

# Emollient Tx From Birth May Prevent Eczema

BY DOUG BRUNK

PORTLAND, ORE. — Beginning emollient therapy at birth is a safe and feasible approach to prevent eczema, results from a small pilot study suggest.

“Decades of research on allergen avoidance has not led to any successful strategy so far,” Dr. Eric Simpson said at the annual meeting of the Pacific Dermatologic Association.

“There are new genetic data showing that eczema is probably a skin barrier disease, at least in a healthy proportion of patients,” he said. “This leads us to the question: Can we focus on skin barrier to prevent eczema?”

The earliest known published study on the topic is from 1991, when researchers in Kenya examined determinants of eczema and whether detergents caused it (*Trop. Doct.* 1991;21:104-6). They

found that the use of petrolatum early in life provided a protective effect.

“This was a case-control study, so it was just one point in time, but it was a surprising finding, and there has not been a follow-up study since that time,” commented Dr. Simpson, who is with the department of dermatology at Oregon Health and Science University in Portland.

More recent studies, he added, have

found that using Aquaphor (Eucerin) in premature neonates from birth can prevent dermatitis, improve skin barrier function, and reduce mortality and sepsis. “But there have been no studies looking specifically at the skin barrier to prevent atopic dermatitis,” he said.

He and his associates were prompted to investigate skin barrier protection after an infant care study at Oregon Health and Science University revealed that 73% of parents and caregivers bathed infants more than three times per week, 91% used soap during bathing, 75% used moisturizers, and 62% regularly used watery lotion.

From that study, Dr. Simpson and his associates concluded that frequent bathing and moisturizer use “is very



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common in patients who develop eczema,” he said. “These skin care practices may be detrimental to the skin. That’s concerning in people who are genetically predisposed to developing eczema. Watery lotions and water alone can disrupt the skin barrier.”

For the pilot study, the researchers enrolled 22 neonates who received Cetaphil cream daily to all body surfaces from day 7. All of the study participants had at least one sibling with clinically confirmed eczema and were studied for a mean of 447 days and a median of 397 days. They underwent regular clinical exams for the development of eczema and barrier function.

To date, only two of the patients (9%) have developed eczema, and there have been no adverse events related to treatment. Dr. Simpson said that the finding is remarkable because previous studies have demonstrated that 40%-50% of infants with an affected sibling develop eczema.

“We’re not really going to know until we have a controlled study, but it is somewhat suggestive that this treatment could be protective against eczema,” he said.

“In addition, barrier protection may reduce IgE sensitization that occurs through the skin. We have a lot of questions to answer. Can it prevent atopic dermatitis? Can it prevent asthma and food allergy down the road? What’s the best barrier protectant?” Dr. Simpson asked.

The study was funded by the Dermatology Foundation and the National Eczema Association.

Dr. Simpson disclosed that he is a paid consultant for Galderma Laboratories, which makes Cetaphil cream. He also has received a research grant from Ceragenix Pharmaceuticals Inc. ■

## DIFFERIN® (adapalene) Gel, 0.3%

### BRIEF SUMMARY

For topical use only. Not for ophthalmic, oral or intravaginal use.

**INDICATIONS AND USAGE:** DIFFERIN® Gel, 0.3% is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

**CONTRAINDICATIONS:** DIFFERIN® Gel, 0.3% should not be administered to individuals who are hypersensitive to adapalene or any of the components in the gel vehicle.

### PRECAUTIONS:

**General:** Certain cutaneous signs and symptoms of treatment such as erythema, scaling, dryness, and stinging/burning may be experienced with use of DIFFERIN® Gel, 0.3%. These are most likely to occur during the first four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Depending upon the severity of these side effects, patients should be instructed to either use a moisturizer, reduce the frequency of application of DIFFERIN® Gel, 0.3% or discontinue use.

If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of “waxing” as a depilatory method should be avoided on skin treated with adapalene.

**Information for Patients:** Patients using DIFFERIN® Gel, 0.3%, should receive the following information and instructions:

1. This medication is to be used only as directed by the physician.
2. It is for external use only.
3. Avoid contact with the eyes, lips, angles of the nose, and mucous membranes.
4. Cleanse affected area with a mild or soapless cleanser before applying this medication.
5. Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.
6. Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis, and eye irritation.
7. This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.
8. Wax epilation should not be performed on treated skin due to the potential for skin erosions.
9. During the early weeks of therapy, an apparent exacerbation of acne may occur. This may be due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy.

**Drug Interactions:** As DIFFERIN® Gel, 0.3% has the potential to induce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN® Gel, 0.3%. If these preparations have been used, it is advisable not to start therapy with DIFFERIN® Gel, 0.3%, until the effects of such preparations have subsided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day, and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day. These doses are up to 3 times (mice) and 2 times (rats) in terms of mg/m<sup>2</sup>/day the potential exposure at the maximum recommended human dose (MRHD), assumed to be 2.5 grams DIFFERIN® Gel, 0.3%. In the oral study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats was observed.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased risk of skin neoplasms with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) and *in vivo* (mouse micronucleus test).

Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day (up to 26 times the MRHD based on mg/m<sup>2</sup> comparisons). No effects of adapalene were found on the reproductive performance or fertility of the F<sub>0</sub> males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F<sub>1</sub> offspring.

**Pregnancy, Teratogenic effects. Pregnancy Category C.** Retinoids may cause fetal harm, when administered to pregnant women. Adapalene has been shown to be teratogenic in rats and rabbits when administered orally (see Animal Data below). There are no adequate and well-controlled studies in pregnant women. DIFFERIN® Gel, 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The safety and efficacy of DIFFERIN® Gel, 0.3% in pregnancy has not been established.

### 1. Human Data

In clinical trials involving DIFFERIN® Gel, 0.3% in the treatment of acne vulgaris, women of child-bearing potential initiated treatment only after having had a negative pregnancy test and used effective birth control measures during therapy. However, 6 women treated with DIFFERIN® Gel, 0.3% became pregnant. One patient elected to terminate the pregnancy, two patients delivered healthy babies by normal delivery, two patients delivered prematurely and the babies remained in intensive care until reaching a healthy state and one patient was lost to follow-up.

### 2. Animal Data

• No teratogenic effects were seen in rats at oral doses of 0.15 to 5.0 mg/kg/day adapalene representing up to 6 times the maximum recommended human dose (MRHD) based on mg/m<sup>2</sup> comparisons. Adapalene has been shown to be teratogenic in rats and rabbits when administered orally at doses  $\geq$  25 mg/kg representing 32 and 65 times, respectively, the MRHD based on mg/m<sup>2</sup> comparisons. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in the rat and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in the rabbit.

• Cutaneous teratology studies in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits. Systemic exposure (AUC<sub>0-24h</sub>) to adapalene 0.3% gel at topical doses of 6.0 mg/kg/day in rats and rabbits represented 5.7 and 28.7 times, respectively, the exposure in acne patients treated with adapalene 0.3% gel applied to the face, chest and back (2 grams applied to 1000 cm<sup>2</sup> of acne involved skin).

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN® Gel, 0.3% is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 12 have not been established.

**Geriatric Use:** Clinical studies of DIFFERIN® Gel, 0.3% did not include subjects 65 years of age and older to determine whether they respond differently than younger subjects. Safety and effectiveness in geriatric patients age 65 and above have not been established.

Rx only

**ADVERSE REACTIONS:** In the multi-center, controlled clinical trial, signs and symptoms of local cutaneous irritation were monitored in 258 acne patients who used DIFFERIN® Gel, 0.3% once daily for 12 weeks. Of the patients who experienced cutaneous irritation (erythema, scaling, dryness, and/or burning/stinging), the majority of cases were mild to moderate in severity, occurred early in treatment and decreased thereafter. The incidence of local cutaneous irritation with DIFFERIN® Gel, 0.3% from the controlled clinical study is provided in the following table:

Table 2: Physician assessed local cutaneous irritation with DIFFERIN® Gel

Incidence of Local Cutaneous Irritation with DIFFERIN® Gel, 0.3% from Controlled Clinical Study (N=253*)			
Maximum Severity Scores Higher Than Baseline			
	Mild	Moderate	Severe
Erythema	66 (26.1%)	33 (13.0%)	1 (0.4%)
Scaling	110 (43.5%)	47 (18.6%)	3 (1.2%)
Dryness	113 (44.7%)	43 (17.0%)	2 (0.8%)
Burning/Stinging	72 (28.5%)	36 (14.2%)	9 (3.6%)

\* Total number of subjects with local cutaneous data for at least one post-Baseline evaluation.

Table 3: Patient reported local cutaneous adverse events with DIFFERIN® Gel

	DIFFERIN® (adapalene) Gel, 0.3%	Vehicle Gel
	N=258	N=134
Related* Adverse Events	57 (22.1%)	6 (4.5%)
Dry Skin	36 (14%)	2 (1.5%)
Skin Discomfort	15 (5.8%)	0 (0.0%)
Desquamation	4 (1.6%)	0 (0.0%)

\* Selected adverse events defined by investigator as Possibly, Probably or Definitely Related

Related adverse events from the controlled clinical trial that occurred in greater than 1% of patients who used DIFFERIN® Gel, 0.3% once daily included: dry skin (14.0%), skin discomfort (5.8%), pruritus (1.9%), desquamation (1.6%), and sunburn (1.2%). The following selected adverse events occurred in less than 1% of patients: acne flare, contact dermatitis, eyelid edema, conjunctivitis, erythema, pruritus, skin discoloration, rash, and eczema.

In a one-year, open-label safety study of 551 patients with acne who received DIFFERIN® Gel, 0.3%, the pattern of adverse events was similar to the 12-week controlled study.

**OVERDOSAGE:** DIFFERIN® Gel, 0.3% is intended for topical use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, scaling, or skin discomfort may occur. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of vitamin A.

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**References:** 1. Data on file. Galderma Laboratories, L.P. 2. Thiboutot D, Arsonnaud S, Soto P. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. *J Drugs Dermatol.* 2008;7(suppl 6):S3-S10.

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