

# Interferon Induces Some Involution of Atypical Nevi

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PARIS — Treatment of atypical nevi with high-dose interferon alfa-2b may induce at least partial involution, based on the results of a small study.

Six of eight atypical nevi demonstrated a decrease in their greatest diameter, perimeter, or surface area, suggesting partial involution following treatment with high-dose interferon alfa-2b, reported Dr. Mona Amini-Adle of the department of dermatology at Hôpital de l'Hôtel Dieu, Lyon, France.

Partial clinical involution of atypical nevi was associated with an upregulation of CD4/CD8 ratio in the intra-nevi compartment, Dr. Amini-Adle said at the annual

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congress of the European Academy of Dermatology and Venereology.

For the study, 10 patients with stage IIB-III melanoma, and at least four atypical nevi from each patient, were enrolled. The four nevi were identified as A-D at enrollment and photographed.

Two nevi were selected at random for removal prior to treatment; the remaining two were removed after 3 months of treatment. All nevi were evaluated clinically, pathologically, and with a double immunohistochemistry procedure (CD4-CD8; CD1a-CD83).

Patients were treated according to their melanoma status. Patients at high risk for melanoma were treated with a regimen of 20 million U/m<sup>2</sup> per day given intravenously five times a week for 4 weeks, followed by 10 million U/m<sup>2</sup> per day given subcutaneously three times a week until 1 year of treatment was reached. Lower-risk patients received 3 million U/day subcutaneously three times a week for 3 months.

Dr. Amini-Adle reported on eight patients with a mean age of 36 years, half of whom were women. Sixteen clinical photos (eight pre- and eight posttreatment) from five patients were informative. Biopsy samples from eight patients were informative for 27 lesions—14 pre- and 13 posttreatment nevi. "We did not observe any histologic regression," said Dr. Amini-Adle.

Clinical atypia and histologic dysplasia were correlated in half of the lesions. The clinical changes were not accompanied by histologic signs of involution. Immunohistochemistry analysis showed alterations in lymphocyte infiltrates in nevi that were focal, with histologic signs of dysplasia and a significant upregulation of the CD4/CD8 ratio in the intra-nevi compartment ( $P = .0076$ ).

of these lesions. With regard to lymphocytic infiltrates, there was a trend of upregulation of CD4 cells and downregulation of CD8 cells, Dr. Amini-Adle said.

This resulted in upregulation of the CD4/CD8 ratio. These changes, however, were observed only in dysplastic nevi, not normal melanocytic nevi.

Dissociated responses of lymphocytes in both normal and atypical nevi suggest differential immunologic response to these entities. The dendritic cell infiltrate

was not found to be influenced either in atypical nevi or normal nevi following treatment.

Atypical nevi have been shown to be nonobligate precursors of, and risk markers for, melanoma. Interferon alfa-2b is the only agent that has been shown to have a consistent and durable impact on relapse-free survival in melanoma patients, but it has not been studied for atypical nevi.

Interferon is known to enhance the im-

munogenicity of tumors. It is also known to suppress immune tolerance and to increase the degree of lymphocytic infiltrate in lesions that progress under treatment. Interestingly, in spontaneous regressive melanoma, the CD4/CD8 ratio is upregulated.

The meaning of upregulation in dysplastic nevi is unclear.

Dr. Amini-Adle noted that CD4 cells appear to play an important role in this regression. ■

**Luxiq**®

(betamethasone valerate) Foam, 0.12%

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Rx Only

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

**CONTRAINDICATIONS**

Luxiq is contraindicated in patients who are hypersensitive to betamethasone valerate, to other corticosteroids, or to any ingredient in this preparation.

**PRECAUTIONS**

**General:** Systemic absorption of topical corticosteroids has caused reversible hypothalamic-pituitary-adrenal (HPA) axis 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 the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. If HPA axis 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, Luxiq should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than 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 Luxiq 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. 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 scalp 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.

5. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

**Laboratory Tests:** The following tests may be helpful in evaluating patients for HPA axis 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 or the effect on fertility of betamethasone valerate.

Betamethasone was genotoxic in the *in vitro* human peripheral blood lymphocyte chromosome aberration assay with metabolic activation and in the *in vivo* mouse bone marrow micronucleus assay.

**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 in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, Luxiq 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 Luxiq is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also 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.

Hypothalamic-pituitary-adrenal (HPA) axis 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.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

**ADVERSE REACTIONS**

The most frequent adverse event was burning/itching/stinging at the application site; the incidence and severity of this event were as follows:

| Product                                  | Total incidence | Incidence and severity of burning/itching/stinging |          |         |
|--|-----------------|--|----------|---------|
|  |                 | Maximum severity                                   |          |         |
|  |                 | Mild   | Moderate | Severe  |
| Luxiq Foam<br>n=63                       | 34 (54%)        | 28 (44%)   | 5 (8%)   | 1 (2%)  |
| Betamethasone<br>valerate lotion<br>n=63 | 33 (52%)        | 26 (41%)   | 6 (10%)  | 1 (2%)  |
| Placebo Foam<br>n=32                     | 24 (75%)        | 13 (41%)   | 7 (22%)  | 4 (12%) |
| Placebo Lotion<br>n=30                   | 20 (67%)        | 12 (40%)   | 5 (17%)  | 3 (10%) |

Other adverse events which were considered to be possibly, probably, or definitely related to Luxiq occurred in 1 patient each; these were paresthesia, pruritus, acne, alopecia, and conjunctivitis.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximately decreasing order of occurrence: irritation; dryness; folliculitis; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; secondary infection; skin atrophy; striae; and miliaria.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

**OVERDOSAGE**

Topically applied Luxiq can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS**.)

**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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