits abnormalities in the SC permeability barrier that are present even in the absence of signs and symptoms of AD, it is important that the clinician integrate proper skin care and barrier repair/maintenance into the regimen. The specific cleanser (body wash) and moisturizer (lotion) discussed in the article incorporate conventional ingredients needed to formulate a quality cleanser and moisturizer, in addition to "special additives" such as a ceramide precursor, FLG degradation

products (arginine, pyrrolidone carboxylic acid), sunflower seed oil, Shea butter, and niacinamide. Beyond the rational theoretical considerations based on the formulations, clinical studies support the use of both the cleanser and moisturizer in all age groups, especially on atopic skin.

DISCLOSURES

Galderma had the opportunity to review the final version of the supplement and provide comments regarding accuracy of content; however, the authors maintained control over the content.

Dr. Del Rosso has served as a consultant, advisory board participant, clinical investigator, and speaker for Galderma, Allergan, Bayer HealthCare, Dermira, Eisai, Ferndale, Leo Pharma, Medicis (a Division of Valeant), Onset Dermatologics, Pharmaderm, Primus, Promius Pharma, Quinnova, Ranbaxy, Taro Pharmaceuticals, TriaBeauty, Unilever, Valeant (Consumer Products), and Warner-Chilcott.

Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Galderma, Allergan, Bayer, Promius Pharma, Quinnova, Stiefel/GSK, LeoPharma, Taro, Valeant, and Warner Chilcott.

REFERENCES

1. Bieber T, Prolss J. Atopic dermatitis. In: Gaspari AA, Tyring SK, eds. *Clinical and Basic Immunodermatology*. London: Springer-Verlag; 2008:193-206.
2. Elliott K, Forrest S. Genetics of atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Marcel Dekker; 2002:81-110.
3. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259-1260.
4. Proksch E, Elias PM. Epidermal barrier in atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Marcel Dekker; 2002:123-143.
5. DiNardo A, Wertz PW. Atopic dermatitis. In: Leyden JJ, Rawlings AV, eds. *Skin Moisturization*. 1st ed. New York: Marcel Dekker; 2002:165-178.
6. Harding CR. The stratum corneum: structure and function in health and disease. *Dermatol Ther*. 2004;17(suppl 1):s6-s15.
7. Yamamoto A, Serizawa S, Ito M, Sato Y. Stratum corneum lipid abnormalities in atopic dermatitis. *Arch Dermatol Res*. 1991;283(4):219-223.
8. Cork MJ, Danby SG, Vasilopoulos Y, et al. Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol*. 2009;129(8):1892-1908.
9. Ogawa H, Yoshiike T. A speculative view of atopic dermatitis: barrier dysfunction in pathogenesis. *J Dermatol Sci*. 1993;5(3):197-204.
10. O'Regan GM, Irvine AD. The role of filaggrin in the atopic diathesis. *Clin Exp Allergy*. 2010:40(7):965-972.
11. Kezic S, Kemperman PM, Koster ES. Loss-of-function mutations in the filaggrin gene lead to reduced level of natural moisturizing factor in the stratum corneum. *J Invest Dermatol*. 2008;128(8):2117-2119.
12. Scott IR, Harding CR. Barrett JG. Histidine-rich protein of the keratohyalin granules. Source of the free amino acids, urocanic acid and pyrrolidone carboxylic acid in the stratum corneum. *Biochem Biophys Acta*. 1982:719(1);110-111.
13. Choi MJ, Maibach HI. Role of ceramides in barrier function of healthy and diseased skin. *Am J Clin Dermatol*. 2005;6(4):215-223.
14. Cork MJ, Moustafa M, Danby S, et al. Skin barrier dysfunction in atopic dermatitis. In: Rawlings AV, Leyden JJ, eds. *Skin Moisturization*. 2nd ed. New York: Informa Health; 2009:211-239.
15. Di Nardo A, Wertz P, Giannetti A, Seidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm Venereol*. 1998;78(1):27-30.
16. Leung DYM. Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic disease. *J Allergy Clin Immunol*. 1995;96(3):302-319.
17. Di Nardo A, Gallo RL. Cutaneous barriers in defense against microbial invasion. In: Elias PM, Feingold KR, eds. *Skin Barrier*. New York: Taylor & Francis; 2006:363-377.
18. Leyden JJ, Marples RR, Kligman AM. Staphylococcus aureus in the lesions of atopic dermatitis. *Br J Dermatol*. 1974;90:525-530.
19. Leung DYM. The role of Staphylococcus aureus in atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. 1st ed. New York: Marcel Dekker; 2002:401-419.
20. Del Rosso JQ. Repair and maintenance of the epidermal barrier in patients diagnosed with atopic dermatitis: an evaluation of the components of a body wash-moisturizer skin care regimen directed at management of atopic skin. *J Clin Aesthet Dermatol*. 2011;4(6):45-55.
21. Del Rosso JQ, Levin J. Clinical relevance of maintaining the structural and functional integrity of the stratum corneum: why is it important to you? *J Drugs Dermatol*. 2011;10(suppl 10):s5-s12.
22. Eichenfield LE. Hot topics in pediatric dermatology. Paper presented at: Winter Clinical Dermatology 2013 in Kauai, Hawaii; Jan 2013.
23. Margolis DJ, Apter AJ, Gupta J, et al. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. *J Allergy Clin Immunol*. 2012;130(4):912-917.
24. 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(2):198-208.
25. Lucky AW, Leach AD, Laskarzewski P, Wenck H. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr Dermatol*. 1997;14(4):321-324.
26. Boguniewicz M. Conventional topical treatment of atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. 1st ed. New York: Marcel Dekker; 2002:453-477.
27. Jalian HR, Kim J. Antimicrobial peptides. In: Gaspari AA, Tyring SK, eds. *Clinical and Basic Immunodermatology*. London: Springer-Verlag; 2008:131-145.
28. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*. 2002;347(15):1151-1160.
29. de Jongh GJ, Zeeuwen PL, Kucharekova M, et al. High expression levels of keratinocyte antimicrobial peptides in psoriasis compared with atopic dermatitis. *J Invest Dermatol*. 2005;125(6):1163-1173.
30. Howell MD, Wollenberg A, Gallo RL, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol*. 2006;117(4):836-841.
31. Leung DY. Infection in atopic dermatitis. *Curr Opin Pediatr*. 2003;15(4):399-404.
32. Morath S, Geyer A, Hartung T. Structure-function relationship of cytokine induction by lipoteichoic acid from Staphylococcus aureus. *J Exp Med*. 2001;193(3):393-398.
33. Fallon PG, Sasaki T, Sandilands A, et al. A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. *Nat Genet*. 2009;41(5):602-608.
34. Martin DB, Gaspari AA. Toll-like receptors. In: Gaspari AA, Tyring SK, eds. *Clinical and Basic Immunodermatology*. London: Springer-Verlag; 2008:67-84.
35. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, et al. The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol*. 2004;113(3):565-567.
36. Zdolsek HA, Jenmalm MC. Reduced levels of soluble CD14 in atopic children. *Clin Exp Allergy*. 2004;34(4):532-539.
37. Rothenbacher D, Weyermann M, Beermann C, Brenner H. Breastfeeding, soluble CD14 concentration in breast milk and risk of atopic dermatitis and asthma in early childhood: birth cohort study. *Clin Exp Allergy*. 2005;35(8):1014-1021.
38. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, et al. The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol*. 2004;113(3):565-567.
39. Kezic S, O'Regan GM, Lutter R, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol*. 2012;129(4):1031-1039.
40. Hara J, Higuchi K, Okamoto R, Kawashima M, Imokawa G. High-expression of sphingomyelin deacylase is an important determinant of ceramide deficiency leading to barrier disruption in atopic dermatitis. *J Invest Dermatol*. 2000;115(3):406-413.
41. Murata Y, Ogata J, Higaki Y, et al. Abnormal expression of sphingomyelin acylase in atopic dermatitis: an etiologic factor for ceramide deficiency? *J Invest Dermatol*. 1996;106(6):1242-1249.
42. Biao L, Elias PM, Feingold KR. The role of the primary cytokines, TNF, IL-1, and IL-6, in permeability barrier homeostasis. In: Elias PM, Feingold KR, eds. *Skin Barrier*. New York, NY: Taylor & Francis; 2006:305-318.
43. Ogawa H, Yoshiike TJ. A speculative view of atopic dermatitis: barrier dysfunction in pathogenesis. *J Dermatol Sci*. 1993;5(3):197-204.
44. Proksch E, Brasch J. Influence of epidermal permeability barrier disruption and Langerhans' cell density on allergic contact dermatitis. *Acta Derm Venereol*. 1997;77(2):102-104.
45. Lee E, Granstein RD. Neuroimmunology. In: Gasapari AA, Tyring SK, eds. *Clinical and Basic Immunodermatology*. London UK: Springer-Verlag; 2008:31-44.
46. Wuthrich B, Schmid-Grendelmeier P. Definition and diagnosis of intrinsic versus extrinsic atopic dermatitis. Conventional topical treatment of atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. 1st ed. New York, NY: Marcel Dekker; 2002:1-20.
47. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol*. 1994;131(3):406-416.

48. Schultz Larsen F, Diepgen T, Svensonn A. Clinical criteria in diagnosing AD: the Lillehammer criteria 1994. *Acta Derm Venereol (Stockh).* 1996;(suppl 76):s115-s119.
49. Diepgen TL, Fartasch M, Hornstein OP. Evaluation and relevance of atopic basic and minor features in patients with atopic dermatitis and in the general population. *Acta Derm Venereol (Stockh).* 1989;(suppl 144):s50-s54.
50. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh).* 1980;(suppl 92):s44-s47.
51. Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease affected skin. *J Clin Aesthet Dermatol.* 2011;4(9):22-42.
52. Rawlings AW, Watkinson A, Rogers J, Mayo A, Hope J, Scott IR. Abnormalities in stratum corneum structure, lipid composition, and desmosome degradation in soap-induced winter xerosis. *J Soc Cosmet Chem.* 1994;45(7):203-220.
53. Elias PM. Stratum corneum defensive functions: an integrated view. *J Invest Dermatol.* 2005;125(2):183-200.
54. Elias PM, Feingold KM. Permeability barrier homeostasis. In: Elias PM, Feingold KR, eds. *Skin Barrier.* New York, NY: Taylor & Francis; 2006:337-361.
55. Rawlings AV, Scott IR, Harding CR, Bowser PA. Stratum corneum moisturization at the molecular level. *J Invest Dermatol.* 1994;103(5):731-741.
56. Menon GK, Norlen L. Stratum corneum ceramides and their role in skin barrier function. In: Leyden J, Rawlings A, eds. *Skin Moisturization.* New York: Marcel Dekker; 2002:31-60.
57. Uitto J, McGrath JA. The role of filaggrin in skin disease. In: Rawlings AV, Leyden JJ, eds. *Skin Moisturization.* 2nd ed. New York, NY: Informa Health; 2009:57-67.
58. Katagiri C, Sato J, Nomura J, Denda M. Changes in environmental humidity affect the water-holding property of the stratum corneum and its free amino acid content, and the expression of filaggrin in the epidermis of hairless mice. *J Dermatol Sci.* 2003;31(1):29-35.
59. Del Rosso JQ. Moisturizers: function, formulation, and clinical applications. In: Draelos ZD, ed. *Cosmeceuticals.* Philadelphia, PA: Saunders Elsevier; 2009:97-102.
60. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol.* 1991;96(4):523-526.
61. Draelos ZD. The effect of ceramide-containing skin care products on eczema resolution duration. *Cutis.* 2008;81(1):87-91.
62. Del Rosso J, Friedlander SF. Corticosteroids: options in the era of steroid-sparing therapy. *J Am Acad Dermatol.* 2005;53(1 suppl 1):s50-s58.
63. Kao JS, Fluhr JW, Man MQ, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *J Invest Dermatol.* 2003;120(3):456-464.
64. Hong SP, Oh Y, Jung M, et al. Topical calcitriol restores the impairment of epidermal permeability and antimicrobial barriers induced by corticosteroids. *Br J Dermatol.* 2010;162(6):1251-1260.
65. Ananthapadmanabhan KP, Moore DJ, Subramanyan K, Misra M, Meyer F. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. *Dermatol Ther.* 2004;17(suppl 1):s16-s25.
66. Frankel A, Sohn A, Patel RV, Lebwohl M. Bilateral comparison study of pimecrolimus cream 1% and a ceramide-hyaluronic acid emollient foam in the treatment of patients with atopic dermatitis. *J Drugs Dermatol.* 2011;10(6):666-672.
67. Castiel-Higounenc I, Chopard M, Ferraris C. Stratum corneum lipids: specificity, role, deficiencies and modulation. *Oleagineux, Corps Gras, Lipides.* 2004;11:401-406.
68. Simpson E, Böhling A, Bielfeldt S, Bosc C, Kerrouche N. Improvement of skin barrier function in atopic dermatitis patients with a new moisturizer containing a ceramide precursor. *J Dermatol Treat.* 2013;24(2):122-125.
69. Eichenfield LF, McCollum A, Msika P. The benefits of sunflower oleodistillate (SOD) in pediatric dermatology. *Pediatr Dermatol.* 2009;26(6):669-675.
70. Piccardi N, Piccirilli A, Choulot JC, et al. Sunflower oil oleodistillate for atopy treatment: an in-vitro and clinical investigation. *J Invest Dermatol.* 2001;117:390-423.
71. Maranz S, Wiesman Z, Garti N. Phenolic constituents of Shea (Vitellaria paradoxa) kernels. *J Agric Food Chem.* 2003;51(21):6268-6273.
72. Obeda M, Sousselier L. Shea butter: the revival of an African wonder. *Global Cosmetic Ind.* 1999;4:36-41.
73. Ghering W, Gloor M. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydration. Results of a human in vivo study. *Arzneimittelforschung.* 2000;50(7):659-663.
74. Ebner F, Heller A, Rippke F, Tausch I. Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol.* 2002;3(6):427-433.
75. Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol.* 2000;143(3):524-531.
76. Simpson E, Dutronc Y. A new body moisturizer improves atopic dermatitis. *J Drugs Dermatol.* 2011;10(7):744-749.
77. Simpson E, Trookman N, Rizer R, et al. 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. *Pediatr Dermatol.* 2012;29(5):590-597.

AUTHOR CORRESPONDENCE

James Q. Del Rosso DO FAOCD

E-mail:.....jqdelrosso@yahoo.com

JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS