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Dermatology for the Clinician

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For adults with plaque psoriasis

betterTOGETHER

The first and only steroid/retinoid therapy, allowing **halobetasol** and **tazarotene** to work together in an advanced, once-daily lotion that can be dosed to clearance[1-3]

DUOBRII™
(halobetasol propionate and tazarotene)
Lotion 0.01% / 0.045%

mechanisms of change

Halobetasol (0.01%)

Provides powerful antiinflammatory effects and reduces skin irritation, which is often associated with retinoids[1,4,5]

Tazarotene (0.045%)

Regulates cell growth and specialization to reduce hyperproliferation, increases collagen, and extends remission post treatment[4,6,7]

The only FDA-approved treatment with a potent-to-superpotent steroid that can be used until control is achieved

The efficacy and safety of DUOBRII Lotion was investigated in two 8-week clinical trials and an additional 1 year safety study.[1,3]
Discontinue treatment with DUOBRII Lotion when control is achieved or if atrophy, striae, telangiectasias, or folliculitis occurs.[1]

American Academy of Dermatology (AAD) Guidelines give the combination of a corticosteroid and a retinoid an A rating with Evidence Level I for the treatment of psoriasis[4]

Indication

DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, is indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Contraindication

DUOBRII Lotion is contraindicated in pregnancy.

Warnings and Precautions

- Women of child-bearing potential should be warned of the potential risk of fetal harm from DUOBRII and use adequate birth-control. A negative result for pregnancy should be obtained within 2 weeks prior to treatment. If the patient becomes pregnant during treatment, discontinue DUOBRII Lotion and advise patient of the potential hazard to the fetus.
- DUOBRII Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during or after treatment and may require that patients be evaluated periodically during treatment.
- Predisposing factors for HPA axis suppression include: use of more potent corticosteroids, use on large areas, use under occlusive dressings, use on altered skin barrier, concomitant use of other steroids, liver failure and young age.
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria.
- Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. If these effects occur, discontinue until the integrity of the skin has been restored. Do not resume treatment if contact dermatitis is identified. DUOBRII Lotion should not be used on eczematous skin, as it may cause severe irritation.
- Avoid exposure to sunlight, sunlamps and weather extremes. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers because of the increased potential for photosensitivity.
- Topical corticosteroids may increase the risk of cataracts and glaucoma; advise patients to report any visual symptoms and refer to an ophthalmologist if needed.

Adverse Events

- The most common adverse events in clinical trials were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on the following page.

References 1. DUOBRII Lotion [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC. **2.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed April 29, 2019. **3.** Data on file. **4.** Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol.* 2009;60(4):643-659. **5.** Orfanos CE, Schmidt HW, Mahrle G, et al. Retinoic acid in psoriasis: its value for topical therapy with and without corticosteroids: clinical, histological and electron microscopical studies on forty-four hospitalized patients with extensive psoriasis. *Br J Dermatol.* 1973;88(2):167-182. **6.** Lesnik RH, Mezick JA, Capetola R, Kligman LH. Topical all-trans-retinoic acid prevents corticosteroid-induced skin atrophy without abrogating the anti-inflammatory effect. *J Am Acad Dermatol.* 1989;21(2 Pt 1):186-190. **7.** Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *J Am Acad Dermatol.* 1997;37(1):85-92.

Learn more at DUOBRII.com

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe DUOBRII safely and effectively. See full Prescribing Information for DUOBRII.

DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% for topical use

INDICATIONS AND USAGE

DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS

Pregnancy

DUOBRII Lotion is contraindicated in pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Risk

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Tazarotene is teratogenic, and it is not known what level of exposure is required for teratogenicity in humans *[see Contraindications and Clinical Pharmacology]*. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits *[see Use in Specific Populations]*.

Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to DUOBRII Lotion therapy. Initiate DUOBRII Lotion therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion therapy *[see Use in Specific Populations]*.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects

DUOBRII Lotion contains halobetasol propionate, a corticosteroid, and has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with DUOBRII Lotion was evaluated in a study of 20 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area. The subjects were treated once daily for 8 weeks and assessed for HPA axis suppression at Weeks 4 and 8. HPA axis suppression occurred in 3 out of 20 (15%) subjects at Week 4 and none (0%) of these 20 subjects had HPA axis suppression at Week 8 *[see Clinical Pharmacology in full Prescribing Information]*.

Because of the potential for systemic absorption, use of topical corticosteroids, including DUOBRII Lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug or reduce the frequency of application. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids because of their larger surface-to-body mass ratio *[see Use in Specific Populations]*.

Local Adverse Reactions

Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. Some local adverse reactions may be irreversible. If these adverse reactions occur, discontinue the medication at least until the integrity of the skin is restored; do not resume treatment if allergic contact dermatitis is identified.

Avoid use of DUOBRII Lotion on eczematous skin, as it may cause severe irritation.

Photosensitivity and Risk for Sunburn

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of DUOBRII Lotion. Patients must be instructed to use sunscreens and protective clothing when using DUOBRII Lotion. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using DUOBRII Lotion.

DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Ophthalmic Adverse Reactions

Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with the use of topical corticosteroid products. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of DUOBRII Lotion until the infection has been adequately treated.

ADVERSE REACTIONS

Clinical Trials Experience

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

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 410 adults with plaque psoriasis were treated with DUOBRII Lotion or vehicle lotion and had post-baseline safety data. Subjects applied DUOBRII Lotion or vehicle lotion once daily for up to eight weeks. The adverse reactions occurring in ≥1% of the subjects treated with DUOBRII through Week 8 were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from DUOBRII Lotion during pregnancy; therefore, DUOBRII Lotion should be discontinued as soon as pregnancy is recognized *[see Contraindications, Warnings and Precautions, Clinical Pharmacology]*.

Observational studies suggest an increased risk of low birthweight in infants with the maternal use of potent or very potent topical corticosteroids *(see Data)*.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose 11 times the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 116 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 9 and 228 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 9 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during the period of organogenesis to pregnant rats and rabbits *(see Data)*. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of DUOBRII Lotion.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (11 times the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5%, 0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (116 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 9 and 228 times, respectively, the MRHD (based on AUC comparisons).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (16 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to 5 times the MRHD (based on AUC comparison).

Lactation

Risk Summary

There are no data on the presence of tazarotene, halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with DUOBRII Lotion.

After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUOBRII Lotion and any potential adverse effects on the breastfed child from DUOBRII Lotion.

Clinical Considerations

Advise breastfeeding women not to apply DUOBRII Lotion directly to the nipple and areola to avoid direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing

DUOBRII Lotion is contraindicated in women who are pregnant. Females of reproductive potential should be warned of the potential risk and use adequate birth-control measures during treatment with DUOBRII Lotion. The possibility that a female of reproductive potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy should be obtained within 2 weeks prior to DUOBRII Lotion therapy, which should begin during menstruation.

Contraception

Based on animal studies, DUOBRII Lotion may cause fetal harm when administered to a pregnant female *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion.

Pediatric Use

Safety and effectiveness of DUOBRII Lotion in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, 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 or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions]*.

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 *[see Warnings and Precautions]*.

Geriatric Use

Of the 270 subjects exposed to DUOBRII Lotion in clinical trials, 39 subjects were 65 years or older. Clinical trials of DUOBRII Lotion did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposure at the highest dose was 35 times the MRHD (based on AUC comparison).

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day, approximately 0.53 times the MRHD based on BSA comparisons, indicated no impairment of fertility or general reproductive performance.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was 5 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced a systemic exposure 17 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced a systemic exposure 30 times the MRHD (based on AUC comparison).

Manufactured for:
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By:
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Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847; 8,809,307 and 10,251,895

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ARAZLO™ (tazarotene) lotion, for topical use
Initial U.S. Approval: 1997
This Brief Summary does not include all the information needed to use ARAZLO safely and effectively; please see full Prescribing Information for ARAZLO.

INDICATIONS AND USAGE
ARAZLO™ (tazarotene) lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS
ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient *[see Warnings and Precautions, Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS
Embryofetal Toxicity Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, discontinue ARAZLO as soon as pregnancy is recognized.

Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for ARAZLO have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications, Use in Specific Populations]*.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. Tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

Advise pregnant patients of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to ARAZLO therapy. Initiate ARAZLO therapy during a menstrual period. Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO *[see Dosage and Administration, Use in Specific Populations]*.

Skin Irritation Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided. Patients with sunburn should be advised not to use ARAZLO until fully recovered.

ARAZLO should be administered with caution if the patient is taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

ADVERSE REACTIONS
The following serious adverse reactions are discussed in more detail in other sections:

- Embryofetal toxicity *[see Warnings and Precautions]*
- Photosensitivity and Risk of Sunburn *[see Warnings and Precautions]*

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

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino and 42% were younger than 18 years of age, fourteen of 779 subjects (1.8%) treated with ARAZLO were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in Table 1. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated. Overall, 2.4% (19/779) of subjects discontinued ARAZLO because of local skin reactions.

Table 1: Adverse Reactions Reported by ≥1% of the ARAZLO Group and More Frequently than the Vehicle Group

Adverse Reactions N (%)		
	ARAZLO Lotion N=779	**Vehicle N=791**
Application site pain[1]	41 (5)	2 (<1)
Application site dryness	30 (4)	1 (<1)
Application site exfoliation	16 (2)	0 (0)
Application site erythema	15 (2)	0 (0)
Application site pruritus	10 (1)	0 (0)

[1]Application site pain defined as application site stinging, burning, or pain

Skin irritation was evaluated by active assessment of erythema, scaling, itching, burning and stinging, with grades for none, mild, moderate, or severe. The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The percentage of subjects with these signs and symptoms at any post-baseline visit are summarized in Table 2.

Table 2: Incidence of Local Cutaneous Irritation at any Post-Baseline Visit

	ARAZLO Lotion N=774 Mild/Moderate/Severe	**Vehicle Lotion N=789** Mild/Moderate/Severe
Erythema	49%	38%
Scaling	51%	23%
Itching	29%	14%
Burning	30%	6%
Stinging	22%	5%

DRUG INTERACTIONS
No formal drug-drug interaction studies were conducted with ARAZLO.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

In a trial of 27 healthy female subjects, between the ages of 20–55 years, receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, the concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and $AUC_{0\text{-}24}$ of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng•hr/mL, respectively) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., minipills) has not been evaluated.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary ARAZLO is contraindicated in pregnancy.

There are no available data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 1 and 30 times, respectively, the MRHD (based on AUC comparison).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

Lactation
Risk Summary There are no data on the presence of tazarotene or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAZLO and any potential adverse effects on the breastfed child from ARAZLO.

Clinical Considerations To minimize potential exposure to the breastfed infant via breast milk, use ARAZLO for the shortest duration possible while breastfeeding. Advise breastfeeding patients not to apply ARAZLO directly to the nipple and areola to prevent direct infant exposure.

Females and Males of Reproductive Potential
Pregnancy Testing Pregnancy testing is recommended for patients of childbearing potential within 2 weeks prior to initiating ARAZLO therapy which should begin during a menstrual period.

Contraception Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO.

Pediatric Use Safety and effectiveness of ARAZLO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 300 pediatric subjects aged 9 to less than 17 years received ARAZLO in the clinical studies *[see Clinical Pharmacology and Clinical Studies]*.

The safety and effectiveness of ARAZLO in pediatric patients below the age of 9 years have not been established.

Geriatric Use Clinical trials of ARAZLO did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

OVERDOSAGE
Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

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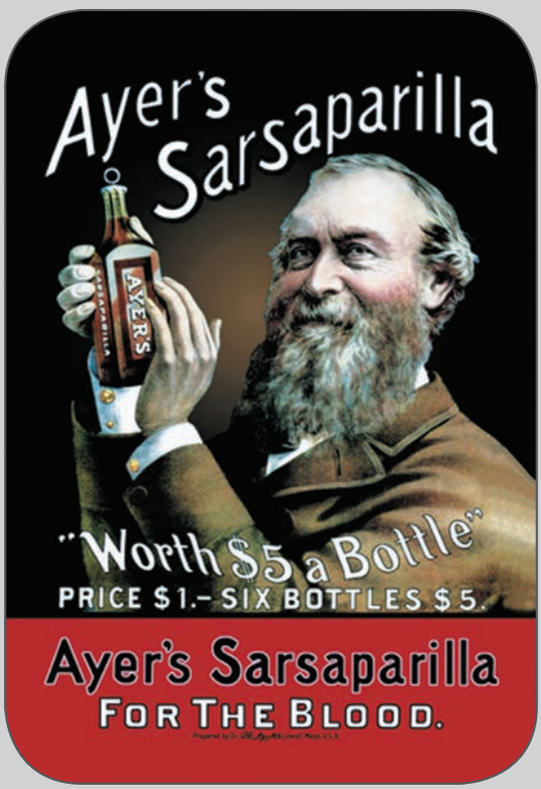

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ABOUT OUR JOURNAL

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Otezla®
(apremilast) 30mg tablets

GETTING OTEZLA GETS EVEN EASIER

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*Basic, Standard, and Advanced Control Formularies. †SafeGuardRx® Program has 1 biologic step for patients on certain Otezla® (apremilast) indications. DMARD, disease-modifying antirheumatic drug.

INDICATIONS

Otezla® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.

IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Please see Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.

Reference: 1. Data on file, Amgen Inc.

Otezla® (apremilast) 30mg tablets

For patients with moderate to severe plaque psoriasis

RESULTS

the way

THEY WANT THEM

Otezla has a proven efficacy and safety profile, oral dosing, and no label-required lab monitoring—making it a treatment experience patients can respond to[1]

Otezla® (apremilast) significantly increased PASI-75 response (n=562) at week 16 (primary endpoint) vs placebo (n=282) (33% vs 5%; P<0.0001) in ESTEEM 1[1,2]

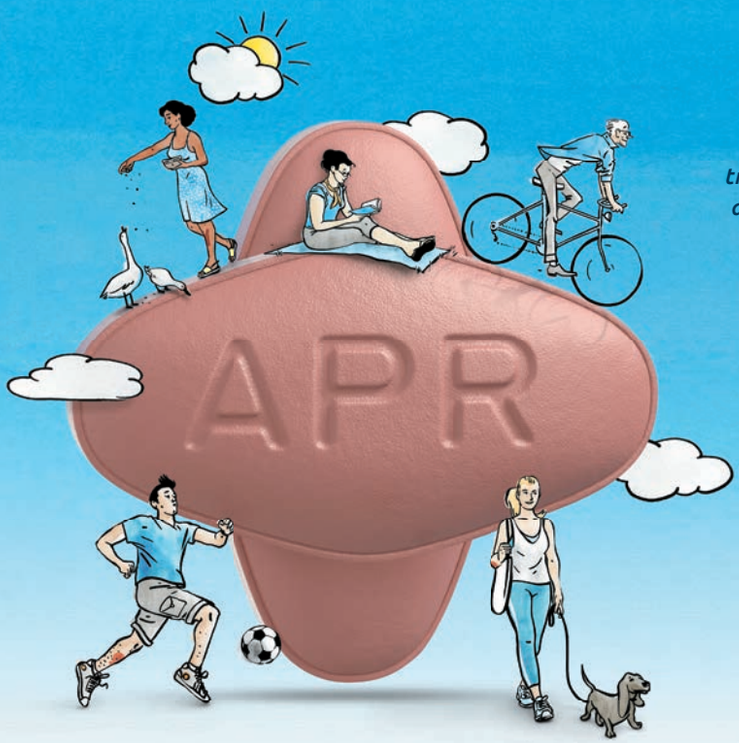
ESTEEM® Study Design

- Evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N=1257) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration[1]
- Selected inclusion criteria: age ≥18 years, BSA ≥10%, sPGA ≥3, PASI ≥12, candidates for phototherapy or systemic therapy[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

- Diarrhea, Nausea, and Vomiting: Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur
- Weight Decrease: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla



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Also approved for the treatment of adults with active psoriatic arthritis

START your patients on Otezla today

- **Convenient oral dosing[1]***
- **No required lab monitoring[1]**
- **Samples available in office**
- **Bridge program offers 3 years for free†**
- **$0 co-pay‡**

- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)

Use in Specific Populations

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Otezla during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

*Following a 5-day titration, the recommended maintenance dosage is 30 mg twice daily.

† To receive a free Bridge supply of Otezla, patients must have an on-label diagnosis and be denied or waiting for coverage.

‡ Certain restrictions apply; eligibility not based on income, must be 18 years or older. This offer is not valid for persons eligible for reimbursement of this product, in whole or in part under Medicaid, Medicare, or similar state or federal programs. Offer not valid for cash-paying patients. People who are not eligible can call **1-844-4OTEZLA** to discuss other financial assistance opportunities.

BSA, body surface area; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.

References: 1. Otezla [package insert]. Thousand Oaks, CA: Amgen Inc. **2.** Papp K, Reich K, Leonardi CL, et al. *J Am Acad Dermatol.* 2015;73(1):37-49.

Please turn the page for Brief Summary of Full Prescribing Information.

AMGEN®

03/20 US-OTZ-20-0415

OTEZLA® (apremilast) tablets, for oral use

RX Only

The following is a Brief Summary of the Prescribing Information; see Full Prescribing Information for complete product information.

4 CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

5.2 Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

5.3 Weight Decrease: During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo.

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo.

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered *[see Adverse Reactions (6.1)]*.

5.4 Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended *[see Drug Interactions (7.1)]*

6 ADVERSE REACTIONS

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

Psoriatic Arthritis Clinical Trials: OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials [Studies PsA-1, PsA-2, and PsA-3] of similar design in adult patients with active psoriatic arthritis. Across the 3 studies, there were 1493 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was used over the first 5 days. Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily at week 16 while OTEZLA patients remained on their initial treatment. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

The majority of the most common adverse reactions presented below occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% Than That Observed in Patients on Placebo on Day 1-5 (Placebo %, OTEZLA %): Diarrhea[a] (1.2%, 9.3%), Nausea[a] (1.4%, 7.4%), Headache[a] (1.8%, 4.8%), Upper respiratory tract infection[b] (0.6%, 0.6%), Vomiting[a] (0.4%, 0.8%), Nasopharyngitis[b] (0.2%, 0.2%), Abdominal pain upper[b] (0.0%, 0.6%).

Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% Than That Observed in Patients on Placebo on Day 6-112 (Week 16) (Placebo %, OTEZLA %): Diarrhea[a] (1.6%, 7.7%), Nausea[a] (3.1%, 8.9%), Headache[a] (2.2%, 5.9%), Upper respiratory tract infection[b] (1.8%, 3.9%), Vomiting[a] (0.4%, 3.2%), Nasopharyngitis[b] (1.6%, 2.6%), Abdominal pain upper[b] (0.2%, 2.0%).

[a] Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.

[b] Of the reported adverse drug reactions none were serious.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

Immune system disorders: Hypersensitivity, Investigations: Weight decrease, Gastrointestinal Disorders: Frequent bowel movement, gastroesophageal reflux disease, dyspepsia, Metabolism and Nutrition Disorders: Decreased appetite*, Nervous System Disorders: Migraine, Respiratory, Thoracic, and Mediastinal Disorders: Cough, Skin and Subcutaneous Tissue Disorders: Rash

*1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

Psoriasis Clinical Trials

The safety of OTEZLA was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

Adverse Reactions Reported in ≥1% of Subjects on OTEZLA and With Greater Frequency Than in Subjects on Placebo; up to Day 112 (Week 16) (Placebo %, OTEZLA %):
Diarrhea (6%, 17%), Nausea (7%, 17%), Upper respiratory tract infection (6%, 9%), Tension headache (4%, 8%), Headache (4%, 6%), Abdominal pain* (2%, 4%), Vomiting (2%, 4%), Fatigue (2%, 3%), Dyspepsia (1%, 3%), Decreased appetite (1%, 3%), Insomnia (1%, 2%), Back pain (1%, 2%), Migraine (1%, 2%), Frequent bowel movements (0%, 2%), Depression (0%, 1%), Bronchitis (0%, 1%), Tooth abscess (0%, 1%), Folliculitis (0%, 1%), Sinus headache (0%, 1%).
*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.
Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with OTEZLA.

7 DRUG INTERACTIONS

7.1 Strong CYP450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Risk Summary: Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

8.2 Lactation

Risk Summary: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed child from OTEZLA or from the underlying maternal condition.

8.4 Pediatric Use: The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use: Of the 1493 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older, including 19 patients 75 years and older. No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

Of the 1257 subjects who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis subjects were 65 years of age and older, including 9 subjects who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly subjects ≥65 years of age and younger adult subjects <65 years of age in the clinical trials.

8.6 Renal Impairment: Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment.

8.7 Hepatic Impairment: Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

10 OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

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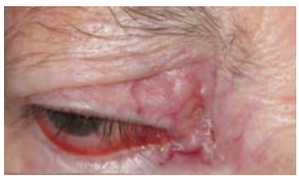
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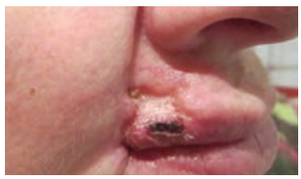
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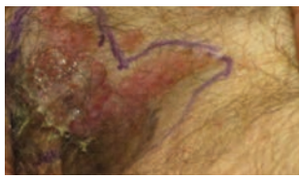
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of lesion reduction in half of patients[1,3*]

*At 30 months, the median duration of response was 26.1 months (95% CI: 10.1 months, NE).[1]

laBCC=locally advanced basal cell carcinoma; NE=not estimable.

1. ODOMZO [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 09/2017. **2.** Data on file. Sun Pharmaceutical Industries, Inc. Princeton, NJ. March 2017. **3.** Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. J Eur Acad Dermatol Venereol. 2018;32(3):372-381.

INDICATION

ODOMZO® (sonidegib) is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. ODOMZO is embryotoxic, fetotoxic, and teratogenic in animals**
- **Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose**
- **Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose**

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Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the following pages of this publication.

Brief Summary of Prescribing Information for ODOMZO® (sonidegib) capsules

This Brief Summary does not include all the information needed to use ODOMZO safely and effectively.

See full Prescribing Information for ODOMZO.

INDICATIONS AND USAGE

ODOMZO is a hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

WARNINGS AND PRECAUTIONS

WARNING: EMBRYO-FETAL TOXICITY
See full Prescribing Information for complete boxed warning.

- **ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is embryotoxic, fetotoxic, and teratogenic in animals.**
- **Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose.**
- **Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose.**

Blood Donations: Advise patients not to donate blood or blood products during treatment with ODOMZO and for at least 20 months after the last dose.

Musculoskeletal Adverse Reactions: Obtain serum creatine kinase (CK) and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated. Temporary dose interruption or discontinuation of ODOMZO may be required based on the severity of musculoskeletal adverse reactions.

Premature Fusion of the Epiphyses: Has been reported in pediatric patients exposed to ODOMZO and other Hh pathway inhibitors. ODOMZO is not indicated for use in pediatric patients.

DOSAGE AND ADMINISTRATION

Recommended dosage: 200 mg taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal.

ADVERSE REACTIONS

The most common adverse reactions occurring in ≥10% of patients are muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

DRUG INTERACTONS

CYP3A Inhibitors: Avoid strong CYP3A inhibitors. Avoid long-term (greater than 14 days) use of moderate CYP3A inhibitors.

CYP3A Inducers: Avoid strong and moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

EMBRYO-FETAL TOXICITY: See boxed warning. ODOMZO can cause fetal harm when administered to a pregnant woman.

Report pregnancies to Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

LACTATION

Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with ODOMZO and for 20 months after the last dose.

PEDIATRIC USE

The safety and effectiveness of ODOMZO have not been established in pediatric patients.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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For more information, call 1-833-786-4636

IMPORTANT SAFETY INFORMATION (continued)

Embryo-fetal Toxicity: ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. *Females of Reproductive Potential:* Verify pregnancy status prior to initiating ODOMZO. Advise females to use effective contraception and not to breastfeed, due to the potential for serious adverse reactions in breastfed infants, during treatment and for at least 20 months after the last dose. Report pregnancies to Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

Males: Advise males to use condoms, even after a vasectomy, and to not donate semen during treatment and for at least 8 months after the last dose to avoid potential drug exposure in pregnant females or females of reproductive potential.

Blood Donation: Advise patients not to donate blood or blood products while taking ODOMZO, and for at least 20 months after the last dose because their blood or blood products might be given to a female of reproductive potential.

Musculoskeletal Adverse Reactions: Musculoskeletal adverse reactions, which may be accompanied by serum creatine kinase (CK) elevations, occur with ODOMZO and other drugs which inhibit the hedgehog (Hh) pathway. Obtain serum CK and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated. Temporary dose interruption or discontinuation of ODOMZO may be required based on the severity of musculoskeletal adverse reactions.

Premature Fusion of the Epiphyses: ODOMZO is not indicated for use in pediatric patients. Premature fusion of the epiphyses has been reported in pediatric patients exposed to ODOMZO and other Hh pathway inhibitors. In some cases, fusion progressed after discontinuation.

Drug Interactions: Avoid concomitant administration of ODOMZO with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, administer for less than 14 days and monitor closely for adverse reactions, particularly musculoskeletal. Avoid concomitant administration of ODOMZO with strong and moderate CYP3A inducers.

Geriatric Use: There was a higher incidence of serious adverse events, Grade 3 and 4, and events requiring dose interruption or discontinuation in patients ≥65 years compared with younger patients; this was not attributable to an increase in any specific adverse event.

Most Common Adverse Reactions: The most common adverse reactions occurring in ≥10% of patients were muscle spasms (54%), alopecia (53%), dysgeusia (46%), fatigue (41%), nausea (39%), musculoskeletal pain (32%), diarrhea (32%), decreased weight (30%), decreased appetite (23%), myalgia (19%), abdominal pain (18%), headache (15%), pain (14%), vomiting (11%), and pruritus (10%).

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on previous pages of this publication.

SUN PHARMA

EDITORIAL

Dermatology Journals and the Impact Factor

Lawrence Charles Parish, MD, MD (HON);[1,2] W. Clark Lambert, MD, PhD[3,4,5]

"There are four types of ignorance: (1) Things which you know and think you know. (2) Things which you know but think you do not know. (3) Things which you do not know and think you do not know. And (4) Things that you do not know but think you know. Beware the last one!"
—Socrates (470–399 BCE)

A half-century ago, journals were usually printed with hot type, set either by a Mergenthaler Linotype or Harris Intertype. The fifth and final edition of the *Index-Catalogue of the Library of the Surgeon-General's Office* had been published. The number of dermatology journals was less than 100,[1] and the Library of the College of Physicians of Philadelphia subscribed to all but two. Even then, librarians and some readers recognized that the annual increase in scientific information had come to exceed anything with which a medical librarian might cope.

Garfield was concerned with not only the expense of subscribing and binding the periodicals but also finding physical space for shelving them. This marked the birth of the Science Citation Index (SCI), the Impact Factor (IF), and the Institute for Scientific Information (ISI) in Philidelphia.[2]

THE PURPOSE

The role of the SCI has expanded over the years. Libraries may still continue to select journals on the basis of their IF, with many institutions subscribing for periodicals digitally or by group selection from the publishers' packages. What was never anticipated, however, is the importance given to the IF, not only by libraries but also by readers and even academia. Unfortunately, this has produced some untoward and even bizarre results.

THE JOURNAL IMPACT FACTOR AND ITS CONSEQUENCES

How is the IF determined? The IF ratings are primarily formulated based on how many citations are made of a paper published in that journal and the IF in turn of each of those papers that cite that paper and of the journals in which those papers appear, performed by staff at the ISI.[2–7] The process is not perfect, and unintended consequences can creep in places[7]; however, there are more important issues to be considered.

Some journals enjoy exceedingly high IFs, although their readability by the average physician is questionable. This is demonstrated for a publication by WCL, who in 1969 described a method for synchronization of all cultured cells into a single phase of the cell cycle.[8] The method has become widely used, is cited in numerous papers, and has earned such a high IF that it has actually been cited specifically as a high-IF paper by the ISI. While this is flattering, the reality is that it is just a methods paper and is not considered by WCL to be among his most important contributions.

Periodicals often wish to maintain or advance their reputation. As a result, not a few have discarded the case report, which, in the case of dermatology, is disappointing, as these papers are often instrumental in advancing knowledge of the discipline. Another "trick of the trade" is to relegate some contributions to online only status; yet, another trick is to initiate a separate publication under the mantra of the main journal. As perspicaciously noted by David Pendlebury of the ISI, "Journal impact factors are frequently misused to assess the influence of individual papers and authors, but such uses were never intended."[5]

To make matters worse, European universities sometimes base promotions on how high are the IFs of the journals in which the candidate has published. The higher the publications' IFs, the more likely the young physician will advance in his or her academic community.[3,4,5]

As noted by C. Northcote Parkinson (1909–1993), a British naval historian, anything given a numerical value tends to be awarded

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outsized importance in making decisions, further exacerbating this issue.[9] The problem is made even worse by the fact that few of us really understand, take the time, or extend the effort needed to comprehend the real meaning of the IF, as its definition is never clearly stated, making it all the more powerful.[10] There should be better ways to determine merit among our endeavors and that of our peers and to determine who among us will be named "The Sweetheart of Sigma Chi."

WHAT CAN BE DONE TO RECTIFY THE PROBLEM?

An author may choose to ignore the IF of a journal and submit his or her work to a publication best suited for his or her presentation. Yes, there is a snob appeal to publishing in a high-IF journal. If the periodical is listed in PubMed and/or PubMed Central, however, as are most peer-reviewed journals, half the battle for recognition is already won.

The other 50% could perhaps be remedied by creating a specialty IF (the dermatology IF) based solely on contributions published in, and cited in, dermatology-related journals. Other specialties and subspecialties of medicine may find it useful to do something similar. This might not be a perfect solution, but maybe there is more than one way to become "The Sweetheart of Sigma Chi."

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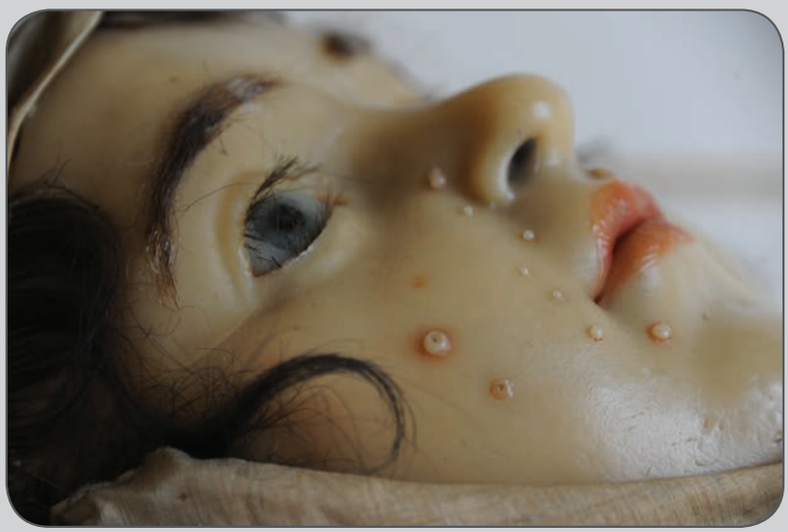

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ORIGINAL CONTRIBUTION

Sexually Transmitted Diseases in the COVID-19 Era

Claire J. Wiggins, BS; Theodore Rosen, MD

ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an infectious disease of recent origin with high transmissibility and mortality. The resulting COVID-19 pandemic has impacted the United States the most, in terms of the number of confirmed cases and fatalities. How other aspects of public health will be impacted by this disease has yet to be fully realized. Sexually transmitted diseases (STDs), already a major public health crisis, will likely be significantly affected by this pandemic. We address some of the potential implications for STDs in the setting of widespread COVID-19, discussing the sexual transmission of COVID-19 itself, STD co-infection with COVID-19, and changes in STD prevalence secondary to COVID-19. (*SKINmed*. 2020;18:210–212)

The global spread of the novel coronavirus (COVID-19) has ushered in new social rules governing human interaction. In the post-coronavirus world, the crowding of people is of great significance: previously normal gatherings of people are now seen as a dangerous violation of public health guidance. Other than slowing the spread of COVID-19, additional benefits of social distancing are only just beginning to unfold. Also, once an individual is infected with COVID-19, it is unclear how this will impact other preexisting infectious diseases. Coronavirus-related policies may also indirectly impact the quality of medical care delivered for other conditions. For example, as public health officials are urgently attending to the pressing issues surrounding the pandemic, it is not known how precisely COVID-19 will affect sexually transmitted diseases (STDs) in the United States or elsewhere, epidemiologically, immunologically, or clinically.

SEXUAL TRANSMISSION OF COVID-19

Viral transmission from person to person requires viral infectivity by the host, adequate pathogenic viral dose, and appropriate route of exposure.[1] More rapid and safer methods of virus detection, such as polymerase chain reaction (PCR), have become common diagnostic tools; however, actual viral isolation, either in laboratory animals or cell culture, is the only definite way to prove viral infectivity.[1] Studies of the Ebola (EBOV) and Zika (ZIKV) outbreaks are pertinent examples where the presence of the viral genome does not necessarily equate to infectivity. While ZIKV ribonucleic acid (RNA) was frequently present in the semen of symptomatic patients, only 4% of these ZIKV RNA-positive samples were infectious.[1,2] The ZIKV RNA has been detected in semen over 9 months after acute infection, but the infectious samples were all collected within 30 days after the onset of symptoms and had a viral load of 7.0 $\log_{10}$ RNA copies/milliliter, suggesting that ZIKV can be transmitted sexually for only a short window of time.[1,2] Similar is the case with EBOV: although viral RNA can persist in semen over 1 year after disease onset, actual sexual transmission of EBOV has been documented extremely rarely.[3,4]

Investigation into whether COVID-19 can be directly transmitted sexually is of particular interest currently. In a descriptive study of 11 recovered patients from COVID-19, aged 22–38 years, semen samples from all subjects tested negative for SARS-CoV-2 RNA.[5] An additional patient in the study, a 67-year-old man who succumbed to COVID-19, underwent a testicular biopsy, which tested negative for COVID-19 RNA.[5] By contrast, however, in a different study of 38 men, 26.7% of actively infected COVID-19 patients' semen and 8.7% of recovering patients' semen tested positive for SARS-CoV-2 RNA.[6] Notably, reverse-transcriptase PCR was used for both studies, so the actual viral infectivity was not confirmed[5,6]; Hence, it is obvious that further research is required to determine if COVID-19 can be directly transmitted sexually,

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due to the potential implications for viral dissemination via the sexual route. This immediately impacts advice given to recovered male patients and their partners. Similarly, the presence of viral RNA in vaginal secretions has yet to be addressed.

Interestingly, viral genomes that are not classically described as STDs, such as flaviviruses, bunyaviruses, adenoviruses, retroviruses, and paramyxoviruses, are more frequently isolated in semen than the genomes of typical STD viruses, further emphasizing that mere detection of viral genetic material alone may have little pragmatic or clinical significance.[7] Further complicating matters, conventional testing for viruses does not account for the potential for dormancy and reactivation, situations where viral shedding is intermittent rather than constant.[1] The significance for sexual transmission of COVID-19, as well as many other viruses, has yet to be established, but in terms of public health policy, preventative measures (e.g., barrier protection) might well be recommended in the present circumstance of a theoretical, but uncertain, degree of risk.

SEXUAL TRANSMISSIBILITY OF COVID-19

One of the challenges in classifying potential sexually transmissible viruses is differentiating the sexually *transmitted*, directly through exchange of or exposure to bodily fluids, from the sexually *transmissible*, which spreads due to the close human contact of sexual activity. In order to reduce the risk of the spread of COVID-19, current evidence indicates that interpersonal contact should take place at least 2 m (6 feet) apart, with all parties wearing masks covering the nose and mouth.[8] As viral transmission occurs through respiratory droplets from coughing, sneezing, or even speaking, and viable aerosolized infectious particles can persist for 3 hours or more,[9] being in close contact with an infected person, let alone kissing, would clearly be considered high risk. In short, if individuals are close enough to have sex, then they are close enough to be exposed to COVID-19. Depending on the sexual partner, however, the degree of risk will vary. Patients should be counseled that sex with an existing partner from the same household likely would not increase risk, as this exposure would have already occurred. On the contrary, precautions should be taken when engaging in sexual activity with partners who reside in different abodes: considering each person's respective other human contacts, engaging in proper hygiene, and cancelling plans for an intimate encounter if either partner develops symptoms suggestive of COVID-19 infection.

COVID-19 AND CLASSIC STDs

Aside from the spread of COVID-19 secondary to sexual contact, how the pandemic will alter the course and prevalence of STDs has yet to be determined. Common venereal diseases, such as gonorrhea, chlamydia, and syphilis, have recently reached all-time highs in the United States.[10] In the setting of a society with relatively pervasive STDs, it is logical to ask: will COVID-19 co-infection alter STD recurrence, morphology, and/or response to therapy?

It is known that human immunodeficiency virus (HIV) co-infection, for example, is positively correlated with persistence of the human papilloma virus (HPV) infection and invasive cervical carcinoma.[11] Herpes simplex virus-2 (HSV2) and HIV are also strongly associated, in that retroviral co-infection can lead to atypical (vegetative or ulcerated) presentation of herpes progenitalis. Men with HIV have been shown to have a high recurrence of asymptomatic chlamydia trachomatis urethritis after treatment.[12] Atypical clinical presentations of syphilis have occurred in the setting of HIV co-infection.[13] Interestingly, lymphocytopenia is a common diagnostic indicator in COVID-19 patients, and SARS-CoV-2 has been found to infect T-cells via receptor-dependent membrane fusion.[14] Given that HIV also infects T-cells, the potential for COVID-19 to impact STDs as in the case of HIV is, at the least, a realistic possibility. Although there is no evidence yet that COVID-19 infection produces atypical STD presentation, reactivates STDs, or reduces the efficacy of STD treatment, we must be prepared to recognize these potential effects.

The COVID-19 pandemic may also indirectly influence the prevalence of STDs globally. The potential for increased STDs may be caused by a variety of COVID-19-related factors. More frequent instances of sexual activity secondary to "sheltering in place" without the typical distractions of everyday life may play a role. For example, a study of female sexual desire and behavior during the COVID-19 pandemic in Turkey has, in fact, shown increased rates of intercourse, a decreased desire for pregnancy, and a decreased use of female contraception.[15] The pandemic has made scarce a variety of resources, including condoms, as the major Asian condom factories have closed down due to extensive infection among the workforce.[16] There is also a shortage of azithromycin, part of the Centers for Disease Control and Prevention (CDC)-recommended treatment for uncomplicated gonococcal infections, as it was being tested as a potential COVID-19 treatment.[17] Individuals have thus obtained and hoarded this antibiotic. Routine STD tracking by epidemiologists, STD awareness promotions, and other public health efforts to combat STDs have been curtailed, as health professionals are focusing their efforts on COVID-19 control instead. Access to testing in city/county STD clinics will likely be limited, as clinics may close or reduce hours of service. Crowding inside a clinic violates social distancing guidelines and may be uncomfortable for patients concerned about contracting COVID-19, which may lead a

lessened interest in visiting clinics for STD testing.[18] Personal protective equipment, other than gloves, is not routinely stored in STD clinics.[18] Telehealth methods of STD screening are largely underdeveloped, and STD testing could be viewed as low priority amid a deadly worldwide pandemic; however, the influence of COVID-19 could, as a silver lining, limit the spread of STDs. Abiding by social distancing should overall reduce each individual's number of new sexual partners during the pandemic. With less social contact, especially at work, rates of infidelity are also likely to decrease. In light of the importance of social distancing measures, self-pleasuring campaigns, connection via dating sites and cellphone apps, and various forms of cybersex activities have been promoted as alternative outlets to partially fulfill the sexual needs of the populace.[19–21]

CONCLUSIONS

It is not known how long COVID-19 will dominate the public health sphere, and how it will shape other aspects of human health. Creating awareness of these potential effects, such as the state of STDs, is important as this critical period unfolds. Coronaviruses have marred the beginning of the 21st century: SARS-CoV-1, MERS-CoV, and now, most significantly, SARS-CoV-2. Although these devastating outbreaks of disease may induce feelings of helplessness, the opportunity to learn about the mechanisms of infectious disease and the strengths and weaknesses of our healthcare system will hopefully mitigate future loss and strengthen public health in the long term. In the words of John Donne, "no man is an island, entire of itself," a truth no more undeniable as a result of the COVID-19 pandemic.

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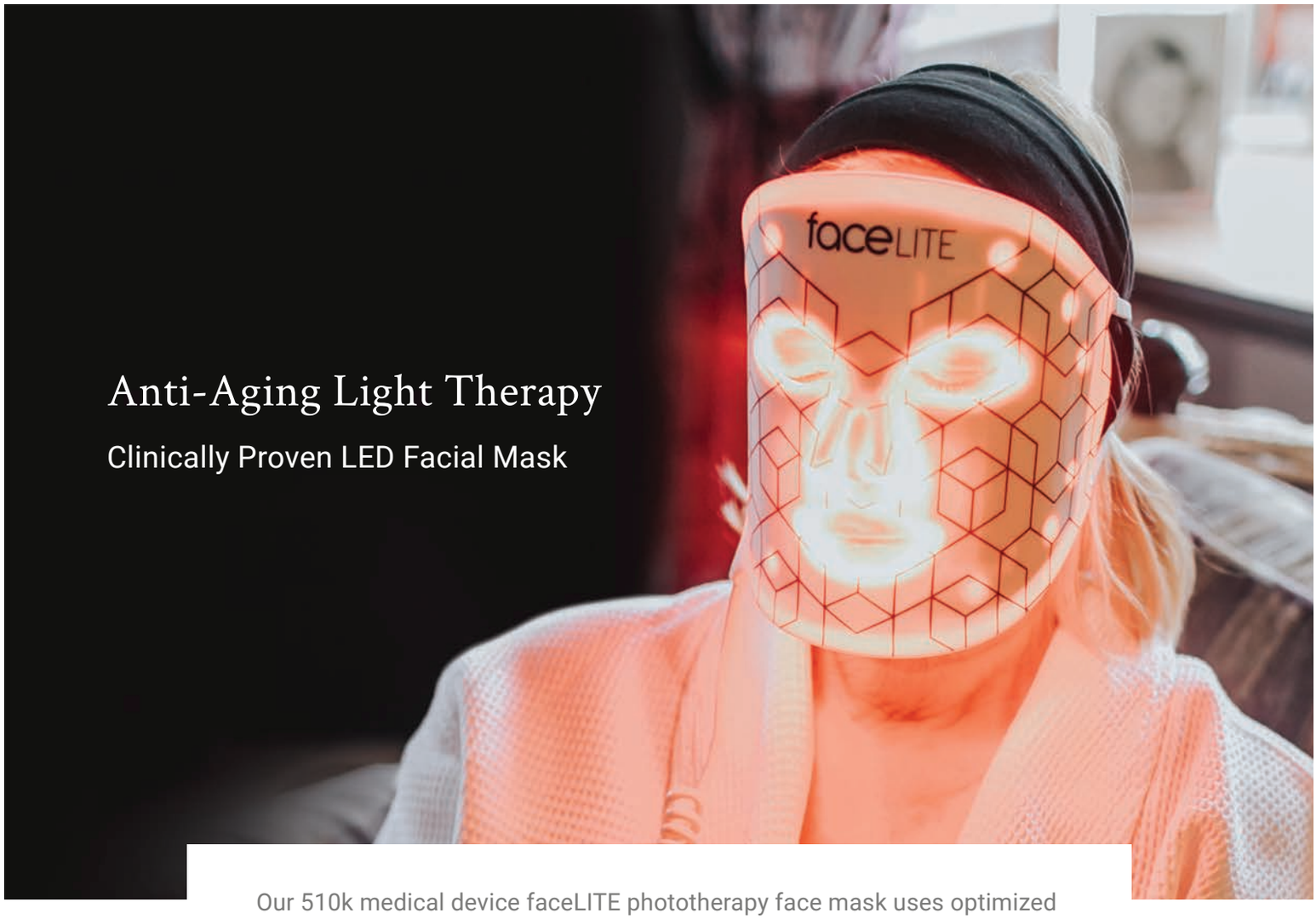

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ORIGINAL CONTRIBUTION

Fractional Ablative Laser-Assisted Photodynamic Therapy as Field Treatment for Actinic Keratoses: Our Anecdotal Experience

Jordan V. Wang, MD, MBE, MBA;[1] Thomas D. Griffin, MD[2]

ABSTRACT

Actinic keratoses (AKs) are common skin lesions that are often considered to be precancerous markers for the future development of skin cancers. There are various treatment options, including cryotherapy, imiquimod, 5-fluorouracil, curettage, lasers, and photodynamic therapy (PDT). Laser-assisted drug delivery, using the combination of a fractional ablative laser with PDT, is an effective therapy. Our clinical experience with six patients demonstrates that the combination of fractional ablative 2,940 nm erbium:yttrium-aluminum-garnet laser with blue light PDT is safe and effective for the field treatment of AKs. (*SKINmed*. 2020;18:214–216)

Actinic keratoses (AKs) are common skin neoplasms that are considered to be precancerous lesions and markers for the future development of cutaneous malignancy. Many treatment modalities currently exist, including cryotherapy, imiquimod, 5-fluorouracil, ingenol mebutate, curettage, chemical peels, lasers, and photodynamic therapy (PDT). Laser-assisted drug delivery (LADD) has recently been pioneered and studied in the management of various skin disorders, including AKs, squamous cell carcinomas, basal cell carcinomas, scars, vitiligo, melasma, hemangiomas, warts, and photoaging.[1–5]

In LADD, a predetermined area of skin is first treated with a laser, such as the 10,600 nm carbon dioxide (CO_2) laser or the 2,940 nm erbium:yttrium-aluminum-garnet (Er:YAG) laser. This creates tiny microchannels in the skin, termed microscopic treatment zones (MTZs), which can more readily uptake topical medications.[6,7] The MTZs allow the drug to penetrate through the laser breakdown of the stratum corneum and increase its local absorption and bioavailability. Soon after the laser treatment, the topical medication is applied.

Laser settings (e.g., wavelength, fluence, pulse width, and spot size) can influence MTZ characteristics, such as depth and density; in turn, both laser settings and drug properties (e.g., vehicle type, lipophilic vs. lipophobic, and pH) can impact drug delivery. LADD has been paired with topical medications, including imiquimod, 5-fluorouracil, ingenol mebutate, bleomycin, cisplatin, vismodegib, timolol, bimatoprost, corticosteroids, and poly-L lactic acid.

Recently, LADD has combined fractional ablative resurfacing with the application of 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) for PDT in the treatment of premalignant and malignant keratinocytic neoplasms.[8–12] Studies have demonstrated the superiority of a single session of LADD, compared to either single or multiple sessions of PDT monotherapy. In addition to the destruction of the epidermis and the superficial portion of the dermis caused by the laser, there is also an increased uptake of the ALA or MAL, which can stimulate a stronger response by either blue or red light PDT.

Ablative fractional lasers can change the kinetics and biodistribution of ALA and MAL, with ALA favoring targeting of deep structures.[13] With an increasing use of LADD in dermatology, we decided to use it in our patients as a field treatment for AKs. We present our experiences with six patients undergoing treatment with fractional ablative laser-assisted PDT.

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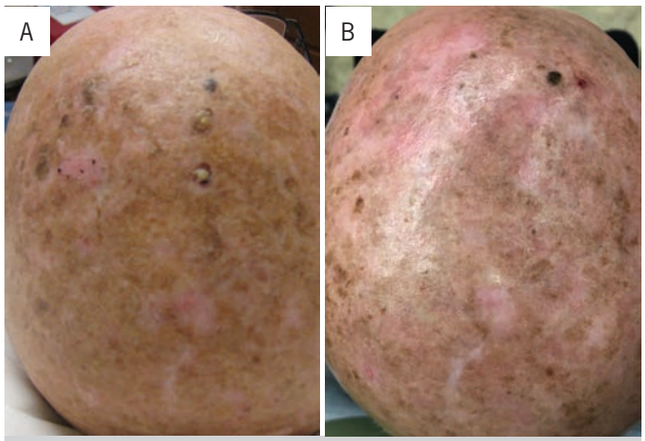

Figure 1. Patient 1 before (A) and several weeks after (B) treatment with fractional ablative laser-assisted photodynamic therapy.

CLINICAL EXPERIENCE

In total, six patients were treated using a fractional ablative 2,940 nm Er:YAG laser (ProFractional, Sciton, Palo Alto, CA). Patient 1 was treated using two passes (5.5% density, 250 um) to the entire scalp with an additional pass (5.5% density, 400 um) for thicker lesions (Figure 1). Patients 2 and 3 were treated using two passes (5.5% density, 100 um) to the entire forehead, with an additional pass using the same settings for thicker lesions (Figure 2). Patient 4 was treated using a single pass (5.5% density, 50 um) to the entire face. Patient 5 was treated using a single pass (5.5% density, 100 um) to the distal arms. Patient 5 had a history of squamous cell carcinomas on his arms and also had numerous AKs that were recalcitrant to multiple courses of topical 5-fluorouracil. Patient 6 was treated using a single pass (11% density, 150 um) to the entire face (Figure 3).

After laser treatment, ALA 20% was applied under occlusion to the designated area for 45 minutes, followed by blue light PDT. With a single treatment session, all patients experienced >95% clearance in AKs and improved satisfaction with their clinical appearance. Side-effect profile was similar to that of PDT monotherapy.

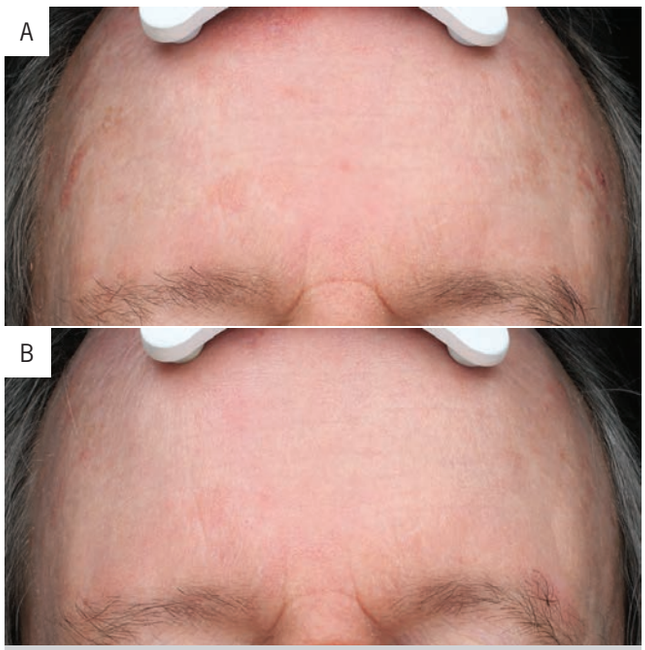

Figure 2. Patient 3 before (A) and 1 year after (B) treatment with fractional ablative laser-assisted photodynamic therapy.

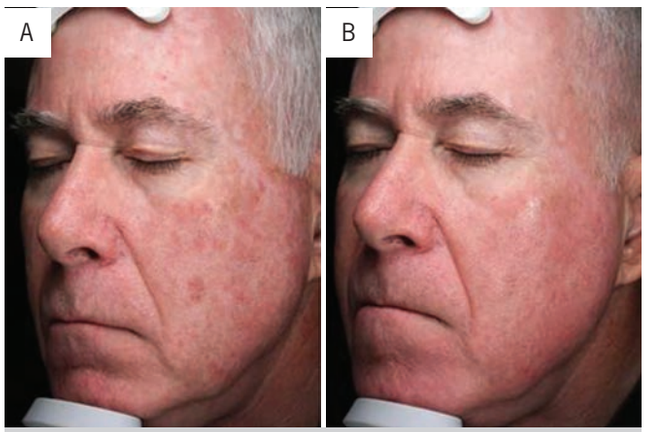

Figure 3. Patient 6 before (A) and 2 months after (B) treatment with fractional ablative laser-assisted photodynamic therapy.

DISCUSSION

Our limited series of patients supports the combination of fractional ablative resurfacing and ALA-PDT for the safe and effective field treatment of AKs on the various sites of the body. Although the scalp is often recalcitrant to topical 5-fluorouracil due to the thickness and depth of lesions, laser-assisted PDT ensures quick healing, with no patient complaints. Fractional ablative treatments, farther off the face, require more healing time. The face takes about 1 week to heal with significant redness for a few days, while the arms require a much longer healing time. Laser settings should be adjusted to obtain the desired depth based on skin thickness of the treatment site.

Fractional ablative laser pretreatment for the creation of MTZs can increase the uptake of topical medications and can improve

topical drug delivery. Various studies have demonstrated the safety and efficacy of laser-assisted PDT in the treatment of keratinocytic neoplasms, and our experience mirrors those in the literature. Our patients also demonstrate that improvements in cosmesis can be attained, which can ensure greater patient satisfaction. Following this positive experience, we look forward to future trials of LADD for treating other cutaneous disorders in our patients.

CONCLUSIONS

LADD using the combination of fractional ablative 2,940nm Er:YAG laser with blue light ALA-PDT is safe and effective for the field treatment of AKs. Further research should investigate the use of LADD for the treatment of other common skin disorders.

DISCLOSURE

Thomas D Griffin, MD, is a consultant for Sciton.

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ORIGINAL CONTRIBUTION

Cutaneous Manifestations of COVID-19: A Report from the United Arab Emirates

Ibrahim Galadari, MD; Amani Al Marzooqi, MD; Ayman Al Naeem, MD; Suad Ali, MD; Meera Adawi, MD; Hassan Galadari, MD

ABSTRACT

Coronavirus disease of 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). In addition to affecting mainly the respiratory tract, there have been many reported cutaneous manifestations of the disease. A retrospective case series based on history and clinical findings was performed across six hospitals in the UAE, including two field hospitals. A total of 324 patients with COVID-19 were identified and divided into three groups based on the severity of the disease. Forty-five (12.5%) patients had clearly identifiable cutaneous manifestation of COVID-19. Two patients each with alopecia areata and sclerosis of the extremities, respectively, were identified in the second group. Cutaneous manifestations of COVID-19 have been well reported across the literature. The experience in the UAE is similar to that of published reports. The occurrence of other cutaneous manifestations with an underlying autoimmune pathogenesis should raise the possibility of such conditions in those with COVID-19. (*SKINmed*. 2020;18:218–220)

Coronavirus disease of 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). It was first reported from the capital city of Wuhan in Hubei Province of China toward the end of the year 2019.[1] In a span of 3 months, it had eventually spread to more than 200 countries in the world, thus culminating into the ongoing 2019–2020 coronavirus pandemic. On January 30, 2020, the World Health Organization (WHO) first declared it a Public Health Emergency of International Concern (PHEIC) and within few weeks realized the imminent threat to the whole world to declare it a "Pandemic" on March 11, 2020. It is commonly characterized by fever, cough, and dyspnea. Other symptoms reported uncommonly associated with it include malaise, muscle pain, nausea, vomiting, diarrhea, sore throat, loss of smell, and abdominal pain.[2] Although vast majority (more than 90%) of the patients report mild or even no symptoms, approximately 10% of patients are believed to require hospitalization; few of the hospitalized patients progress to develop severe pneumonia and eventually multiorgan failure, and they require intensive care with external support to vital organs.[3]

In the United Arab Emirates (UAE), the first COVID-19-positive patient was reported in January 2020 in a family of four. All four recovered from the condition. Subsequent cases were later reported and began to spread. This mandated a nationwide lockdown in March 2020. To date, at the time of writing this article in May 2020, there have been 35,645 active patients, 243 deaths, and 22,374 recoveries.

There have been reported many positive patients with COVID-19-related skin changes. These include mostly urticaria, drug-related eruptions, and chickenpox-like vesicles.[4] In addition, cutaneous lesions referred to as acute acro-ischemia have been reported as a possible sign of SARS-CoV-2 infection. In this article, we discuss the cutaneous findings that have been reported from the COVID-19 outbreak in the UAE, including a number of newly described sclerotic lesions on the extremities of one patient.

METHODS

A retrospective case series based on history and clinical findings was performed across six hospitals in the UAE, including two field hospitals.

Each patient underwent a complete blood cell count; biochemistry tests for liver and kidney function, erythrocyte sedimentation rate, and levels of ferritin, lactate dehydrogenase, and C-reactive

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protein; coagulation tests, including levels of D-dimer, cryoglobulins, and proteins C and S; urine sediment examination; and autoimmunity tests for antinuclear antibodies. Antineutrophil cytoplasmic antibodies; antiphospholipid antibodies; tests for immunoglobulin (Ig) G, IgM, and IgA (COVID-19 ELISA Kit, Vircell; sensitivity and specificity for IgG and IgM + IgA joint detection of 70% and 98%); and reverse transcriptase–polymerase chain reaction (RT-PCR) by nasopharyngeal swab for SARS-CoV-2 (Viasure SARS-CoV-2 Real-Time PCR Detection Kit, CerTest Biotec; detection limit ≥10 RNA copies per reaction for the ORF1ab and N genes).

Patients with cutaneous manifestations were identified and divided into three groups: asymptomatic (did not require hospitalization), mild-moderate (required hospitalization, but did not require intensive care), and severe (required hospitalization and intensive care). As part of the inclusion criteria, all patients did not have any skin conditions or underlying dermatologic disease. Patients with longstanding conditions, such as psoriasis and atopic dermatitis, were excluded.

RESULTS

A total of 324 patients with COVID-19 were identified. Forty-five (12.5%) patients had clearly identifiable cutaneous manifestation of COVID-19. All patients reported the occurrence of these lesions approximately 10 days (SD ± 2.7 days) after the initial diagnosis.

Patients were divided into three groups:

Group 1 (asymptomatic) had 194 patients. All patients in this group complained of pruritus and xerosis. There was no other skin eruption.

Group 2 (mild-moderate) had 85 patients. Patients who fell in this group complained of urticaria, petechiae, and ecchymoses. In this group, one patient complained of new onset alopecia areata (Figure 1), and one patient, who did not have a history of connective tissue disease, developed a new onset sclerosis of the dorsum hands bilaterally (Figure 2).

Group 3 (severe) had 45 patients. Patients in this group complained of a vesiculobullous eruption and a morbilliform rash (Figure 3). Four patients who were in critical condition in the ICU also developed gangrene in the lower extremities.

DISCUSSION

The UAE declared a major lockdown in March 2020 given the spread of the COVID-19 across the population. The country began to take steps to curb the infection by imposing a strict stay-at-home rule. In addition, movement from and to the country was minimized and restricted for repatriation purposes only. Different facets of society including education and businesses were shifted online.

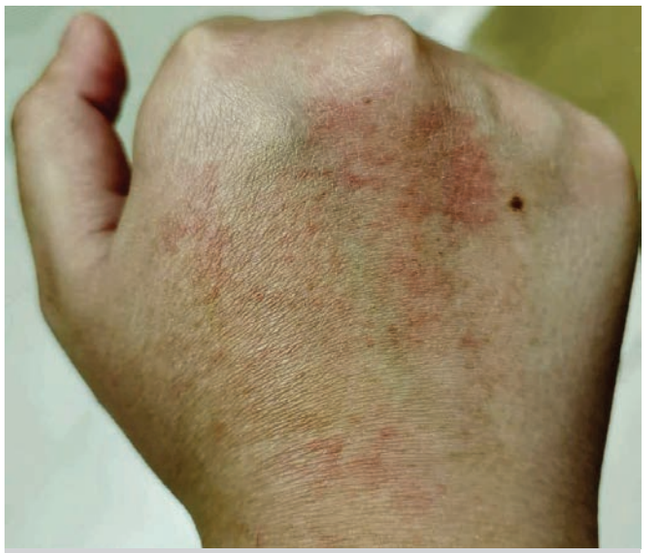

Figure 1. Petechiae and ecchymoses on the dorsum of the hand of a 43-year-old female patient.

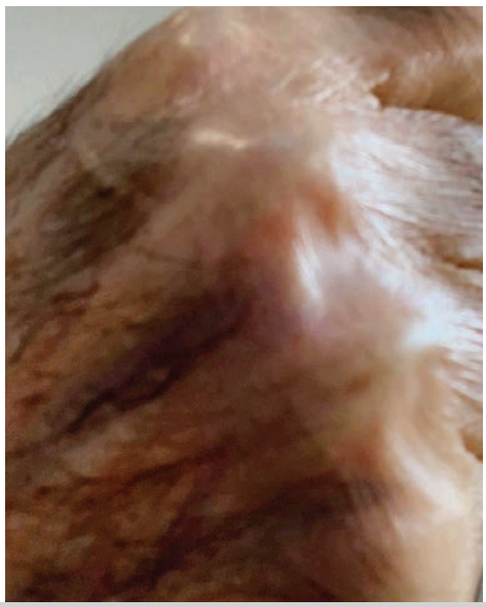

Figure 2. New onset sclerosis of the dorsum hands bilaterally of a 47-year-old male patient.

Given the increasing number of affected patients, reports of diverse cutaneous lesions as possible symptoms of COVID-19 were made. This led to the investigation of the cutaneous

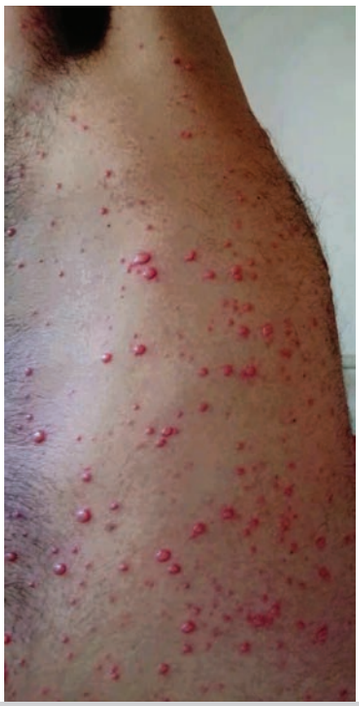

Figure 3. Vesiculobullous eruption in a 32-year-old male patient.

manifestations of the disease by a team of dermatologists. In this article, we report 324 patients with cutaneous lesions that are classifiable based on the severity of the underlying condition.

When evaluating the pathogenesis of these lesions, several possibilities emerge. The number of affected patients reported in the literature has developed in a short space of time, generally with an onset in the second to third week of the pandemic.[5–8]

The findings were consistent with other published reports.[7] The first group included patients who were positive, were asymptomatic, and did not develop specific findings. This group mainly complained of xerosis and pruritus. The second group included patients who were much sicker and required hospitalization. This group did not require intubation or care in an intensive care setting. In the third group, most of the patients had similar reported features such as a vesiculobullous eruption and a morbilliform rash, while two patients each reported alopecia areata and sclerotic changes of skin on the extremities, respectively.

CONCLUSIONS

Although a causal link between SARS-CoV-2 and the appearance of autoimmune and autoinflammatory skin diseases has not yet been firmly established, it is suggested by the temporal association with the current COVID-19 pandemic and the history of exposure of affected patients to SARS-CoV-2 that this may be a possibility.[9] Dermatologists should become aware of this association.

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ORIGINAL CONTRIBUTION

Postinflammatory Hyperpigmentation following Electrodesiccation with a Eutectic Mixture of Local Anesthetics

Rahul Nagar, DNB; Saurabh Dubey, MD; Danish Anwar, MD; Sushil Yadav, MD; Sanjay Khare, MD

ABSTRACT

We assessed the effects of prior application of a eutectic mixture of local anesthetics (EMLA) on the appearance of dyschromia at the site of superficial electrodesiccation in an observer-blind, case–control study in 60 patients. Thirty subjects each were assigned to Groups A and B; both groups underwent radiofrequency (RFC) ablation for facial dermatosis papulosa nigrans (DPN). Group A received RFC ablation with prior application of EMLA, whereas Group B did not. No significant difference was observed in the dyschromia between both groups. EMLA cream was well tolerated by the study participants. (*SKINmed*. 2020;18:222–225)

Dyschromia is one of the most common pigmentary problems encountered in dermatologic practice, especially among persons of color. Epidemiologic studies reveal that dyschromias, including postinflammatory hyperpigmentation (PIH), are among the most frequent reasons for darker-skin racial/ethnic groups seeking the care of a dermatologist.[1] Although this condition is benign, it has a significant psychologic impact on the quality of life. The occurrence of PIH is characterized by increased melanocytic activity and dermal melanophages, whereas hypopigmentation can result from the inhibition of melanogenesis.[2]

The eutectic mixture of local anesthetics (EMLA) cream contains a mixture of lidocaine 2.5% and prilocaine 2.5%,which is useful in minor dermatologic procedures. It is usually well tolerated, but there are reports of irritant and allergic contact dermatitis to the mixture and its individual constituents.[3] EMLA alters keratinocyte structure, dermal vessel diameter, and dermal fibroblast structure and function.[4,5] These properties are significant, because keratinocytes and dermal fibroblasts regulate the function of melanocytes through the paracrine effects.[6] Could EMLA cream influence melanocytes via the modulation of keratinocytes (Figure 1)?[7] No study has implicated EMLA in inducing pigmentary changes; however, there is a single case report of PIH following EMLA.[8]

At our outpatient department (OPD), prior to the removal of superficial cutaneous lesions, such as dermatosis papulosa nigra (DPN) by electrodessication, patients are routinely offered EMLA, because the procedure is well tolerated, even without anesthesia. Apprehensive patients usually prefer the application of EMLA before the procedure, whereas others avoid the anesthetic cream. We studied these patients to assess the effects of EMLA on the appearance of postinflammatory dyschromia.

MATERIALS AND METHOD

The single-center, nonrandomized, open-label, observer-blind, prospective case–control study was performed over a period of 12 months in the Department of Dermatology, Venereology, & Leprosy of Mahatma Gandhi Memorial Medical College, in association with Maharaja Yashwantrao Hospital, Indore, India. Permission was obtained from our institutional ethics committee prior to the initiation of the study. Written informed consent was obtained from all patients for participation in the study, publication of clinical photographs, and the radiofrequency (RFC) procedure.

Patients with DPN over the face were screened for the study. Individuals aged 25–45 years and with Fitzpatrick skin type III/IV were eligible to participate. Those with a history of

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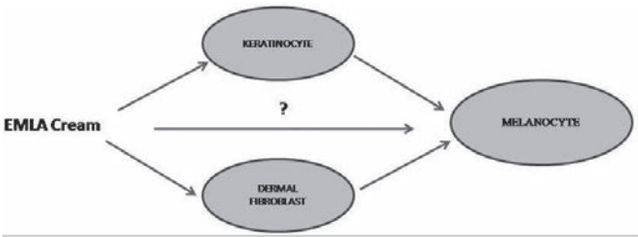

Figure 1. Eeutectic mixture of local anesthetics (EMLA) cream alters keratinocyte and dermal fibroblast structure and function. Furthermore, keratinocytes and dermal fibroblasts regulate the functioning of melanocytes. It is unknown whether EMLA cream influences melanocytes via the modulation of keratinocytes/fibroblasts.

photosensitivity, pacemaker use, keloidal tendency, and excessive sun exposure over the past 6 weeks were excluded. Subjects with thyroid disorders, diabetes mellitus, Addison disease, vitamin B-12 deficiency, or *Herpes simplex* labialis, as well as those taking concomitant medication were also excluded.

Baseline photographs of each patient were taken at the first visit. To avoid biases, all photographs were taken with an external flash using the same lens and the same focal length. A white card was used to maintain the white-balance of the camera [Nikon^{R}D5500 DSLR Camera (Nikon Corporation, Tokyo, Japan), Nikkor 35 mmf/1.8G prime lens, and Nikon SB-300 external flashlight]. A RFC cautery machine was used at 3.7 MHz for the ablation of DPN; for all participants, a ballpoint probe was used for RFC ablation. Also, the same operator performed the procedures for all study participants.

Uniform postprocedural care was provided in the form of the meticulous use of sunscreen and the application of mupirocin ointment over the wounds. Follow-up visits were scheduled in weeks 2 and 4, during which time photographs were taken. When a subject dropped out, a replacement was added to the respective group.

A total of 60 eligible candidates were consecutively recruited into two equal groups [Group A (cases) and Group B (controls)]. Group A received RFC ablation with prior application of EMLA, whereas Group B did not receive EMLA. Detailed personal and clinical histories, including past and present medical history and past and concomitant drug use, were recorded. Hyperpigmentation and hypopigmentation were noted and evaluated for each subject by an independent observer using clinical photographs.

A single brand of EMLA cream (Prilox® cream, Neon, Mumbai, India) was applied under occlusion 30 minutes prior to the procedure.

STATISTICAL ANALYSIS

All qualitative parameters were presented using descriptive statistical methods. Nominal values were expressed as percentages and proportions, and continuous variables were presented as means and standard deviations. Two-sample *t*-tests were used for intergroup comparison of dyschromic lesion counts. Chi-square test was performed to analyze the proportion of subjects who were affected by dyschromias in both the groups.

OBSERVATIONS AND RESULTS

A total of 60 patients, aged 25–45 years, successfully completed the study. The male:female ratio was 7:3. All study subjects had Fitzpatrick skin type III or IV. Baseline characteristics of the study participants are presented in Table 1. The case and control groups were comparable with respect to baseline characteristics.

The lesions were most commonly distributed over the malar region, followed by the temples and the forehead. Of 3269 lesions, 2126 were present over the malar region, whereas 856 and 314 over the temples and the forehead, respectively. The lower half of the face was less commonly involved. Seven of 60 patients complained of itching over the DPN lesions. The sizes of individual DPN lesions were not recorded.

The prevalence of dyschromia in the study group did not differ significantly from controls on statistical analysis (Table 2). Also, there was no significant difference in dyschromia between genders (data not shown). The clinical progression of several participants is shown in Figure 2.

Mild burning and stinging sensation were seen in five patients after the application of EMLA. Immediately after the procedure, the participants all noted mild pain, erythema, and edema, which resolved without any medication. Scarring was present in

Table 1. Baseline Characteristics of the Study Population

	Group A (Cases)	Group B (Controls)
N	30	30
Male	10	8
Female	20	22
Mean age	33	33.3
Number of lesions treated (no. of patients)	1641 (30)	1628 (30)
Mean lesions per person	54.7	54.2

Table 2. Effect of the Application of Eutectic Mixture of Local Anesthetics on the Appearance of Post-procedural Dyschromia

Total Number of Lesions With Change/ (Total Subjects With The Change)	Group A (Cases)	Group B (Controls)	*P*-value* (According To The Number of Affected Patients)**
Hypopigmentation			
Week 2	662 (17)	477 (15)	**0.259 (0.71)**
Week 4	48 (2)	65 (2)	**0.813 (1.0)**
Hyperpigmentation			
Week 2	979 (29)	1151 (29)	**0.293 (1.0)**
Week 4	866 (20)	897 (21)	**0.868 (0.78)**

"Total subjects with the change" may sum up to more than the total study participants because some subjects manifested both hypopigmentation and hyperpigmentation.
Abbreviation: EMLA, eutectic mixture of local anesthetics.
**P*-values obtained from two sample *t*-tests.
***P*-values obtained from Chi-square test.

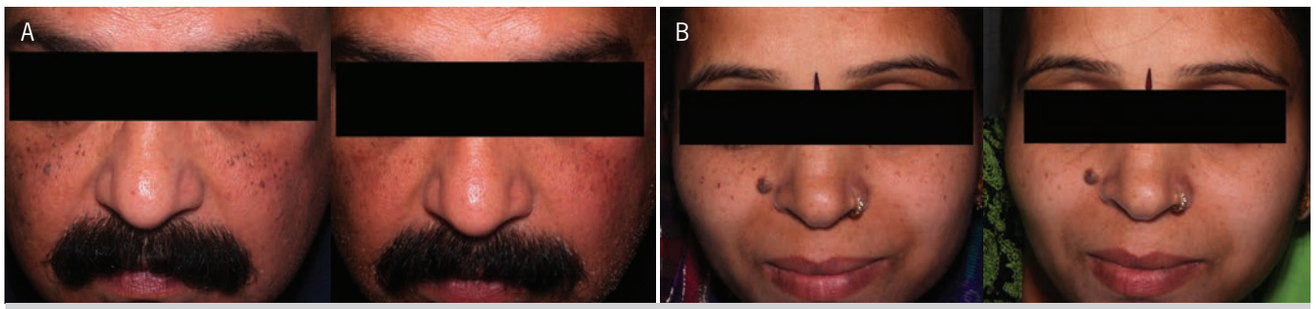

Figure 2. Clinical progression of several study participants. The subject in picture (A) received the eutectic mixture of local anesthetics cream before the procedure, and the subject in picture (B) did not.

two and three patients at the first and second follow-ups, respectively. One patient complained of dryness after 2 weeks of the procedure.

The procedures were well tolerated, and there was no significant intergroup or intragroup variation in side-effect profiles between participants (Table 3).

DISCUSSION

We compared the appearance of postinflammatory dyschromia with the prior use of an anesthetic cream to the nonuse of the same. We did not observe any significant difference in the appearance of dyschromia between the groups. Therefore, we conclude that the application of EMLA cream prior to electrodesiccation for DPN does not increase the likelihood of postinflammatory dyschromia.

No similar study has ever been performed. In darker-skin individuals, any inflammation or injury to the skin can be accompanied by hyperpigmentation or hypopigmentation, on which there is limited information. The term "individual chromatic tendency" (autosomal dominant) has been proposed. Melanocytes can react with normal, decreased, or increased melanin production in response to cutaneous inflammation. People with weak melanocytes are more likely to develop hypopigmentation, and those with strong melanocytes tend to develop hyperpigmentation. PIH is characterized by increased melanocytic activity and dermal melanophages, whereas hypopigmentation can result from the inhibition of melanogenesis.[2]

EMLA is known to induce histologic changes in the skin[4] and to affect dermal fibroblasts and keratinocytes,[5] thereby influencing melanogenesis. Therefore, EMLA might affect melanogenesis and thus the appearance of postinflammatory dyschromia;

Table 3. Number of Subjects with Side Effects

	First Follow-up		Second Follow-up	
Side Effects[a]	Group A	Group B	Group A	Group B
Pain	6	5	2	1
Redness	5	5	1	0
Swelling	0	0	0	0
Crusting	2	3	0	0
Bruising	2	1	0	0
Scarring	1	1	1	2
Dryness	0	1	0	0
Itching	7	9	3	2
Burning	3	2	0	0
Paresthesias	1	0	1	0

[a] Only effects lasting more than a day were recorded here.

however, we did not observe PIH at the site of EMLA application or any influence on the appearance of postinflammatory dyschromia. We selected DPNs as the dermatoses for our study, because they are common, noninflammatory lesions. In our study, women were predominantly affected, and the malar region was the most commonly affected area. These findings are consistent with previous studies.[9]

Our study was limited by its case-control study design and because it employed only an observer-blind assessment. Study photographs were assessed by an independent blinded observer. We did not perform a split-face study, as this would not be ethically appropriate for measuring melanin.

EMLA cream can cause itching,[10] and in such a scenario, scratching could be a confounding factor. EMLA-induced contact urticaria has also been reported.[11] To minimize confounding effects, all subjects were instructed not to scratch their scabs and to apply the mupirocin ointment twice daily over the wound. The ointment base provided an additional moisturizing effect. Subjects who received EMLA prior to their procedure had a greater chance of obtaining higher RFC energies, thereby increasing their risk for postinflammatory dyschromia. To avoid this scenario, all RFC procedures were performed by the same physician, and similar energy modes were used during the procedure.

CONCLUSIONS

The application of EMLA cream does not influence the likelihood of postinflammatory dyschromia. The use of EMLA cream as a topical anesthetic is well-tolerated and convenient.

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Are your patients looking for a well-tolerated treatment they can depend on for the long haul?

RESPONSE THAT LASTS THROUGH WEEK 148

91%

Based on responders at Week 28 who participated in the extension study (reSURFACE 1 and 2)

MAINTAINED PASI 75
THROUGH WEEK 148
in an as-observed analysis[1]*

Co-primary endpoints: PASI 75 and PGA 0/1 with at least a 2-point improvement, both at Week 12[2]

- **After 2 doses**, by Week 12, 64% and 61% achieved PASI 75 (reSURFACE 1 and reSURFACE 2, respectively)
  - vs placebo: 6% (reSURFACE 1) and 6% (reSURFACE 2)
- **After 2 doses**, by Week 12, 58% and 55% achieved PGA 0/1 (reSURFACE 1 and reSURFACE 2, respectively)
  - vs placebo: 7% (reSURFACE 1) and 4% (reSURFACE 2)

DURABLE SAFETY PROFILE

ADVERSE EVENTS[2†]	SERIOUS ADVERSE EVENTS[2†]	LOW DISCONTINUATION RATE DUE TO AEs

Placebo 54% | ILUMYA™ 48%

Placebo 2% | ILUMYA™ 1%

Only 3.4% and 2.3% of patients who entered the extension studies discontinued due to singular-event AEs (reSURFACE 1 and reSURFACE 2, respectively).[4,5]

- **Through Week 148**, ILUMYA™ was well-tolerated with a low rate of adverse events of interest[1‡]
- ILUMYA™ may increase the risk of infection[2]
- The most common (≥1%) adverse reactions associated with ILUMYA™ treatment that were more frequent than in the placebo group are upper respiratory infections, injection-site reactions, and diarrhea[2]

*From a post hoc pooled analysis extension study of reSURFACE 1 and 2. No imputation of missing data.
†From the placebo-controlled period of the trial: Weeks 0–12.
‡AEs of interest include: Serious infections, malignancies, non-melanoma skin cancer, melanoma, extended MACE, deaths, injection site reactions, and drug-related hypersensitivity AEs.
All results based on the recommended 100 mg dose of ILUMYA™.
AE=adverse event; MACE=major adverse cardiovascular events; PASI=Psoriasis Area and Severity Index; PGA=Physician Global Assessment.

reSURFACE 1 and 2 were Phase 3, double-blind, placebo-controlled trials of ILUMYA™ given at Weeks 0, 4, and every 12 weeks thereafter. Patients in reSURFACE 1 (N=463) and reSURFACE 2 (N=463) with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy were randomized to ILUMYA™ 100 mg or placebo. At Week 28, patients in reSURFACE 1 initially randomized to ILUMYA™ who achieved at least PASI 75 were re-randomized to either continue initial treatment or to receive placebo up to 64 weeks. The co-primary endpoints of both trials were: 1) the proportion of subjects who achieved at least PASI 75 and 2) the proportion of subjects with a PGA 0 or 1 and at least a 2-point improvement, both at Week 12. Other evaluated outcomes included PASI 90/100 at Week 12 and PASI 75 at Week 28. reSURFACE 1 also measured maintenance of efficacy in responders up to Week 64.[2,3]

INDICATION

ILUMYA™ (tildrakizumab-asmn) is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

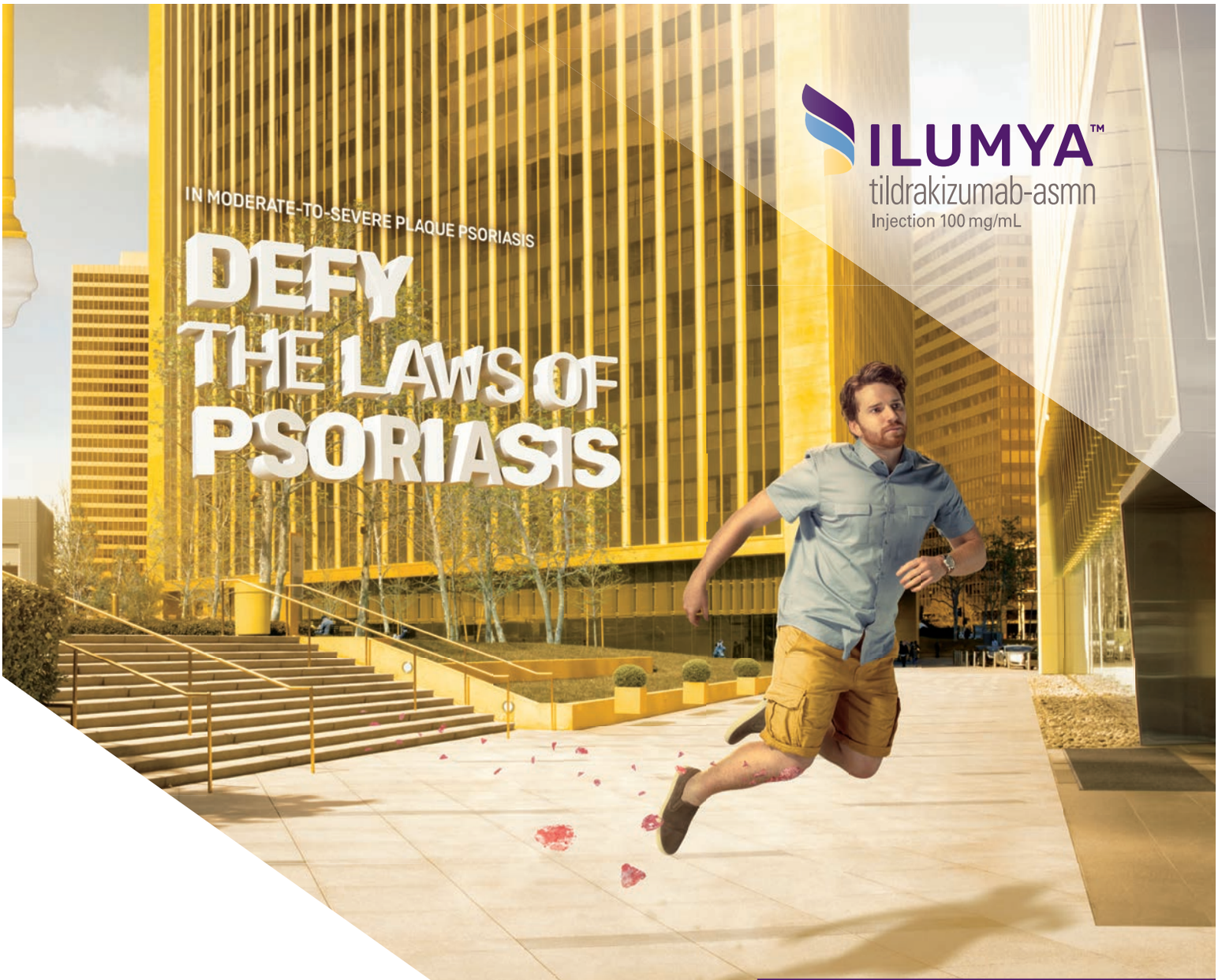
IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ILUMYA™ is contraindicated in patients with a previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity
Cases of angioedema and urticaria occurred in ILUMYA™-treated subjects in clinical trials. If a serious allergic reaction occurs, discontinue ILUMYA™ immediately and initiate appropriate therapy.



ILUMYA™
tildrakizumab-asmn
Injection 100 mg/mL

DISCOVER THE *WHY* BEHIND
DEFY AT **ILUMYAPRO.COM**

Infections
ILUMYA™ may increase the risk of infection. Treatment with ILUMYA™ should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated.

Consider the risks and benefits of treatment prior to prescribing ILUMYA™ in patients with a chronic infection or a history of recurrent infection. Instruct patients receiving ILUMYA™ to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection, or is not responding to standard therapy, closely monitor and consider discontinuation of ILUMYA™ until the infection resolves.

Pretreatment Evaluation for Tuberculosis
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with ILUMYA™. Do not administer ILUMYA™ to patients with active TB infection. Initiate treatment of latent TB prior to administering ILUMYA™. Consider anti-TB therapy prior to initiation of ILUMYA™ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving ILUMYA™ should be monitored closely for signs and symptoms of active TB during and after treatment.

Immunizations
Prior to initiating therapy with ILUMYA™, consider completion of all age-appropriate immunizations according to current immunization guidelines. Patients treated with ILUMYA™ should not receive live vaccines.

Adverse Reactions
The most common (≥1%) adverse reactions associated with ILUMYA™ treatment that were more frequent than in the placebo group are upper respiratory infections, injection-site reactions, and diarrhea.

Please see Brief Summary of Full Prescribing Information on the next page or visit ILUMYApro.com.

References: 1. Thaçi D, Iversen L, Pau-Charles I, et al. Long-term efficacy and safety of tildrakizumab in patients with moderate-to-severe psoriasis who were responders at week 28: pooled analysis through 3 years (148 weeks) from reSURFACE 1 and reSURFACE 2 phase 3 trials. Paper presented at: 27th Congress of the European Academy of Dermatology and Venereology (EADV); September 12-16, 2018; Paris, France. **2.** ILUMYA™ [package insert]. Princeton, NJ: Sun Pharmaceuticals, Inc. **3.** Data on File. Sun Pharmaceutical Industries, Inc. **4.** Tyring SK, Spelman L, Igarashi A, et al. Efficacy and safety of long-term tildrakizumab for plaque psoriasis: 3-year results from reSURFACE 1. Poster presented at: American Academy of Dermatology Annual Meeting; March 1-5, 2019; Washington DC. **5.** Gooderham M, Papp KA, Blauvelt, A, et al. Efficacy and safety of long-term tildrakizumab for plaque psoriasis: 3-year results from reSURFACE 2. Poster presented at: American Academy of Dermatology Annual Meeting; March 1-5, 2019; Washington DC.

SUN DERMATOLOGY

Brief Summary of Prescribing Information for ILUMYA™ (tildrakizumab-asmn)
ILUMYA™ (tildrakizumab-asmn) injection, for subcutaneous use
See package insert for full Prescribing Information

INDICATIONS AND USAGE ILUMYA™ is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS
ILUMYA is contraindicated in patients with a previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS
Hypersensitivity: Cases of angioedema and urticaria occurred in ILUMYA treated subjects in clinical trials. If a serious hypersensitivity reaction occurs, discontinue ILUMYA immediately and initiate appropriate therapy *[see Adverse Reactions]*.

Infections: ILUMYA may increase the risk of infection. Although infections were slightly more common in the ILUMYA group (23%), the difference in frequency of infections between the ILUMYA group and the placebo group was less than 1% during the placebo-controlled period. However, subjects with active infections or a history of recurrent infections were not included in clinical trials. Upper respiratory infections occurred more frequently in the ILUMYA group than in the placebo group *[see Adverse Reactions]*.

The rates of serious infections for the ILUMYA group and the placebo group were ≤0.3%. Treatment with ILUMYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing ILUMYA. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and consider discontinuation of ILUMYA until the infection resolves *[see Adverse Reactions]*.

Pretreatment Evaluation for Tuberculosis: Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with ILUMYA. Initiate treatment of latent TB prior to administering ILUMYA. In clinical trials, of 55 subjects with latent TB who were concurrently treated with ILUMYA and appropriate TB prophylaxis, no subjects developed active TB (during the mean follow-up of 56.5 weeks). One other subject developed TB while receiving ILUMYA. Monitor patients for signs and symptoms of active TB during and after ILUMYA treatment. Consider anti-TB therapy prior to initiation of ILUMYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer ILUMYA to patients with active TB infection.

Immunizations: Prior to initiating therapy with ILUMYA, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid the use of live vaccines in patients treated with ILUMYA. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
Hypersensitivity Reactions *[see Warnings and Precautions]*
Infections *[see Warnings and Precautions]*

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

In clinical trials, a total of 1994 subjects with plaque psoriasis were treated with ILUMYA, of which 1083 subjects were treated with ILUMYA 100 mg. Of these, 672 subjects were exposed for at least 12 months, 587 for 18 months, and 469 for 24 months.

Data from three placebo-controlled trials (Trials 1, 2, and 3) in 705 subjects (mean age 46 years, 71% males, 81% white) were pooled to evaluate the safety of ILUMYA (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 12 weeks [Q12W]) *[see Clinical Studies]*.

Placebo-Controlled Period (Weeks 0-16 of Trial 1 and Weeks 0-12 of Trials 2 and 3)
In the placebo-controlled period of Trials 1, 2, and 3 in the 100 mg group, adverse events occurred in 48.2% of subjects in the ILUMYA group compared to 53.8% of subjects in the placebo group. The rates of serious adverse events were 1.4% in the ILUMYA group and 1.7% in the placebo group.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the ILUMYA group than in the placebo group.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects in the ILUMYA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Trials 1, 2, and 3

Adverse Reaction	ILUMYA 100 mg (N=705) N (%)	Placebo (N=355) N (%)
Upper respiratory infections*	98 (14)	41 (12)
Injection site reactions†	24 (3)	7 (2)
Diarrhea	13 (2)	5 (1)

* Upper respiratory infections include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, and pharyngitis.

† Injection site reactions include injection site urticaria, pruritus, pain, reaction, erythema, inflammation, edema, swelling, bruising, hematoma, and hemorrhage.

During the placebo-controlled period of Trials 1, 2, and 3, adverse reactions that occurred at rates less than 1% but greater than 0.1% in the ILUMYA group and at a higher rate than in the placebo group included dizziness and pain in extremity.

Specific Adverse Reactions
Hypersensitivity Reactions
Cases of angioedema and urticaria occurred in ILUMYA-treated subjects in clinical trials *[see Warnings and Precautions]*.

Infections
Infections were slightly more common in the ILUMYA group. The difference in frequency of infections between the ILUMYA group (23%) and the placebo group was less than 1% during the placebo-controlled period. The most common (≥1%) infections were upper respiratory infections. The rates of severe infections for the ILUMYA group and the placebo group were ≤0.3%.

Safety Through Week 52/64
Through Week 52 (Trials 1 and 3) and Week 64 (Trial 2), no new adverse reactions were identified with ILUMYA use and the frequency of the adverse reactions was similar to that observed during the placebo-controlled period.

Immunogenicity
As with all therapeutic proteins there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to tildrakizumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Up to Week 64, approximately 6.5% of subjects treated with ILUMYA 100 mg developed antibodies to tildrakizumab. Of the subjects who developed antibodies to tildrakizumab, approximately 40% (2.5% of all subjects receiving ILUMYA) had antibodies that were classified as neutralizing. Development of neutralizing antibodies to tildrakizumab was associated with lower serum tildrakizumab concentrations and reduced efficacy.

DRUG INTERACTIONS
Live Vaccinations
Avoid use of live vaccines in patients treated with ILUMYA *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary
Limited available data with ILUMYA use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Human IgG is known to cross the placental barrier; therefore, ILUMYA may be transferred from the mother to the fetus. An embryofetal developmental study conducted with tildrakizumab in pregnant monkeys revealed no treatment-related effects to the developing fetus when tildrakizumab was administered subcutaneously during organogenesis to near parturition at doses up to 159 times the maximum recommended human dose (MRHD). When dosing was continued until parturition, a small increase in neonatal death was observed at 59 times the MRHD *[see Data]*. The clinical significance of this nonclinical finding is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data: *Animal Data*
In an embryofetal developmental study, subcutaneous doses up to 300 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to gestation day 118 (22 days from parturition). No maternal or embryofetal toxicities were observed at doses up to 300 mg/kg (159 times the MRHD of 100 mg, based on AUC comparison). Tildrakizumab crossed the placenta in monkeys.

In a pre- and postnatal developmental study, subcutaneous doses up to 100 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks from gestation day 50 to parturition. Neonatal deaths occurred in the offspring of one control monkey, two monkeys at 10 mg/kg dose (6 times the MRHD based on AUC comparison), and four monkeys at 100 mg/kg dose (59 times the MRHD based on AUC comparison). The clinical significance of these nonclinical findings is unknown. No tildrakizumab-related adverse effects were noted in the remaining infants from birth through 6 months of age.

Lactation: Risk Summary
There are no data on the presence of tildrakizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Tildrakizumab was detected in the milk of monkeys *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ILUMYA and any potential adverse effects on the breastfed child from ILUMYA or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of ILUMYA in pediatric patients (<18 years of age) have not been established.

Geriatric Use: A total of 1083 subjects were exposed to ILUMYA 100 mg during Phase 2 and 3 trials. A total of 92 subjects were 65 years or older, and 17 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

OVERDOSAGE: In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

PATIENT COUNSELING INFORMATION: Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Instruct patients and/or caregivers to read the Medication Guide before starting ILUMYA therapy and to reread the Medication Guide each time the prescription is renewed. Advise patients of the potential benefits and risks of ILUMYA.

Hypersensitivity
Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions]*.

Infections
Instruct patients of the importance of communicating any history of infections to the doctor and contacting their doctor if they develop any symptoms of infection *[see Warnings and Precautions]*.

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SUN PHARMA

NEW THERAPY UPDATE

William Abramovits, MD; Aditya K. Gupta, MD, PhD, FRCPC, Section Editors

Enstilar® (Calcipotriene and Betamethasone Dipropionate) Foam for Plaque Psoriasis in Adolescents Aged 12–17 Years

William Abramovits, MD;[1] Joyce M.C. Teng, MD, PhD;[2] Kimberly Dawn Vincent, MD;[3] Aditya K. Gupta, MD, PhD, FRCPC[1,4,5]

Enstilar® is a topical foam medication composed of the combination of 0.005% calcipotriene (Cal), a vitamin D analog, and 0.064% betamethasone dipropionate (BD), a corticosteroid. It was initially approved by the U.S. Food and Drug Administration (FDA) in 2015 to treat adult patients with plaque psoriasis.[1,2] In pivotal clinical trials in adult patients aged 18 years or older, Cal/BD foam demonstrated superior efficacy over Cal/BD suspension (gel formulation), Cal/BD ointment, Cal, BD, and foam vehicle, as well as a favorable safety profile.[3–6] More recently, Cal/BD foam was evaluated in adolescent patients, aged 12 to <17 years, with plaque psoriasis of the body and scalp in a prospective, multicenter, open-label, single-group, Phase 2 trial (NCT02387853).[7] Favorable results from this study led to the expansion of the Cal/BD foam indication to include adolescent patients aged 12 years or older.[1,8]

INDICATIONS, DOSAGE, AND ADMINISTRATION

Cal/BD foam is indicated for the topical treatment of plaque psoriasis in patients aged 12 years and older.[1] One pressurized aluminum spray can contains 60 g of product, whereby 1 g delivers 50 mcg Cal and 0.643 mg of BD. Cal/BD foam should be self-administered to the affected areas once daily for up to 4 weeks until control has been achieved.[1] The maximum 4-day dose limit is 60 g.[1]

MECHANISM OF ACTION

Corticosteroids (e.g., BD) are thought to exert anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive effects through binding of intracellular glucocorticoid receptors and regulation of gene transcription, particularly genes encoding for pro-inflammatory cytokines.[9] Vitamin D analogs (e.g., Cal) are thought to inhibit the proliferation and promote the differentiation of keratinocytes through binding of vitamin D receptors.[9] The combination of BD and Cal may have synergistic effects in the treatment of psoriasis.[10] Bioavailability is enhanced with the aerosol foam formulation, which enables rapid evaporation of the volatile propellants and supersaturation of the active ingredients.[11]

PHARMACOKINETICS

The metabolites of Cal and BD are MC1080 and betamethasone 17-propionate (B17P), respectively. In adolescent patients (n=33) with psoriasis of the body and scalp treated with Cal/BD foam, very low levels of these metabolites were detected.[7] The full B17P pharmacokinetic profile was quantifiable in only one patient, while Cal and MC1080 were not detectable in any patient sample, suggesting minimal systemic exposure to both Cal and BD.[7] In adult patients (n=35) with psoriasis of the body and scalp treated with once-daily Cal/BD foam for 4 weeks, mean maximal serum concentrations (Cmax) of BD and B17P (quantifiable in five and 27 patients, respectively) have been reported to be 52.2 pg/mL and 147.9 pg/mL, respectively.[1] Cmax of Cal and mean Cmax of MC1080 (quantifiable in one and three patients, respectively) were 55.9 pg/mL and 24.4 pg/mL, respectively.[1]

Enstilar® is manufactured by LEO Laboratories Ltd. (Dublin, Ireland) and distributed by LEO Pharma Inc. (Madison, NJ, USA). It is available in 60-g spray cans.

From the Dermatology Treatment & Research Center and Department of Dermatology, Baylor University Medical Center and the University of Texas Southwestern School of Medicine, Dallas, TX;[1] Department of Dermatology, Stanford University School of Medicine, Palo Alto, CA;[2] Belle Meade Dermatology, Nashville, TN;[3] Division of Dermatology, Department of Medicine, University of Toronto School of Medicine, Toronto, ON, Canada;[4] Mediprobe Research, London, ON, Canada[5]

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CLINICAL STUDY IN ADOLESCENT PATIENTS

The Phase 2, multicenter, open-label, noncontrolled, 4-week study (NCT02387853) conducted in 106 adolescent patients (aged 12 to <17 years) with at least mild psoriasis on the body and scalp evaluated the safety and efficacy of once-daily Cal/BD foam in the treatment of plaque psoriasis.[7] The patients' mean age was 14.2 years, and 43% of the patients were male. Disease severity on the body, as assessed by the Physician's Global Assessment (PGA), was moderate for 76% and severe for 2% of the patients; on the scalp, it was moderate for 73% and severe for 13% of the patients.

Patients in the hypothalamic–pituitary–adrenal (HPA) axis cohort (n = 34) were required to have greater disease severity (≥10% body surface area [BSA] involvement, ≥20% scalp surface area involvement, and PGA ≥ moderate) and normal baseline adrenal function (measured using the adrenocorticotropic–hormone [ACTH] challenge test).[7] Weekly dose of Cal/BD foam in this cohort was not limited.[7] The remaining 72 patients were enrolled in the non-HPA cohort, in which patient dosage was based on age and BSA: patients aged 12 to <15 years with BSA ≤1.3 m^2 or >1.3 m^2 received 60 g or 90 g per week, respectively, and patients aged ≥15 to <17 years with BSA ≤1.7 m^2 or >1.7 m^2 received 90 g or 120 g per week, respectively.[7] Baseline demographics were similar between the HPA-axis and non-HPA cohorts.[7] Primary endpoints included treatment-emergent adverse events (TEAEs) and albumin-corrected serum calcium concentration from baseline to week 4 in the overall population, and serum cortisol concentration in the HPA-axis cohort.[7] Secondary endpoints included assessments of the efficacy of Cal/BD foam in the overall population and in the HPA-axis cohort.[7]

SAFETY/ADVERSE EVENTS

In the Phase 2 study, TEAEs occurring in ≥1% of patients included upper respiratory tract infection, nasopharyngitis, and acne (Table 1).[7] Few TEAEs were considered related or possibly related to treatment; the ones that were included acne, erythema, skin reaction, application site pain, product physical consistency issue, and myopia. Local reactions were either mild or moderate and improved in intensity over time; no moderate local reaction was observed at week 4 (Table 1).[7] No serious or severe TEAEs were reported, and there were no fatalities.[7] The TEAE profile in adolescents was consistent with that reported in adults.[7]

Assessments of albumin-corrected serum calcium concentration at week 4 showed a mean change of –0.016 mmol/L (standard deviation [SD], 0.119) from baseline for the overall population.[7] In the HPA-axis cohort, changes from baseline in excreted urinary calcium (Table 2) were not considered to be clinically relevant or different from those observed in other studies of calcium homeostasis.[7] All patients in the HPA-axis cohort had normal 24-hour urinary calcium: creatinine ratio at baseline and week 4.[7] Only two evaluable patients had slight decreases in serum cortisol, which normalized at 60 minutes post-ACTH challenge, suggesting no clinical relevance. These changes did not appear to be associated with BSA, pharmacokinetic parameters, or the amount of Cal/BD foam consumed.[7]

EFFICACY

Treatment success was defined as a PGA rating of "clear" or "almost clear" at week 4 in patients whose baseline PGA score indicated moderate or severe disease, and of "clear" in patients with a baseline PGA score indicating mild disease. Rates of PGA treatment success for body and scalp psoriasis were 71.8% and 75.7%, respectively, in the overall population.[7] The respective rates for treatment success according to the Patient's Global

Table 1. Treatment-Emergent Adverse Events by Preferred Term, and Local Safety Profile of Cal/BD Foam[7]

Adverse event/local reaction	Subjects (N = 106)
Treatment-emergent adverse events occurring in ≥1% of subjects at week 4, n (%)	
Upper respiratory tract infection	8 (7.5)
Nasopharyngitis	4 (3.8)
Acne	2 (1.9)
Local safety and tolerability profile, baseline/week 2/week 4, %[a]	
Erythema	
Mild	4.7 / 5.8 / 3.9
Moderate	2.8 / 1.0 / 0
Dryness	
Mild	4.7 / 3.9 / 3.9
Moderate	3.8 / 2.9 / 0
Erosion	
Mild	0.9 / 1.9 / 0
Moderate	0.9 / 0 / 0
Edema	
Mild	0.9 / 1.0 / 0
Moderate	0.9 / 0 / 0

[a]≤2 cm from border of treated lesion.

Table 2. Calcium Metabolism in the HPA-Axis Cohort From Baseline to Week 4[7]

Level (baseline, week 4)	24-Hour Urinary Calcium Excretion (n = 34)[a]	24-Hour Urinary Calcium:Creatinine Ratio (n = 34)[a]
Low, Low	14	0
Low, Normal	3	0
Normal, Low	9	0
Normal, Normal	6	31

Abbreviation: HPA, hypothalamic–pituitary–adrenal.
[a]Includes only those patients with laboratory parameter values below, within, or above the reference range.

Assessment (PaGA; defined as "clear" or "very mild") were 83.5% and 81.6%.[7] PGA and PaGA treatment success rates at week 4 for both body and scalp were higher in the HPA-axis cohort than in the non-HPA cohort (Table 3).[7] The PGA treatment success rates were higher than those reported in adult trials[1] and may potentially be attributed to a high compliance rate among the adolescent patients (95.3% with no missed application).[7]

The mean change in scores on the Psoriasis Area and Severity Index (PASI) were consistent with the PGA and PaGA treatment success results, with 59.1% (95% confidence interval [CI]: 54.7%, 63.5%) and 82.0% (95% CI: 78.6%, 85.5%) reductions by week 2 and week 4, respectively.[7] Mean PASI reductions were similar between the HPA-axis and the non-HPA cohorts at both week 2 and week 4 (Table 3).[7] For itch, the mean change from baseline in itch intensity score on the visual analog scale (VAS) at week 4 in the overall population and in the HPA-axis and non-HPA cohorts was –32.5, –42.5, and –27.7, respectively (Table 3).[7]

DISCUSSION

In July 2019, the FDA approved the use of Cal/BD foam in adolescent patients aged 12 years or older.[8] The expansion of the indication was based on the results of the Phase 2 study described here, which demonstrated that Cal/BD foam was safe and well tolerated in adolescent patients with psoriasis. Systemic exposure to Cal and BD metabolites was minimal. The TEAE profile was comparable to that reported in the adult population, and no clinically relevant abnormal changes in calcium metabolism or serum cortisol occurred. Cal/BD foam also appeared to be effective in these adolescent patients, with a reported rate of PGA treatment success of more than 70%, along with

Table 3. Cal/BD Foam Efficacy in Adolescent Patients[7]

Endpoint	Full Analysis Set (n = 106)	Non-HPA Cohort (n = 72)	HPA-Axis Cohort (n = 34)
Patients achieving PGA treatment success, %			
Week 2, body/scalp	30.1/40.8	28.6/32.9	33.3/57.6
Week 4, body/scalp	71.8/75.7	61.4/65.7	93.9/97.0
Patients reporting PaGA treatment success, %			
Week 2, body/scalp	46.6/52.4	50.0/44.3	39.4/69.7
Week 4, body/scalp	83.5/81.6	78.6/74.3	93.9/97.0
Mean change in PASI scores from baseline, %			
Week 2	–59.1	–59.9	–58.7
Week 4	–82.0	–85.9	–80.2
Mean itch score (assessed using visual analog scale)			
Baseline	39.3	43.5	37.3
Week 2	10.2	10.7	9.9
Week 4	6.5	1.0	9.1

Abbreviations: HPA, hypothalamic–pituitary–adrenal; PGA, Physician's Global Assessment; PaGA, Patient's Global Assessment; PASI, Psoriasis Area and Severity Index.

improvements in PASI score (82% reduction) and itch intensity (32.5-point reduction in VAS scores). Taken together, these results provide evidence that Cal/BD foam can be an important treatment option for adolescent patients with psoriasis.

To date, few clinical trials have been conducted in pediatric patients with psoriasis, and therefore clinicians often resort to using many of the available treatment options, off-label, for their younger patients.[10] The most recent joint guideline from the American Academy of Dermatology and the National Psoriasis Foundation for the management of pediatric psoriasis supports the use of products containing a combination of Cal and BD, such as Cal/BD ointment and topical suspension.[10] Cal/BD foam is not among the recommended treatment options, as the timing of the guideline development and its subsequent publication (November 2019) may have precluded consideration of the Phase 2 clinical trial data.

In adults, the foam formulation of Cal/BD has demonstrated superior efficacy to that of its fixed-combination counterparts of ointments and suspensions.[12] The availability of a fixed-dose combination product may improve compliance and effectiveness in adolescent patients, similar to those seen in the Phase 2 study. For psoriasis in such locations as the scalp, hands, and feet, application of foam may be preferred. For the appropriate adolescent patient, Cal/BD foam is an option to be considered prior to initiating systemic therapy. In addition, in those who do require systemic therapy, use of concurrent optimized topical treatment may be considered to reduce the dosage and duration of treatment with the systemic agent. The new expanded indication for Cal/BD foam provides both patients and physicians an important treatment option for managing psoriasis.

CONCLUSIONS

The extension of this Cal/BD foam indication to adolescents aged 12 to <17 years should provide an additional option for this age group.

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RHYTIDECTOMY: A SOCIAL MEDIA ANALYSIS

Adam Honeybrook, MB, BS

Department of Otolaryngology, Louisiana State University Health Sciences Center, New Orleans, LA

Very few studies have been published on patient satisfaction with the facelift procedure. Data were extracted from 1876 consecutive rhytidectomy online reviews from RealSelf®. The majority of reviewers were women (88.3%) aged 60–69 years (40.1%). The predominant reasons behind reviewers choosing their surgeons were related to favorable surgeon personality/demeanor (20.0%) and to having established a positive rapport (17.7%). Of the reviewers, 85.0% (1045) believed surgery was "worth it," 0.7% (8) were undecided, and 14.4% (177) did not consider it worthwhile. The main reasons for those who liked their surgical outcome were related to looking younger and "fresher" (31.1%) and to looking natural (18.4%). Many patients chose their surgeon based on favorable personality traits and emotional connections.

UNRECOGNIZED FACIAL PYODERMA GANGRENOSUM—A RARE COMPLICATION OF MOHS MICROGRAPHIC SURGERY

Patrick M. Zito, DO, PharmD

Department of Dermatology & Cutaneous Surgery, Larkin Community Hospital—Palm Springs, Hialeah, FL

Pyoderma gangrenosum (PG) is a rare, inflammatory skin condition with ulcerative lesions. There is no standard treatment protocol for facial PG. An 85-year-old patient underwent Mohs micrographic surgery and subsequently developed a painful progressive ulcer at the surgical site, which was treated with debridement and negative pressure without improvement. Biopsies were consistent with PG without systemic disease, for which he was treated with topical tacrolimus, systemic corticosteroids, and cyclosporine, with total resolution by the eighth week.

PRIMARY CUTANEOUS ANAPLASTIC LARGE-CELL LYMPHOMA IN A PATIENT WITH LONGSTANDING STABLE PATCH STAGE MYCOSIS FUNGOIDES

Jeave Reserva, MD;[1] Kumaran Mudaliar, MD;[2] Madhu Dahiya, MD;[3] David Eilers, MD[1]

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Primary cutaneous anaplastic large-cell lymphoma (pcALCL) is a CD30+ T-cell lymphoproliferative disorder (CD30+ LPD) that manifests as recurrent solitary or multifocal nodules on the head, neck, or extremities, and is associated with a favorable prognosis. Distinguishing this entity from its histologic mimic CD30-rich transformed mycosis fungoides (MF) is crucial, given the latter's association with poor outcomes. We present a patient with pcALCL coexistent with patch stage MF, highlighting the importance of longitudinal clinicopathologic correlation in the diagnosis and management of CD30+LPD.

DISSEMINATED PRESENTATION OF ORF DISEASE IN A BURN PATIENT

Betul Macit, MD;[1] Fatih Göktay, MD;[1] Sema Aytekin, MD;[1] Pembegül Güneş, MD[2]

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Orf is caused by a parapoxvirus that commonly infects sheep, goats, and cows. Human infection is due to contact with an infected animal or fomites. We present a patient with disseminated orf disease who sustained a burn following a tanker explosion. Orf following extensive burns is an unusual situation.

THE CONTENTS OF THE ESTHETIC UNIT OF BOTULINUM NEUROTOXIN–A PRODUCTS

Tiffany Alexander, MD

Department of Dermatology, Duke University Medical Center, Durham, NC

The amount of total protein and pure neurotoxin in botulinum neurotoxin–A products for the FDA-approved esthetic glabellar doses was studied. A systematic review and personal correspondence with industry leaders were performed to determine the contents of an esthetic unit of the available approved toxins. The FDA-approved esthetic glabellar doses of onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxin A, daxibotulinumtoxin A, and prabotulinumtoxin A are 20 units, 50 units, 20 units, 40 units, and 20 units, respectively. The amount of total protein for each is 1.00 ng, 0.43 ng, 0.08 ng, >0.2 ng, and 1.00 ng, respectively. The neurotoxin amounts are 0.18 ng, 0.33 ng, 0.08 ng, 0.18 ng, and 0.15 ng, respectively. Based on this analysis, it was determined that abobotulinum contains the highest amount of neurotoxin protein per esthetic dose injected, and incobotulinum contains the least.

COSMETIC RED EYE RELIEF: CURE OR CURSE?

Peter M. Kally, MD;[1] Ann Q. Tran, MD;[1,2] Andrea A. Tooley, MD;[1,2] Eleanore Kim, MD[1]

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Red or bloodshot eyes can be a distressing concern to the cosmetic patient. The condition is frequently treated with topical, over-the-counter redness relief drops. The current medications consist of active decongestants with varying alpha-adrenergic receptor-binding activity. Such agents, which are often abused, comprise the following agents listed from low to high: brimonidine, naphazoline, tetrahydrozoline, and phenylephrine. These medications can cause rebound redness, ocular irritation, tachyphylaxis, and carry the risk of provoking angle-closure glaucoma. Unfortunately, their use can mask signs of active infectious or inflammatory disease, delaying treatment. Given these risks, the American Academy of Ophthalmology instead recommends the use of preservative-free artificial tears as first-line treatment.

PREDICTORS OF SUN PROTECTIVE BEHAVIOR OF FLORIDA RESIDENTS

Sergey Arutyunyan, DO

Dermatology Resident, Larkin Community Hospital, Miami, FL

A total of 619 Florida residents, aged 18 years or older, were recruited to complete an anonymous, cross-sectional survey that consisted of 79 questions on knowledge, attitudes, and sun-protective behaviors. Multiple regression analysis revealed that being more educated (95% CI = 0.15–0.79, $p < 0.004$), having a lighter color of untanned skin (95% CI = 0.74–1.6, $p < 0.001$), performing skin self-exam (95% CI = 1.26–3.09, $p < 0.001$), having high salience of skin cancer risk (95% CI = 0.22–0.44, $p < 0.001$), having more positive attitudes toward sun protection (95% CI = 0.55–0.78, $p < 0.001$), and having increased perceived vulnerability to skin cancer (95% CI = 0.14–0.62, $p < 0.002$) predicted sun-protective behaviors. With additional research, encouraging attitudinal change may be a viable strategy to improve sun-protective behaviors.

SAFETY OF COMPOUNDED TRIAMCINOLONE FOR INTRADERMAL AND SUBCUTANEOUS INJECTION

Chelsea A. Luther, MD

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Intralesional injection of sterile medications remains an integral practice in dermatology. This study assesses infection associated with in-office intralesional triamcinolone. A retrospective chart review identified Henry Ford Dermatology subjects who received in-office intralesional corticosteroid injections in 2016. Medical documentation within 30 days of injection was reviewed for cases of clinician suspected infection. Eleven suspected localized infections occurred across the 3,174 intralesional triamcinolone injections assessed by chart review, giving an infection rate of 0.6%. Of these, 7/11 occurred after injection of an "inflamed cyst." In-office compounding for dermal and subcutaneous administration yields a low infection rate.

SKIN WOUNDING AND WOUND INFECTION ALTERS BEHAVIOR AND COGNITION IN MICE

Yasmin Hadian, MS;[1,2] Daniel R. Fregoso;[1] Melanie G. Gareau, PhD;[3] R. Rivkah Isseroff, MD[1,2]

[1]Department of Dermatology, University of California at Davis, School of Medicine, Davis, CA; [2]Dermatology Section, Northern California Health Care System, Mather, CA; [3]Department of Anatomy, Physiology, Cell Biology, School of Veterinary Medicine, University of California at Davis, Davis, CA

The hypothesis that a wound/wound infection contributes to cognitive impairment and depressive behaviors was tested, using wounded mice infected with *Pseudomonas aeruginosa,* a common wound pathogen. Wounded, wounded/infected, or unwounded control C57Bl mice were examined with the forced swim test for depressive behavior,[1] light/dark box test for anxiety,[2] and novel object recognition test for decreased memory.[3] Wounded and wounded/infected animals exhibited increased depressive behavior, increased anxiety, and decreased cognition relative to unwounded animals. Pain medication did not alter findings. Recognition of the role of the skin–microbiota–brain axis in cognitive function may improve outcomes of patients with chronic, infected wounds.

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PHOTO CAPSULE

Snejina Vasilleva MD, PhD, Section Editor

A Reticulated Eruption of the Trunk

Anissa Zaouak, MD; Houda Hammami, MD; Samy Fenniche, MD

A 23-year-old woman with a medical history of esophageal atresia, which was treated surgically in the neonatal period, was referred to our department for a papular reticulate pigmented eruption on the trunk, present for 2 months. There were no similar afflictions in her family, and she was not obese. There had been no treatment prior to her developing the papular eruption.

Dermatologic examination of the trunk revealed multiple pigmented macules and papules with a scaly surface and peripheral reticulate pattern (Figure 1). She had no acne, hirsutism, or acanthosis nigricans. Dermatoscopy using the DermLite DL4 revealed a pigmented background with brown polygonal globules separated by whitish striae creating a cobblestone pattern (Figure 2). Direct mycologic examination was unremarkable. A skin biopsy showed compact hyperkeratosis with parakeratosis and hyperpigmentation of the basal layer and a perivascular mononuclear infiltrate in the upper portion of the dermis. Laboratory tests, including fasting blood sugar and thyroid function, were normal. We then diagnosed reticulated papillomatosis of Gougerot-Carteaud. She was treated with doxycycline 100 mg daily for 1 month with a significant improvement in her skin condition.

DISCUSSION

Reticulated papillomatosis of Gougerot-Carteaud is an acquired keratinization disorder of unknown etiology.[1] It classically presents with asymptomatic gray-brown scaly flat papules that coalesce into larger patches with a reticular pattern at the edges and mainly affects the trunk.[2] The diagnosis of this rare dermatosis relies mainly on the clinical presentation with histopathologic confirmation. Dermatoscopic examination, as an adjuvant tool, would show homogenous flat globules separated by whitish scales on a fair pigmented background and a cobblestone pattern.[2] The differential diagnosis includes tinea versicolor, lichen planus pigmentosus, Dowling-Degos disease, and terra firma-forme dermatosis.[1,2]

In our patient, tinea versicolor was ruled out, because a mycologic examination was negative. In lichen planus pigmentosus,

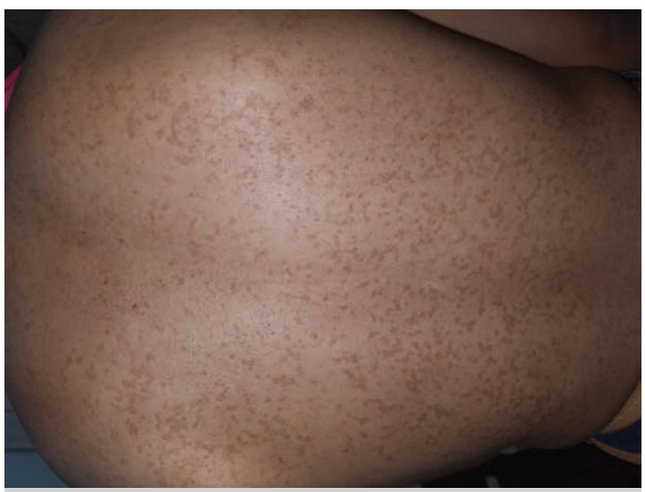

Figure 1. Multiple pigmented macules and papules on the trunk with a scaly surface and peripheral reticulate pattern.

Figure 2. Clear visualization of pigmented background with ill-defined borders, whitish scales, and flat brown globules in a cobblestone pattern (DermLite DL4) (×20).

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dermatoscopy usually shows dots or a globular pattern with yellow-brown pigmentation and structureless brownish areas.[3] Dowling-Degos disease is characterized in dermatoscopy by the regular arrangement of brown spots with star-shaped hyperpigmented outline on a diffuse light brown background.[4] Terra firma-forme dermatosis usually shows in dermatoscopy large polygonal, plate-like brown scales arranged in mosaic pattern[5] There are other treatment alternatives, such as oral retinoids or antifungals, as well as topical treatments with corticosteroids or antifungals. Recurrences are often observed after therapy discontinuation.[1]

Confluent and reticulated papillomatosis of Gougerot-Carteaud is known to be associated with polycystic ovarian syndrome in women. Some patients may have impaired glucose tolerance, hyperinsulinemia, or diabetes mellitus.[6,7]

CONCLUSIONS

When flat pigmented globules separated by whitish scales on a light brown pigmented background are seen in dermatoscopy, the diagnosis of confluent and reticulated papillomatosis of Gougerot-Carteaud is most likely and should avoid unnecessary skin biopsies.

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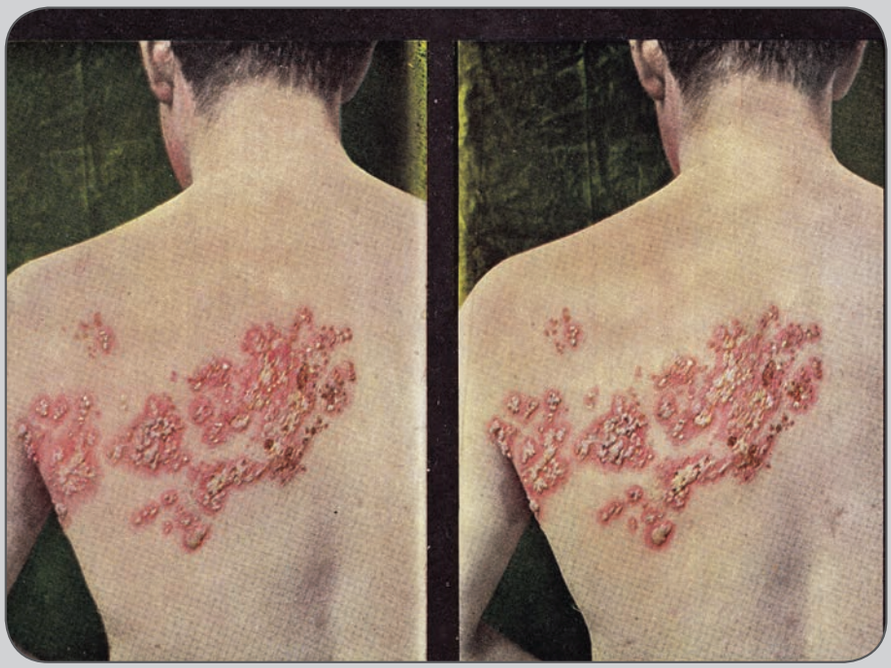
HISTORICAL DIAGNOSIS AND TREATMENT: ZOSTER



(Continued on page 245)

PHOTO CAPSULE

Snejina Vassileva, MD, PhD, Section Editor

Localized Hypertrichosis of the Thigh

Khadija Sellami, MD; Hamida Turki, MD

A 45-year-old woman presented to our department with a slightly brownish patch on her right thigh which was covered with numerous dark hairs (Figure 1). The same thigh had been injured by blunt trauma a few months earlier. On examination, there was an infiltrated patch with no sclerosis, but no other abnormalities. Laboratory tests, including a complete blood count, C-reactive protein, erythrocyte sedimentation rate, chemical profile, serum protein electrophoresis test, and antinuclear antibodies, were all normal. Histopathologic examination showed lobular panniculitis. A month later, the skin discoloration spontaneously resolved, but the hypertrichosis remained.

There are only a few reports of similar traumatic panniculitis, accompanied by localized hypertrichosis in women and afflicting the legs.[1] There is also a report of a patient with localized hypertrichosis and lupus panniculitis.[2]

Acquired and localized hypertrichosis may be associated with local inflammation, inducing abundant arterial hyperemia and stimulating the affected follicles. The resulting angiogenesis may prolong the anagen phase of the follicles.[1]

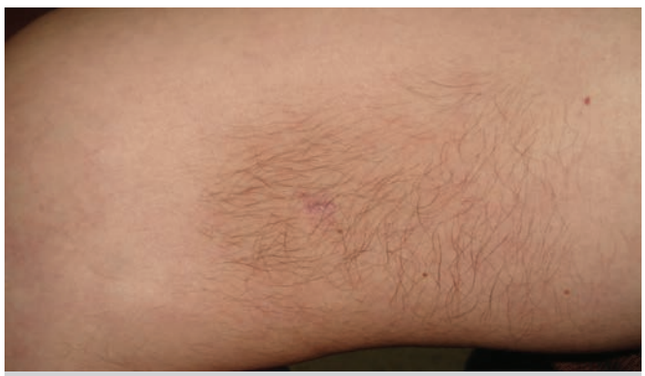


Figure 1. Brownish patch with dark hairs on the inner aspect of the right thigh.

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PHOTO CAPSULE

Snejina Vassileva, MD, PhD, Section Editor

Uremic Frost: Dialytic Emergency

Estefanía Galeano-Piedrahita, MD;[1] Susana Chiquito-García, MD;[2]
Ana María Mejía-Giraldo, MD;[1] J. Andrés Díaz-Ruiz, MD[3]

Uremic frost is a specific finding of end-stage renal disease. It involves serious metabolic alterations and, if not corrected, results in irreversible complications. It was first described by Harald Hirschprung (1839–1916) in 1865.[1] Its clinical manifestations appear on the skin and are specific to advanced chronic renal disease with azotemia. Uremic frost is infrequent, given the vast availability of renal substitution therapy. In India, uremic frost occurs in 3% of terminal chronic renal illnesses and in 1% of other conditions.[2–4]

It is important to treat an uremia patient, given its potentially fatal consequences. The management of uremic frost, as implied by its name, aims to control the uremia. This condition is observed infrequently due to early control and replacement therapies in patients with end-stage renal disease, and it is a preventable entity.

CLINICAL CASE

A 69-year-old man with a history of chronic renal illness, without any other major medical history, had been treated by a general internist in a high-quality hospital. His findings were dyspnea at rest, oliguria, nausea, and loss of weight. The initial chemical analysis reported 37.2 mg/dL creatinine, 470 mg/dL urea, 220 mg/dL blood urea nitrogen (BUN), 7.26 mEq/L potassium, arterial gases with pH 7.25, 10.3 mEq/L sodium bicarbonate, 21 mm Hg PCO_2, and 68 mm Hg PO_2. Physical examination revealed hypertension; the odor of urine; and well-defined, generalized, multiple plaques with white desquamation. Some had an erythematous base and were predominantly found on the abdomen (Figure 1), arms, and legs (Figure 2).

Chronic renal illness was diagnosed with dialytic urgency, and uremic frost was found on the skin. The patient was admitted to

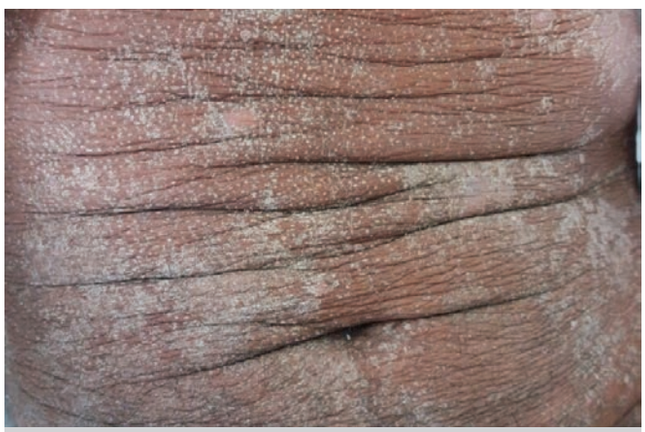

Figure 1. Multiple plaques with white desquamation that are well-defined and generalized—some with an erythematous base on the abdomen.

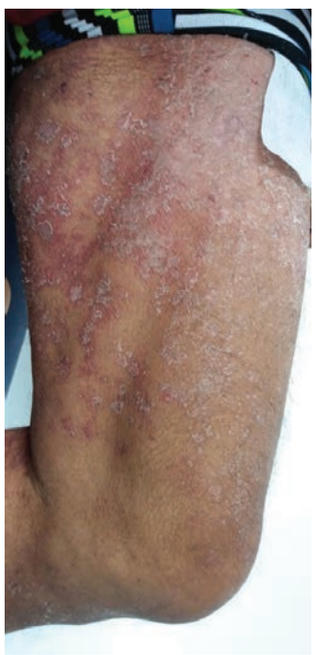

Figure 2. Multiple plaques with white desquamation, well-defined and generalized—some with an erythematous base on the legs.

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the intensive care unit; hemodialysis was started, which improved the patient's breathing and lessened his skin lesions. Unfortunately, his condition deteriorated, and he died.

DISCUSSION

Uremic frost is a sign of chronic renal illness, with serious complications and a high mortality rate, given the advanced state of the renal illness. Fortunately, cases of uremic frost are rare due to the current modality of management and dialysis. It is caused by kidney damage, resulting in the accumulation of urea in the blood. It involves high urea levels in the blood—200 mg/dL[2] or greater—which increases its concentration in sweat, and then evaporates, crystallizes, and deposits itself on the skin. In addition, urea can permeate sweat due to problems with the vasculature and eccrine glands.[4,5]

Men who have hypertension, diabetes, with renal disease are more vulnerable to uremic frost. The average age for developing uremic frost is 54 years, with BUN and creatinine levels approximating 199 mg/dL and 17.5 mg/dL, respectively.[3,4] The nine published cases include changes in mental state, difficulty breathing, azotemia, and hyperkalemia.[4] On physical examination, there are small, yellow-white crystals with the frost on the face, neck, arms, and legs.[6] Clinically, there is dermatitis, xerosis, and desquamation.[7]

CONCLUSIONS

Patients with uremic frost should undergo immediate hemodialysis.[4] Uremic frost occurs less frequently today and is preventable.[6]

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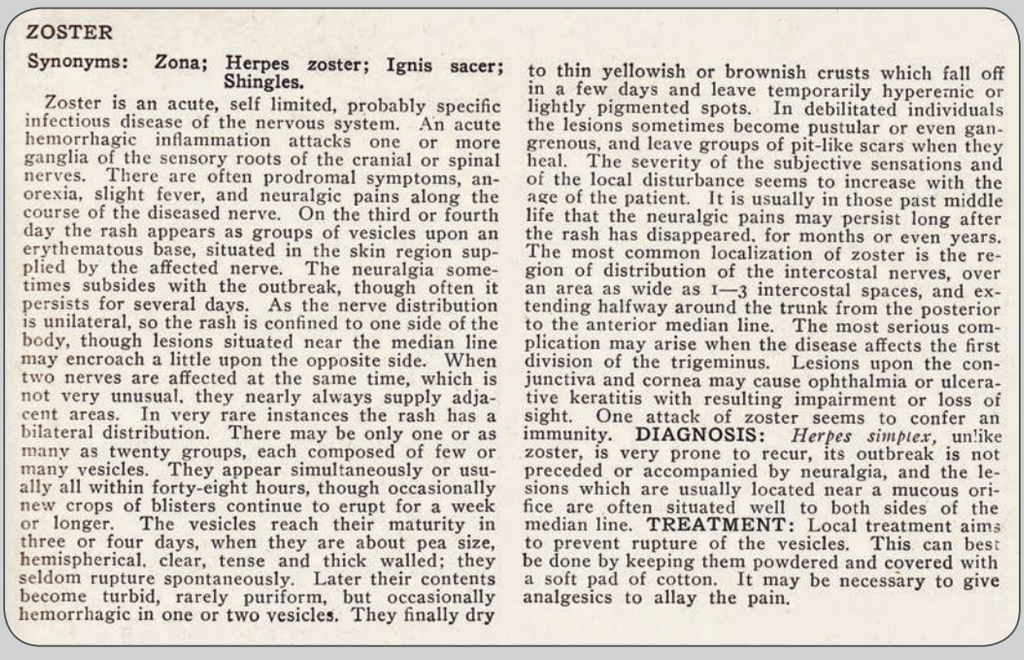
HISTORICAL DIAGNOSIS AND TREATMENT: ZOSTER

(Continued from page 241)



ZOSTER

Synonyms: Zona; Herpes zoster; Ignis sacer; Shingles.

Zoster is an acute, self limited, probably specific infectious disease of the nervous system. An acute hemorrhagic inflammation attacks one or more ganglia of the sensory roots of the cranial or spinal nerves. There are often prodromal symptoms, anorexia, slight fever, and neuralgic pains along the course of the diseased nerve. On the third or fourth day the rash appears as groups of vesicles upon an erythematous base, situated in the skin region supplied by the affected nerve. The neuralgia sometimes subsides with the outbreak, though often it persists for several days. As the nerve distribution is unilateral, so the rash is confined to one side of the body, though lesions situated near the median line may encroach a little upon the opposite side. When two nerves are affected at the same time, which is not very unusual, they nearly always supply adjacent areas. In very rare instances the rash has a bilateral distribution. There may be only one or as many as twenty groups, each composed of few or many vesicles. They appear simultaneously or usually all within forty-eight hours, though occasionally new crops of blisters continue to erupt for a week or longer. The vesicles reach their maturity in three or four days, when they are about pea size, hemispherical, clear, tense and thick walled; they seldom rupture spontaneously. Later their contents become turbid, rarely puriform, but occasionally hemorrhagic in one or two vesicles. They finally dry to thin yellowish or brownish crusts which fall off in a few days and leave temporarily hyperemic or lightly pigmented spots. In debilitated individuals the lesions sometimes become pustular or even gangrenous, and leave groups of pit-like scars when they heal. The severity of the subjective sensations and of the local disturbance seems to increase with the age of the patient. It is usually in those past middle life that the neuralgic pains may persist long after the rash has disappeared, for months or even years. The most common localization of zoster is the region of distribution of the intercostal nerves, over an area as wide as 1—3 intercostal spaces, and extending halfway around the trunk from the posterior to the anterior median line. The most serious complication may arise when the disease affects the first division of the trigeminus. Lesions upon the conjunctiva and cornea may cause ophthalmia or ulcerative keratitis with resulting impairment or loss of sight. One attack of zoster seems to confer an immunity. **DIAGNOSIS:** *Herpes simplex*, unlike zoster, is very prone to recur, its outbreak is not preceded or accompanied by neuralgia, and the lesions which are usually located near a mucous orifice are often situated well to both sides of the median line. **TREATMENT:** Local treatment aims to prevent rupture of the vesicles. This can best be done by keeping them powdered and covered with a soft pad of cotton. It may be necessary to give analgesics to allay the pain.

CASE STUDY

Successful Use of Rituximab and Intravenous Gamma Globulin to Treat Checkpoint Inhibitor-Induced Severe Lichen Planus Pemphigoides

Matthew Brennan, MD;[1] Marissa Baldissano, MD;[1] Lauren King, MS;[2] Anthony A. Gaspari, MD[1,3]

In 2015, a 73-year-old Caucasian woman with a history of multiple nonmelanoma skin cancers was diagnosed with malignant melanoma located on the forehead (0.85 mm in thickness, with a low mitotic rate of <1 mm/m^2 and desmoplastic changes with regression, BRAF [a human gene that encodes a protein called B-raf, which is formally known as murine sarcoma viral oncogene homologue B] V600 negative). The lesion was excised with wide margins and with sentinel nodes negative for metastatic lesions. Three years later, she developed back pain, was found to have metastatic lesions on her spine, and underwent surgical de-bulking of metastatic lesions and radiation to the spine (Stage IV unresectable metastatic disease). She also had developed metastatic lesions in her lungs and brain, found on positron emission tomography positron emission tomography (PET) scan, for which she was treated with the gamma knife to the brain. She then received nivolumab 480 mg infusions for eight monthly cycles of treatment. Due to an episode of sepsis and compromised renal function, immunotherapy was discontinued a year later. Restaging PET scan taken at this time revealed diminished mediastinal/hilar activity and response in bones; her brain magnetic resonance imaging magnetic resonance imaging (MRI) was now negative. These evaluations suggested a complete clinical response to nivolumab infusions, with no metastatic lesions being detectable during the restaging process. Four months later, she was hospitalized twice for sepsis-like episodes that resolved spontaneously, and the patient was found to have adrenal insufficiency. (*SKINmed*. 2020;18:246–249)

After this hospitalization, she presented to the dermatology service with a highly pruritic eruption on her arms and legs (Figure 1A), ongoing for 4 months. Histologic analysis of a punch biopsy specimen revealed lichenoid dermatitis, consistent with immunotherapy-induced lichen planus (LP) (Figure 1B). She was treated with a single intramuscular injection of 1 mL of triamcinolone acetonide, 40 mg/mL and topical corticosteroids (triamcinolone 0.1% twice a day, BID). As this regimen did not adequately control the manifestations of LP, oral prednisone therapy was initiated at 20 mg/day, and eventually increased to 40 mg/day (0.5 mg/kg) over the subsequent 4 months.

This treatment was effective, but after a taper of the oral corticosteroids, she presented 2 months later with severe exacerbation of her itching along with blisters (Figure 2A). Histopathologic examination using direct immunofluorescence (strong linear deposits of C3 and IgG along the basement membrane zone of the epidermis) pointed toward a diagnosis of lichen planus pemphigoides (LPP) (Figure 2B). Oral prednisone at 1 mg/kg/day did not control her pruritic blistering, and she was admitted to a local hospital for pulse intravenous (IV) corticorticosteroids (solumedrol, 1 g daily IV for 3 days). She was discharged with oral prednisone 1 mg/kg/day, topical clobetasol diproprionate cream 0.05%, and hydroxyzine 25 mg by mouth every 6 hours for itching. Due to the recurrence of the blistering and severe pruritus, she was again hospitalized for another round of pulse IV corticosteroids (solumedrol, 1 g daily IV for 3 days), followed by oral corticosteroids at 1 mg/kg/day. Tapering of the corticosteroids to below 20 mg/day resulted in a relapse of her blisters and itching. Four months after the onset of her eruption, rituximab (a single 1-g pulse IV infusion was initiated, with a second pulse administered 1 month later). This was followed by intravenous gamma globulin (IVIG), started at 1 g/kg, administered IV daily BID, with a plan for 4 monthly infusions if needed. Nine months after the diagnosis of LP, there were no blisters, or LP-like lesions, or pruritus. Our patient successfully underwent a slow corticosteroid taper from 1 mg/kg/day of oral prednisone, and has recently discontinued

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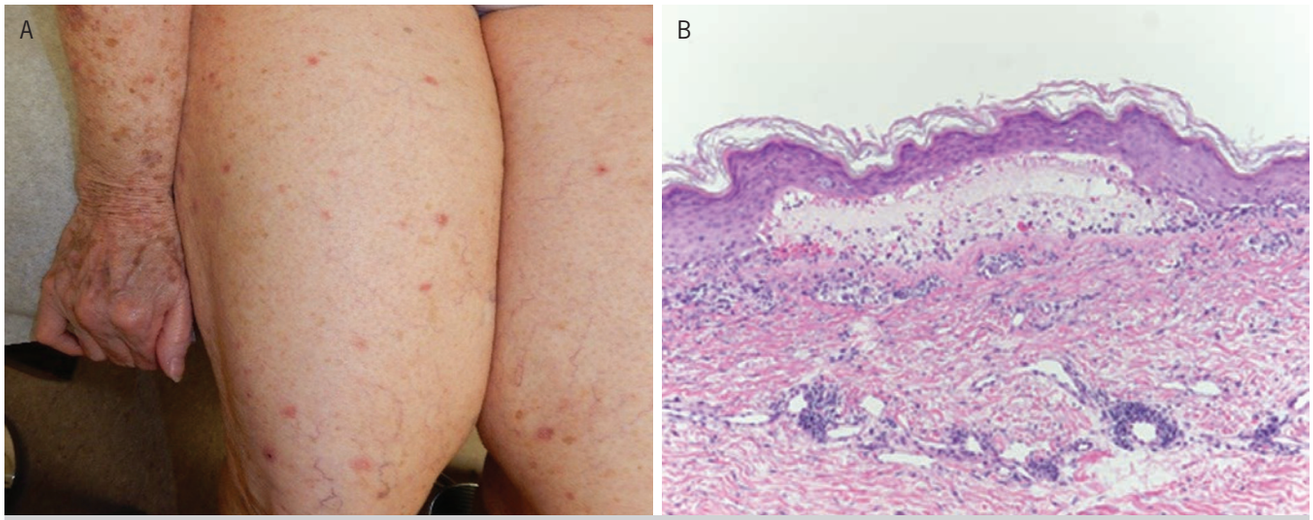

Figure 1. (A) Lichenoid papules and macules on arms and legs at presentation in May 2019. These skin lesions were widespread over the trunk and extremities; no blisters were present on physical examination. (B) The hematoxylin and eosin stained sections of a biopsy specimen show lichenoid interface dermatitis with necrotic keratinocytes at the dermo-epidermal junction and associated subepidermal cleft/bullae on one edge. There is epidermal hyperplasia, wedge-shaped hyper-granulosis, and overlying slightly thickened compact orthokeratosis. The infiltrate is composed of mostly lymphocytes with a few admixed neutrophils in the dermis and bullae cavity (100× magnification). Clinicopathologic correlation was consistent with a lichenoid drug eruption.

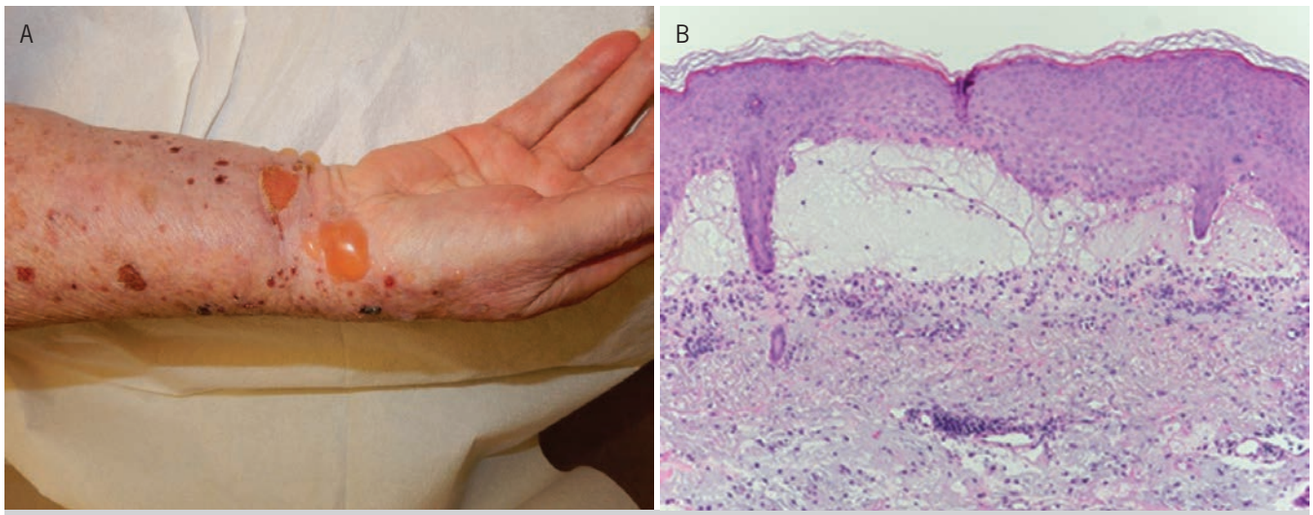

Figure 2. (A) Bullae, vesicles, and erosions on the wrist at presentation in September 2019. These blisters and erosions were widely distributed over the patient's trunk and extremities. (B) The hematoxylin and eosin stained sections of a biopsy specimen show a central subepidermal bulla with scant cells (including lymphocytes, neutrophils, and eosinophils), with a superficial perivascular lymphocytic infiltrate with eosinophils and neutrophils. There is adjacent broad interface dermatitis with necrotic keratinocytes, eosinophils, and neutrophils at the dermo-epidermal junction (100×). Direct immunofluorescence study of a perilesional biopsy specimen revealed strong linear deposits of C3 and IgG along the basement membrane zone (not shown). Clinicopathologic correlation was consistent with lichen planus pemphigoides.

systemic corticosteroids without a relapse of her LPP. Recent CT scan of her chest did not reveal detectable metastatic lesions, and a MRI of her head was also clear of detectable metastatic lesions, suggesting her immunotherapy-induced remission was sustained despite the use of rituximab.

DISCUSSION

Nivolumab is a monoclonal antibody, which acts by modulating a checkpoint control molecule by binding to the programmed cell death 1 (PD-1) receptor on T-cells.[1] This antibody blocks

the interaction of PD-1 on T-cells with PD-1 Ligand (PD-1L) on tumor cells, which is thought to be an important tumor escape mechanism for preventing tumor-specific T-cells from mounting an effective immune response. This biologic agent ultimately leads to the enhancement of an anti-tumor T-cell response by overcoming tumor cell escape mechanisms. It is considered an immune stimulatory therapy in the treatment of unresectable, metastatic cancers. Nivolumab, as well as other checkpoint inhibitors, such as pembrolizumab, have been used in the treatment of non–small cell lung cancers, melanoma, and other cancers.[1] Nivolumab has demonstrated durable responses in patients with metastatic melanoma with overall survival and progression-free survival of 44% and 29%, respectively, at 5 years. A total of 19% of the patients may experience complete remissions that may last beyond their last course of immunotherapy.[2]

Cutaneous adverse events (AEs) occur frequently and are estimated to occur in between 20% and 50% of treated patients during checkpoint inhibitor immunotherapy for advanced cancers,[3] presenting within the first 8–10 months of treatment. The most common cutaneous AEs include pruritus, dermatitis, vitiligo, and other eruptions, such as lichenoid dermatitis and psoriasiform eruptions. Bullous pemphigoid (BP), erythema multiforme, Steven–Johnson syndrome, and drug-related eosinophilia with systemic symptoms (DRESS) are less common.[4] LPP is a rare, distinct, overlap syndrome of LP and bullous pemphigoid. It may occur spontaneously, be induced by medications or infections, or be associated with cancer.[5] Of the numerous cutaneous AE associated with checkpoint inhibitor therapy, BP is an uncommon complication, occurring in approximately 2.4% of patients in a series of over 500 patients treated with checkpoint inhibitors.[3] A total of 22 cases of PD-1 inhibitor-induced BP have been reported,[4–13] but LPP is rarer, with only two other cases being reported.[14,15] Management of BP involves discontinuation of checkpoint inhibitor therapy, the use of topical and systemic corticosteroids, and the use of oral antihistamines to induce a remission.

Our patient's LPP developed approximately 5 months after discontinuing nivolumab (due to AEs of pseudosepsis with renal compromise), with a highly pruritic lichenoid eruption that progressed rapidly to severe LPP, which required multiple hospitalizations with pulse IV corticosteroids to control her blistering and severe pruritus. Because rituximab has been used successfully in the treatment of BP, with a response rate of 75% and an excellent safety profile,[12] we utilized this pulse therapy with this biologic along with a single infusion of IVIG to successfully induce a remission in late-onset, severe LPP. Similarly, IVIG (alone or in combination with other drugs) has been used to treat autoimmune blistering skin diseases.

CONCLUSIONS

In spite of the potential for immune suppression, which may occur with transient B-lymphocyte depletion from rituximab infusions, the patient's metastatic melanoma remains undetectable (maintenance of a complete clinical response to nivolumab). This treatment approach may be worth considering in other patients who present with severe variants of this rare, cutaneous complication of checkpoint inhibitor therapy for metastatic cancer.

ACKNOWLEDGMENTS

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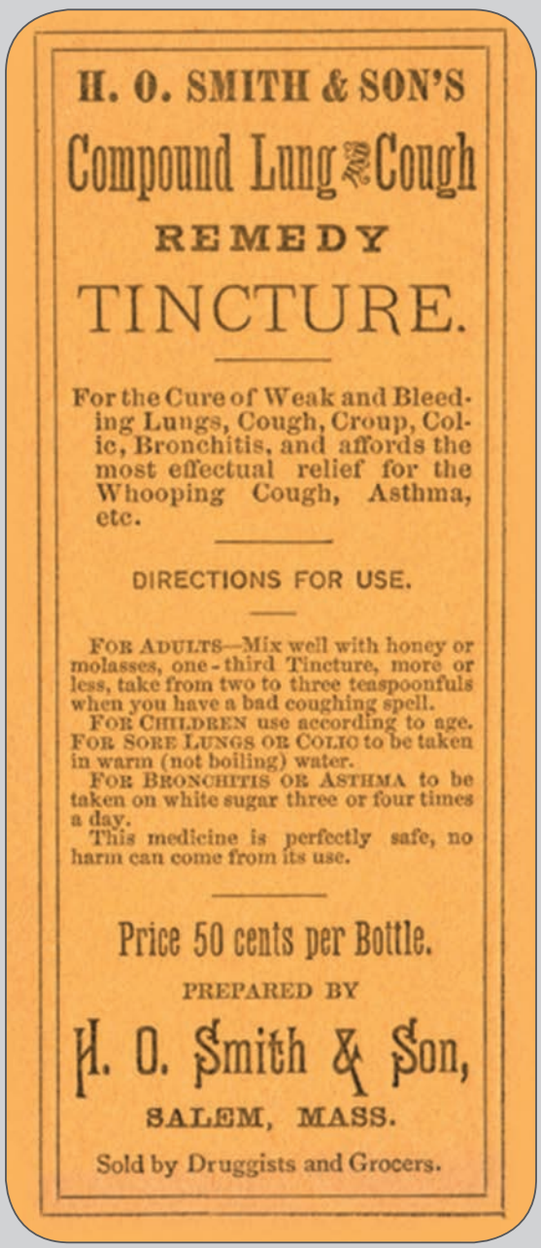

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CASE STUDY

Pemphigus Vulgaris Localized to a Surgical Scar

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Dermatology consultation was sought for a woman in her fifties for a well-defined painful erosion prior overlying a pre-existing scar on the back present for the past 18 months (Figure 1). The patient recalled being operated on for a lump at the same site 10 years. The surgical incision site healed with the formation of a hypertrophic scar for which she was treated with 4 intralesional triamcinolone acetonide injections 6 years ago. One and a half years ago, the patient developed multiple fluid-filled blisters overlying the scar, which ruptured to form the erosion. The erosion persisted, increasing in size but remained restricted to the hypertrophic scar. Local examination revealed a well-defined erosion of approximately 10×7 cm size overlying the scar with healthy granulation tissue at base and superficial whitish slough. No mucosal involvement was observed, and the rest of the cutaneous examination was normal. Pathologic examination of the skin biopsy taken from the edge of the lesion revealed intraepidermal suprabasal split. Mildly dense lymphocytic infiltrate was also present around the vessels (Figure 2). Direct immunofluorescence of skin taken from the perilesional skin revealed immunoglobulin deposits in a fishnet-like pattern (IgG: 2+ and C3: 1+). A diagnosis of pemphigus vulgaris was reached based on the above findings, and the patient was started on oral prednisolone 0.5 mg/kg/day and cyclophosphamide 100 mg per day. At a follow-up visit 4 months later, the erosion had healed with keloidal scarring (Figure 3). (*SKINmed*. 2020;18:252–253)

DISCUSSION

Pemphigus is a group of rare autoimmune bullous dermatoses associated with significant morbidity and mortality. The incidence of pemphigus (including its variants) restricted to a surgical scar or keloid is rare with only a few reported cases in the literature to date.[1–5] The exact etiopathogenesis of pemphigus being localized to the scar/keloid is largely unknown; however, a few hypotheses have been put forward to explain such a phenomenon. An isomorphic response may play a role in the occurrence of pemphigus limited to scar or keloid. Unlike classic Köebner's response,

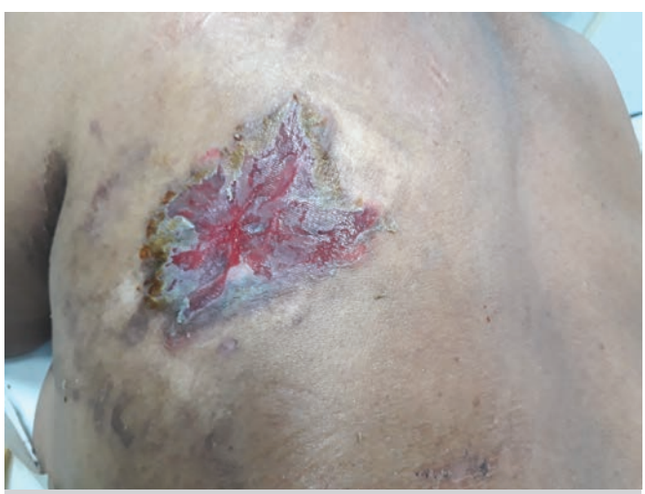

Figure 1. Well-defined erosion overlying a scar on the back.

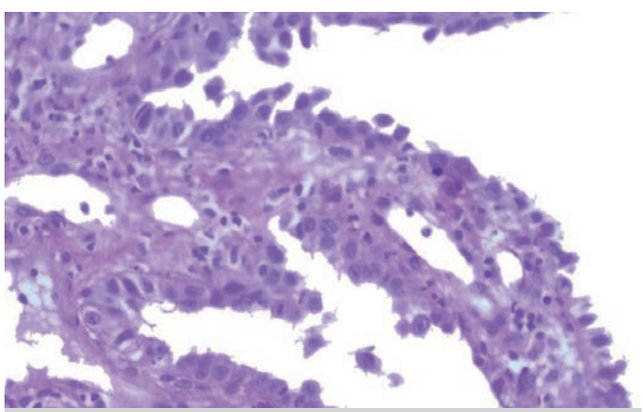

Figure 2. Loss of the stratum malphigi with remaining basal layer keratinocytes in a row of tombstone pattern. Acantholytic cells are also seen (hematoxylin and eosin stain, original magnification ×100).

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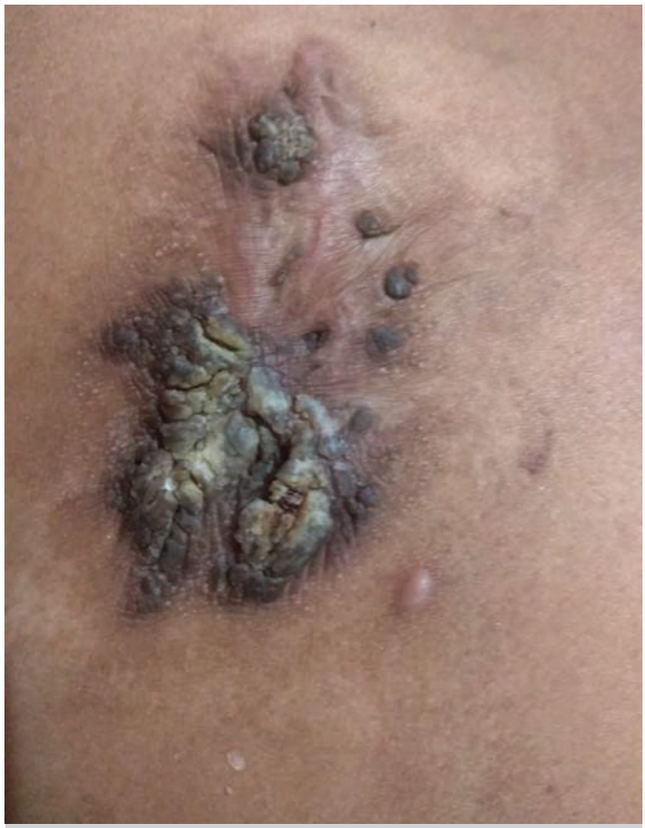

Figure 3. Healing with keloidal formation at a follow-up visit.

patients did not have a history of pre-existing pemphigus in most of these reports.[6] Our patient did not have any history suggestive of prior pemphigus, and the disease remained localized to the scar even 18 months prior to the onset. Another hypothesis proposes that trauma leads to the expression of cryptic antigens allowing either the onset of autoantibody production or the augmentation of the autoimmune response in those having low levels of autoantibodies, ultimately resulting in the development of pemphigus. Other researchers have suggested that scarring, trauma, or inflammation causes an alteration in connective tissue and vascular functions, thus leading to the phenomenon of Ruocco's "immunocompromised cutaneous district" (locus minoris resistentiae), that is, the creation of sites with reduced resistance to disease.[6,7] Apart from pemphigus, there are a few reports of bullous pemphigoid developing at surgical sites.[8–10]

Such atypical cases may be misdiagnosed as post-traumatic or post-surgical infections,[6] especially those caused by atypical mycobacteria and treated with long courses of empirical antimicrobials. Accordingly, a high index of suspicion with pathologic and immunofluorescence studies of these lesions is essential for their diagnosis and management.

CONCLUSIONS

This case study illustrates that due awareness among clinicians about the presentation and management of autoimmune bullous disease developing on traumatic/surgical scars is required to avoid mismanagement. Long-term follow up of these patients is indispensable to evaluate the prognosis and to find out whether the disease remains localized to the scar or involves the normal skin.

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CORRESPONDENCE

Snejina Vassileva, MD, PhD, Section Editor

Thalidomide Should Be Tested as a Therapeutic Option in COVID-19 Pneumonia

Jorge E. Tiscornia, MD;[1] Thelma V. Poggio, PhD;[2] Daniel G. Feinsilber, MD;[1] Anton E. Coleman, MD[3]

To the Editor:

Leprosy reactions represent episodes of acute hypersensitivity to antigens of Mycobacterium *leprae*. In lepromatous lepra reactions (type 2 reactions), a cytokine storm affects the general condition of the patient, the skin, and the internal organs. In these type 2 reactions, thalidomide resolves the fever, and markedly improves the general condition and skin lesions over the course of 48 to 72 hours. In addition to its teratogenic action, the side effect profile of thalidomide is usually mild, particularly when the drug is ingested for a short period of time. Currently, thalidomide is being used in several countries for this indication. In the United States, thalidomide has been in use for over 30 years, and has been approved by the Food and Drug Administration for the treatment of lepromatous lepra reactions.

CLINICAL OBSERVATIONS

We had the opportunity to see a patient with a lepromatous lepra reaction who also had respiratory signs and symptoms, which in retrospect suggested a concomitant COVID-19 infection. It should be pointed out that pulmonary signs and symptoms are not part of lepromatous lepra reactions.[1]

The patient was treated with thalidomide. The fast and effective resolution of the respiratory manifestations on treatment strongly suggests that this drug could be a potential candidate for a clinical trial in acute viral respiratory syndromes.

BACKGROUND OF THALIDOMIDE

Previous research has shown that thalidomide protects experimental mice from the pulmonary consequences of H1N1[2] and in humans diminishes cough in idiopathic pulmonary fibrosis[3] as well as in bleomycin-induced pulmonary fibrosis.[4] To date, there is only one publication on COVID-19 pneumonia that was successfully treated with thalidomide and low-dose steroids[5]. The extensive mechanisms of action of thalidomide have not yet been fully dilucidated.

Thalidomide acts via the decreased synthesis of TNF- and IL-6, in addition to other cytokines, but the precise pathway is unknown.

1) Does thalidomide in COVID-19 pneumonia cause improvement in the inflammatory status?
2) Would thalidomide inhibit the progression of mild cases to moderate-severe cases with COVID-19 pneumonia?

RECOMMENDATIONS

A cytokine storm is considered to be the mechanism that accounts for much of the morbidity and mortality of the current cases of COVID-19. Several medications that have no direct antiviral action have been used to treat this cytokine storm. Among these is chloroquine or its derivatives.[6] Thalidomide is an inexpensive medication, which is available in many countries. Its administration to men and post-menopausal women solely would prevent the possibility of teratogenic complications. A short clinical trial with thalidomide would be useful to answer the aforementioned questions.

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The Spectrum of Dermatoses during the Lockdown Period of COVID-19 Pandemic: Are Papulosquamous Disorders on the Rise?

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To the Editor:

Globally, the currently evolving COVID-19 pandemic has crippled everybody equally, in terms of the basic amenities, emotions, freedom, and health issues. One can only imagine the extent of the sufferings endured due to the coronavirus. In this context, the technology of teledermatology has been immensely useful, as it enables us to virtually attend to a patient who is need of a consultation, and also prescribe the necessary treatment.[1]

In a study conducted in India during the COVID-19-related lockdown, that is, March 28 to May 15, 2020, a total of 161 patients with various skin conditions were consulted via teledermatology (i.e., WhatsApp, Zoom, Google Meet, and other online platforms). Almost 50% (84/161) of these patients were men. After a comprehensive history taking and a careful analysis of pictures/videos of the skin lesions of interest, the dermatologist could provide a probable diagnosis and recommendations for further management.

We came across papulosquamous disorders, such as psoriasis in 35 (21.7%) patients, lichen planus in 19 (11.8%) patients, seborrheic dermatitis in 17 (10.5%) patients, pityriasis rosea (PR) in seven patients, and nummular dermatitis in five patients. Cases involving an infective etiology included tinea corporis, tinea cruris, candidal balanoposthitis, folliculitis, paronychia, herpes zoster, herpes labialis, and scabies. Other dermatologic disorders diagnosed comprised acne vulgaris, hand dermatitis, atopic dermatitis, contact dermatitis, miliaria, androgenetic alopecia, and even Dowling-Degos disease (Table 1).

Due to the unforeseen crisis during the total lockdown in India, there was a massive upsurge in unemployment from 6.7% to 26% during our study period.[2] The resultant financial constraint further added to the preexisting psychological stress, which aggravates itching in patients with psoriasis and lichen planus. As a consequence, exacerbation of new scaly lesions and Koebnerization was noted in these patients. Stress, a well-known precipitating factor for inflammatory skin conditions, may act as a causal link for the flare-ups. We believe that there is a *brain–skin pathway*, as evidenced by a stress-mediated increase in the circulating inflammatory cells, along with altered expressions of cutaneous neuropeptides.[3]

Psoriasis patients experienced increased scaling and erythema over the lesions, dissemination of the lesions due to increased pruritus, and an increase in the Psoriatic Area Severity Index (PASI) score. Patients with PR had most of their lesions on the back. Whether there is a temporal relation of these lesions to the COVID-19 pandemic or whether it is due to the presumed infection with a herpetic virus is still unknown, as currently testing for COVID-19 is being performed only in suspects with respiratory and constitutional findings.

PR is being reported as a possible cutaneous manifestation of COVID-19.[4–6] If we consider it to be a part of COVID-19 manifestations, the possible hypothesis could be an immunologic reaction as a post-asymptomatic viral disease or a part of a peculiar anti-viral immune response.[7]

With the compulsion to adhere the precautionary norm of hand hygiene, regular washing with alkaline pH soaps and exposure to sanitizers have resulted in dry and itchy lesions, especially in patients with psoriasis, lichen planus, and nummular dermatitis. This could be attributed to the increase in transepidermal water loss (TEWL) caused by these agents; however, other possible reasons for the aggravation of these conditions could be the sudden unavailability of dermatologists round the clock and the scarcity

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Table 1. Distribution of Cases Consulted through Teledermatology during the Lockdown

Diagnosis	Distribution	Men	Women
Papulosquamous disorders			
Psoriasis vulgaris	35 (21.7%)	21	14
Lichen planus	19 (11.8%)	10	9
Seborrheic dermatitis	17 (10.5%)	10	7
Pityriasis rosea	7 (4.3%)	5	2
Infections and infestations			
Fungal	34 (21.1%)	11	23
Bacterial	9 (5.5%)	5	4
Viral	7 (4.3%)	4	3
Infestations	14 (8.6%)	9	5
Acne vulgaris	9 (5.5%)	3	6
Hair disorders	3 (1.8%)	2	1
Others	7 (4.3%)	4	3
	161 (100%)	84 (52.1%)	77 (47.9%)

of pertinent medications in the neighborhood pharmacies, due to the restrictions on the supply chain with the lockdown in place.[8,9]

As this COVID era continues to pose new challenges, the most advanced economies are plunging into recession, which will result in a considerable lowering of the socioeconomic status of individuals around the globe. The resulting psychosocial stress will only accentuate the stress-reactive disorders that will continue long after the pandemic dies down.

Although these circumstances have brought our lives to a state of limbo, giving our utmost attention to patients with dermatologic conditions remains our priority. We, as dermatologists, can productively deal with any preexisting or evolving skin conditions effectively during these challenging times! As this pandemic has modified our approach toward patients, it is time to adapt and turn to technology, rather than in-person consultations. We have been able to devise therapeutic plans and counsel our patients, as part of our contribution to humanity and our endeavor to curb the spread of this contagion.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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INDICATIONS AND USAGE

LEVULAN KERASTICK for topical solution, a porphyrin precursor, plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the photodynamic therapy (treatment) of minimally to moderately thick actinic keratoses of the face or scalp, or actinic keratoses of the upper extremities.

DOSAGE AND ADMINISTRATION:

The LEVULAN KERASTICK topical solution 20% is intended for direct application to individual lesions diagnosed as actinic keratoses and not to perilesional skin. This product is not intended for application by patients or unqualified medical personnel. Application should involve lesions on the scalp, face or upper extremities; multiple lesions can be treated within a treatment region, but multiple treatment regions should not be treated simultaneously.

The recommended treatment frequency is one application of the LEVULAN KERASTICK topical solution and one dose of illumination per treatment region per 8-week treatment session. Each individual LEVULAN KERASTICK applicator should be used for only one patient.

LEVULAN KERASTICK photodynamic therapy for actinic keratoses is a two-stage process involving application of the LEVULAN KERASTICK topical solution to the target lesions and then illumination with blue light using the BLU-U Blue Light Photodynamic Therapy Illuminator after 3 hours for upper extremity lesions or after 14-18 hours for face or scalp lesions.

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.

WARNINGS AND PRECAUTIONS

Transient Amnestic Episodes

Transient amnestic episodes have been reported during postmarketing use of LEVULAN KERASTICK in combination with BLU-U Blue Light Photodynamic Therapy Illuminator. Inform patients and their caregivers that LEVULAN KERASTICK in combination with PDT may cause transient amnestic episodes. Advise them to contact a healthcare provider if the patient develops amnesia after treatment.

Photosensitivity

After LEVULAN KERASTICK topical solution has been applied, the treatment site will become photosensitive and 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) for 40 hours. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Therefore, before exposure to sunlight, patients should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material, and/or a long-sleeved shirt and/or gloves. 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 the eye or surrounding skin.

Application of LEVULAN KERASTICK topical solution to perilesional areas of photodamaged skin of the face, scalp or upper extremities may result in photosensitization. Upon exposure to activating light from the BLU-U, 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 KERASTICK Photodynamic Therapy. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK topical solution should be used by a qualified health professional to apply drug to no more than 5mm of perilesional skin surrounding the target actinic keratosis lesions. If for any reason the patient cannot return for blue light treatment during the prescribed period after applying LEVULAN KERASTICK topical solution, 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.

Irritation

The LEVULAN KERASTICK topical solution contains alcohol and is intended for topical use only. Irritation may be experienced if this product is applied to eyes or mucous membranes. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion longer than 3 hours.

Coagulation Defects

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

ADVERSE REACTIONS

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

In clinical trials, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK photodynamic therapy.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK photodynamic therapy (PDT) was observed in all clinical trials for actinic keratoses treatment.

Local skin reactions at the application site were observed in 99% of subjects treated with LEVULAN KERASTICK topical solution and BLU-U Blue Light Photodynamic Therapy Illuminator. The most common local adverse reactions (incidence ≥ 10%) were application site stinging/burning, erythema, edema, scaling/crusting, hypo/hyperpigmentation, itching, erosion, oozing/vesiculation/crusting, dryness.

In the trials for face and scalp lesions, severe stinging and/or burning at one or more lesions during light treatment was reported by at least 50% of subjects. Severe stinging and/or burning also occurred during light treatment in 9% of subjects receiving treatment for upper extremity lesions.

In trials for the face or scalp lesions, 99% of the active treatment group and 79% of the vehicle group experienced erythema shortly after treatment. In the trial for the upper extremity lesions, 99% of LEVULAN KERASTICK topical solution treatment group and 52% of the vehicle group experienced erythema on visit Days 2-3. Approximately 35% of LEVULAN KERASTICK topical solution group had edema, while edema occurred in <1% of the vehicle group. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy for face or scalp. Edema resolved by 4 weeks and erythema resolved to baseline by 8 weeks for upper extremities. The application of LEVULAN KERASTICK topical solution to perilesional skin resulted in stinging, burning, erythema and edema similar to treated actinic keratosis

Other Localized Cutaneous Adverse Experiences: Table 1 depicts the incidence and severity of cutaneous adverse events in trials for the face and scalp. Table 2 depicts the percentage of subjects with cutaneous adverse reactions by the most severe grade reported in course of the trial for the upper extremity lesions.

TABLE 1 Post-PDT Cutaneous Adverse Events – ALA-018/ALA-019 For the Face and Scalp

	FACE				SCALP			
	LEVULAN KERASTICK Topical Solution + PDT (n=139)		Vehicle + PDT (n=41)		LEVULAN KERASTICK Topical Solution + PDT (n=42)		Vehicle + PDT (n=21)	
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/hyper-pigmentation	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%

TABLE 2 Percentage of Subjects with Cutaneous Adverse Reactions by the Most Severe Grade Reported Post-Baseline – CP0108 For Upper Extremities

	LEVULAN KERASTICK Topical Solution + PDT (N=135)			Vehicle + PDT (N=134)		
Degree of Severity	Minimal/ Mild	Moderate/ Severe	Total	Minimal/ Mild	Moderate/ Severe	Total
Edema	51%	4%	56%	7%	1%	8%
Erythema	35%	65%	100%	63%	12%	75%
Hyper-pigmentation	64%	9%	73%	57%	10%	66%
Hypo-pigmentation	46%	4%	50%	50%	5%	55%
Oozing/Vesiculation/ Crusting	36%	5%	41%	8%	2%	10%
Scaling and Dryness	65%	22%	87%	58%	7%	64%
Stinging/Burning	23%	73%	96%	23%	0%	23%

In the trial for upper extremity lesions, itching and scabbing occurred in 8% and 4%, respectively, of the subjects in the LEVULAN KERASTICK photodynamic therapy group. No subjects in the vehicle group reported itching or scabbing.

Common (>2%, <10%) local cutaneous adverse reactions for face, scalp and upper extremities in the LEVULAN KERASTICK topical solution group included wheal, scabbing, pustules, ulceration, bleeding, tenderness and dysesthesia.

Uncommon (<2%) local cutaneous adverse reactions for face, scalp and upper extremities in the LEVULAN KERASTICK topical solution group were flaking, pain, peeling, perilesional pruritic rash, excoriation and blistering.

Common (>2%, <10%) adverse reactions not limited to the application site for upper extremities and occurring more frequently in the LEVULAN KERASTICK topical solution group than in the vehicle group were sinusitis, squamous cell carcinoma, and squamous cell carcinoma of skin.

Postmarketing experience:

The following adverse reactions have been reported during post-approval use of LEVULAN KERASTICK. 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.

Nervous system disorders: transient amnestic episodes

DRUG INTERACTIONS

There have been no formal studies of the interaction of LEVULAN KERASTICK 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 St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with LEVULAN KERASTICK topical solution.

USE IN SPECIFIC POPULATIONS:

Pregnancy

Limited available data with LEVULAN KERASTICK topical solution use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Animal developmental toxicology studies were not conducted with aminolevulinic acid. LEVULAN KERASTICK solution has low systemic absorption following topical administration, and the risk of maternal use resulting in fetal exposure to the drug is unknown.

Lactation

There are no data on the presence of LEVULAN KERASTICK topical solution in either human or animal milk, the effects on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEVULAN KERASTICK topical solution and any potential adverse effects on the breastfeeding child from LEVULAN KERASTICK topical solution or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness in pediatric patients below the age of 18 have not been established. Actinic keratosis is not a disease generally seen in the pediatric population.

Geriatric Use

Of the 512 subjects in Phase 3 clinical trials of LEVULAN KERASTICK topical solution, 63% (321/512) were 65 years old and over, while 24% (123/512) were 75 years old and over. No overall differences in safety or substantial differences in effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

In the 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 after ingestion. The consequences of exceeding the recommended topical dosage are unknown. There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK topical solution application.

PATIENT COUNSELING

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Transient Amnestic Episodes

Transient episodes of amnesia have been reported with LEVULAN KERASTICK in combination with BLU-U Blue Light Photodynamic Therapy Illuminator. Advise patients and their families or caregivers to contact their healthcare provider if memory impairment, confusion, or disorientation is observed.

Photosensitivity

Advise patients that after LEVULAN KERASTICK topical solution has been applied, the treatment site will become photosensitive and that they 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) for 40 hours. Advise patients to protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material, and/or a long-sleeved shirt and/or gloves. Advise patients 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 the eye or surrounding skin.

If for any reason the patient cannot return for blue light treatment during the prescribed period after applying LEVULAN KERASTICK topical solution, advise patients to call the doctor. Advise patient to continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. Advise patients to avoid certain medications that may enhance the phototoxic reaction to PDT.

Common Adverse Reactions

Inform patients that treatment with LEVULAN KERASTICK topical solution plus BLU-U Blue Light Photodynamic Therapy Illuminator may result in sensitivity to light, skin irritation and local skin reactions including erythema, edema, stinging/burning, scaling, crusting, oozing, vesiculation, wheal, scabbing, pustules, ulceration, itching, erosion, hypo/hyperpigmentation, bleeding, tenderness, dysesthesia, and dryness.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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Important Safety Information

LEVULAN® KERASTICK® (aminolevulinic acid HCl) for topical solution, 20%, 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 of the face or scalp, or actinic keratosis of the upper extremities.

Contraindicated in patients with cutaneous photosensitivity at wavelengths of 400–450 nm, porphyria, known allergies to porphyrins, and/or known sensitivity to any of the components of the LEVULAN KERASTICK. LEVULAN KERASTICK topical solution has not been tested on patients with inherited or acquired coagulation defects.

Transient amnestic episodes have been reported during postmarketing use of LEVULAN KERASTICK in combination with BLU-U Blue Light Photodynamic Therapy Illuminator. Inform patients and their caregivers that LEVULAN KERASTICK in combination with PDT may cause transient amnestic episodes. Advise patients to contact a healthcare provider if amnesia develops after treatment. Do not apply to the eyes or to mucous membranes as irritation may be experienced. Excessive irritation may occur if LEVULAN KERASTICK is applied under occlusion for longer than 3 hours. Occlusion is used only in the treatment of lesions of the upper extremities. LEVULAN KERASTICK topical solution should be applied by a qualified health professional to no more than 5 mm of perilesional skin surrounding each target lesion. During light treatment, both patients and medical personnel should be provided with blue blocking protective eyewear.

Patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light for 40 hours after LEVULAN KERASTICK topical solution application. Advise patients to protect treated areas with light-opaque clothing, such as long sleeves or a hat. Sunscreens will not protect the patient against photosensitivity reactions caused by visible light.

Concomitant use of other known photosensitizing agents such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, and tetracyclines might increase the photosensitivity reaction.

The most common local adverse reactions (incidence ≥ 10%) were erythema, edema, stinging/burning, scaling/crusting, itching, erosion, hypo/hyperpigmentation, oozing/vesiculation/crusting, scaling, and dryness. In clinical trials, severe stinging and/or burning was reported by at least 50% of face and scalp patients and 9% of upper extremity patients at some time during treatment.

Please see a Brief Summary of the full Prescribing Information on the following page.

References: 1. Symphony Health. Actinic Keratosis Total Patient Share. June 2018. **2.** Data on file, Sun Pharma. **3.** LEVULAN KERASTICK (Prescribing Information). Sun Pharma; April 2018.

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