

UV Exposure May Be Tied to Dermatomyositis in Women

BY JEFF EVANS

The intensity of exposure to ambient ultraviolet radiation appears to determine the prevalence of dermatomyositis and an autoantibody specific to the disease in women, based on a recent study.

The UV Index across geographical re-

gions of the United States also significantly correlated with the presence of an autoantibody unique to dermatomyositis (DM)—known as anti-Mi-2—and not to autoantibodies more commonly found in polymyositis (PM). The association between UV radiation and DM was strongest in a collective group of European, Hispanic, and Asian American women, but it also was significant among black women.

This is the first study to show evidence of the influence of sex on the association between UV radiation and autoimmune disorders, commented Dr. Victoria P. Werth, professor of dermatology at the University of Pennsylvania, Philadelphia, and chief of dermatology at the Philadelphia Veterans Affairs Medical Center.

The study brings up many “intriguing kinds of things that we don’t totally understand,” such as differences in risk factors and responses to UV radiation between men and women and between PM and DM. These types of “interesting epidemiologic observations” may help in the future to understand more about the differences in pathogenesis, Dr. Werth said in an interview.

In the cross-sectional, retrospective study, Dr. Lori A. Love of the National Institute of Environmental Health Sciences and her coinvestigators gathered clinical data and serum samples from 202 PM and 178 DM patients at referral centers across the United States.

The investigators detected myositis-specific autoantibodies in 172 patients (45%), some of which were found in both PM and DM patients, whereas others were found only in each particular phenotypic type of myositis, such as anti-SRP in 21 PM patients and anti-Mi-2 in 23 DM patients.

PM occurred in a significantly greater proportion of black patients (66%) than among nonblack patients (48%). Most (86%) of the patients with anti-SRP antibodies were black, Dr. Love and her associates reported (*Arthritis Rheum.* 2009;60:2499-504).

The proportion of patients in the study who had anti-Mi-2 autoantibodies was significantly associated with the UV Index for the seven regions (comprising 37 states) that the investigators categorized according to shared geoclimatic factors. However, the UV Index was not associated with the proportion of patients with DM. Both of these comparisons proved to be significant for women but not for men.

The investigators noted that the study may be limited by the following: referral bias; the use of state-level UV radiation intensities; the lack of accounting for individual-level exposure; differences in UV radiation exposure at different locations over time; and the use of personal photoprotective measures.

The study was funded in part by the intramural research programs of the National Institute of Environmental Health Sciences. Dr. Werth said she had no relevant disclosures.

The intensity of UV radiation exposure may be tied to the prevalence of dermatomyositis in women, shown here.



COURTESY DR. VICTORIA P. WERTH

VECTICAL™ (calcitriol) OINTMENT, 3 mcg/g

For topical use only.

Not for oral, ophthalmic, or intravaginal use.
Not to be applied to the eyes, lips, or facial skin.

BRIEF SUMMARY INDICATIONS AND USAGE:

VECTICAL Ointment is a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Effects on Calcium Metabolism

In controlled clinical trials with VECTICAL Ointment, among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the upper limit of normal.

If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

Ultraviolet Light Exposure

Animal data suggest that the vehicle of VECTICAL Ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumors.

Subjects who apply VECTICAL Ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use VECTICAL Ointment.

Unevaluated Uses

The safety and effectiveness of VECTICAL Ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated. The safety and effectiveness of VECTICAL Ointment in patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated.

ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience

VECTICAL Ointment was studied in two vehicle-controlled studies (419 subjects), and in one open label study (324 subjects). The table below describes exposure to VECTICAL Ointment in 743 subjects, including 239 exposed for 6 months and 116 exposed for one year.

Four hundred and nineteen subjects were treated with VECTICAL Ointment twice daily for 8 weeks. The population included subjects ages 13 to 87, males (284) and females (135), Caucasians (372) and non-Caucasians (47); with mild (105) to moderate (313) chronic plaque psoriasis.

Selected Adverse Events Occurring in at least 1% of Subjects in the Two Pooled Vehicle-Controlled Studies

	VECTICAL Ointment (n=419)	Vehicle Ointment (n=420)
Discomfort skin	3%	2%
Pruritus	1%	1%

Among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle, however the elevations were less than 10% above the upper limit of normal. The open label study enrolled 324 subjects with psoriasis who were then treated for up to 52 weeks. Adverse events reported at a rate of greater than or equal to 3% of subjects treated with VECTICAL Ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hypercalciuria (3%), and pruritus (3%). Kidney stones were reported in 3 subjects and confirmed in two.

Postmarketing Experience

The following adverse reactions have been identified during worldwide post-approval use of VECTICAL Ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, and skin discomfort. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

VECTICAL Ointment should be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies for VECTICAL Ointment in pregnant women. VECTICAL Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcitriol were performed in which rats were treated orally at dosages up to 0.9 mcg/kg/day (5.4 mcg/m²/day) and in which rabbits received topical application of calcitriol ointment (3 ppm) to 6.4% of the body surface area. No effects on reproductive or fetal parameters were observed in rats. In rabbits, topically applied calcitriol induced a significantly elevated mean post-implantation loss and an increased incidence of minor skeletal abnormalities due to retarded ossification of the pubic bones. A slightly increased incidence of skeletal variation (extra 13th rib, reduced ossification of epiphyses) was also observed. These effects may have been secondary to maternal toxicity. Based on the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

Nursing Mothers

It is not known whether calcitriol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VECTICAL Ointment is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VECTICAL Ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcitriol was applied topically to mice for up to 24 months, no significant changes in tumor incidence were observed. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated.

A two-year carcinogenicity study was conducted in which calcitriol was orally administered to rats at dosages of approximately 0.005, 0.03, and 0.1 mcg/kg/day (0.03, 0.18, and 0.6 mcg/m²/day, respectively). The incidence of benign pheochromocytomas was significantly increased in female rats. No other significant differences in tumor incidence data were observed.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcitriol ointment, a reduction in the time required for UVR to induce the formation of skin tumors was observed in all groups that received the ointment base, including the vehicle-treated control group, relative to animals that received no ointment but which were exposed to UVR. The time required for UVR to induce the formation of skin tumors did not differ between animals that received plain vehicle and those that received vehicle that contained calcitriol. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. These data suggest that the vehicle of VECTICAL Ointment may enhance the ability of UVR to induce skin tumors.

Calcitriol did not elicit genotoxic effects in the mouse lymphoma TK locus assay.

Studies in which male and female rats received oral doses of calcitriol of up to 0.6 mcg/kg/day (3.6 mcg/m²/day) indicated no impairment of fertility or general reproductive performance.

Based upon the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposure in these studies.

PATIENT COUNSELING INFORMATION

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. Patients using VECTICAL Ointment should receive the following information:

Instructions for Use

This medication is to be used as directed by the physician. It is for external use only. This medication is to be applied only to areas of the skin affected by psoriasis, as directed. It should be gently rubbed into the skin so that no medication remains visible.

Adverse Reactions

Patients should report any signs of adverse reactions to their physician.

Marketed by:

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Manufactured by:

Galderma Production Canada Inc.
Baie d'Urfé, QC, H9X 3S4 Canada
Made in Canada.

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References: 1. Data on file. Galderma Laboratories. 2. Leibold M, Ortonne JP, Andres P, Briantais P. Calcitriol ointment 3 µg/g is safe and effective over 52 weeks for the treatment of mild to moderate plaque psoriasis. *Cutis.* 2009;83:205-212. 3. VECTICAL™ Prescribing Information. Fort Worth, TX: Galderma Laboratories, L.P.; 2009.

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