# Melanoma Regression Alone Doesn't Justify an SLN Biopsy

BY DAMIAN McNAMARA
*Miami Bureau*

MONTREAL — Regression of a thin melanoma should not be the sole criterion to justify a sentinel lymph node biopsy, according to a retrospective study.

Regression alone is insufficient in the absence of other recognized high-risk predictors of sentinel lymph node (SLN) involvement, Dr. Pierre-Luc Dion said. More established risk factors include Breslow thickness greater than 1 mm, Clark level IV or V, and lesion ulceration.

Prognosis generally is better with thinner melanoma. Identification of the minority of thin melanoma patients who are at high risk for metastasis, however, remains a clinical challenge.

"There is an ongoing debate if regression is good news or bad news for patients. Some think it shows an immune response against tumor cells, but others say it can lead to an underestimation of the real thickness," Dr. Dion said at the annual conference of the Canadian Dermatology Association.

**'Some think [regression] shows an immune response against tumor cells, but others say it can lead to an underestimation of the real thickness.'**

There is no consensus in the literature. One study of 65 thin melanomas with regression found that only 2 lesions (3%) had a positive SLN biopsy result (Ann. Surg. Oncol. 2003;10:558-61).

Another study found only 1 patient with a positive SLN biopsy among 344 who had thin melanomas (mean Breslow thickness of 1.1 mm) that had shown histologic regression (Ann. Surg. Oncol. 2008;15:316-22).

Other investigators have proposed that tumor regression predicts a higher risk of sentinel node involvement in thin melanomas (Br. J. Dermatol. 2003;149:662-3).

Dr. Dion and his colleagues assessed 693 patients treated at the melanoma clinics for Le Centre Hospitalier Universitaire de Québec–L'Hôtel-Dieu de Québec in Saint-Nicolas and Québec City. All of the patients underwent sentinel lymph node biopsy between 1996 and 2007. The median Breslow thickness was 2.28 mm and mean age was 55 years.

A total of 653 patients had a lesion that was greater than 1 mm. Their prognoses were compared with those of a group of 40 others with thinner melanoma and regression. Regression was determined by a pathologist, who found at least a 15% reduction in the lesion size on multiple slides.

Among the patients with regression, none had a positive lymph node, compared with 146 (22%) in the control group, suggesting regression alone is not a reliable predictor, said Dr. Dion of the hospital in Saint-Nicolas.

Of the 40 patients, 1 experienced complete regression. Another six patients in this group developed in situ melanoma. The median Breslow thickness among the remaining 33 patients was 0.6 mm. At a mean follow-up of almost 4 years, recurrence occurred in two patients, including one local recurrence and one transit metastasis, Dr. Dion said. ■

## VERBATIM

*'The [Food and Drug Administration] wants us to believe that an advisory committee member can receive $49,999 from a company and still make an unbiased decision. I don't buy it and the research doesn't support it.'*

Diane Zuckerman, Ph.D., who believes that the FDA's $50,000 cap on advisers' financial interests is too high, p. 77

Olux
(clobetasol propionate) Foam, 0.05%

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Rx Only
**For Dermatologic Use Only**
**Not for Ophthalmic Use**

**CONTRAINDICATIONS**

Olux Foam is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

**PRECAUTIONS**

**General: Clobetasol propionate is a super-potent topical corticosteroid that has been shown to suppress the adrenals at 7.0 g of Olux Foam per day. Lesser amounts of Olux Foam were not studied.** Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which augment systemic absorption include the application of more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression. If adrenal suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. See **PRECAUTIONS-*Pediatric Use***.

If irritation develops, Olux Foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than by noting a clinical exacerbation, as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of Olux Foam should be discontinued until the infection has been adequately controlled.

**Information for Patients:** Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report to their physician any signs of local adverse reactions.

**Laboratory Tests:** The following tests may be helpful in evaluating patients for adrenal suppression:

ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Studies in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

**Pregnancy: *Teratogenic Effects: Pregnancy Category C:*** Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity by the topical route; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of Olux based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 0.003 and 0.01 mg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Olux based on body surface area comparisons. Abnormalities seen included cleft palate, craniioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Olux Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.**

***Nursing Mothers:*** Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Olux Foam is administered to a nursing woman.

***Pediatric Use:*** Safety and effectiveness of Olux Foam in pediatric patients have not been established; therefore, use in children under 12 years of age is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of adrenal suppression and Cushing's syndrome when they are treated with topical corticosteroids. Pediatric patients are therefore at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

Adrenal suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

***Geriatric Use:*** Clinical studies of Olux Foam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**ADVERSE REACTIONS**

In a controlled pharmacokinetic study, 5 of 13 subjects experienced reversible suppression of the adrenals at any time during the 14 days of Olux Foam therapy to at least 20% of the body surface area. Of the 13 subjects studied, 1 of 9 with psoriasis were suppressed after 14 days and all 4 of the subjects with atopic dermatitis had abnormal cortisol levels indicative of adrenal suppression at some time after starting therapy with Olux Foam. (See Table 3 below.)

Table 3: Subjects with reversible HPA axis suppression at any time during treatment

| | |
|---|---|
| Dermatosis | Olux Foam |
| Psoriasis | 1 of 9 |
| Atopic Dermatitis* | 4 of 4 |

*Olux Foam is not indicated for non-scalp atopic dermatitis, as the safety and efficacy of Olux Foam in non-scalp atopic dermatitis has not been established. Use in children under 12 years of age is not recommended.

Systemic absorption of topical corticosteroids has produced reversible adrenal suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients (see PRECAUTIONS).

In a controlled clinical trial (188 subjects) with Olux Foam in subjects with psoriasis of the scalp, there were no localized scalp adverse reactions reported in the Olux Foam treated subjects. In two controlled clinical trials (360 subjects) with Olux Foam in subjects with psoriasis of non-scalp regions, localized adverse events that occurred in the Olux Foam treated subjects included application site burning (10%), application site dryness (<1%), and other application site reactions (4%).

In larger controlled trials with other clobetasol propionate formulations, the most frequently reported local adverse reactions have included burning, stinging, irritation, pruritus, erythema, folliculitis, cracking and fissuring of the skin, numbness of the fingers, skin atrophy, and telangiectasia (all less than 2%).

The following additional local adverse reactions have been reported with topical corticosteroids, but they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids such as Olux Foam. These reactions are listed in an approximate decreasing order of occurrence: dryness, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, striae, and miliaria.

**OVERDOSAGE**

Topically applied Olux Foam can be absorbed in sufficient amounts to produce systemic effects. ***See PRECAUTIONS.***

**DOSAGE AND ADMINISTRATION**

Note: For proper dispensing of foam, hold the can upside down and depress the actuator.

Olux Foam should be applied to the affected area twice daily, once in the morning and once at night. Invert the can and dispense a small amount of Olux Foam (up to a maximum of a golf-ball-size dollop or one and a half capfuls) into the cap of the can, onto a saucer or other cool surface, or to the lesion, taking care to avoid contact with the eyes. Dispensing directly onto hands is not recommended (unless the hands are the affected area), as the foam will begin to melt immediately upon contact with warm skin. When applying Olux Foam to a hair-bearing area, move the hair away from the affected area so that the foam can be applied to each affected area. Pick up small amounts with fingertips and gently massage into affected area until the foam disappears. Repeat until entire affected area is treated.

Apply the smallest amount possible that sufficiently covers the affected area(s). No more than one and a half capfuls of foam should be used at each application. Do not apply to face or intertriginous areas.

Olux Foam is a super-high-potency topical corticosteroid; therefore, treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/week should not be used. Use in pediatric patients under 12 years of age is not recommended.

Unless directed by a physician, Olux Foam should not be used with occlusive dressings.

**WARNING**

***FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.*** Keep out of reach of children. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120°F (49°C).

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