

# 'Extreme Parent Education' Warranted for Atopy

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SAN DIEGO — Parents of children newly diagnosed with atopic dermatitis can be riddled with angst.

Some gravitate to guilt and self-blame, figuring "we did something wrong to our child" or "it must be something we're giving him" that's causing the atopic dermatitis, Dr. Magdalene A. Dohil said at a meeting sponsored by Rady Children's Hospital.

Others believe that baths are bad for their child, and many are frightened to use topical steroids to treat the disease. "They may say things like, 'there are so many creams, we can't remember what goes on and where it goes,'" said Dr. Dohil, a pediatric dermatologist at Rady Children's Hospital, San Diego. "They want a simple and easy cure so they can control the disease."

Many parents find it hard to accept the fact that there is no treatment that com-

pletely cures atopic dermatitis. That is why she practices "extreme parent education" from the get-go.

"We have to battle myths and misperceptions," said Dr. Dohil, also of the University of California, San Diego. "We have some good safety data on atopic dermatitis treatments out there. It's just not common knowledge, and they are not that easy to explain."

## Patient Resources

Web-based resources she points parents and patients to include The Eczema Center at Rady Children's Hospital ([www.eczemacenter.org](http://www.eczemacenter.org)), the National Eczema Association ([www.nationaleczema.org](http://www.nationaleczema.org)), and Under My Skin: A Kid's Guide to Atopic Dermatitis ([www.undermyskin.com](http://www.undermyskin.com)).

Management of atopic dermatitis is currently based on the number, location, and intensity of lesions, persistence of disease, frequency of flares, patient age, and quality of life and emotional issues.

Dr. Dohil focused her discussion on

topical corticosteroids and topical calcineurin inhibitors. "We have to stress for our patients that this is what it boils down to; this is our primary anti-inflammatory armamentarium right now," she said.

## Topical Corticosteroids

Topical corticosteroids have been a mainstay of inflammatory atopic dermatitis treatment for decades. They are also used to manage acute flares and as maintenance therapy.

"We can start as low potency as needed or start high, control, and go back to low potency as needed," she said.

"This is my preference because I feel it gives you that initial trust and compliance if parents see their child getting better. It allows you to taper down and reassure parents that you are no longer at that very potent level of topical steroids," Dr. Dohil added.

The choice of topical corticosteroid is influenced by what prior agents have been used, the age of the patient, severity and localization of



respond adequately to other topical prescription treatments, or when those treatments are not advisable.

After a Food and Drug Administration black box warning was issued in January 2006 related to concerns about skin malignancies and lymphoma from the use of topical calcineurin inhibitors, several case-control studies, long-term registries, ongoing clinical studies, and data safety monitoring boards were launched to continue to assess their safety.

A 10-year study, A Prospective Pediatric Longitudinal Evaluation Study, will examine 8,000 pediatric subjects treated for at least 6 weeks.

Another 10-year trial, The Pediatric Eczema Elective Registry, is an observational parent-report registry designed to assess the risk of malignancies in 5,000 children aged 2-17 years who were treated with pime-

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DR. DOHIL

crolium for at least 6 weeks.

One recent study found that the patients with severe atopic dermatitis were 2.4 times more likely to develop lymphoma, compared with

controls. However, use of pimecrolimus and tacrolimus conferred a protective effect, with odds ratios of 0.8 each (*J. Invest. Dermatol.* 2007;127:808-16).

A separate case-control study of patients with inflammatory dermatitis found that those who used pimecrolimus and tacrolimus had almost a 50% reduction in the risk of developing non-melanoma skin cancer (*Dermatology* 2007;214:289-95).

The odds ratio of association for non-melanoma skin cancer decreased as the number of tubes used and the potency of the agent increased. "There was no clear explanation for this," Dr. Dohil said. "There's still a lot of discussion going on."

She added that studies of the blood levels of topical calcineurin inhibitors indicate that they "appear to be negligible when used appropriately."

In clinical practice these agents are commonly used for the face and genital area and for other so-called hot spots with high risk of atrophy.

They are often used in patients with concerns about steroids due to quantity of use in delicate locations, need for constant or near constant therapy, or in those with an adverse event history such as striae or systemic effects.

"Many people feel that topical calcineurin inhibitors can help patients experience a longer flare-free interval and then further transition from this maintenance treatment to maybe just a topical moisturizer if you give enough time for the skin to settle down," Dr. Dohil said.

Dr. Dohil disclosed that the department at Rady has received grant and research support from Hill Pharmaceuticals. She has also received honoraria from Medicis and Dermik. ■

## BRIEF SUMMARY

(see package insert for full prescribing information)

## Atralin™

(tretinoin) gel 0.05%

For topical use only

### INDICATIONS AND USAGE

Atralin Gel is a retinoid indicated for topical treatment of acne vulgaris.

### Important Limitations of Use

The safety and efficacy of the use of this product in the treatment of any other disorders have not been evaluated.

### CONTRAINDICATIONS

None

### WARNINGS AND PRECAUTIONS

#### Skin Irritation

The skin of certain individuals may become dry, red, or exfoliated while using Atralin Gel. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use altogether. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Mild to moderate skin dryness may also be experienced; if so, use of an appropriate moisturizer during the day may be helpful.

Tretinoin has been reported to cause severe irritation on eczematous or sunburned skin and should be used with caution in patients with these conditions.

Topical over-the-counter acne preparations, concomitant topical medication, medicated cleansers, topical products with alcohol or astringents, when used with Atralin Gel, should be used with caution. [see Drug Interactions (7)]

#### Ultraviolet Light and Environmental Exposure

Unprotected exposure to sunlight, including sunbaths, should be minimized during the use of Atralin Gel. 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 of at least SPF 15 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 tretinoin.

#### Fish Allergies

Atralin Gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish. Patients who develop pruritus or urticaria should contact their health care provider.

### ADVERSE REACTIONS

#### Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, controlled trials, 674 subjects received treatment for up to 12 weeks with Atralin Gel [see Clinical Studies (14)]. In these studies, 50% of the subjects who were treated with Atralin Gel reported one or more adverse reactions; 30% of the subjects reported treatment-related adverse reactions. In the vehicle group, 29% of the 487 randomized subjects reported at least one adverse reaction; 5% of the subjects reported events that were treatment-related.

There were no serious, treatment-related adverse reactions reported by subjects in any of the treatment groups.

Selected adverse reactions that occurred in at least 1% of subjects in the two studies combined, are shown in Table 1 (below). Most skin-related adverse reactions first appear during the first two weeks of treatment with Atralin Gel, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persist throughout the treatment period.

**Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)**

Event	Atralin Gel (n = 674)	Vehicle Gel (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/Flaking Skin	78 (12%)	7 (1%)
Skin Burning Sensation	53 (8%)	8 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

### DRUG INTERACTIONS

When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

**Pregnancy Category C.** There are no well-controlled trials in pregnant women treated with Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atralin Gel at doses of 0.1, 0.3 and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately 4 times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities (hydrocephaly), asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were noted in the fetuses of Atralin Gel treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the Atralin Gel treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of Atralin Gel applied daily to a 50-kg person.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately 8 times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased

skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface area comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

**Nonteratogenic effects on fetuses:** Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on a body surface area comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 8 times the clinical dose based on a body surface area comparison.

#### 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 Atralin Gel is administered to a nursing woman.

#### Pediatric Use

Safety and effectiveness in children below the age of 10 have not been established.

A total of 381 pediatric subjects (aged 10 to 16 years), treated with Atralin Gel were enrolled into the two clinical studies. Across these two studies, comparable safety and efficacy were observed between pediatric and adult subjects.

#### Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical studies of Atralin Gel did not include any subjects over age 65 to determine whether they respond differently than younger subjects.

#### Marketed by:



CORIA LABORATORIES, LTD.  
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#### Manufactured by:

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