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Dermatology for the Clinician

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Published by: ***Pulse Marketing & Communications, LLC***

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

Ortho | Dermatologics

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:
Bausch Health Americas, Inc.
Bridgewater, NJ 08807 USA

By:
Bausch Health Companies Inc.
Laval, Quebec H7L 4A8, Canada

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

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Perils of Dermatopathology
W. Clark Lambert, MD, PhD, FRCP Edin., Section Editor

CASE STUDIES

References: 1. ARAZLO Lotion [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol*. 2019;18(6):542-548. **3.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 10, 2019. **4.** Data on file.

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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Dermatology for the Clinician
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CORRESPONDENCE

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ABOUT OUR JOURNAL

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Dermatology Insights and Inquiries

Otezla®
(apremilast) 30mg tablets

GETTING OTEZLA GETS EVEN EASIER

8 out of 10 commercially insured lives in the US have preferred access with **no biologic step** required for Otezla.[1]

LOWEST BRANDED COPAY†

Otezla is listed as preferred, with no biologic step requirement, on:

Aetna Prescription Drug Benefit

Cigna Prescription Drug List

CVS Caremark Formularies*

Express Scripts National Preferred Formulary†

OptumRx ✓

Prime Therapeutics

UnitedHealthcare ✓

✓ **Indicates no DMARD or biologic step-edit required.**

Contact your Otezla representative or visit OtezlaPro.com for a complete list of plans

*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]

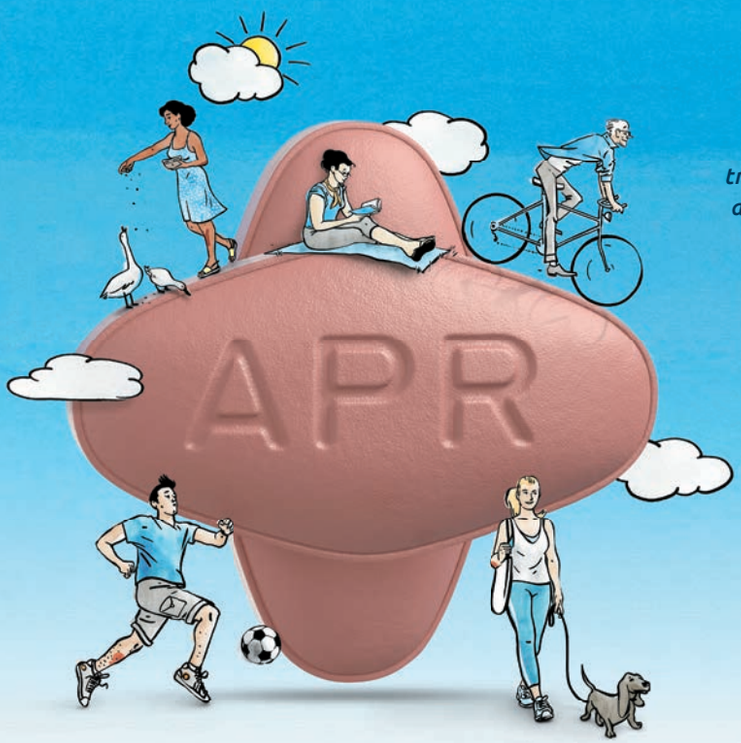
ESTEEM® Study Design

- 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



Learn more at
OtezlaPro.com

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.

Manufactured for: Celgene Corporation, Summit, NJ 07901

OTEZLA® is a registered trademark of Celgene Corporation.

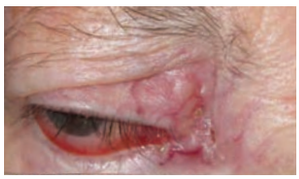
Pat. http:www.celgene.com/therapies

Based on APRPI.007 OTZ_PsA_PsO_HCP_BSv.007 07_2019

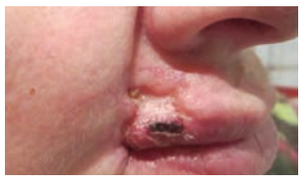
THE TREATMENT JOURNEY STARTS WITH YOU.

For patients with locally advanced basal cell carcinoma (laBCC) who are not a candidate for surgery or radiation. Learn about the latest FDA-approved hedgehog pathway inhibitor (HHI)...

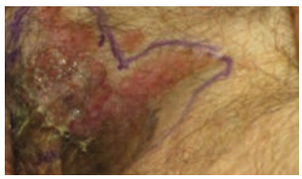
Odomzo®
(sonidegib) capsules 200mg



Eye lesion



Lip lesion



Groin lesion

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

ODOMZO is the only HHI that:

Showed
>90%
of the most common ARs were mild or moderate[1,3]

In a 12-month interim analysis of the BOLT trial
82%
(n=31/38) had an **ongoing response to ODOMZO as of last follow-up** (1.9 to 18.6)[2]

Provides FDA-approved
clear guidance
on dose interruption and discontinuation[1]

>2 years
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**

SUN PHARMA

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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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

COMMENTARY

Kojic Acid for Melasma: Popular Ingredient in Skincare Products

Cameron M. Zachary, MS;[1] Jordan V. Wang, MD, MBE, MBA;[2] Nazanin Saedi, MD[2]

ABSTRACT

Melasma is a common skin condition that affects many patients with hyperpigmented patches on sun-exposed facial skin. It disproportionately affects people of Asian, African, and Hispanic descents. Unfortunately, there are not many lasting and effective treatment options available, which has led many practitioners and skincare companies to trial various topical ingredients. In the past several years, kojic acid has gained popularity as a skincare ingredient to treat hyperpigmentation and melasma. Kojic acid has more recently become popular in over-the-counter skincare products. We discuss the background of kojic acid, its suggested mechanism, and the available studies evaluating its utility in treating melasma. (*SKINmed*. 2020;18:271–273)

Dermatologists have long been searching for an effective topical agent to treat melasma. Although some common formulations can offer clinical results, they may be transient or associated with adverse effects that can hamper long-term adherence and patient satisfaction. This has led many practitioners and skincare companies to search for alternative topical therapies that may offer patients and consumers some clinical benefit. In the recent past, kojic acid (KA) has been in use as a popular skincare ingredient in the treatment of hyperpigmentation and melasma.

BACKGROUND

Aspergillus oryzae, commonly known as kōji mold, is a fungus used in the fermentation of a variety of Japanese staples, including soy sauce, miso, and sake.[1] KA was originally a byproduct isolated from this process, which is where its name originated from. KA is also a chemical product of similar fungal species, including *A. flavus*, *A. tamarri*, and *A. parasiticus*.[2]

Historically, KA was first marketed in 1955 by Charles Pfizer and Company. Since then, the number of companies that mass produce KA has grown as its potential applications have generated increasing demand worldwide.[1,2] It is used throughout various industries, such as food, environment, pharmaceuticals, cosmetics, and agriculture. KA is widely marketed for its abilities to preserve or alter color both of food and skin, such as preventing oxidative browning in cut fruits and treating disorders of skin pigmentation.

Cutaneous hyperpigmentation is modulated by a variety of factors, including genetics, endocrine abnormalities, and hormone imbalances.[3] Melasma is an acquired skin disease characterized by hyperpigmented gray-brown patches, usually on the face and seen more often in women. While the cause of melasma is not fully understood, common triggers include sun exposure, changes in hormones (e.g., pregnancy, oral contraception, hormone replacement), and some skincare products.

Management typically includes long-term treatment with topical agents, such as KA, tretinoin, corticosteroids, hydroquinone (HQ), arbutin, and tranexamic acid.[4] These can be combined with oral agents, such as oral tranexamic acid, or various laser and energy-based device procedures. In non-prescription cosmetics, KA is safe to be used in concentrations of 1% or less according to the Cosmetic Ingredient Review Expert Panel (CIREP);[2] however, KA can be readily found at concentrations of 1%–4%. Although KA is typically well-tolerated, the most common side effect encountered by patients is contact dermatitis.

MECHANISM

Within the epidermis, melanocytes use the enzyme tyrosinase to catalyze the conversion of the amino acid tyrosine into the

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pigment melanin. Tyrosinase contains a copper ion in its active site, and when that copper ion is exposed to ultraviolet (UV) rays, tyrosinase becomes upregulated and melanocytes synthesize melanin.[2] Melanin synthesis in the skin is necessary to protect the tissue from DNA damage caused by UV radiation; however, disorders of hyperpigmentation can occur when melanocytes overproduce melanin in response to various triggers.

KA works by shielding the copper ion within the active site of tyrosinase, which subsequently blocks the UV activation, and ultimately inhibiting the production of melanin. Therefore, KA can be helpful in the management of disorders of hyperpigmentation, where there is an accumulation of tyrosinase and melanin in epidermal and dermal skin cells.

REVIEW

Standard topical treatments for hyperpigmentation, such as combinations of HQ, tretinoin, and corticosteroids, have been shown to produce satisfactory clinical results; however, these mainstay treatments come with potential side effects, which can include irritation, contact dermatitis, skin atrophy, and ochronosis.[5] KA can potentially offer a low-risk safety profile, which makes it a safe long-term treatment option for melasma, especially for regular maintenance and prevention between other treatments.

A multi-center prospective clinical study evaluated 100 patients with mild-to-moderate melasma, who were treated with a novel skin care regimen: (1) A day cream containing KA, vitamin E, vitamin A, and Aquaxyl™ complex, (2) A night cream containing KA, glycolic acid, Aquaxyl™ complex, and scrubbing beads, and (3) A preparation cleanser.[5] Aquaxyl™ complex is a blend of ingredients, which work to moisturize dry and dehydrated skin by controlling water circulation and reserves. A significant decrease in pigmentation was observed at both 45 days and 90 days of treatment. Treatment effectiveness was seen in all three types of melasma that were evaluated, including epidermal, dermal, and mixed. The regimen was demonstrated to be safe and effective without any reported side effects. Due to the nature of the study, it is difficult to determine how much, if any, of the clinical improvements were attributable to KA alone.

A recent systematic review compiled the randomized control trials (RCT) of various topical agents for the treatment of melasma.[6] The study found two "poorly designed" RCTs that examined the use of KA as a topical therapy for melasma.

In one of the studies, four different formulations were compared in an 80-patient single-blind RCT.[7] The once-daily formulations included: (1) 1% KA cream, (2) 1% KA + 2% HQ cream, (3) 1% KA + 0.1% betamethasone valerate cream, and (4) 1% KA + 2% HQ + 0.1% betamethasone valerate cream. The severity of melasma was calculated using the melasma area severity index (MASI) score and responses to treatment were compared using the percentage of change in MASI scores. After 12 weeks of treatment, all four patient groups had significantly decreased MASI scores. The study concluded that group 2 (1% KA + 2% HQ cream) was superior to the other regimens, followed closely by groups 4 (1% KA + 2% HQ + 0.1% betamethasone valerate cream) and 1 (1% KA cream). KA topical was demonstrated to offer clinical benefit; however, all groups contained KA, and there was no placebo group.

The other RCT was a prospective clinical study involving 60 patients with facial melasma.[8] The two study groups were split to be treated with once-daily application of either 4% HQ cream or 0.75% KA cream with 2.5% vitamin C for 12 weeks. MASI scores were utilized to determine clinical efficacy. At 4 weeks of treatment, facial hyperpigmentation responded earlier to the HQ group than the KA group. After 12 weeks of treatment, both groups showed significant decreases in MASI scores, but the HQ cream was associated with overall clinical superiority when compared to the KA cream. This study demonstrates that a topical containing KA can be effective, but may not be as effective as HQ. However, KA may be better tolerated and safer.

CONCLUSIONS

Although limited, the current available evidence suggests that KA may be an effective and well-tolerated therapy when included in a topical regimen for the treatment of melasma. Its over-the-counter availability and limited safety profile can encourage regular daily topical application and maintain patient satisfaction. Additional larger, placebo-controlled RCTs are still needed, and comparative studies should evaluate KA against other common topical therapies. KA may have clinical utility either in a daily regimen for mild melasma, in conjunction with oral agents or laser therapies, and/or as maintenance therapy in combination treatment regimens.

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ORIGINAL CONTRIBUTION

Successful Use of Secukinumab in Various Scenarios of Psoriasis

Geetika Chhabra, MD; Prashant Verma, MD; Niti Khunger, MD

ABSTRACT

Psoriasis is a chronic, immune-mediated, genetically determined inflammatory disease, which afflicts the skin and joints. There is a dearth of literature on situations where psoriasis is complicated by significant disability and associated comorbidities. In such situations, conventional treatments are fraught with challenges, which in turn limit their efficacy. We highlight the successful use of secukinumab in unusual and complicated scenarios of psoriasis. (*SKINmed*. 2020;18:274–276)

Psoriasis due to skin and/or joint symptoms per se, associated comorbidities, and coexisting pathologic states can pose a significant challenge in its management. Conventional treatments have limitations, while secukinumab, an IL 17-A antagonist, can effectively circumvent these situational adversities of psoriasis. We describe the use of secukinumab, an IL 17-A antagonist, in special situations where psoriasis is associated with active pulmonary tuberculosis, chronic recalcitrant pustular psoriasis with vitreous hemorrhage, pregnancy, metabolic syndrome, psoriatic arthritis with severe anemia, and recalcitrant erythroderma. In all of the cases presented secukinumab (Scapho®) was administered as a subcutaneous injection. The results have been encouraging, with secukinumab demonstrating an excellent response as well as a safety profile and long-term sustainability.

Case 1: A 42-year-old man presented to our department with extensive plaque psoriasis and a psoriasis area and severity index (PASI) of 24. The patient was diagnosed with sputum-positive pulmonary tuberculosis during his hospital stay and was started on World Health Organization category 1 anti-tubercular treatment (ATT), along with acitretin 50 mg once daily and apremilast 30 mg twice daily. No improvement was observed in his skin condition, and he was started on secukinumab 300 mg once weekly for 5 weeks, followed by a monthly maintenance doses of 150 mg. There was a 50% reduction in the PASI after 2 weeks of treatment. At the end of 2 months of treatment, the patient was in complete remission, and pulmonary opacities had regressed. Both ATT and secukinumab were well-tolerated by the patient.

Case 2: A 25-year-old man with psoriasis vulgaris for 12 years presented to us with a severe pustular exacerbation for the past 10 days. Four days later, he suffered a sudden absence of pain and profound vision loss in both eyes. B-scan showed bilateral vitreous hemorrhage. Topical eye drops were started, and oral prednisolone 60 mg per day for 2 weeks was prescribed but was later withdrawn due to lack of response and worsening of the skin condition. Secukinumab 300 mg once weekly for 5 weeks was begun and acitretin continued. By the fourth week, there was complete regression of the skin lesions. Also, visual acuity in both eyes improved with marked resolution of the hemorrhages. He continued on a monthly maintenance doses of 150 mg. The patient is now able to perform his daily activities.

Case 3: A 26-year-old woman gravida 2 parity 1 live 1 ($G_2P_1L_1$) with impetigo herpetiformis (IH), presented to us at 22 weeks gestation (Figure 1a). She failed to respond to a combination of oral prednisolone and cyclosporine. She also developed uncontrolled diabetes. At 27 weeks, she developed intrauterine growth restriction and was subsequently given secukinumab 300 mg once weekly for 5 weeks, with regular ultrasound monitoring for fetal well-being. Her skin lesions regressed completely in 2 weeks (Figure 1b), and prednisolone was reduced to 30 mg daily. Unfortunately, intrauterine death (IUD) occurred at 38 weeks.

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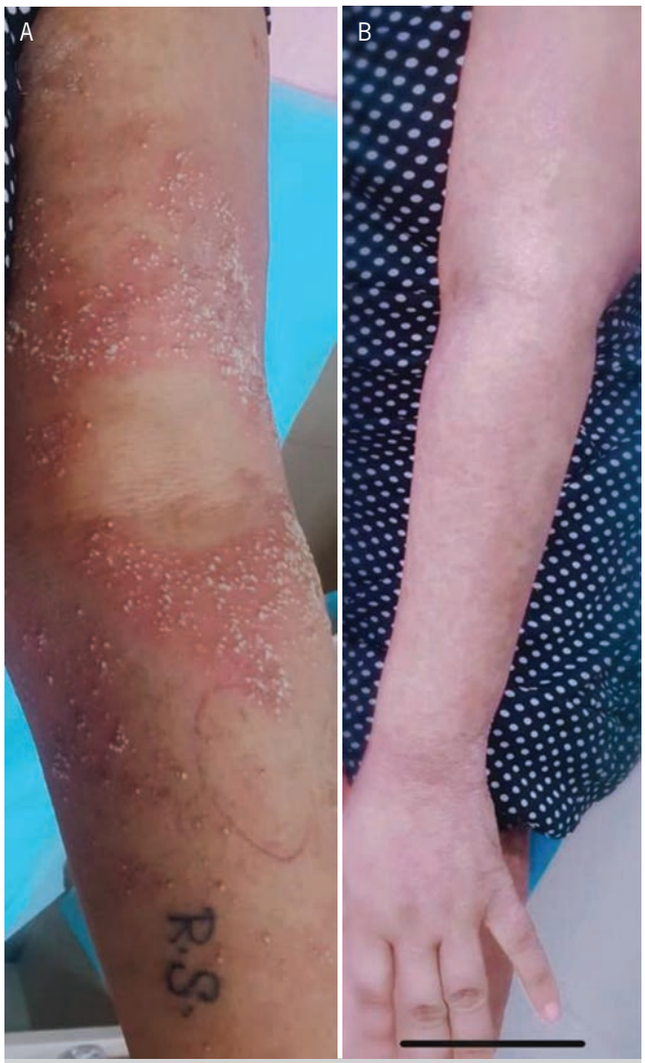

Figure 1. (A) Multiple pustules studded over an erythematous base on the left arm. (B) Regression of the pustules after secukinumab therapy.

Her skin condition then continued to improve during the postpartum period, and prednisolone was gradually tapered.

Case 4: A 36-year-old man with psoriatic arthritis for 2 years consulted us with an exacerbation of his condition during the past 8 months. His PASI at the time of admission was 27, and his body mass index was 22.39. Diabetes, hypertension, dyslipidemia, and nonalcoholic steatohepatitis were detected on FibroScan®. He was started on metformin, telmisartan, atorvastatin, and apremilast 30 mg given twice daily; however, his skin condition did not improve. He was then given secukinumab 300 mg once weekly for 5 weeks, followed by monthly maintenance doses of 150 mg for 3 months. At the end of the fourth week, there was complete clearance of his skin lesions, his PASI had improved to 2.1, and there was marked improvement in his metabolic parameters.

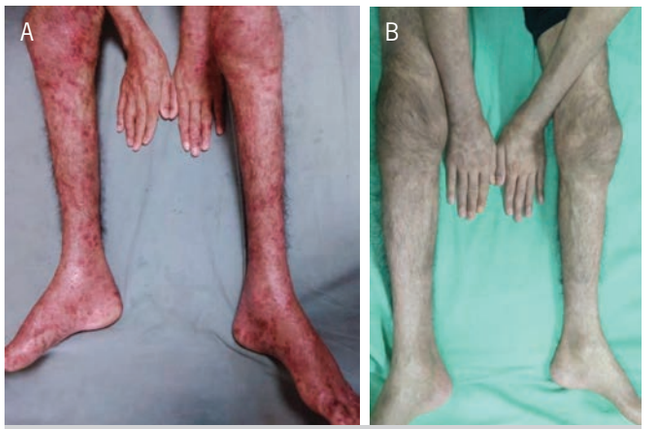

Figure 2. (A) Multiple psoriatic plaques over the arms and legs but with swelling of both knees. (B) Regression of skin lesions secukinumab therapy.

Case 5: A 22 year-old-man presented to us with recalcitrant psoriatic erythroderma for the past 1 year and a Dermatology Life Quality Index (DLQI) of 24. He was treated with acitretin, phototherapy, mycophenolate mofetil, methotrexate, azathioprine, and oral steroids. There was a partial response to cyclosporine with recurrent exacerbations. He was given secukinumab 300 mg once a week for 5 weeks. His condition began to improve after the third week, and the erythroderma cleared by the fifth week. His DLQI improved to 6. The patient has continued monthly maintenance doses of 150 mg with remission since then. Due to financial restraints, he discontinued secukinumab, which led to a flare up of his psoriasis. When he was able to resume therapy with secukinumab, his lesions completely cleared by the fourth week.

Case 6: A 21-year-old man, with a 1 year history of psoriasis and psoriatic arthritis for 10 years, presented with a severe exacerbation of psoriasis for the past 2 months (Figure 2a). His hemoglobin count was 6.7 g/dL, and his baseline PASI was 19.2, and DLQI was 22. He had developed steroid-induced bilateral avascular necrosis, Ficat stage 4, with secondary degenerative changes and reduced femoral acetabular joint space, as revealed by X-ray of both hips and the pelvis. His unman leukocyte antigen B27 (HLA B27) was positive, while the rheumatoid factor was negative. He received secukinumab 300 mg weekly, taking into account his severe arthritis and anemia. At the end of the first week, the skin lesions had regressed as had the arthritis. His PASI improved to 8.2, and DLQI was 10 (Figure 2b). Currently, the patient receives secukinumab 300 mg weekly for 4 weeks.

Case 7: A 45-year-old man presented with psoriatic erythroderma for the past 2 months. He was nonresponsive to both methotrexate and cyclosporine. He was then prescribed 300 mg of secukinumab; however, within a few minutes of the injection, he developed acute urticaria. He was given levocetirizine 5 mg once. The episode resolved within a day and did not recur. The patient refused further treatment with secukinumab.

DISCUSSION

The prevalence of latent tuberculosis infection is as high as 18%.[1] Three per cent of prismatic patients receiving TNF-alpha blockers, even while on chemoprophylaxis for tuberculosis, are known to still revert to active tuberculosis[1] Secukinumab does not have an effect on *Mycobacterium tuberculosis* dormancy or for reactivation *in vitro*.[2] This is the first report on the successful use of secukinumab in a patient with both pulmonary tuberculosis and psoriasis.

Vitreous hemorrhage is a rare ocular finding in psoriasis and may occur due to uveitis.[3] IL 17 levels, in addition to TNF-alpha levels, are higher in the aqueous humor of psoriasis patients with uveitis.[4] This may explain the efficacy of secukinumab in the present patient.

IH is associated with several fetal and maternal complications. Treatment modalities are limited and often teratogenic. To date, there are only two reports of the successful use of secukinumab in severe and persistent IH.[5]

Long-term, conventional, systemic treatment of psoriasis may have an adverse effect on coexisting metabolic disorders and consequently lead to cardiovascular complications. We know of a 66-year-old woman with psoriasis, whose comorbidities included myocardial infarction, hypertension, chronic renal failure, hyperthyroidism, and morbid obesity. She had a remarkable improvement in her skin, joint findings, and metabolic parameters following 48 weeks of secukinumab monotherapy.[6]

There have been long-term remissions of psoriatic erythroderma with secukinumab.[7] For example, a 13 year-old obtained long-term remission of refractory psoriatic erythroderma with secukinumab.[8]

Psoriasis can be associated with anemia induced by proinflammatory cytokines, primarily TNF-alpha and IL-6. Conventional immunosuppressants, methotrexate and mycophenolate mofetil, are cytotoxic and can negatively affect hemoglobin levels. TNF-alpha blockers could possibly lessen the anemia;[9] however, the role of secukinumab in anemia is unknown.

An incidence rate of 0.6%–1.2% of urticaria due to secukinumab has been reported to the United States Food and Drug Administration (FDA). The present case developed acute urticaria after the first dose of secukinumab.

CONCLUSIONS

This series highlights unusual and complicated scenarios of psoriatic patients successfully treated with secukinumab. Even though only one patient with psoriatic erythroderma developed secukinumab-induced urticaria, we believe that secukinumab can be used as a therapeutic modality in patients with a number of comorbities.

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ORIGINAL CONTRIBUTION

Characteristics of Vitiligo in Children and Adolescents

Pushpinder Singh Chauhan, MD; Hitender Sharma, MBBS; Niharika Dhattarwal, MD; Vikram K. Mahajan, MD; Karaninder S. Mehta, MD; Anuj Sharma, MD; Reena Sharma, MD; Yog Raj Verma, MBBS; Monika Chandel, MBBS

ABSTRACT

Vitiligo in children and adolescents displays some distinct features, which may affect its clinical course, therapeutic outcome, and prognosis. We studied 579 children and adolescents with vitiligo, comprising 275 (47.5%) boys and 304 (52.5%) girls (male:female ratio [m:f], 1:1.1) aged between 2 and 19 years (mean ± SD 11.13 ± 4.23 years). The majority of children (301, 52%) were aged >5–12 years, and 221 (38.2%) were adolescents; onset of vitiligo in the above groups occurred between the ages of 2 and 19 years (mean ± SD 9.18 ± 4.08 years). The majority of patients (337, 58.2%) had developed vitiligo between 5 and 12 years of age, and 332 (57.4%) patients had a medical consultation within 1 year of the onset of the disease. The involvement of up to 10% of body surface area in 569 (98.3%) patients, generalized vitiligo in 328 (56.7%) patients, and focal vitiligo in 158 (27.3%) patients were the major presentations. Only 150 (15.9%) patients had family members affected by vitiligo, and associated systemic disorders, predominately thyroid abnormalities, occurred in three (0.5%) patients. Vitiligo was more frequent in children aged 5–12 years, and it affected girls with a slight preponderance, commonly presenting as generalized vitiligo and focal/localized vitiligo. Patients with a family history of vitiligo had an earlier onset but without a statistically significant difference. Local trauma is an important trigger, and screening for thyroid disorders appears important. (*SKINmed*. 2020;18:278–285)

Vitiligo affects 1%–2% of the population of all races and ethnicities worldwide.[1,2] Clinically, depigmented macules of variable sizes and patterns vary from being localized to a small area to almost generalized depigmentation. It is a disease of a complex pathogenesis affecting genetically predisposed patients. Prevalence of family member(s) affected by vitiligo ranges from 11% to 46% in general; however, its poorly understood inheritance pattern is mostly considered polygenic or an autosomal dominant trait with variable penetrance.[3,4] Autoimmune etiopathogensis remains the most plausible pathomechanism due to its association with autoimmune thyroiditis, Grave's disease, diabetes mellitus, Addison's disease, pernicious anemia, and alopecia areata among patients or their immediate relatives.[5] Trauma; infection; sepsis; poor nutrition; physical or psychologic stress; and exposure to drugs, chemicals, toxins, and sun are the commonly suspected inciting factors.[6] Both genders of any age are affected, with some predilection for girls and women.[1,2] Its onset in 50% of patients is prior to 20 years of age, mostly between 18 and 21 (mean 24) years, below the age of 10 years in 10% of cases, and before 8 years of age in 25% of cases. Vitiligo has even appeared as early as 6 months of age.[7–9] The existence of congenital vitiligo remains debatable, as robust evidence is lacking.[10]

Although childhood vitiligo is clinically similar to adult onset vitiligo, there is a preponderance in girls and women, segmental vitiligo being more common than other varieties, and an association with autoimmune or endocrine disorders being uncommon are distinct to childhood vitiligo, which may affect treatment outcome and prognosis.[3,7] Vitiligo remains a common cause for parental anxiety and distress. Early-onset childhood vitiligo, together with features of trichrome vitiligo, confetti-like lesions, and the Koebner's phenomenon, is considered a sign of extensive and progressive clinical course, treatment recalcitrance, and poor prognosis, particularly during adulthood.[11,12]

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MATERIALS AND METHODS

The medical records from January 2015 to March 2018 of children and adolescents with vitiligo were analyzed retrospectively after approval from the institutional ethics committee. Subjects were grouped as preschool children (aged 2–5 years), and school-going children (>5–12 years), and adolescents (>12–19 years). The diagnosis was clinical, and lesions without highlighting under Wood's light were excluded. The extent of body involvement was measured by the Wallace rule of nine for body surface area, and clinical patterns of vitiligo were defined as per guidelines issued by the Vitiligo Global Issues Consensus Conference, 2011–2012.[13]

STATISTICAL METHODS

The data obtained were tabulated and analyzed using Office™ Excel® software. The continuous data are presented as mean ± standard deviation (SD), and categoric variables are presented as frequencies and percentages. Chi-square test

Table 1. Clinico-epidemiologic Features of Vitiligo Patients

Features	Number of Patients (%) *n* = 579
Gender	
Boys	275 (47.5)
Girls	304 (52.5)
Male:Female	1:1.1
Age	
Range	2–19 y
Mean ± SD	11.13 ± 4.23
2–5 y	57 (9.8)
>5–12 y	301 (52)
>12–19 y	221 (38.2)
Age at onset of vitiligo	
Range	2 y–19 y
Mean ± SD	9.18 ± 4.08
≤5 y	118 (20.4)
>5 to 12 y	337 (58.2)
>12 to 19 y	124 (21.4)
Duration of disease	
Range	1 w–19 y
Mean ± SD	2.03 ± 2.58
≤1 m	68 (11.7)
>1 to 6 m	161 (27.8)
>6 m to 1 y	103 (17.8)
>1 to 5 y	185 (32.0)
>5 to 10 y	54 (9.3)
>10 y	08 (1.4)
Sites of onset	
Scalp, face, and neck	164 (28.3)
Lower limbs	135 (23.3)
Eyelids	129 (22.3)
Trunk	90 (15.5)
Upper limbs	33 (5.7)
Lips	17 (2.9)
Mucosal/anogenital skin	11 (2)
Triggering factors	
Identified by patients/parents	**47 (8.1)**
Physical trauma	44
Surgery	01
Medical illness	01
Psychological stress	01
Family history of vitiligo and age of onset	
Present	**53 (9.2)**
First-degree relatives	31
Second-degree relatives	07
Third-degree relatives	15
Age at onset, mean ± SD (range)	8.63 ± 4.03 (6 m–19 y)
Absent	**526 (90.8)**
Age at onset, mean ± SD (range)	9.23 ± 4.08 (1.5 y–18 y)
***P* value**	0.30

Abbreviations: SD, standard deviation; m, months; w, weeks; y, years. $P < 0.05$ calculated at 5% level (95% confidence limit) was considered statistically significant.

and student *t*-test were used for statistical analysis of the categoric and parametric data, respectively. $P < 0.05$ calculated at 5% level (95% confidence limit) was considered statistically significant.

RESULTS

There were 275 (47.5%) boys and 304 (52.5%) girls (m:f 1:1.1), aged between aged 2 and 19 years (mean ± SD 11.13 ± 4.23 years), at the time of presentation. Tables 1 and 2 depict their demographic and clinical characteristics, plus the frequency of vitiligo patterns. Reports of thyroid function tests were available for only 67 patients.

The majority were 301 (52%) children aged >5–12 years. There were 221 (38.2%) adolescents, and 57 (9.8%) were preschool children. The duration of vitiligo varied between 1 week and 19 years (mean ± SD 2.03 ± 2.58 years), with the majority of 332 (57.4%) patients presenting within 1 year of the onset of vitiligo. The age at onset was between 2 and 19 years (mean ± SD 9.18 ± 4.08 years), and the majority (337, 58.2%) of the patients had developed vitiligo between 5 and 12 years of age. In order of frequency, scalp, face, and neck in 164 (28.3%); legs in 135 (23.3%); eyelids in 129 (22.3%); trunk in 90 (15.5%); arms in 33 (5.7%); and lips in 17 (2.9%) patients were the usual sites of the onset of vitiligo. Eleven (1.9%) patients noted the initial lesion appearing over the mucosal/anogenital area.

Only 47 (8.1%) patients identified triggering factors; physical trauma was implicated by 44 patients while one patient each blamed surgery, medical illness, or psychologic stress. Fifty-three (9.2%) patients had a family history of vitiligo, comprising first-degree relatives in 31 patients and second-/third-degree relatives in 22 patients. In patients with family members affected by vitiligo, the mean age at the onset of vitiligo was 8.63 years (range: 6 months–19 years), compared to 9.23 years (range: 1.5–18 years) in the remaining 526 patients. The difference was not statistically significant.

The majority (564, 97.4%) of patients had nonsegmental vitiligo, involving multiple body sites, whereas only 15 (2.6%) patients had segmental vitiligo (Figure 1). In order of frequency, the commonest forms of nonsegmental vitiligo were generalized vitiligo (vitiligo vulgaris) in 328 (56.7%) patients (Figure 2), focal vitiligo in 158 (27.3%) patients (Figure 3), and acrofacial vitiligo in 37 (6.4%) patients. Vitiligo was localized only to the face in 18 (3.1%) patients or the acral areas in 16 (2.8%) patients. Two (0.4%) patients each had vitiligo universalis (Figure 4), mucosal involvement (Figure 5), and mixed pattern (Figure 6). The extent of body involvement was up to 10% in 569 (98.3%) patients, comprising the majority. Leukotrichia (Figure 7) and kobnerization (Figure 8) occurred in 126 (21.8%) and 111 (19.2%) patients, respectively. Twenty six (4.5%) patients had trichrome morphology (Figure 9).

Table 2. Clinical Patterns of Vitiligo and Body Surface Area Involvement

Clinical Patterns	Number of Patients (%) $n = 579$
Clinical patterns	
Segmental	**15 (2.6)**
Nonsegmental	**564 (97.4)**
Generalized vitiligo (vitiligo vulgaris)	328 (56.7)
Localized/focal	158 (27.3)
Acrofacial	37 (6.4)
Facial	18 (3.1)
Acral	16 (2.8)
Vitiligo universalis	2 (0.4)
Mucosal involvement	2 (0.4)
Mixed pattern	2 (0.4)
Genital involvement	1 (0.2)
Other features	
Leukotrichia	126 (21.8)
Koebner's phenomenon	111 (19.8)
Trichrome	26 (4.5)
Body surface area involved	
≤1%	420 (72.5)
>1%–10%	149 (53.7)
>10%–50%	09 (1.6)
>50%–80%	01 (0.2)

Only three (0.5%) patients had associated systemic disorders (Table 3), which comprised newly diagnosed hypothyroidism, elevated serum anti-thyroperoxidase antibody levels (autoimmune thyroiditis), and rheumatic heart disease in one patient each. No patient had diabetes mellitus. Other notable dermatoses in 35 (9%) patients were canities without scalp vitiligo in 21 patients (Figure 10), halo nevus in 12 patients (Figure 2), and ichthyosis vulgaris and alopecia areata in one patient each.

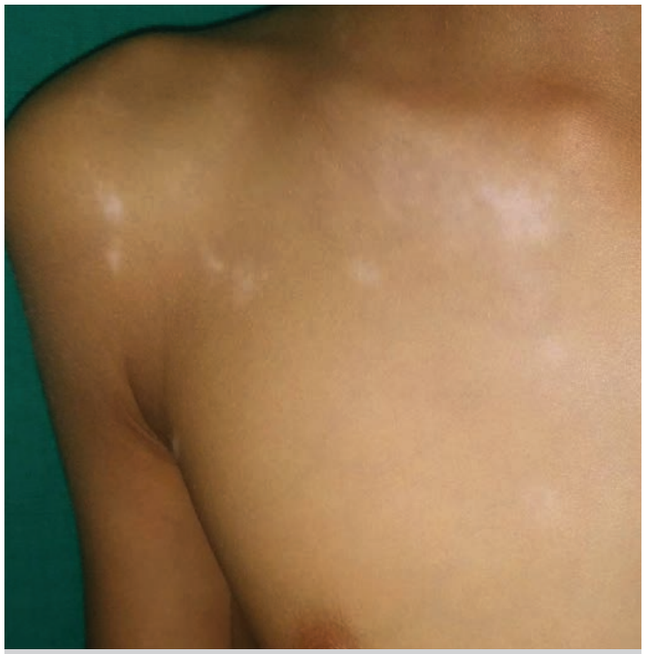

Figure 1. Segmental vitiligo involving the right side of the chest.

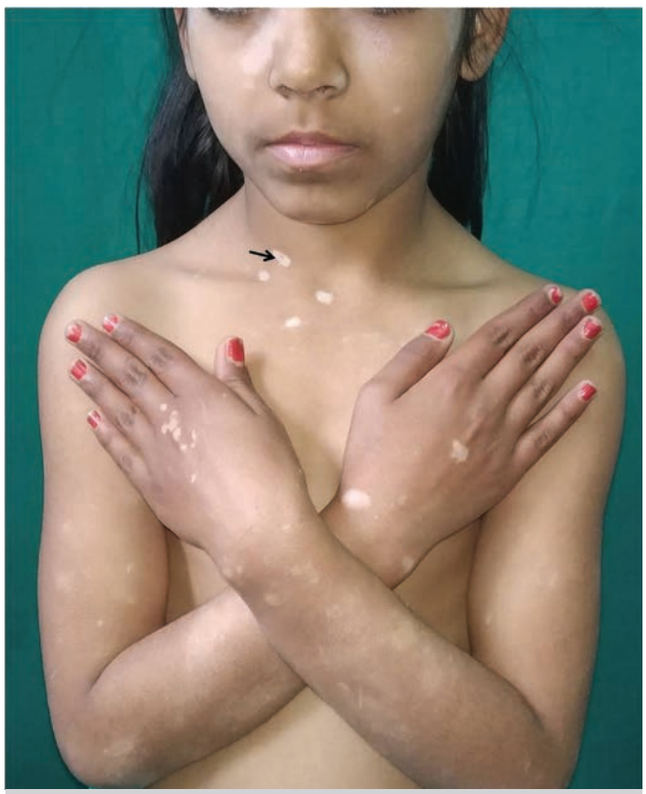

Figure 2. Depigmented macules over the face, chest, and extremities in generalized vitiligo. A halo nevus is also seen (arrow).

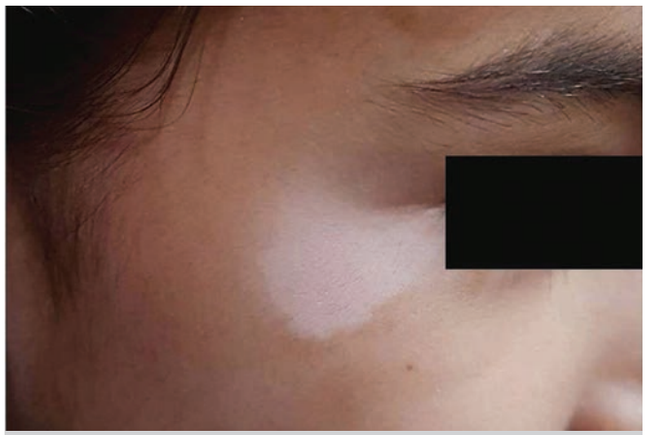

Figure 3. Focal vitiligo macule over the right periocular area. It did not evolve to any pattern within one year.

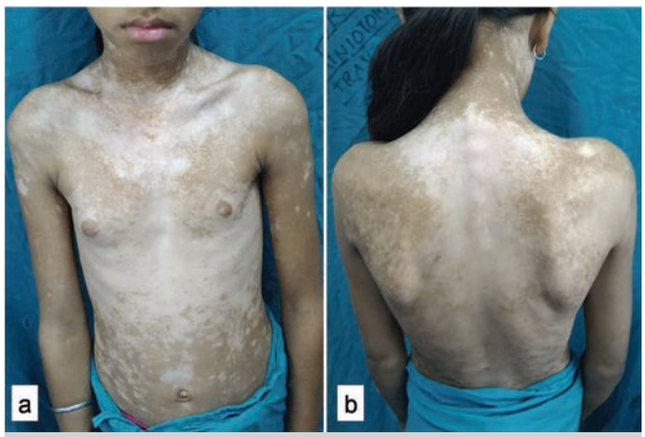

Figure 4. Extensive body involvement in vitiligo vulgaris with impending vitiligo universalis.

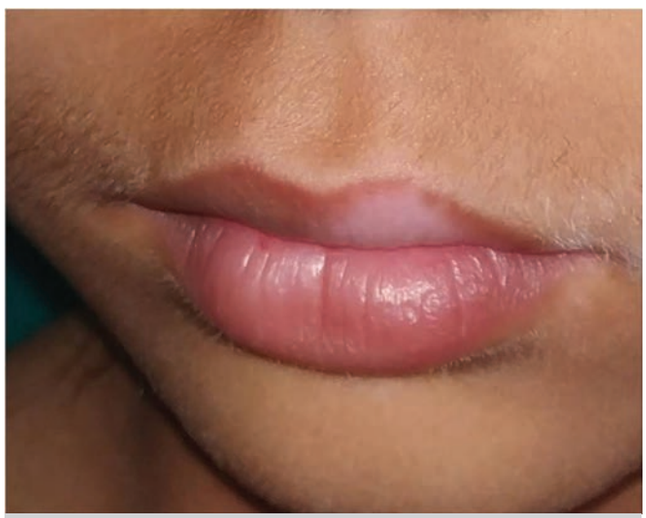

Figure 5. Mucosal vitiligo involving the upper lip.

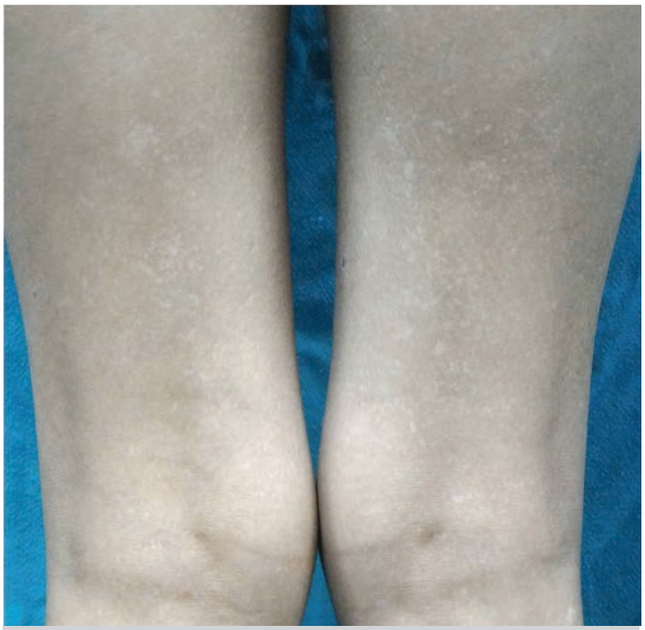

Figure 6. Confetti-like depigmented macules over the legs or vitiligo punctata in a patient with vitiligo denotes progressive disease.

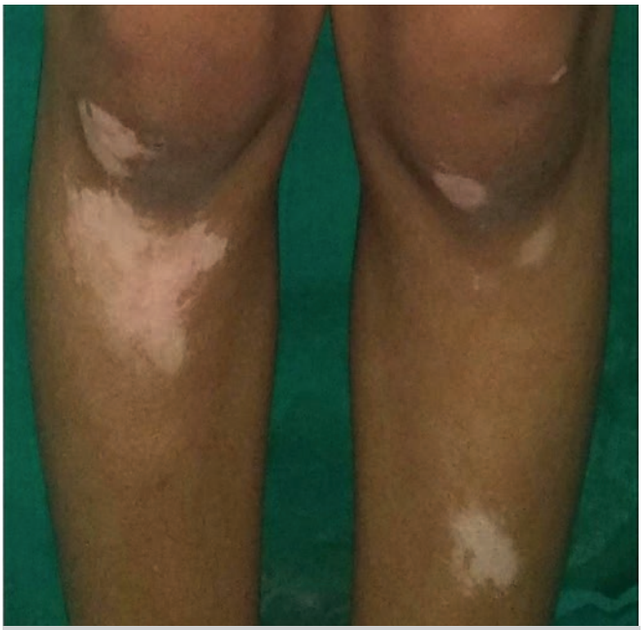

Figure 8. Koebner's isomorphic phenomenon: vitiligo lesions localizing over friction-prone areas around the knees and shins.

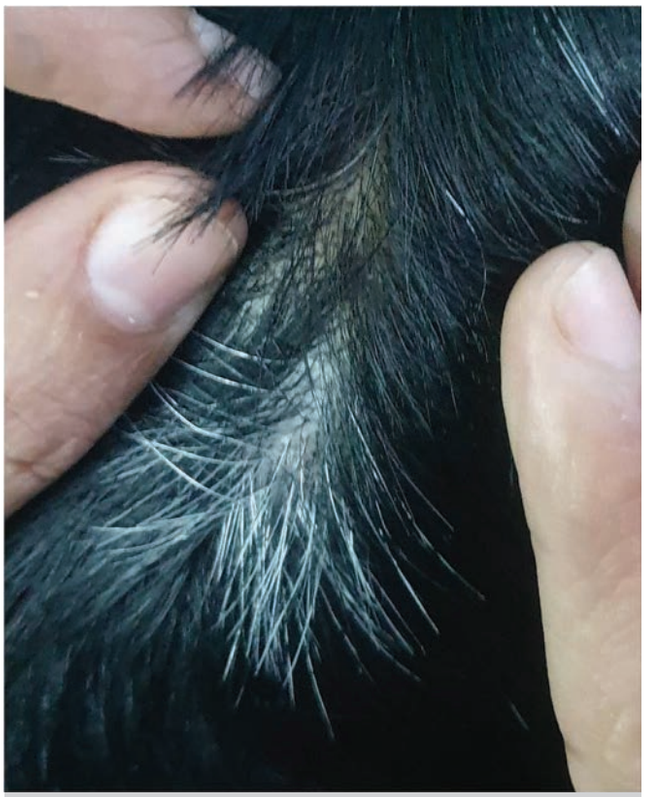

Figure 7. Leukotrichia in vitiligo lesions over the scalp.

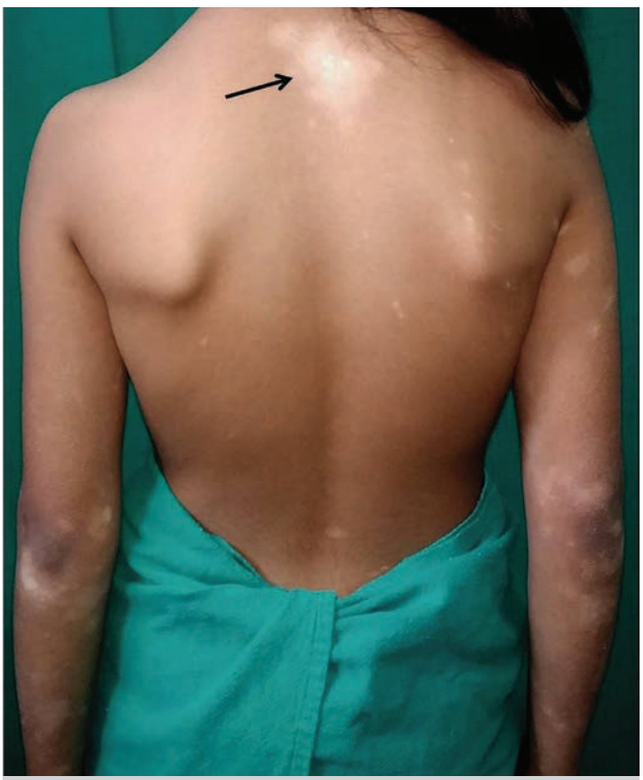

Figure 9. Trichrome vitiligo (arrow) showing zones of varied hues of depigmentation and hyper pigmentation in a child with generalized vitiligo.

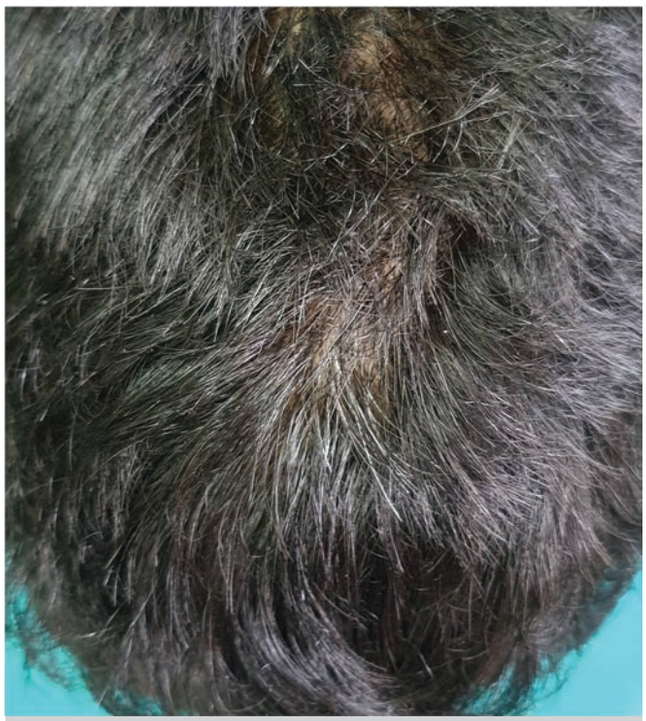

Figure 10. Canities or premature graying of scalp hair with no underlying vitiligo macule (*cf.* leukotrichia) in a vitiligo patient is considered its *forme fruste*.

Table 3. Associated Disorders in Vitiligo Patients

Associated Disorders	Number of Patients (%) *n* = 579
Associated systemic disorders	**03 (0.52)**
Rheumatic heart disease	01
Newly diagnosed hypothyroidism	01
Abnormal serum anti-TPOAb levels and no clinical thyroid disease	01
Associated cutaneous disorders	**35 (8.98)**
Canities	21
Halo nevus	12
Alopecia areata	01
Ichthyosis vulgaris	01

Abbreviation: anti-TPOAb, antithyroid peroxidase antibodies.

DISCUSSION

Vitiligo in children aged <12 years has been reported to be between 23% and 26% in two Indian studies, compared to 16% and 24% among the Koreans and the Chinese, respectively.[14,15] Although understudied, its prevalence among adolescents was 21.7% of 945 patients in one study.[16] The reported mean age of onset ranged from 5.6 to 7.4 years in most studies.[14,15] Except for a few exceptions, both genders are affected almost equally or with a slight preponderance of girls (m:f 1.1.1), which can be attributed to parents seeking early medical consultation for cosmetic concerns.[14,16] The mean age of 9.2 years at onset in this study also conforms to most of the above-mentioned epidemiologic characteristics. The fact that the majority (332, 57.4%) of cases in this study sought medical consultation within 1 year of the onset of the disease corroborates with previous reports that cited 1.9 years (range: 2 months–11 years) and was in contrast to 5 years among adults.[16,17] It perhaps reflects parental concern for vitiligo-associated stigma, as often cited by them, and accounts for the early medical consultation in case of children, and girls in particular.

The reported prevalence of affected family members in childhood vitiligo varies between 11% and 46%, and these children are said to have a lower age of onset.[2,4] In comparison, only 9.2% children in our study had other family members affected by vitiligo, the majority being first-degree relatives; however, there was no statically significant difference in age of onset of vitiligo in children having affected family members, compared to those having no family members with vitiligo.

In general, the clinical forms of vitiligo in our study were distributed similar to their occurrence in adults with minor differences. In order of frequency, prevalence of generalized vitiligo (56.7%), localized/focal vitiligo (27.3%), and acrofacial vitiligo (6.4%) in our study conforms to their respective prevalence of 42%–61%, 23%–24%, and up to 10% reported among all vitiligo cases.[17,18] Only 2.6% of patients had segmental vitiligo in our study corroborating its reported prevalence of up to 12% among all vitiligo cases.[4,13] Vitiligo universalis and mucosal vitiligo in 0.4% patients each, and trichrome vitiligo in 5% of our patients remain uncommon forms in childhood, compared to adulthood cases.[14,18] Focal vitiligo may evolve into a more generalized variety and involve extensive body involvement, but most children have <20% body surface area (BSA) involvement. It was <10% in 98.3% of our cases, constituting the majority.[14,18]

Although factors inciting vitiligo and its continued development may not be always identified, physical trauma is the most implicated factor among a plethora of triggers.[18,19] This is evident from the tendency of vitiligo, irrespective of the clinical type, to involve trauma-prone sites (Koebner's phenomenon). The majority (29%) of our patients had the onset of vitiligo over extremities, the sites which are more prone to friction and injuries, especially in children

who are agile and playful by nature. Onset of vitiligo over scalp, face, and/or neck has been frequently reported in 28.3% of our patients, alluding to koebnerization due to sunlight/ultraviolet light.[19,20] Koebner's phenomenon in 19.2% of patients, indicating continued disease activity, is almost in sync with its reported prevalence of between 21% and 34% among all vitiligo patients.[4,17,18]

Vitiligo may have associated endocrinopathies or other autoimmune disorders (diabetes mellitus, pernicious anemia, Addison's disease, thyroid disease), and circulating antibodies against gastric parietal cells, thyroid gland, and adrenal gland occurred in up to 13% of children with vitiligo, more so in cases with nonsegmental vitiligo.[7,14,21] Clinically, hypothyroidism was almost six times more common in childhood vitiligo, compared to controls in a study.[7] Autoimmune thyroiditis may manifest as elevated serum antithyroid antibodies (antiperoxidase antibodies, thyroid microsomal antibodies, antithyroglobulin antibodies) in 24% of children and adolescents with vitiligo.[7] Out of 67 thyroid function test reports, one patient each in this study had newly diagnosed hypothyroidism and elevated serum anti-TPO (antithyroid peroxidase) antibody levels, suggesting autoimmune thyroiditis with euthyroid state.

Of the 35 patients with concurrent dermatoses, we observed canities in 21 and halo nevi in 12 patients. Halo nevus, a paradigm of cell-mediated immunity against abnormal melanocytes/nevocytes, is often considered to herald the onset of vitiligo in children, and it occurs in 2.5%–34% cases of childhood vitiligo, particularly in the nonsegmental form.[14,15] Presence of canities, a vitiligo-associated disorder or its *forme fruste* that may or may not evolve to classic vitiligo, conforms to the earlier views on the involvement of an autoimmune pathway.[22] Similarly, alopecia areata coexisting with vitiligo, both sharing common immunopathogenesis, observed in one of our patients reportedly occurs in 2.4%–3.4% cases of childhood vitiligo.[17,23] The presence of rheumatic heart disease and ichthyosis vulgaris appears fortuitous.

LIMITATIONS

Small sample size; observational, hospital-based, single-center, cross-sectional study design; and no follow-up remain major limitations. Recall or selection bias is possible due to retrospective study design. All patients could not be assessed for all autoimmune disorders.

CONCLUSIONS

Vitiligo appears to affect both genders with slight preponderance of girls, mostly between the ages of 5 and 12 years, and has an early age of onset, especially in children with a first-degree family member affected by vitiligo. Vitiligo vulgaris and focal/localized vitiligo remain the two commonest varieties. Trauma remains an important inciting factor in childhood vitiligo, as well. The presence of concurrent thyroid disorders, which may affect prognosis and treatment protocols, appears more common in children, compared to adults with vitiligo having diabetes or other autoimmune disorders.

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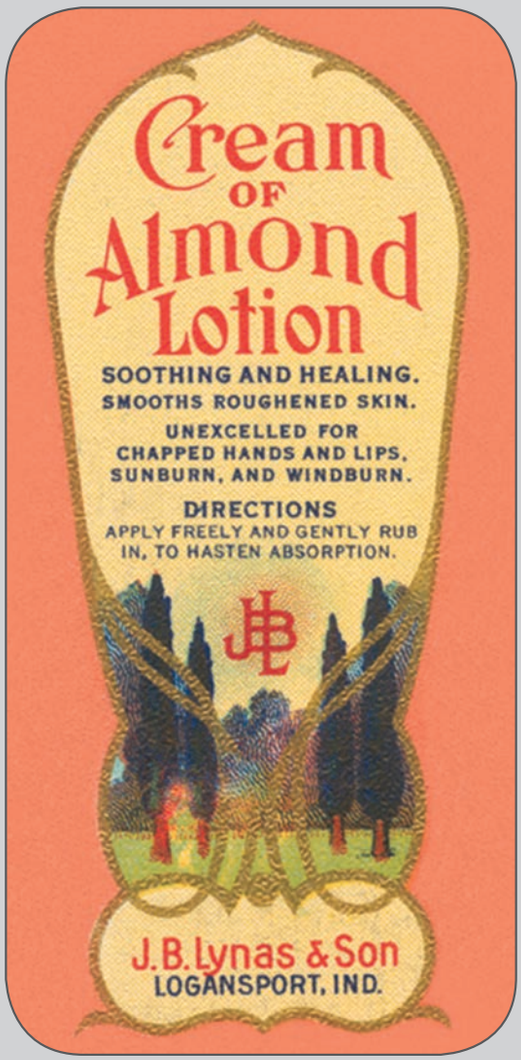

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REVIEW

Dermatofibrosarcoma Protuberans: The Current State of Multidisciplinary Management

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ABSTRACT

Dermatofibrosarcoma protuberans (DFSP) is a rare, infiltrative, soft tissue tumor. It has a propensity for deep invasion but a low risk for distant metastasis. The classic presentation is a slowly progressive, painless, and erythematous to purpuric patch on the trunk or arms. A deep, subcutaneous punch biopsy or incisional biopsy should be performed for diagnosis in all suspected cases; wide undermining of the skin is to be avoided for minimizing the risk of tumor seeding and for retaining the feasibility of histopathologic examination of re-excisions. Histopathologic distinction of DFSP from dermatofibroma requires immunohistochemical assessment for CD34, factor XIIIa, nestin, apolipoprotein D, and cathepsin K. Management of this cutaneous sarcoma involves a multidisciplinary oncologic approach. Surgical excision is usually the first step in management. DFSP has a high propensity for local recurrence, even when surgical margins are negative; therefore, radiation therapy or rarely systemic therapy is recommended, especially for locally advanced or metastatic cases. The indolent nature of DFSP requires lifelong surveillance for recurrence; however, most recurrences occur within 3 years of the primary excision. The median time for the development of a local recurrence is estimated to be 32 months. An emerging theragnostic transmembrane receptor target, folate hydrolase-1 (FOLH1; prostate-specific membrane antigen), has been expressed in benign dermatofibromas and in high-grade sarcomatous phenotypes. These findings suggest that DFSP may also express FOLH1, which could allow for surveillance with FOLH1 PET/CT and antibody-mediated brachytherapy. (*SKINmed*. 2020;18:288–293)

Dermatofibrosarcoma protuberans (DFSP) was first described by Jean Darier (1856–1938) in 1924 as a progressive and recurring dermatofibroma.[1] In 1925, Erich Hoffman (1868–1959) coined the term DFSP,[2] which is a relatively uncommon, low-grade, slow-growing, soft tissue neoplasm of mesenchymal origin. While DFSP is the most common type of cutaneous sarcoma, it represents less than 0.1% of all malignant neoplasms and 1% of all soft tissue sarcomas (STS).[3] The estimated annual incidence of DFSP is 4.2–4.5 cases per million persons in the United States.[4] DFSP is locally aggressive and is associated with recurrence rates of 10%–60% with failure likely related to the tumor's irregular morphology, which is characterized by frequent finger-like extensions.[5] In spite of high recurrence rates, DFSP rarely produces regional (1% of the cases) or distant metastasis (4%–5% of the cases).[6]

DFSP is most commonly found on the trunk (42%–72% of the cases), followed by the extremities (20%–30% of the cases), and the head and neck (10%–16% of the cases)[7] (Figures 1–3). Presenting locations for DFSP are associated with sites of prior trauma, such as old burn sites, surgical scars, vaccination sites, central venous line puncture sites, arthropod bites, and radiation dermatitis.[7]

DFSP is most commonly found in adults aged between 20 and 50 years[8]; however, incidence rates between 6% and 20% have been reported in children.[9] Although early reports on DFSP showed no racial predilection, the incidence rate among darker Fitzpatrick

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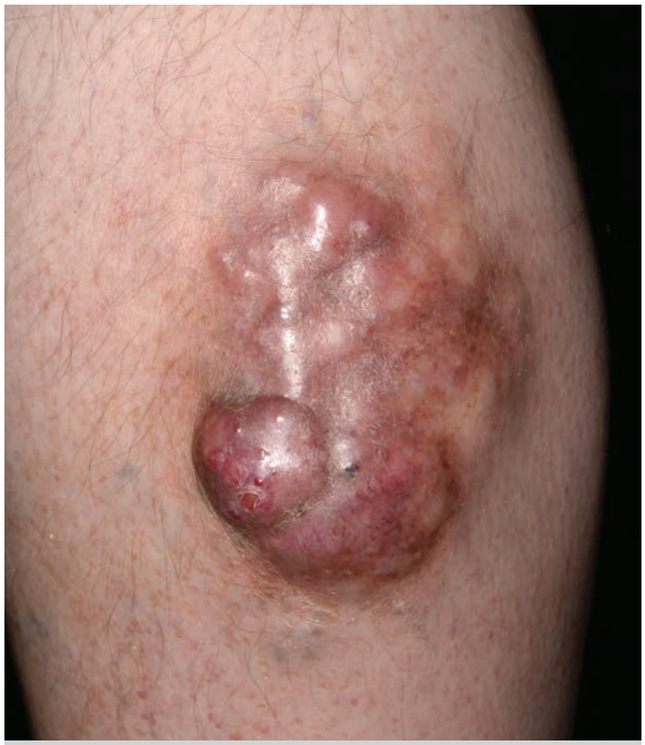

Figure 1. Locally advanced, nodular dermatofibrosarcoma protuberans, with erythematous, violacious, and hyperpigmented discoloration, located on the left shin of a middle-aged man.

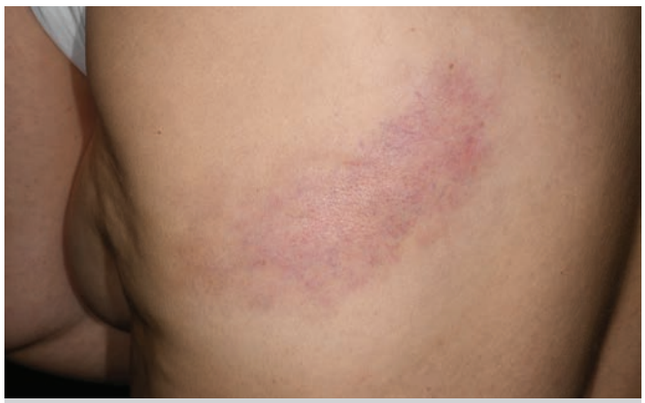

Figure 2. Erythematous to violacious patchy discoloration of a dermatofibrosarcoma protuberans located on the back of a middle-aged woman.

skin types was nearly double the incidence rate among lighter Fitzpatrick skin types (6.5 cases vs. 3.9 cases per million population).[4] The Bednar tumor is an extremely rare, pigmented variant of DFSP, which accounts for approximately 1% of all DFSP cases; the annual incidence rate of the Bednar tumor among darker Fitzpatrick skin types is 7.5 times higher than that of the lighter

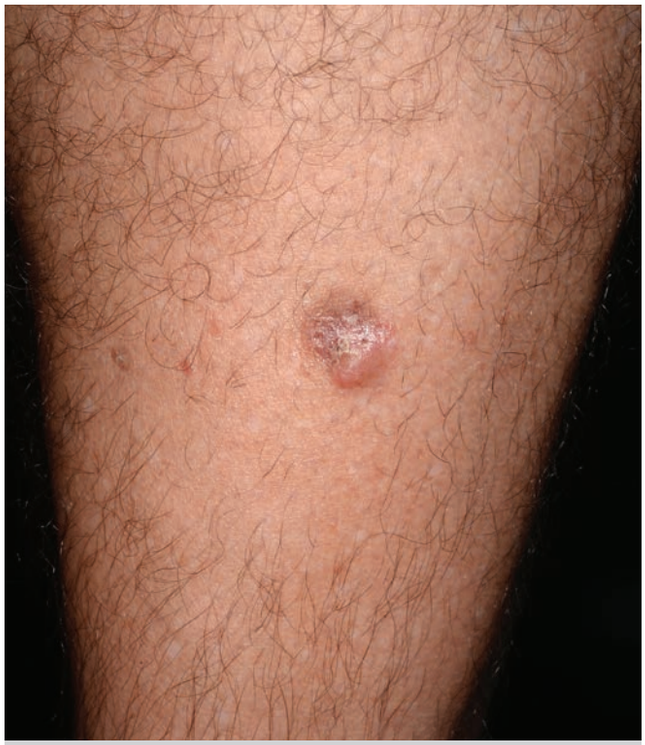

Figure 3. Erythematous and scaly dermatofibrosarcoma protuberans papule on the right calf of a middle-aged man.

Fitzpatrick skin types.[10] Women have higher incidence rates compared to men (4.4 vs. 4.2 cases per million per year); however, this gender difference is negligible in the geriatric population.[4]

PATHOPHYSIOLOGY

DFSP is a slow-growing, malignant, mesenchymal skin tumor that arises in the dermis and invades the subcutaneous tissues, fascia, muscle, and bone. DFSP is thought to arise from pluripotent mesenchymal progenitor cells with the capacity to differentiate into fibroblastic, histiocytic, or neuroectodermal cells found in these tumors.[11–13]

Platelet-derived growth factor-beta (PDGF-β) enhances the growth rate of DFSP tumor cells. Specific cytogenetic abnormalities, such as reciprocal translocations of chromosomes 17 and 22, t(17;22), and supernumerary ring chromosomes composed of interspersed sequences from bands 17(17q22) and 22(22q12), have been identified in DFSP tumor cells. These readjustments fuse the collagen type I alpha 1 (COL1A1) and the PDGF-β chain genes. The collagen promoter drives the production of the COL1A1 and PDGF-β fusion protein. The fusion protein is then processed into a functional PDGF-B and later interacts with the PDGF receptor on the cell surface of DFSP tumor cells.

The activation of the PDGF receptor tyrosine kinase triggers the proliferation of DFSP tumor cells.[14]

CLINICAL PRESENTATION

The diagnosis of DFSP is often delayed by months to years, as the tumor initially presents as asymptomatic, erythematous to violaceous patches (Figure 1) that progress slowly to plaque or papule (Figure 2) and then to nodular/tumoral phases (Figure 3).[15] In the early stages of the disease, DFSP should be differentiated from hypertrophic scars, keloids, epidermal cysts, lipomas, dermatofibromas, and nodular fasciitis.[16] With progression of the disease, DFSPs can grow radially, become atrophic, sclerotic, ulcerative, and protuberant, with subsequent invasion of subcutaneous tissues, fascia, muscles, and bone.[7,17] In the latter disease states, the differential diagnosis should consider amelanotic melanoma, pyogenic granuloma, Kaposi sarcoma, and other STS.[18]

DIAGNOSIS

Clinical suspicion is confirmed by histopathologic assessment, as is the case with most solid tumors.[19]

Histopathologically, DFSP typically presents as a storiform or fascicular proliferation of bland spindled cells that extend from the dermis into the subcutis. DFSP is largely CD34-positive and factor XIIIa-negative[20,21]; distinction of DFSP from dermatofibroma requires immunohistochemical assessment for CD34, factor XIIIa, nestin, apolipoprotein D, and cathepsin K.[22–24]

Routine diagnostic imaging is not generally performed at the initial presentation unless metastatic disease is suspected. A chest x-ray may be prescribed for baseline screening for pulmonary metastasis in high-risk cases, such as recurrence or suspicion of fibrosarcomatous changes (typically found in more than 5% of the surgical specimens).[25] Computed tomography (CT) scanning is indicated if direct bone involvement or metastasis is suspected.[2] Medical literature supports magnetic resonance imaging (MRI) for preoperative assessment in larger or atypical lesions and in recurrent disease.[25–27] MRI may be helpful for defining the approximate tumor border and the depth of invasion.[28] Ultrasonography (US) is utilized for monitoring local DFSP or evaluation of regional lymph node metastases. US examination indicated that DFSPs are mostly hypoechoic or mixed hyperechoic/hypoechoic, with well-defined margins and projections similar to pseudopodia.[29] Fluorodeoxyglucose (FDG)–positron emission tomography scanning may be helpful in monitoring metastatic disease.

STAGING

The American Joint Committee on Cancer is yet to develop a TNM staging system for DFSP. In general, owing its low risk for regional and distant metastasis, DFSP is viewed as a local disease. The following staging system[25] may be helpful in clinical practice:

- Stage I—localized disease
- Stage II—lymph node metastasis
- Stage III—distant metastasis

CURRENT STATE OF MULTIDISCIPLINARY MANAGEMENT

Surgical Oncology

The initial management of DFSP is surgical.[19] The operative approach to DFSP must be methodically planned. Size and location of the tumor, risk for seeding, as well as cosmesis, will determine the most appropriate surgical procedure.[5,30,31]

Due to the proclivity for irregular and frequent, deep, subclinical extensions, every effort should be made toward a complete resection (R0) during the primary surgery.[32] To ensure a complete resection, histopathologic assessment of all surgical margins is required prior to deficit reconstruction; reconstruction without confirmation of negative surgical margins is discouraged, as the undermining procedures and tissue movement can result in tumor seeding, which may complicate the ability to achieve future R0 surgeries.[19]

If positive margins are identified during histopathologic analysis of the resected specimen, re-resection is recommended whenever possible in order to achieve clear margins. There is a discrepancy in the literature about the optimal margins for DFSP; generally, 2 to 4 cm to the investing fascia is deemed necessary.[31,33,34] A series of 204 patients with DFSP showed a very low local recurrence rate (1%) using wide excision (median 2 cm margin) with a standardized surgical approach; however, a major criticism of this series is that the authors underscored the importance of meticulous pathologic margin evaluation after surgical excision.[34] An alternative to radical surgical resection is Mohs micrographic surgery, which is considered by some authors as the treatment of choice for DFSP.[15,35] The operative technique consists of successive horizontal sectioning (5–7 μm) during resection and immediate frozen microscopic examination until a tumor-free margin is attained.[7] The reported local control rates range from 93% to100%.[36,37]

Medical Oncology

Conventional chemotherapy is rarely used in the management of DFSP. Limited case reports have failed to show a significant value for conventional chemotherapy in the treatment of DFSP.[38]

The Food and Drug Administration has approved imatinib mesylate for the treatment of partially resectable, unresectable,

recurrent, and/or metastatic DFSP.[39] The targeted therapy is based on the finding of a translocation between chromosomes 17 and 22 [t(17;22)(q22;q13)], resulting in the overexpression of PDGF-B receptor.[14,40] Imatinib mesylate, a tyrosine kinase inhibitor, some clinical activity against localized and metastatic DFSP tumors containing t(17;22)(q22;q13).[25,41] The recommended oral dose is 800 mg/day.[42] DFSP tumors lacking the t(17;22) translocation may not respond to imatinib mesylate, therefore molecular analysis of the tumor using cytogenetics may be helpful prior to the initiation of therapy with imatinib mesylate.[2]

Some studies have suggested neoadjuvant imatinib mesylate therapy for DFSP.[43,44] Utilizing imatinib mesylate as a neoadjuvant therapy in locally advanced or recurrent DFSP may promote tumor cell apoptosis, reduce the tumor burden, and consequently reduce the extent of surgery.[44]

Radiation Oncology

DFSP has a high propensity for local recurrence, even with negative margins; therefore, adjuvant (i.e., postoperative) or definitive radiation is commonly recommended, especially for locally advanced or metastatic cases. Radiotherapy is generally recommended in the adjuvant setting, specifically in situations where the margins of resection are positive or in circumstances where wide radical excision alone may result in major cosmetic or functional deficits.[7] Adjuvant irradiation may reduce the risk of recurrence when clear surgical margins are not obtained.[7] A retrospective review of 53 patients demonstrated that surgery and radiation yielded an excellent local control rate and disease-free survival of 93% at 10 years.[45]

Radiation in the definitive setting leads to improved cosmesis compared to surgery, but the risk of late toxicities related to functionality is dependent on whether the radiation field contains major joints and on the patient's compliance with postirradiation physical therapy. Frequent follow-up after radiotherapy is warranted, as a subset of DFSP tumors may transform into more aggressive sarcomatous phenotypes.[25,46] In situations where radiation is advisable, the radiotherapeutic dose used in the management of DFSP ranges from 50 to 70 Gy, which is clinically determined based on whether the radiotherapy is being prescribed adjuvantly or definitively, the tumor bulk, and the presence of histopathologic, high-risk features for recurrence.[2,25,46]

Investigational Use of Antibody-Based Brachytherapy

An emerging theragnostic transmembrane receptor target, folate hydrolase-1 (FOLH1; prostate-specific membrane antigen), has been notably expressed in benign dermatofibromas and in high-grade sarcomatous phenotypes.[47] These findings indicate that DFSP may also express FOLH1.

Monoclonal antibody J591 has demonstrated excellent tumor specificity in prostate cancer and virtually all solid tumor neovessels through targeting of membrane-expressed FOLH1 (prostate-specific membrane antigen, glutamate carboxypeptidase II).[48–51] J591 has been shown to undergo endocytosis upon binding to FOLH1,[52] thereby providing a promising target for antibody-mediated brachytherapy (e.g., J591-brachytherapy).

CONCLUSIONS

There is no consensus on how the follow-up of patients with DFSP should be undertaken. Due to the high local recurrence rates for DFSP, the National Comprehensive Cancer Network (NCCN) guidelines recommend ongoing follow-up with focus on the primary site every 6 to 12 months, and re-biopsy of any suspicious regions.[19] Although metastatic disease is rare, a guided history and physical examination should be performed as well. Most recurrences occur within 3 years of the primary excision.[25] A series of 159 patients treated at Memorial Sloan-Kettering Cancer Center showed that the median time for the development of a local recurrence was 32 months.[53] The indolent nature of DFSP requires lifelong surveillance for recurrence. For patients with high-risk features or who have undergone extensive surgery, additional imaging studies may be useful in detecting recurrence.

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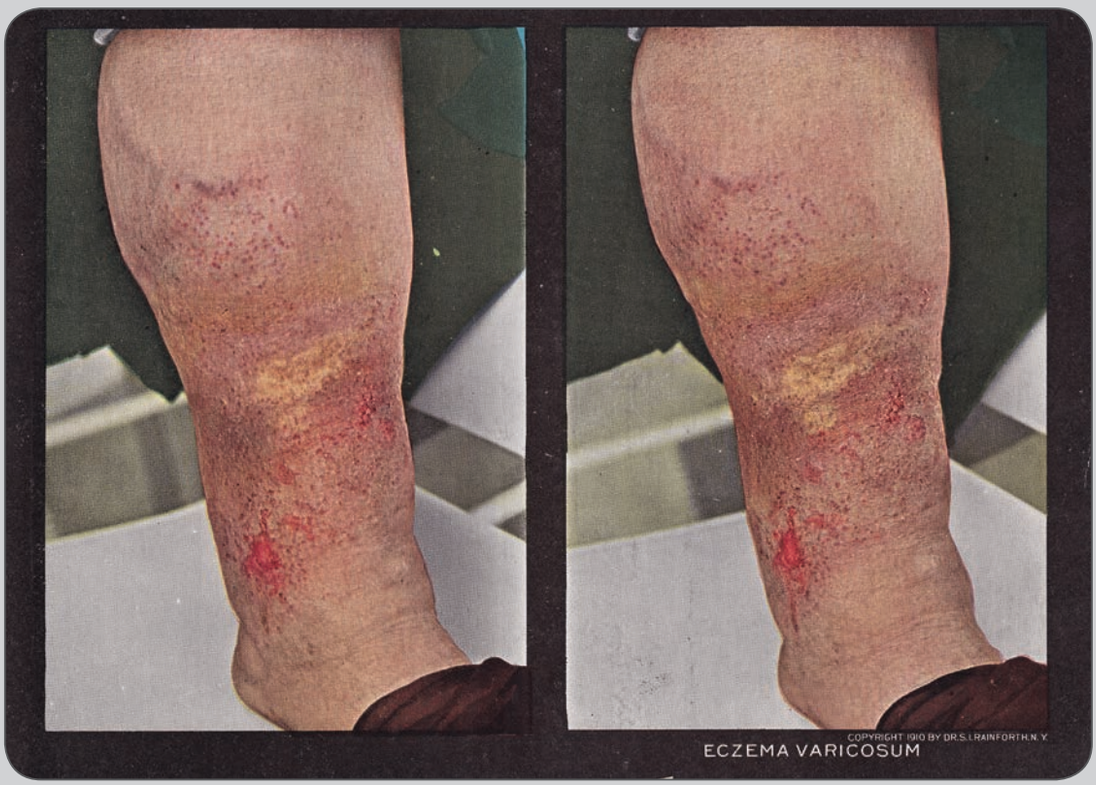
HISTORICAL DIAGNOSIS AND TREATMENT: ECZEMA VARICOSUM



(Continued on page 303)

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- **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.

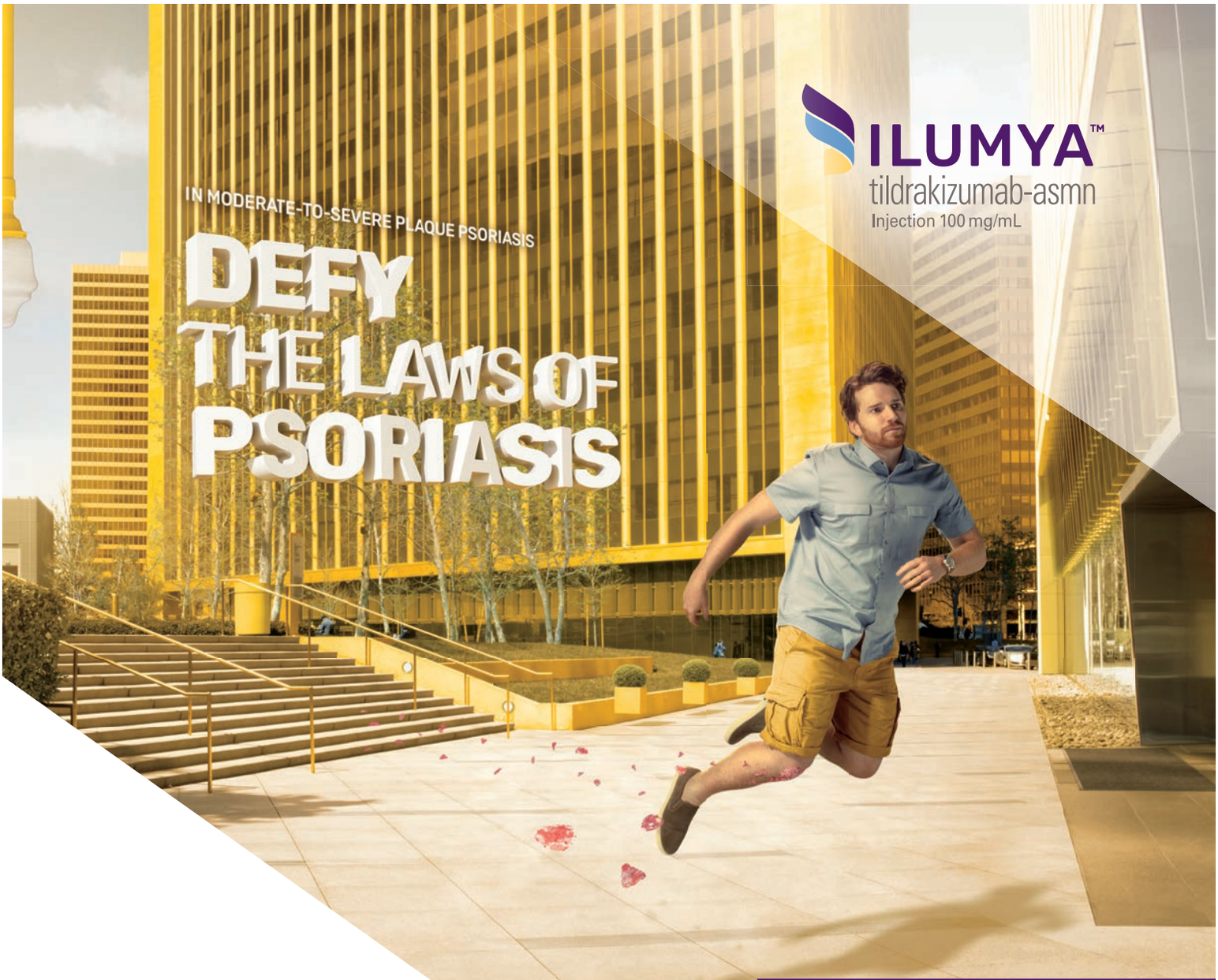
IMPORTANT SAFETY INFORMATION

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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AESTHETIC DERMATOLOGY

Philip R. Cohen, MD, Section Editor

Hypertrichosis and Genital Rejuvenation: Cutaneous Adverse Events Associated with Pubic Hair Grooming

Philip R. Cohen, MD[1,2]

ABSTRACT

Pubic hair grooming is practiced by women and men who consider themselves to have hypertrichosis of their genitals. Of the several modalities that can be used to remove the excess hair—the nonelectric razor is the most common. In addition to laceration, several other adverse cutaneous events have been observed in individuals who groom their own pubic hair. (*SKINmed*. 2020;18:297–299)

Genital hypertrichosis is excessive hair growth involving the penis, scrotum, or vulva.[1] For aesthetic purposes, it also includes the suprapubic region, the perineum, and the perianal area. Hair removal at these sites, referred to as pubic hair grooming, is the treatment for genital hypertrichosis.

Pubic hair grooming is commonly practiced by both men and women.[2] Men prefer their female sexual partners to be hairless, whereas women prefer their male sexual partners to have some pubic hair.[3] Indeed, film and magazine pornography idealizes a new societal norm of hairlessness in the female genital area.[4–6]

DEMOGRAPHICS

Most women currently or previously have removed some or all of their pubic hair; in a study involving 663 women aged 18–24 years enrolled in a public college, only 3.2% had never experienced pubic hair grooming.[7] The women who groom their pubic hair tend to be Caucasian, young, educated, underweight or normal weight, and they tend to have a greater interest in sex and/or have five or more lifetime sexual partners.[2,7,8] The onset of grooming in women is often during adolescence; however, it can begin as early as menarche and usually prior to 20 years of age.[8,9]

Men also practice pubic hair grooming. Men who have sex with women (MSW), men who have sex with men (MSM), and men who have sex with both women and men (MSWM) practice pubic hair grooming. Compared to MSW, MSM not only groom more frequently but also remove all pubic hair more than five times a year. For MSM, the receptive partner grooms more frequently than the insertive partner.[5]

GROOMING REASONS

Women groom for several reasons; common reasons—summarized from two studies—include appearance, cleanliness or hygiene, religious practices, and sensation.[7,9] Other common reasons shared by women for pubic hair grooming include pleasing their sexual partner, complying with cultural and social norms, addressing sexual appeal and pleasure, providing a positive genital self-image, receiving cunnilingus, and pressure applied by family or friends.[3,7,9,10] Compared to MSM, MSW are more likely to prefer their partner(s) to be groomed; however, MSM groom more for both sex and vacation.[5]

GROOMING METHODS

A nonelectric razor is the most common method women use for pubic hair grooming, because it is low cost, readily available, and easy to use[2,3,7–9,11]; in contrast, trimming with scissors or clippers is the most frequent method employed by men for grooming.[3]

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Other grooming methods include depilatory cream, tweezing, electric razor, and dyeing and/or bleaching. Hair removal strategies that usually require assistance include laser, waxing, sugaring, threading, and electrolysis.[8,9] Hair clipping and the use of electric razor are safer methods to use for pubic hair grooming.[5,11]

COMPLICATIONS

In a study of 400 Saudi women, 75.5% (302 women) self-reported a complication, and 17.9% (54 women) required treatment[9]; however, both men and women have experienced complications from pubic hair grooming. Investigators who were evaluating injuries from pubic hair grooming found that those who removed all their pubic hair 11 times or more had an increased chance of injury.[2] Other researchers evaluated individuals with injuries related to pubic hair grooming who presented to emergency departments; 97.3% of the patients (56.7% women, and 43.3% men) were treated and discharged, 1.2% had to be admitted for treatment, and 1.5% left without being seen.[11]

In a study evaluating the prevalence of injuries related pubic hair grooming, women most commonly injured the pubis, followed by the inner part of the thigh, labia majora, and perineum.[2] In men, the most frequent injury sites were the scrotum, penis, and pubis.[2] MSM had more grooming-related injuries to the anus.[5]

The minor cutaneous adverse events associated with pubic hair grooming include erythema, irritation known as razor burn, and pain. Other common complications include folliculitis (Figure 1), genital burns (from waxing), pseudofolliculitis (Figure 2), and pruritus. The most frequent injuries are lacerations from razors and scissors.[2,4,7–9,11,12]

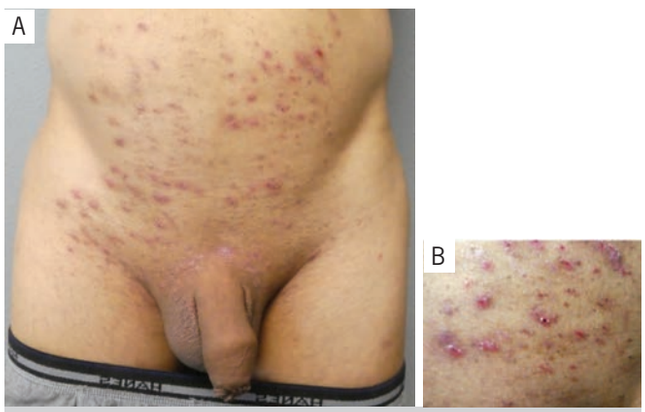

Figure 1. Grooming-associated folliculitis. Distant (a) and closer (b) views of a 45-year-old man who developed folliculitis (with a positive bacterial culture for methicillin-susceptible *Staphylococcus aureus* and *Pseudomonas luteola*) involving not only his scrotum but also his suprapubic area and lower abdomen after waxing these areas to remove all of the hair.

Less common, but more serious, adverse pubic hair grooming skin events have also been observed. These include abscesses and bacterial infection. Pubic hair grooming techniques have been associated with either an epidermoid cyst or hair-containing abscesses of the periclitoral area in three women after waxing and/or shaving their vulva or genital hair.[13]

In addition, there are also several individual case reports of grooming-related serious sequelae. A 31-year-old man developed eruptive syringomas in the pubic region after waxing,[14] while a 20-year-old woman had recurrent episodes of both *Herpes simplex* infection and cellulitis, from which *Streptococcus pyogenes* was cultured, following hair removal initially with hot wax and subsequently with a razor.[15] A shaving-associated vulvar inverted

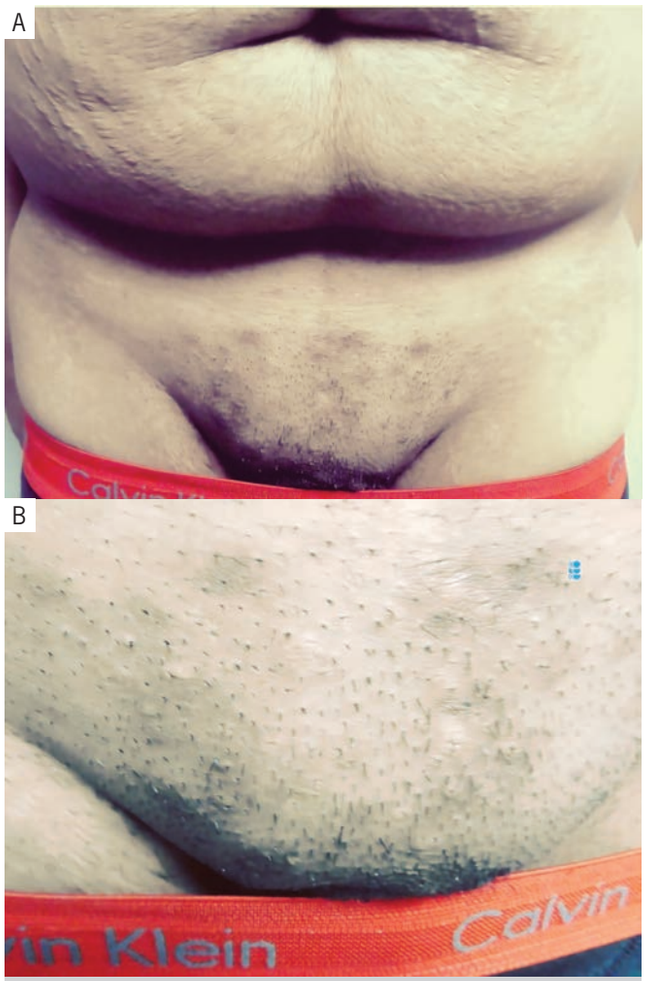

Figure 2. Pubic hair grooming pseudofolliculitis. Distant (a) and closer (b) views of the suprapubic region of a 23-year-old man who developed multiple ingrown hairs after removing all of the hair by shaving the affected areas with a nonelectric razor.

follicular keratosis, morphologically mimicking a squamous cell carcinoma, occurred in a 27-year-old woman, which required excision.[16]

A decrease in the incidence of pubic lice has been associated with pubic hair grooming[17]; however, other sexually transmitted infections, such as condyloma acuminata, *Herpes simplex* infection, molluscum contagiosum, and syphilis, have been observed in people who engage in pubic grooming.[18,19] A study showed that MSM had more lifetime sexually transmitted infections, while anogenital grooming may increase the risk for a sexually transmitted disease.[5] Curiously, a more recent study of 310 individuals (247 men, 58 women, and five transgender participants) did not observe any association between recent grooming and sexually transmitted genital infections[20]; however, gay and bisexual men who were anal groomers were three times more likely to have a sexually transmitted rectal infection.

CONCLUSIONS

Men and women with actual or perceived genital hypertrichosis commonly practice pubic hair grooming to remove some or all of the hair in the genital area. Razor blade shaving remains the most commonly used method for grooming. Laceration is the most common complication occurring in patients grooming their pubic hair; however, other cutaneous adverse events may also occur. Relatively safer methods for pubic hair grooming are hair clipping and using the electric razor.

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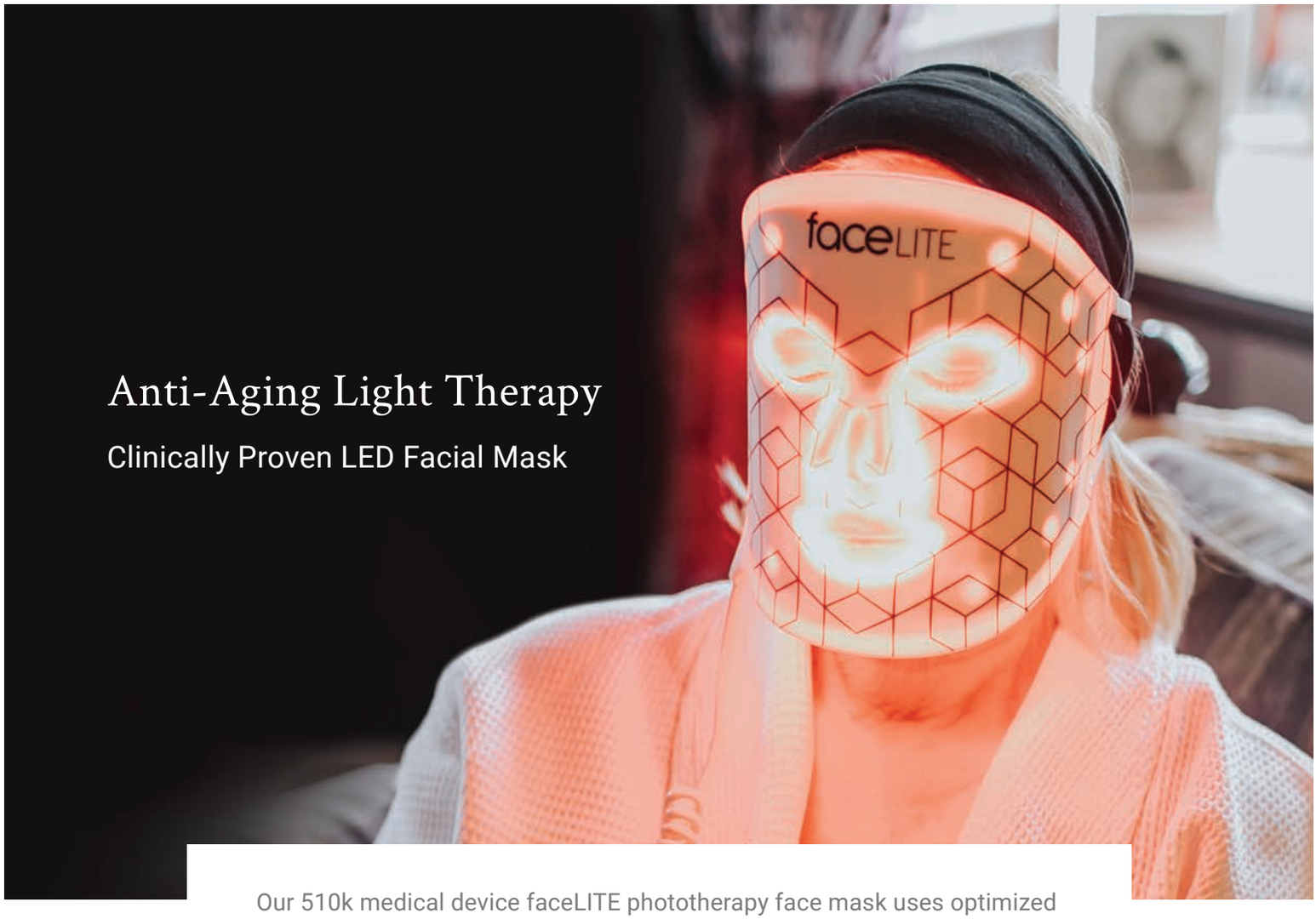

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PERILS OF DERMATOPATHOLOGY

W. Clark Lambert, MD, PhD, FRCP Edin, Section Editor

Dermatopathologic Signs of Systemic Disease I: Acquired Perforating Dermatosis and Kyrle Disease

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SERIES INTRODUCTION

Irwin M. Braverman, in his classic textbook, *Skin Signs of Systemic Disease*, Editions 1 and 2,[1] electrified medicine in the later 20th century with the stunning idea that internal/systemic diseases could be recognized and diagnosed, at least in part, by recognizing diagnostic signs on the skin and mucous membranes. Recall that in those days, there were no Computer Assisted Tomography (CAT), Magnetic Resonance Imaging (MRI), or similar scans or scanning devices available, and many laboratory tests which are now routine were not yet developed. Devoted medical students and physicians carefully memorized information from any source they could find, especially from books on signs of disease detected by probing the abdomen or chest. In this environment Braverman's book dropped like a bombshell, inspiring many young physicians, including one of us (WCL) to apply for and then enroll into dermatology residencies. This series of papers, in which signs of systemic disease detectable microscopically are presented, is dedicated to Irwin and is named *Dermatopathologic Signs of Systemic Disease* in tribute to Irwin (happily, later a mentor of WCL) and his classic textbook.

The perforating dermatoses are a collection of skin disorders thought to be characterized by transepidermal elimination of dermal components.[2] The perforating dermatoses are commonly divided into two groups, primary and secondary. Four diseases have been described in the primary type: Kyrle disease (KD), reactive perforating collagenosis (RPC), elastosis perforans serpiginosum (EPS), and perforating folliculitis (PF).[2] The secondary form is the acquired perforating dermatoses (APD).[1] APD were originally proposed by Ronald Rapini in 1989 and used to describe all perforating dermatoses, irrespective of the eliminated dermal material, affecting patients with diabetes mellitus (DM) and chronic renal failure (CRF).[1,2] APD especially affect patients on hemodialysis. More recently, this group of diseases has been expanded considerably and now includes a number of systemic diseases, especially drug reactions.

APD affect men and women equally and usually arise in patients in their 40s.[3] The pathophysiology of APD is uncertain, but there have been several proposed mechanisms. One such mechanism is the Koebner phenomenon, in which lesions appear at sites of prior trauma or excoriation.[4] Other possible theories include leukocyte infiltration leading to the degradation of extracellular matrix components.[1]

The diagnoses of APD require skin biopsy. APD do not have a uniform pathology, and lesions may resemble the primary perforating dermatoses. On histology, APD demonstrate epidermal invagination. It is said to involve, in many cases, a dilated hair follicle with a keratotic plug composed of collagen, keratin, or elastic fibers.[5] Clinically, APD manifest as several polymorphous skin lesions, often hyperkeratotic and umbilicated.[1,6] The lesions range in size from 2 to 10 mm and have a predisposition for the extremities, especially the legs.[4,5]

In KD, it is currently believed that there is transdermal elimination of keratin, with no collagen or elastic fibers.[7–9]

Dedicated to Irwin M. Braverman MD, teacher, counselor, colleague, and friend.

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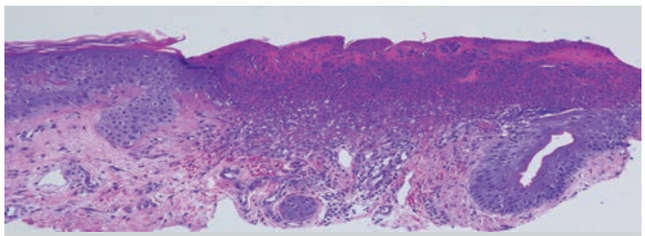

Figure 1. Case 1: Acquired perforating dermatosis. Note the debris being transferred via transepidermal elimination directly from the dermis to the surface. No hyperkeratosis or parakeratosis is involved (hematoxylin and eosin, magnification ×66).

CASE REPORTS

Case 1

A 60-year-old man presented to the clinic with markedly pruritic lesions located primarily on the legs. Clinical examination revealed 2–5 mm papular lesions filled with dense hard cores which were in the process of being extruded in places where the patient had previously expressed these cores.

Histologic findings are shown in Figure 1. Histologic examination revealed foci of transepidermal elimination of degenerating collagen and possibly other materials. The lesion avoided, rather than preferentially involved, hair follicles. Figure 1 presents such a lesion adjacent to a hair follicle and abutting onto it which, nevertheless, does not directly involve the follicle in any way. Overlying the lesion, is degenerating material arising in the dermis and undergoing transepidermal elimination, not keratin.

Case 2

A 59-year-old man presented to the clinic with markedly pruritic lesions located primarily on the legs. Clinical examination revealed 2–5 mm papular lesions at sites of hair follicles. They showed irregular keratotic centers. Biopsy was performed (Figure 2).

Histologic examination revealed the lesion clearly occupying and involving the hair follicle. Note the marked asymmetry of the lesion; one side of the hair follicle is much more involved than the other. The lesion shows degeneration of a column of material extending through the stratum corneum, and not hyperkeratosis or parakeratosis.

Note that hyperkeratosis and/or parakeratosis is/are present in neither lesion, contrary to the current beliefs regarding the pathology of APD and KD. As pointed out by Rapini, it may be necessary to take many sections in order to see the diagnostic lesions of APD or KD, and in many cases it is therefore missed altogether.[10] We found this to be true in the cases presented, both

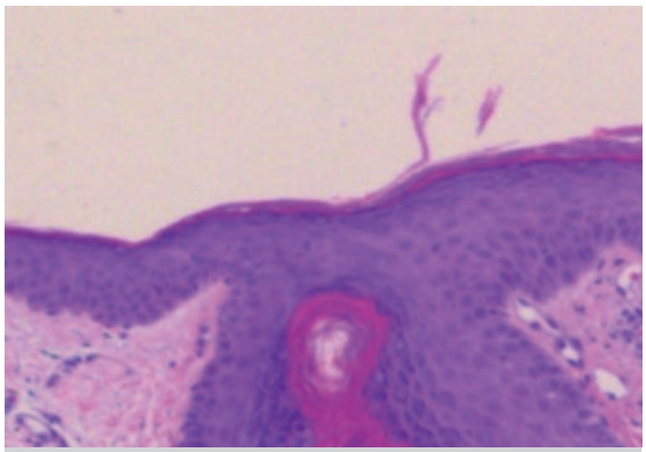

Figure 2. Case 2: Kyrle disease. Note the degeneration of tissue lining an apocrine duct entering the hair follicle (hematoxylin and eosin, magnification ×78).

or which required many serial sections to reveal the diagnostic tissue (38 and 67 sections, respectively). Whenever the clinical diagnosis is a perforating dermatosis or folliculitis and the histopathology only shows dermatitis, additional sections should be taken.

We present two cases of acquired perforating dermatosis (APD). APD often arises in patients with CRF and DM, especially those receiving hemodialysis.[8] Many theories exist attempting to explain the pathogenesis of the APD, as well as to propose an explanation for the association with CRF and DM patients receiving hemodialysis.[8] In the setting of renal disfunction, metabolic disturbances or microdeposition of substances such as calcium salts, may cause an alteration in collagen or elastic fibers.[9] Alternatively, the underlying dermal microvasculopathy in DM may induce a hypoxic state. Irritation and inflammation from this hypoxia can lead trauma and dermal necrosis due to excoriations. The presence of a positive stain (of tissue, not of dermatophytes) with the periodic acid-Schiff stain (PAS) and thickening of the vessel walls in the upper dermis of diabetic patients with APD support this hypothesis.[4] Treatment of the underlying associated disease provides the most therapeutic outcome. Other effective treatments include cryotherapy, systemic and topical retinoids, narrow band UVB, and keratolytics, such as salicylic acid.[1,5]

CONCLUSIONS

Dermatopathologic diagnosis in both the cases presented required examination of multiple levels. When a history of folliculitis/perforating disease is associated with a dermatopathologic picture of dermatitis, multiple levels should be obtained.

The current literature does not appear to elaborate on the biopsy techniques needed to identify either KD or APD. Either pathology is usually assessed by commercial laboratories, with limited willingness or ability to perform multiple layers on blocks while staying within their financial constraints. In our case reports, we performed 38 levels in case 1 and 67 levels in case 2 in order to identify the histopathology needed to diagnose KD and APD. It is important that dermatologists be aware of these diseases and of these limitations of their laboratories and consider related comorbidities which include not only DM and renal disease but also many other systemic disorders, especially drug reactions.[10] A handful of cases of APD/KD have been reported in patients with no known systemic disease at the time of biopsy.[10] KD/APD are important to recognize as they may be the presenting sign that anything is amiss.

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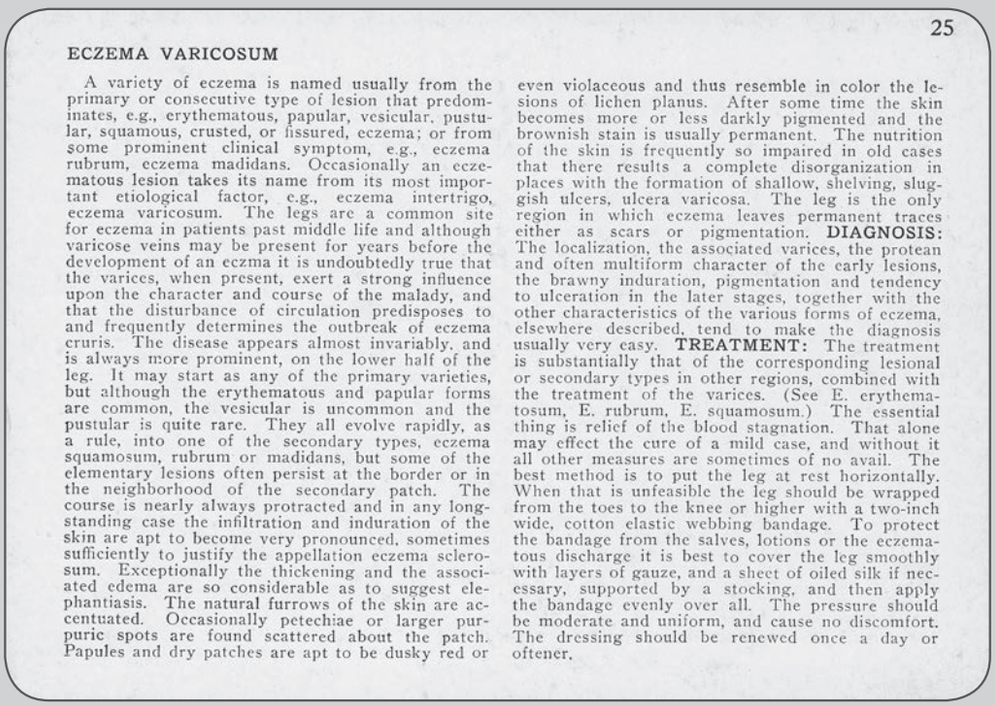
HISTORICAL DIAGNOSIS AND TREATMENT: ECZEMA VARICOSUM

(Continued from page 293)



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ECZEMA VARICOSUM

A variety of eczema is named usually from the primary or consecutive type of lesion that predominates, e.g., erythematous, papular, vesicular, pustular, squamous, crusted, or fissured, eczema; or from some prominent clinical symptom, e.g., eczema rubrum, eczema madidans. Occasionally an eczematous lesion takes its name from its most important etiological factor, e.g., eczema intertrigo, eczema varicosum. The legs are a common site for eczema in patients past middle life and although varicose veins may be present for years before the development of an eczma it is undoubtedly true that the varices, when present, exert a strong influence upon the character and course of the malady, and that the disturbance of circulation predisposes to and frequently determines the outbreak of eczema cruris. The disease appears almost invariably, and is always more prominent, on the lower half of the leg. It may start as any of the primary varieties, but although the erythematous and papular forms are common, the vesicular is uncommon and the pustular is quite rare. They all evolve rapidly, as a rule, into one of the secondary types, eczema squamosum, rubrum or madidans, but some of the elementary lesions often persist at the border or in the neighborhood of the secondary patch. The course is nearly always protracted and in any long-standing case the infiltration and induration of the skin are apt to become very pronounced, sometimes sufficiently to justify the appellation eczema sclerosum. Exceptionally the thickening and the associated edema are so considerable as to suggest elephantiasis. The natural furrows of the skin are accentuated. Occasionally petechiae or larger purpuric spots are found scattered about the patch. Papules and dry patches are apt to be dusky red or even violaceous and thus resemble in color the lesions of lichen planus. After some time the skin becomes more or less darkly pigmented and the brownish stain is usually permanent. The nutrition of the skin is frequently so impaired in old cases that there results a complete disorganization in places with the formation of shallow, shelving, sluggish ulcers, ulcera varicosa. The leg is the only region in which eczema leaves permanent traces either as scars or pigmentation. **DIAGNOSIS:** The localization, the associated varices, the protean and often multiform character of the early lesions, the brawny induration, pigmentation and tendency to ulceration in the later stages, together with the other characteristics of the various forms of eczema, elsewhere described, tend to make the diagnosis usually very easy. **TREATMENT:** The treatment is substantially that of the corresponding lesional or secondary types in other regions, combined with the treatment of the varices. (See E. erythematosum, E. rubrum, E. squamosum.) The essential thing is relief of the blood stagnation. That alone may effect the cure of a mild case, and without it all other measures are sometimes of no avail. The best method is to put the leg at rest horizontally. When that is unfeasible the leg should be wrapped from the toes to the knee or higher with a two-inch wide, cotton elastic webbing bandage. To protect the bandage from the salves, lotions or the eczematous discharge it is best to cover the leg smoothly with layers of gauze, and a sheet of oiled silk if necessary, supported by a stocking, and then apply the bandage evenly over all. The pressure should be moderate and uniform, and cause no discomfort. The dressing should be renewed once a day or oftener.

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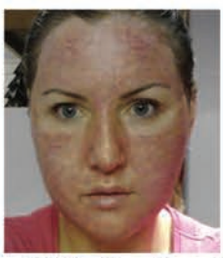

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CASE STUDY

Pyemotes ventricosus Dermatitis: Comet-Shaped Skin Lesions after Contact with Woodworm-Infested Furniture

Javier Sánchez-Bernal, MD;[1] Beatriz Aldea-Manrique, MD;[2] Mar Ramírez-Lluch, MD;[2] Marcial Álvarez-Salafranca, MD;[2] Mariano Ara-Martín, PhD[2]

A 23-year-old woman presented to our dermatology clinic for the sudden onset of pruritic lesions on her forearms and legs for the past two days ago. She had been restoring used furniture infested with woodworm. We observed many oval "comet-shaped" erythematous maculopapules with a serpiginous track on the exposed parts of her forearms and legs (Figure 1). Considering the temporal relationship and the contact with woodworm, we were able to diagnose it as *Pyemotes ventricosus*. We prescribed topical corticosteroids twice daily. By the 8th day, the lesions had cleared. (*SKINmed*. 2020;18:305–306)

DISCUSSION

Pyemotes spp. is an ectoparasitic mite that usually infests cereals, legumes, straw, tobacco, grass, and woods. Most outbreaks are related to occupational tasks in the countryside[1,2] or contact with infested timber furniture.[3] There is a worldwide distribution, and it only infests humans temporarily following contact with infested material.[1] The dermatitis generally occurs during spring and summer.[2,3]

Pyemotes ventricosus acts as a parasite to the larvae of *Anobium punctatum*, known as the common furniture beetle. As a consequence, many outbreaks of this kind of dermatitis have been described due to close contact with woodworm-infested wood or timber furniture.[1,3,4] There are distinctive skin lesions characterized as erythematous macules and papules with a central vesicle, which correspond to the mite bite, creating a characteristic serpiginous or linear track, resembling a comet with its tail—"comet sign."[3,4] The self-limited skin lesions are seen a few hours after contact and usually resolve within 1 to 3 weeks.[3–5]

The diagnosis was clinical based on typical cutaneous lesions from recent contact with infested wood. Blood tests were within normal limits.[4] Histopathologic findings were nonspecific with perivascular dermal inflammatory infiltrate, mostly comprising eosinophils, plus neutrophils and lymphocytes. There was no epidermal involvement or vasculitis. Neither mites nor foreign bodies were found on biopsy.[4]

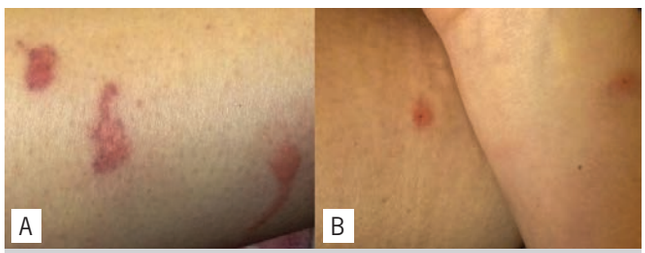

Figure 1. (A) Erythematous maculopapules, oval-shaped, with a serpinginious track on the right leg, extending from one of the openings. (B) Erythematous comet-shaped lesions with a central vesicle on the forearms.

There is a report of a mite found in the skin scraping of a 20-month-old patient, who had typical lesions and was in contact with *Anobium punctatum*-infested furniture.[5] Frequently, the mites are found in the plant or wood debris of infested furniture.[2–4]

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CONCLUSIONS

The combination of comet-shaped lesions and a history of contact suggests an infestation with *Pyemotes ventricosus*. Recognizing the self-limited nature of this dermatitis and its etiology, one may avoid unnecessary diagnostic tests and treatment.

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WAX MOULAGE

"Smallpox" *(Vaiolo umano florido all'apice dell'eruzione pustolosa)*

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CASE STUDY

Nail Fold Dermatoscopic Findings in Scleroderma Patients

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Case 1: A 28-year-old woman with previously excellent health presented with pain, swelling, and stiffness on the face and hands, which had persisted for over 18 months. She had initially experienced intermittent pain in both knees. Skin hardening spread to both hands until the fingers could no longer be straightened. There were intermittent pain and skin hardening on the cheeks extending to the neck. These were accompanied by breathing difficulty, especially during high-intensity activity. (*SKINmed*. 2020;18:308–310)

Dermatologic examination revealed sclerosis on the fingers (sclerodactyly) of both hands. Hypopigmented macules with ill-defined borders and diffusely hyperpigmented macules were observed on the clavicle, upper part of the back, nape, occiput, and retroauricular regions, resulting in a salt-and-pepper appearance.

The rheumatoid factor was elevated (41.1 [normal: <30 IU/mL]). Spirometry showed moderately restricted pulmonary function, and antinuclear antibody (ANA) status for anti-ScL70 was +++. Histopathologic analysis of the biopsy from the left arm revealed a hyperkeratotic epidermis, packed connective tissue collagen with wedged adnexal tissue in the dermis, and mild perivascular lymphocyte infiltration, confirming the diagnosis of scleroderma. Dermatoscopic examination revealed multiple capillary hemorrhages, several giant capillaries, and a slightly disorganized capillary structure in the nail fold of the right first digit. The left fourth digit also showed minor disorganization of giant capillaries (Figure 1).

The patient was diagnosed with systemic sclerosis (SSc) and was given 15 g of topical 0.25% desoximetasone and 30 g Vaseline. The patient was referred to the rheumatology department for systemic therapy and received 10 mg/24 hours oral nifedipine, 10 mg/week oral methotrexate, 0.5 mg/24 hours oral colchicine, and 8 mg/12 hours oral methylprednisolone. By the fifth month, there was some improvement.

Case 2: A 46-year-old woman presented with skin hardening on the chest and the upper part of the back with pain for the last 2 years. Sclerosis first occurred on the fingers, and then spread to the arms and the remainder of the trunk. As a result, the patient experienced difficulty in grasping, along with intermittent pain. She had undergone a mastectomy 3 years ago for breast cancer and had subsequently received chemotherapy. She was currently in remission. There was no history of similar complaints.

Additional findings showed sclerosis with ill-defined hypopigmented and diffusely hyperpigmented macules on the right and left arms, resulting in a salt-and-pepper appearance. Edema was detected on the right third and fifth digits, and pitting scars were present on the fingertips. ANA immunofluorescence analysis showed a speckled pattern with a titer of >1:1000 (normal: <1:100), consistent with progressive sclerosis. Anti-ScL70 antibody status was +++. A biopsy from the right arm revealed irregular epidermal thickness due to reduced keratinization and thickening of the collagen layer, accompanied by a compressed adnexal structure in the dermal layer, mild lymphocyte infiltration, and perivascular macrophages, supporting the scleroderma.

Dermatoscopic examination showed bushy capillaries and severely avascular areas on the right first and third digits. Capillary branches in severely avascular areas were observed on the right second and left fourth digits (Figure 2). SSc was diagnosed based on the above findings.

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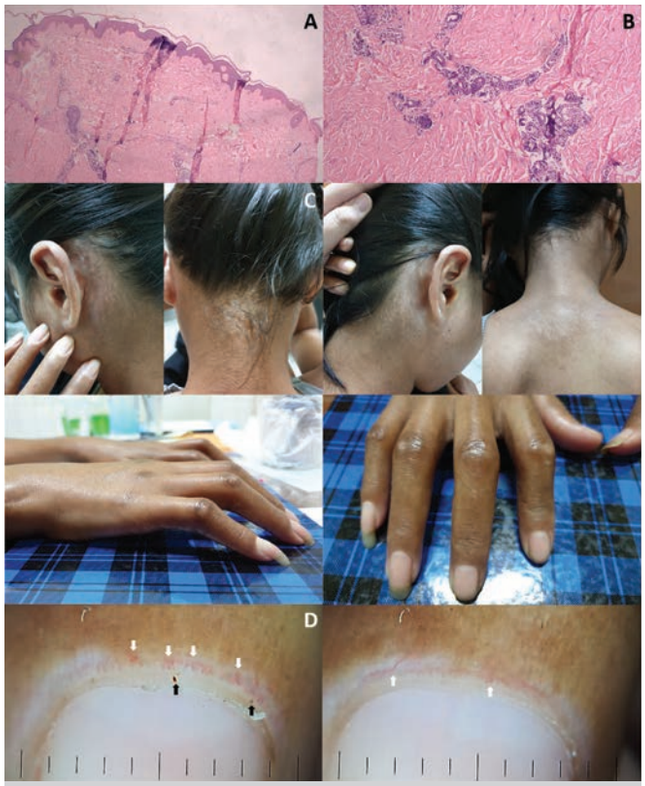

Figure 1. Histopathologic and dermatoscopic findings for Patient 1. (A) Hyperkeratosis of the epidermis packed connective tissue collagen with wedged adnexal tissue in the dermis and mild perivascular lymphocyte infiltration (4× magnification). (B) Dense collagen in the dermis and perivascular lymphocyte infiltration (10×). (C) Hypopigmented macules with ill-defined borders and diffuse hyperpigmented macules on the neck, chest, and trunk. Sclerosis (sclerodactyly) was detected on the right and left fingers. (D) (Left) Hemorrhage (black arrows) and mildly disorganized giant capillaries (white arrow) on the first digit of the right hand. (Right) Mildly disorganized giant capillaries (white arrows) on the fourth digit of the right hand.

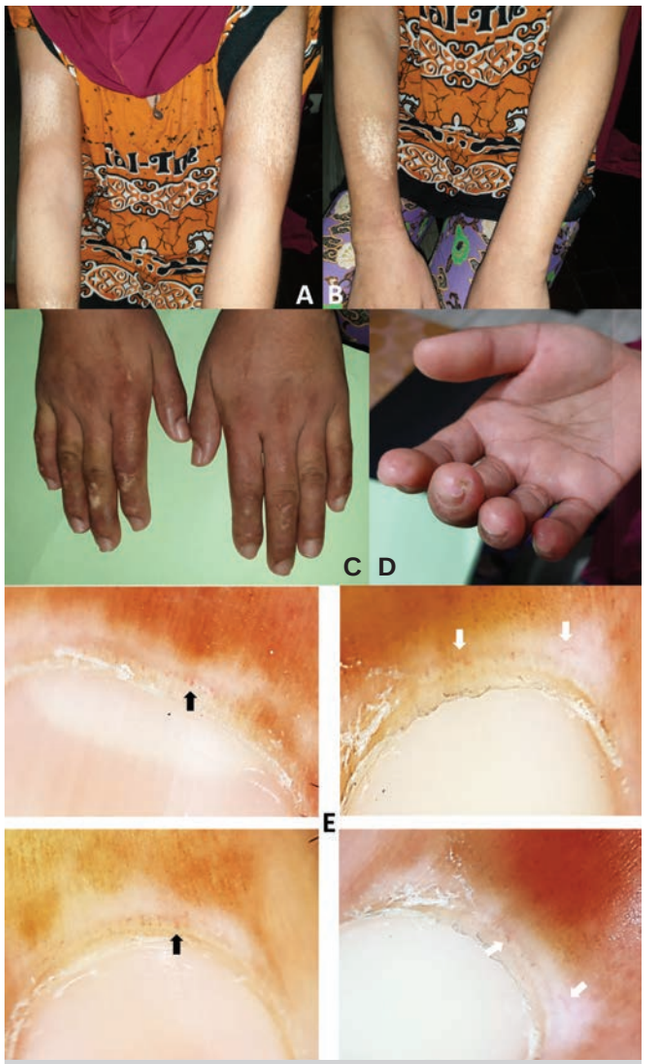

Figure 2. Histopathologic and dermatoscopic findings for Patient 2. (A, B) Sclerotic right and left upper extremities accompanied by ill-defined hypopigmented and diffusely hyperpigmented macules. (C) Hypopigmented macules on most of the distal fingers. (D) Pitting scars on the edematous third and fifth digits. (E) Dermatoscopic findings. (Upper left) First digit of the right hand. (Lower left) Bushy capillaries (black arrows) and large avascular areas on the third digit of the right hand. (Upper right) Second digit of the right hand. (Lower right) Capillary branching and large avascular areas (white arrows) on the fourth digit of the left hand.

DISCUSSION

SSc or scleroderma is a multisystemic immune disease, characterized by autoantibody production, vascular endothelial injury, and fibroblast activation.[1,2] The most commonly affected organs are skin, esophagus, lungs, heart, and kidney. SSc has variable clinical manifestation, disease course, and prognosis. Women are more commonly affected, with a male-to-female ratio ranging from 3:1 to 14:1.[2]

SSc is characterized by perturbation of angiogenesis, immune activation by autoantibody production, and tissue sclerosis resulting from the deposition of collagen and other extracellular matrix components.[1] Endothelial injury precedes fibrosis. Endothelial cell activation leads to upregulation of adhesion molecules and an increase in circulating inflammatory cells. Scleroderma renal crisis and pulmonary arterial hypertension are manifestations of large blood vessel dysregulation.[1]

Microangiopathy in SSc involves capillary enlargement or loss as well as reactive neoangiogenesis and capillary branching.[3] Different patterns (i.e., early, active, and advanced) of nail fold microvascular damage have been found to be correlated with SSc duration or progression[4] and may represent the evolution

of SSc microangiopathy from capillary enlargement to loss to telangiectasia.[3]

Assessment of nail fold microcirculation by nail fold video capillaroscopy (NVC) at 200× magnification is the gold standard for identifying nail fold capillary abnormalities across the SSc spectrum and can be used to diagnose and monitor disease progression. This simple, noninvasive method can be implemented in routine clinical practice but has not been widely adopted due to the inaccessibility of equipment and requirement for technical expertise. Although it cannot replace laboratory or radiologic examination, dermatoscopy—a noninvasive skin imaging method used by dermatologists—at 10× magnification can also detect nail fold capillary abnormalitiess,[5–7] such as dilation, hemorrhage, reduced or irregular distribution, and branching in the nail fold (i.e., a scleroderma pattern) of SSc patients.[8–10]

Capillaries typically have a hairpin shape and are homogeneously distributed in a parallel pattern without avascular areas.[11,12] In cases of scleroderma, capillaries are enlarged or dilated, absent, or disorganized, with an irregular distribution; this may be accompanied by abnormal branching and hemorrhage.[4,10] Absence of vascular abnormalities in the nail fold excludes a diagnosis of SSc and other autoimmune diseases, such as dermatomyositis and lupus erythematosus.[10]

Capillary enlargement is an aberrant angiogenic response to peripheral ischemia and is observed in >80% of SSc patients and can thus be considered as a marker of SSc. Microcapillary hemorrhage in peripheral capillaries and multiple hemorrhages due to ischemia or reperfusionn[11] are observed in SSc. Dermatoscopic examination of Patient 1 revealed multiple capillary hemorrhages, several giant capillaries, and a mildly disorganized capillary structure, reflecting an active scleroderma pattern.

SSc patients often exhibit ulceration on their fingers along with branched or bushy capillaries in hypovascularized areas. Dermatoscopic examination of Patient 2 revealed bushy capillaries and severely avascular areas with several capillary branches, which were consistent with an advanced scleroderma pattern. This finding was accompanied by pitting scars on the patient's fingers.

A comparison of nail fold capillaries in SSc patients and healthy control subjects evaluated by dermatoscopy (10×) and NVC (300×) showed that the former was a more accessible tool with sufficient capacity to detect nail fold capillary abnormalities, in spite of having a lower rate of subjective gradeability than the gold standard NVC.[5] Dermatoscopic findings in both of our patients were in accordance with NVC references. Thus, dermatoscopic analysis of nail fold capillaries can effectively classify the disease status of SSC patients as early, active, or advanced.

CONCLUSIONS

SSc or scleroderma is an autoimmune disease affecting the connective tissue in skin, blood vessels, and internal organs. Impaired angiogenesis is an early event in SSc pathogenesis. Affected blood vessels range from the small capillaries in the proximal nail fold to large arteries in the lungs. Dermatoscopy is a cost-effective, accessible, simple, sensitive, and specific method, which can be used to examine nail fold capillaries and classify SSc as early, active, or advanced.

ACKNOWLEDGMENTS

Charlesworth Author Services edited the contribution for English language.

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CASE STUDY

Refractory Human Cutaneous Protothecosis

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Samuel H. Allen, FRCP, FRCPS;[3] Alexander Waters, MB BCh, PhD;[4]
Margaret Strick, MbbCh, MSc, DPD, FRCS, FRCS(Plast);[5]
Maha Elgoweini, MBChB, MSc, MD, FRCPath[6]

A 67-year-old Scottish woman presented to her general practitioner with a subcentimeter lump between her shoulder blades. The lump was suspected to be an epidermal cyst and was excised. The patient had a history of controlled diabetes. Most summers, she spent a month near a beach resort in Mexico. The lump reappeared after 6 months within the scar area and was re-excised. Both skin excisions were performed in the primary care setting without histologic assessment. (*SKINmed*. 2020;18:312–314)

After 12 months, the patient visited her general practitioner, as the lesion was enlarging. She was referred for a dermatologic opinion. Examination revealed a 1 cm erythematous indurated patch with central hyperkeratosis. The skin biopsy showed a central ulceration surrounded by an inflammatory cell infiltrate, which included lymphocytes, plasma cells, eosinophils, and epithelioid histiocytes, without evidence of dysplasia or malignancy (Figure 1A). Over the next 6 months, the lesion became itchy with the appearance of discrete papules raising the possibility of cutaneous sarcoidosis. A repeat biopsy showed a similar dermal inflammatory cell infiltrate with prominent eosinophils and epithelioid histiocytes but without ulceration. Periodic Acid-Schiff (PAS) stain revealed sporangia, up to 15 μm in diameter, with occasional morula-like appearances, characteristic of *Prototheca* species. A retrospective review of the previous biopsy, which was reported by another pathologist, with the addition of PAS stain, showed the presence of the same organism (Figure 1B). Pan-fungal polymerase chain reaction (PCR) was weakly positive, but species identification was not possible from the paraffin blocks.

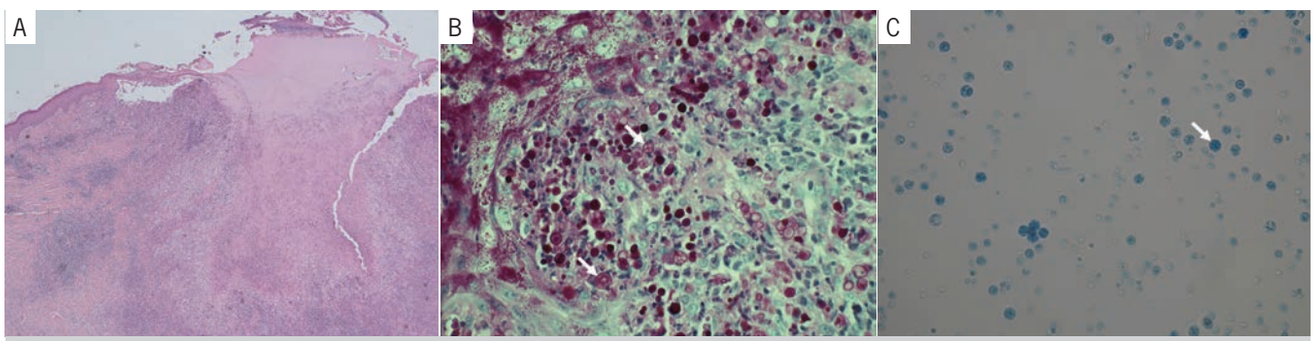

Figure 1. Microscopic examination: (A) Hematoxylin and eosin stain shows skin with central ulceration and surrounding inflammatory infiltrate (×4). (B) PAS stain shows morula-like sporangia (white arrow) at the edge of the ulceration (×60). (C) Lactophenol cotton blue stain shows prominent sporangia (white arrow) from tissue culture (×60).

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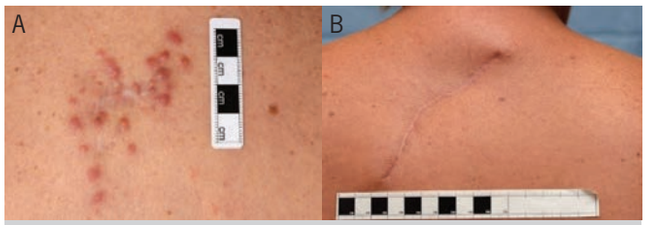

Figure 2. (A) Discrete papules over 7 × 4 cm area. (B) Healed scar with no recurrence at 8 months after excision.

Microbiologic culture on Sabouraud agar with subsequent wet mount microscopy identified numerous sporangia (Figure 1C). *Prototheca wickerhamii* was confirmed by Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-ToF-MS) technology.[1]

The patient was given oral itraconazole 200 mg/day for 4 months but without improvement. She was then switched to 200 mg fluconazole daily for 6 months. In spite of azole therapy, the affected area continued to increase in size to 7 × 4 cm (Figure 2A). A trial of daily weight-adjusted intravenous Amphotericin B was stopped after two doses owing to renal impairment. She was referred for curative excision with 1 cm clinical margin, down to the fascia barrier, followed by an appropriate defect reconstruction. There was no recurrence (Figure 2B) at the 14-month follow-up.

DISCUSSION

Protothecosis is caused by achlorophyllic algae of the genus *Prototheca*, which are ubiquitous in nature and found worldwide.[2,3] Human protothecosis is rare, with less than 200 case reports or small case series appearing in the English language literature. The first cutaneous protothecosis infection was reported in 1964 from Africa.[3] To our knowledge, this is the first case of protothecosis reported from Scotland. *Prototheca wickerhamii* is the species most commonly implicated in human infection.[4] Protothecosis is usually associated with conditions that compromise the immune system, such as diabetes.[5] Infection is thought to be acquired through traumatic skin inoculation[5,6] and can be located anywhere on the body. The most common sites of involvement are the extremities.[4]

Protothecosis has no definitive clinical manifestations. It can manifest as ulcerations, erythematous plaques, eczematous patches, subcutaneous papules, vesicles, nodules, verrucous or herpetiform lesions, or pyoderma-like lesions.[2,4,5] Misdiagnosis is common occurring in up to 50% of the cases.[7] The travel history of our patient suggested a possible clinical diagnosis of paracoccidioidomycosis (South American blastomycosis).[8] Diagnosis and differentiation mainly relies on histopathology[3] in conjunction with newer diagnostic methods, such as MALDI-ToF-MS and the next generation sequencing (NGS) methodologies.[1]

Human cutaneous protothecosis typically follows a chronic, indolent, progressive course.[9] Various antifungal treatment regimens, most notably with the azole drug class, have yielded inconsistent outcomes.[5,6,10,11] In our patient, available medical treatment failed. Fortunately, the lesion was in a nonexposed body area and could be excised. The successful outcome replicates results achieved by other centers and reinforces the effectiveness of surgery, with or without antifungal therapy, as a curative option for localized cutaneous protothecosis.[11–13]

CONCLUSIONS

Human cutaneous protothecosis is a rare, indolent infection with no specific clinical features. Management of human cutaneous protothecosis is challenging and requires a multidisciplinary approach. The diagnosis relies on recognition of characteristic histopathologic features in conjunction with microbiologic confirmation. Response to medical therapy is variable. Surgical excision with wide margins is an effective therapeutic option for localized lesions, especially when medical treatment fails.

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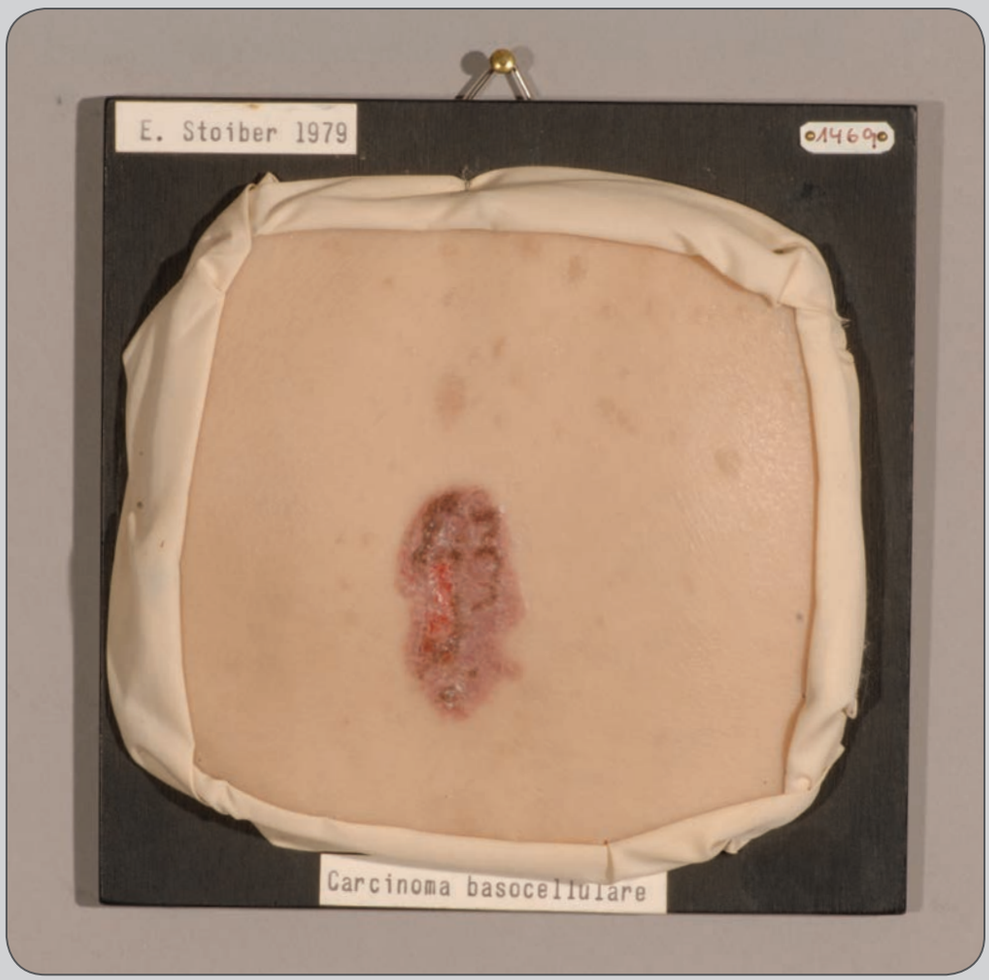

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CORRESPONDENCE

Virtual Clinical Rotations during the COVID-19 Pandemic: A Perspective on the Pros and Cons

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To the Editor:

Coronavirus disease 2019 has catalyzed a change in medical education, with medical student clinical rotations being greatly affected. Clinical "away rotations" are an essential part of the residency application process in a competitive specialty like dermatology.[1] Rotations give the medical students a glimpse of life in their chosen specialty and also enable them to "audition" for the residency program of their choice.[2] They are integral in facilitating medical student interaction with prospective peers and mentors. In addition, odds of acceptance are two times higher for those with dermatology rotations during medical school,[1] and about 50% of the students match either at a program at which they completed an away rotation or their home institution.[2]

ROLE OF PRIOR KNOWLEDGE AND ROTATIONS

A program director survey cited prior knowledge of applicants and rotation in their own department as important criteria in selecting candidates to interview.[3] Clinical rotations can yield letters of recommendation and research projects, which may be pivotal in a residency application.[1] Successful candidates are more likely to have letters of recommendation from dermatologists.[1] As these letters are usually based on interpersonal and clinical skills observed during the rotation, the effect of virtual rotations on letters of recommendation, residency applications, and matching for medical students applying in 2020 is as yet unknown.

The Coalition for Physician Accountability has discontinued "away rotations" via the Visiting Student Learning Opportunities platform. The work group instead recommends online interviews for this residency match cycle.[4] For the most part, programs have adopted virtual clinical rotations (tele-rotations) instead of traditional in-person clinical clerkships, as the former enables virtual discussion of cases and conferences, which provides medical students with an opportunity to showcase their clinical knowledge or oratory skills. The advantages of tele-rotations are the elimination of travel and lodging costs associated with away rotations, greater scheduling flexibility, and lower carbon footprint.

Disadvantages of virtual clinical rotations include the lack of exposure to patients in clinics or floors and the limited time medical students get to spent with the faculty and residents. This is important given that the more time the students spend with their evaluators, the more likely they are to receive clinical honors.[5] Dermatology being a visual field, the inability to physically see the patients, visualize the morphology and the distribution of the lesions, perform dermatoscopy, and closely observe procedures denies the medical students a clinic experience in the truest sense.

Students who complete in-person clerkships at their home institutions will probably have an advantage over students who, for want of dermatology clerkships at their home institutions, complete tele-rotations. In the past, program directors have given considerable weight to letters of recommendation while ranking residency applicants; however, this may change in the present scenario.[3] The lack of human interaction in web-based platforms may also pose a challenge for the faculty in judging a rotating student's clinical abilities and/or character, which, in turn, can compromise the strength of the recommendations. One solution may be to accord more importance to nondermatology letters than earlier. Another solution may be to prioritize other criteria, such as medical school performance, United States Medical Licensing Examination (USMLE) scores, and research work. This unfortunately may work against those who are unable to improve upon their low STEP 1 grades owing to STEP 2 clinical knowledge (CK) exam cancellations and delays. No solution is perfect, but both the teacher and the student could adapt to continue medical education and thrive in this changed scenario.

CONCLUSIONS

At this point in time, concrete data are unavailable, and the effect of tele-rotations compared with in-person rotations on the strength of the letters of recommendation and matching into dermatology programs should be studied. This information would be especially important in this technology-driven world, as

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programs look to make tele-rotations and/or interviews an option in the future beyond COVID-19.

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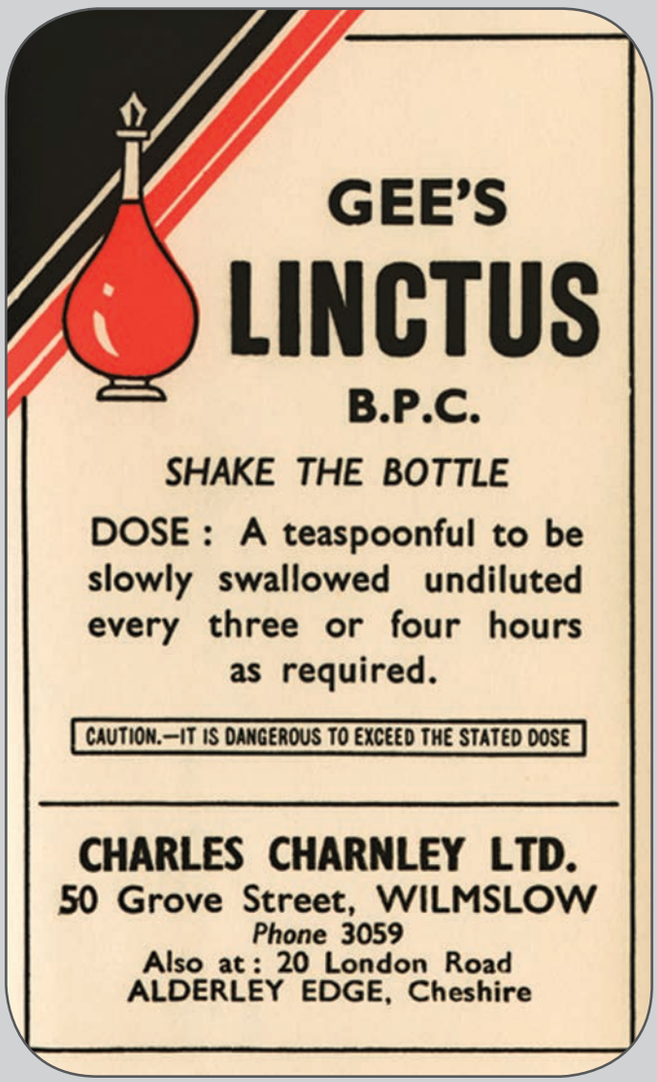

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CONTRAINDICATIONS

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.

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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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