

Isotretinoin's Mechanism of Action Explored

BY KERRI WACHTER

PHILADELPHIA — Isotretinoin appears to derive its effectiveness from increased production of the antimicrobial protein neutrophil-gelatinase associated lipocalin in the skin, reducing sebum levels, and in turn reducing levels of *Propionibacterium acnes*, according to new data.

While isotretinoin is the most effective

agent for patients with moderate to severe acne, the drug's teratogenicity makes alternative therapies desirable. A better understanding of the drug's mechanism of action could direct the investigation of new therapies, Kimberly Lumsden, an MD/PhD student at Pennsylvania State University, Hershey, said at the annual meeting of the Society for Pediatric Dermatology.

In vivo neutrophil-gelatinase associ-

ated lipocalin (NGAL) levels are highest 1 week after the start of isotretinoin treatment.

In addition, the study showed that in vivo sebum and *P. acnes* levels start to decrease during the first week of treatment with isotretinoin and continue to decrease for up to 8 weeks.

Dr. Lumsden and her colleagues recruited a patient on isotretinoin and evaluated the level of NGAL present on the

skin using a tape-stripping method at weeks 1, 4, and 8.

"At 1 week we saw the greatest increase in the level of NGAL, which levels off at 4-8 weeks," she said.

Next, they used recombinant NGAL protein and solution with *P. acnes* in vitro to determine if isotretinoin is antibacterial. They found a dose response. Increasing NGAL concentration led to decreased survival of *P. acnes*.

For the last phase, they recruited a cohort of nine patients to try to determine whether decreases in sebum and *P. acnes* coincide with the initial increase in NGAL levels with isotretinoin.

"We did see a decrease in sebum at 1 week and it's further decreased by 8 weeks," she said.

However, sebum levels start to recover by about 8 weeks. As for *P. acnes*, there was a trend toward decreased levels at week 1 and levels continued to decrease through weeks 4 and 8.

Consider Nevus Simplex in Atypical Sites

PHILADELPHIA — Infants with at least one typical site of nevus simplex involvement are likely to have involvement in less typical sites as well, according to a retrospective study of 28 infants.

Nevus simplex—the most common birthmark of infancy—typically affects the forehead, glabella, upper eyelids, and nape.

Among the patients in this study, approximately two-thirds had scalp involvement (69%), 64% had nose involvement, 64% had upper- or lower-lip involvement, and more than half (54%) had lumbosacral involvement, reported Dr. Anna Juern and colleagues in a poster at the annual meeting of the Society for Pediatric Dermatology.

For the study, the researchers identified 28 infants with nevus simplex who were seen at two tertiary care centers. The infants (15 girls and 13 boys) had a median age of 4.5 months.

The infants also had at least one typical site of involvement, noted Dr. Juern, a pediatric dermatology research fellow at the Medical College of Wisconsin in Milwaukee.

"It's important to recognize that widespread involvement beyond the typical sites does occur," the researchers wrote. Nevus simplex involvement of less-typical areas may lead to confusion with port-wine stains and other vascular birthmarks.

"Using the name 'nevus simplex' to describe these [atypical] lesions will aid in the correct diagnosis of these lesions and provide reassurance to parents, due to their benign nature," the researchers concluded.

—Kerri Wachter

Levulan® Kerastick®

(aminolevulinic acid HCl) for Topical Solution, 20%

For Topical Use Only • Not for Ophthalmic Use

Brief Summary (For full prescribing information, see physician's insert)

INDICATIONS AND USAGE

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses (Grade 1: slightly palpable, better felt than seen or Grade 2: moderately thick, easily seen and felt) of the face or scalp.

CONTRAINDICATIONS

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

WARNINGS

The LEVULAN KERASTICK for Topical Solution contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

PRECAUTIONS

General: During the time period between the application of LEVULAN KERASTICK Topical Solution and exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a widebrimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution outside the treatment site to eye or surrounding skin.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN PDT. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK for Topical Solution should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin.

The LEVULAN KERASTICK for Topical Solution has not been tested on patients with inherited or acquired coagulation defects.

Information for Patients:

LEVULAN Photodynamic Therapy for Actinic Keratoses. The first step in LEVULAN KERASTICK photodynamic therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK for Topical Solution to actinic keratoses located on the patient's face or scalp. After LEVULAN KERASTICK for Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light. Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment. The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, pricking or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment. Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

Photosensitivity

After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient should avoid exposure of the photosensitive actinic keratoses to sunlight or bright indoor light (e.g., from examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. If the patient feels stinging and/or burning on the actinic keratoses, exposure to light should be reduced. Before going into sunlight, the patient should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect the patient against photosensitivity reactions.

If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

Drug Interactions: There have been no formal studies of the interaction of LEVULAN KERASTICK for Topical Solution with any other drugs, and no drug-specific interactions were noted during any of the controlled clinical trials. It is, however, possible that concomitant use of other known photosensitizing agents such as griseofulvin, thiazide diuretics, sulfonureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with the LEVULAN KERASTICK for Topical Solution.

Carcinogenesis, Mutagenesis, Impairment to Fertility: No carcinogenicity testing has been carried out using ALA. No evidence of mutagenic effects was seen in four studies conducted with ALA to evaluate this potential. In the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay (Ames mutagenicity assay), no increases in the number of revertants were observed with any of the tester strains. In the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay in the presence of solar light radiation (Ames mutagenicity assay with light), ALA did not cause an increase in the number of revertants per plate of any of the tester strains in the presence or absence of simulated solar light. In the L5178Y TK- mouse lymphoma forward mutation assay, ALA was evaluated as negative with and without metabolic activation under the study conditions. PpIX formation was not demonstrated in any of these in vitro studies. In the in vivo mouse micronucleus assay, ALA was considered negative under the study exposure conditions. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after ALA exposure with PpIX formation. Other studies have documented oxidative DNA damage in vivo and in vitro as a result of ALA exposure.

No assessment of effects of ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to ALA HCl might have on fertility or reproductive function.

Pregnancy Category C: Animal reproduction studies have not been conducted with ALA HCl. It is also not known whether LEVULAN KERASTICK Topical Solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. LEVULAN KERASTICK Topical Solution should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The levels of ALA or its metabolites in the milk of subjects treated with LEVULAN KERASTICK Topical Solution have not been measured. Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution is administered to a nursing woman.

ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the treatment. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment. The majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

The most common changes in lesion appearance after LEVULAN KERASTICK for Topical Solution Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response. (see Precautions).

Other Localized Cutaneous Adverse Experiences: Table 1 depicts the incidence and severity of cutaneous adverse events, stratified by anatomic site treated.

Adverse Experiences Reported by Body System: In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

TABLE 1 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019

	FACE		VEHICLE (n=41)		SCALP		VEHICLE (n=21)	
	LEVULAN (n=139)				LEVULAN (n=42)			
Degree of Severity	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyperpigmentation		22%		20%		36%		33%
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose: LEVULAN KERASTICK Topical Solution overdose have not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U® Light Overdose: There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

HOW SUPPLIED

The LEVULAN KERASTICK for Topical Solution, 20%, is a single-unit dosage form, supplied in packs of 6. Each LEVULAN KERASTICK for Topical Solution applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle. The other ampule contains 354 mg of aminolevulinic acid HCl. The applicator is covered with a protective cardboard sleeve and cap.

Product Package

Individual LEVULAN KERASTICK for Topical Solution, 20% 67308-101-01
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20% 67308-101-06

NDC number

Storage Conditions: Store between 20°– 25°C (68°– 77°F); excursions permitted to 15°– 30°C (59°– 86°F) [See USP Controlled Room Temperature]. The LEVULAN KERASTICK for Topical Solution should be used immediately following preparation (dissolution). Solution application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and a new LEVULAN KERASTICK for Topical Solution used, if needed.

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