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 **Ebglyss**[®]
(lebrikizumab-lbkz)
250mg/2mL injection

A Lilly Medicine

Deliver
CALM TO AD
that can go
ON AND ON¹

Help give your patients calm skin for the long term with EBGLYSS, a first-line biologic following topical therapy that can provide lasting relief from the burden of the signs and symptoms of moderate-to-severe atopic dermatitis (AD)¹

INDICATION

EBGLYSS is **indicated** for the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. EBGLYSS can be used with or without topical corticosteroids.

SELECT IMPORTANT SAFETY INFORMATION

Contraindication

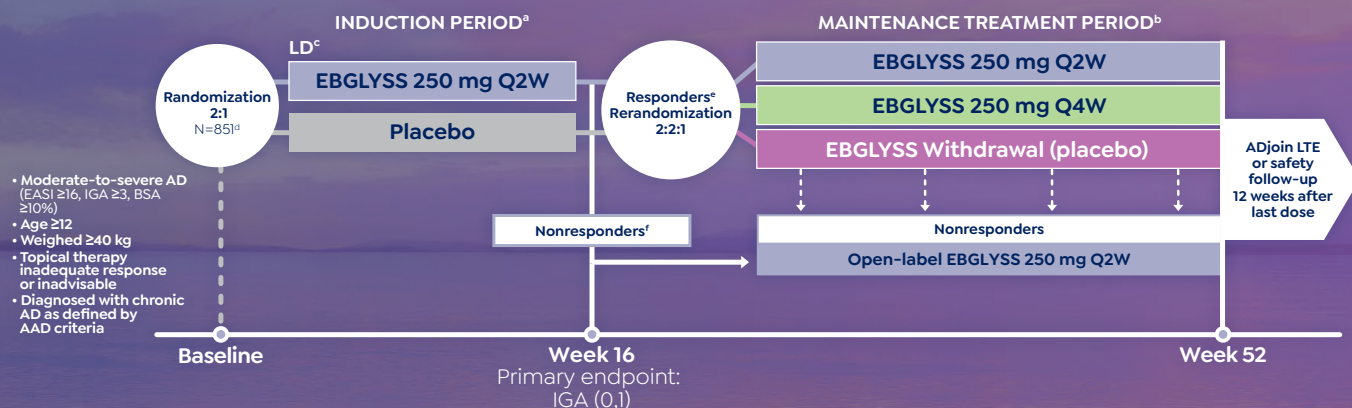
EBGLYSS is contraindicated in patients with prior serious hypersensitivity to lebrikizumab-lbkz or any excipients of EBGLYSS.

Actor portrayals.

EBGLYSS MONOTHERAPY

The efficacy and safety of EBGLYSS were evaluated over the course of 1 year in 2 monotherapy trials with the same design (ADvocate 1, ADvocate 2)¹

ADvocate 1 and ADvocate 2 study design^{1,2}



See Long-Term Efficacy Data on subsequent pages.



EXPLORE EBGLYSS BY VISITING
ebglyss.lilly.com/hcp

^aUse of topical/systemic treatments for atopic dermatitis (AD) was prohibited.²

^bUse of intermittent topical rescue medications for AD was permitted in the maintenance phase.²

^cTwo 250-mg injections at week 0 and week 2.¹

^dAt baseline, there were 424 patients enrolled in ADvocate 1, and 427 patients enrolled in ADvocate 2.²

^eResponders were defined as patients who achieved IGA 0,1 with ≥ 2 -point improvement or EASI 75 at week 16 without the use of rescue medication.²

^fNonresponders were defined as participants who did not achieve IGA 0,1 or EASI 75 at week 16 and participants who required rescue therapy during the first 16 weeks.³

AAD=American Academy of Dermatology; BSA=body surface area; EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LD=loading dose; LTE=long-term extension study; Q2W=every 2 weeks; Q4W=every 4 weeks.

SELECT IMPORTANT SAFETY INFORMATION

Hypersensitivity

Hypersensitivity reactions, including angioedema and urticaria, have been reported with use of EBGLYSS. If a serious hypersensitivity reaction occurs, discontinue EBGLYSS and institute appropriate therapy.

See Important Safety Information and Brief Summary of Prescribing Information on subsequent pages.

Ebglyss®

(lebrikizumab-lbkz)
250mg/2mL injection

A Lilly Medicine

ADvocate 2 (N=427): 33% of patients who received EBGLYSS monotherapy achieved IGA 0 or 1 vs 11% with placebo at week 16 ($P<0.001$).^{1,2}

^aResponder was defined as a patient with an IGA 0 or 1 ("clear" or "almost-clear") and a reduction of ≥ 2 points on a 0-4 IGA scale.¹

^bPatients received 500 mg of EBGLYSS at week 0 and week 2, and 250 mg Q2W through week 16.¹

^cPatients who received rescue therapy or discontinued treatment due to lack of efficacy were analyzed as nonresponders. Data after treatment discontinuation due to any other reason were considered missing. Any missing data were imputed using MCMC-MI.¹

MCMC-MI=Markov chain Monte Carlo multiple imputation.

^{*}IGA: A 5-point clinical assessment measure of atopic dermatitis (AD) severity in which 0="clear," 1="almost-clear," 2="mild," 3="moderate," and 4="severe."^{1,4}

Primary endpoint was the proportion of subjects who achieved IGA 0 or 1 with ≥ 2 -point change from baseline at week 16.¹

SELECT IMPORTANT SAFETY INFORMATION

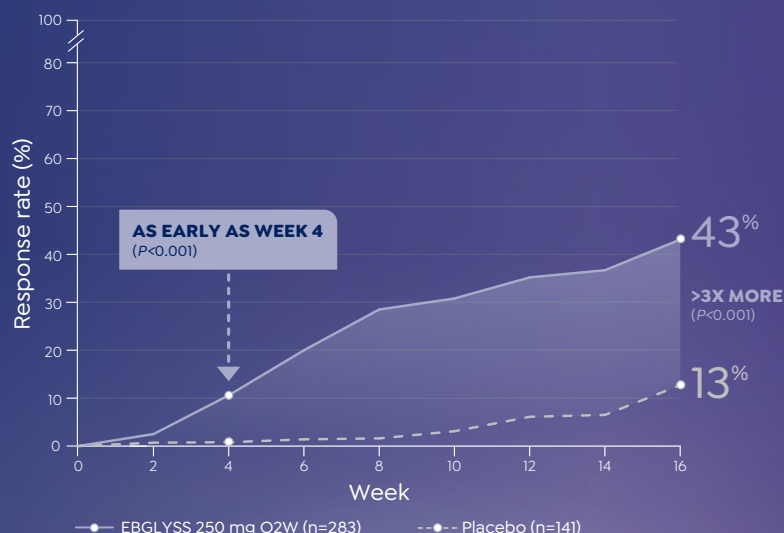
Conjunctivitis and Keratitis

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials. Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received EBGLYSS compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered during the treatment period. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

References:

- EBGLYSS (lebrikizumab-lbkz). Prescribing Information. Lilly USA, LLC.
- Silverberg JI, Guttman-Yassky E, Thaçi D, et al; for ADvocate1 and ADvocate2 Investigators. Two phase 3 trials of lebrikizumab for moderate-to-severe atopic dermatitis. *N Engl J Med*. 2023;388(12):1080-1091. doi:10.1056/NEJMoa2206714
- Data on File. Lilly USA, LLC. DOF-LK-US-0010.
- Data on File. Lilly USA, LLC. DOF-LK-US-0007.
- Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. *Br J Dermatol*. Published online March 30, 2023. doi:10.1093/bjd/ljad022

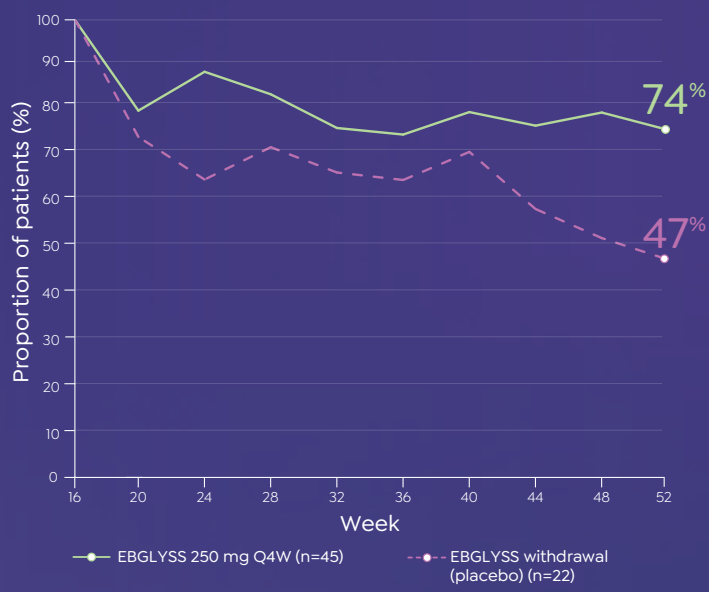
Primary endpoint: IGA* (0,1) responders through week 16 in ADvocate 1 (N=424)^{1,2,a,b,c}



See Important Safety Information on next page and Brief Summary of Prescribing Information on subsequent pages.

Actor portrayal.

Long-lasting clearance: IGA (0,1) responders through week 52 in ADvocate 1^{1,5,a}



ADvocate 2: 81% of patients who achieved clear or almost-clear skin (IGA 0 or 1) at week 16 and then received EBGLYSS monthly maintained clearance at 1 year (n=32); 50% with EBGLYSS withdrawal (placebo) (n=16).¹

Primary endpoint was the proportion of subjects who achieved IGA 0 or 1 with ≥ 2 -point change from baseline at week 16.¹

The recommended dosage of EBGLYSS is an initial dose of 500 mg (two 250-mg injections) at week 0 and week 2, followed by 250 mg every 2 weeks until week 16 or later, when adequate clinical response is achieved. The maintenance dose is 250 mg every 4 weeks.

^aPatients who received systemic rescue therapy or discontinued treatment due to lack of efficacy were analyzed as nonresponders. Data after topical rescue medication or treatment discontinuation due to any other reason were considered missing. Any missing data were imputed using MCMC-MI.¹

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: EBGLYSS is contraindicated in patients with prior serious hypersensitivity to lebrikizumab-lbkz or any excipients of EBGLYSS.

WARNINGS AND PRECAUTIONS
Hypersensitivity

Hypersensitivity reactions, including angioedema and urticaria, have been reported with use of EBGLYSS. If a serious hypersensitivity reaction occurs, discontinue EBGLYSS and institute appropriate therapy.

Conjunctivitis and Keratitis

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials. Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received EBGLYSS compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered during the treatment period. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if EBGLYSS will influence the immune response against helminth infections by inhibiting IL-13 signaling. Treat patients with pre-existing helminth infections before initiating treatment with EBGLYSS. If patients become infected while receiving EBGLYSS and do not respond to antihelminth treatment, discontinue treatment with EBGLYSS until the infection resolves.

Vaccinations

EBGLYSS may alter a patient’s immunity and increase the risk of infection following administration of live vaccines. Prior to therapy with EBGLYSS, complete all age-appropriate vaccinations according to current immunization guidelines. Avoid use of live vaccines immediately prior to or during treatment with EBGLYSS. No data are available on the response to live vaccines.

ADVERSE REACTIONS

The most common ($\geq 1\%$) adverse reactions are conjunctivitis, injection site reactions, and herpes zoster.

EBGLYSS is available as a 250mg/2mL subcutaneous injection prefilled pen or prefilled syringe.

See Brief Summary of Prescribing Information on subsequent pages.
Please see Instructions for Use included with the device.

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PP-LK-US-0711-003 03/2025
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EBGLYSS™ (lebrikizumab-lbkz) 250mg/2mL injection for subcutaneous use, available in a prefilled pen or prefilled syringe.
Brief Summary: Consult the Package Insert for complete Prescribing Information.

INDICATION AND USAGE

EBGLYSS is indicated for the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. EBGLYSS can be used with or without topical corticosteroids.

CONTRAINDICATION

EBGLYSS is contraindicated in patients with prior serious hypersensitivity to lebrikizumab-lbkz or any excipients of EBGLYSS (*see Warnings and Precautions*).

WARNINGS AND PRECAUTIONS

Hypersensitivity

Hypersensitivity reactions, including angioedema and urticaria, have been reported with use of EBGLYSS. If a serious hypersensitivity reaction occurs, discontinue EBGLYSS and institute appropriate therapy.

Conjunctivitis and Keratitis

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials. Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received EBGLYSS compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered during the treatment period (*see Adverse Reactions*). Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if EBGLYSS will influence the immune response against helminth infections by inhibiting IL-13 signaling. Treat patients with pre-existing helminth infections before initiating treatment with EBGLYSS. If patients become infected while receiving EBGLYSS and do not respond to antihelminth treatment, discontinue treatment with EBGLYSS until the infection resolves.

Vaccinations

EBGLYSS may alter a patient's immunity and increase the risk of infection following administration of live vaccines. Prior to therapy with EBGLYSS, complete all age-appropriate vaccinations according to current immunization guidelines. Avoid use of live vaccines immediately prior to or during treatment with EBGLYSS. No data are available on the response to live vaccines.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying and controlled 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.

Atopic Dermatitis

The safety of EBGLYSS was evaluated across 4 randomized, double-blind, placebo-controlled, multicenter trials in subjects with moderate-to-severe atopic dermatitis including 3 phase 3 trials (ADvocate 1, ADvocate 2, ADhere) and 1 phase 2 dose ranging trial (KGAF). In these 4 trials, mean age was 37 years; 50% of subjects were male; 62% were White, 13% were Black, and 20% were Asian. In terms of co-morbid conditions, in the phase 3 trials, 30% of the subjects had asthma, 50% had allergic rhinitis, 31% had food allergy, and 14% had allergic conjunctivitis at baseline.

A total of 891 subjects were treated with EBGLYSS for at least 1 year in the atopic dermatitis development program. ADvocate 1, ADvocate 2, and KGAF compared the safety of EBGLYSS monotherapy to placebo. ADhere compared the safety of EBGLYSS + TCS to placebo + TCS through 16 weeks. All subjects from the phase 3 trials were allowed to enroll in the long-term extension study.

Weeks 0 to 16

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the EBGLYSS 250 mg every 2 weeks monotherapy group, or in the EBGLYSS 250 mg every 2 weeks + TCS group, all at a higher rate than placebo during the first 16 weeks of treatment.

EBGLYSS™ (lebrikizumab-lbkz) 250mg/2mL injection for subcutaneous use

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Table 1: Adverse Reactions Occurring in ≥1% of the EBGLYSS Monotherapy Group or the EBGLYSS + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reactions	EBGLYSS Monotherapy ^a		EBGLYSS + TCS ^b	
	EBGLYSS 250 mg Q2W ^c N=638 n (%)	Placebo N=338 n (%)	EBGLYSS 250 mg Q2W ^c + TCS N=145 n (%)	Placebo + TCS N=66 n (%)
Conjunctivitis ^d	61 (10)	10 (3)	7 (5)	0
Injection Site Reactions ^e	16 (3)	4 (1)	4 (3)	1 (2)
Herpes Zoster	3 (<1)	0	2 (1)	0

^aIntegrated analysis of ADvocate 1, ADvocate 2, and the phase 2 dose finding trial (KGAF)

^bAnalysis of TCS concomitant therapy trial ADhere

^cEBGLYSS 500 mg at Week 0 and Week 2, followed by 250 mg every two weeks

^dConjunctivitis cluster includes conjunctivitis, conjunctivitis allergic, and conjunctivitis bacterial

^eInjection Site Reactions cluster includes injection site-related: pain, erythema, reaction, discomfort, dermatitis, pruritis, swelling and rash

In the monotherapy trials (ADvocate 1, ADvocate 2, and KGAF) through Week 16, the proportion of subjects who discontinued treatment due to adverse events was 2.4% in the EBGLYSS 250 mg every 2 weeks group and 1.8% in the placebo group. In the TCS trial (ADhere) through Week 16, the proportion of subjects who discontinued treatment due to adverse events was 2.1% in the EBGLYSS 250 mg every 2 weeks + TCS group and 0% in the placebo + TCS group. The most common adverse reactions leading to discontinuation of EBGLYSS compared to the placebo group were conjunctivitis and keratitis (0.6% vs. 0.3%), and injection site reactions (0.2% vs. 0) in the monotherapy trials; and conjunctivitis (0.7% vs. 0), and injection site reactions (0.7% vs. 0) in the TCS trial.

Eosinophilia

Increased post-baseline blood eosinophils were observed at a higher frequency in EBGLYSS-treated subjects compared to placebo. During the first 16 weeks, eosinophilia (>5000 cells/mcL) was observed in 0.4% in the EBGLYSS-treated subjects and 0% in subjects receiving placebo. Blood eosinophil elevations were generally transient and did not result in discontinuation.

Safety Weeks 16 to 52

Among those EBGLYSS-treated subjects who responded at Week 16 and who were re-randomized in the maintenance period of the monotherapy trials ADvocate 1 and ADvocate 2, a total of 113 and 118 subjects received EBGLYSS 250 mg every 2 weeks or every 4 weeks, respectively. The safety profile of EBGLYSS 250 mg every 4 weeks was generally consistent with EBGLYSS every 2 weeks during Weeks 16 to 52. The safety profile of EBGLYSS during maintenance treatment was generally consistent with the safety profile observed through Week 16.

Specific Adverse Drug Reactions

Conjunctivitis and Keratitis

Conjunctivitis was the most frequently reported eye disorder. Most cases of conjunctivitis and keratitis were mild or moderate in severity and recovered or resolved without treatment interruption or discontinuation.

During the initial 16-week treatment period of the monotherapy trials, conjunctivitis, including allergic conjunctivitis, was reported by 61 subjects (10%) in the EBGLYSS 250 mg every 2 weeks group and 10 subjects (3%) in the placebo group. In the TCS concomitant therapy trial, conjunctivitis was reported by 7 subjects (5%) in the EBGLYSS 250 mg every 2 weeks + TCS group compared to 0% in the placebo + TCS group. During the 16-week placebo-controlled induction period, 68 subjects reported 73 events of conjunctivitis. All events were nonserious and mild or moderate in severity. Conjunctivitis led to treatment discontinuation in 3 subjects. The exposure adjusted incidence rate of conjunctivitis for subjects treated with EBGLYSS 250 mg every 2 weeks was 30.6 events per 100 patient years through Week 16 (KGAF, ADvocate 1, ADvocate 2, ADhere).

During the maintenance treatment period of the monotherapy trials (ADvocate 1 and ADvocate 2) from 16 to 52 weeks, conjunctivitis, including allergic conjunctivitis, was reported by 2 subjects (1.8%) in the EBGLYSS 250 mg every 2 weeks group and 12 subjects (10.1%) in the EBGLYSS 250 mg every 4 weeks group, compared to 5 subjects (8.3%) in the placebo group. During the maintenance treatment period, 14 subjects treated with EBGLYSS reported 18 events of conjunctivitis.

See Brief Summary of Prescribing Information continued on adjacent page.

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All events were mild or moderate in severity. Conjunctivitis led to treatment discontinuation in 2 subjects in the EBGLYSS 250 mg every 4 weeks group. The exposure adjusted incidence rate of conjunctivitis for subjects treated with EBGLYSS 250 mg every 2 weeks was 18.3 events per 100 patient years and for those treated with EBGLYSS 250 mg every 4 weeks was 20.6 events per 100 patient years through Week 52 (ADvocate 1, ADvocate 2, ADhere + the long-term extension study).

During the initial 16-week treatment period of the monotherapy trials, keratitis, including atopic and vernal keratoconjunctivitis, was reported by 4 subjects (0.6%) in the EBGLYSS 250 mg every 2 weeks group and 1 subject (0.3%) in the placebo group. In the TCS concomitant therapy trial, vernal keratoconjunctivitis was reported by 1 subject (0.7%) in the EBGLYSS 250 mg every 2 weeks + TCS group, compared to 0% in the placebo + TCS group. During the 16-week placebo-controlled induction period, 5 subjects reported 7 events of keratitis. All events were nonserious and mild or moderate in severity. Keratitis led to treatment discontinuation in 2 subjects. The exposure adjusted incidence rate of keratitis for subjects treated with EBGLYSS 250 mg every 2 weeks was 2.2 events per 100 patient years through Week 16 (KGAF, ADvocate 1, ADvocate 2, ADhere).

During the maintenance treatment period of the monotherapy trials (ADvocate 1 and ADvocate 2) from 16 to 52 weeks, atopic keratoconjunctivitis was reported by 1 subject (0.8%) in the EBGLYSS 250 mg every 4 weeks group, and vernal keratoconjunctivitis was reported by 1 subject (0.9%) in the EBGLYSS 250 mg every 2 weeks group, compared to 0% in the placebo group. One (0.9%) event of severe vernal keratoconjunctivitis in an EBGLYSS 250 mg every 2 weeks subject led to treatment discontinuation. The exposure adjusted incidence rate of keratitis for subjects treated with EBGLYSS 250 mg every 2 weeks was 1.0 event per 100 patient years and for those treated with EBGLYSS 250 mg every 4 weeks was 0.7 events per 100 patient years through Week 52 (ADvocate 1, ADvocate 2, ADhere + the long-term extension study).

Injection Site Reactions

Injection site reactions were reported by 3% of the EBGLYSS group and 1% of the placebo group in the first 16 weeks of the monotherapy trials. Incidence of injection site reactions declined with continued treatment. Most events were mild or moderate and recovered without treatment discontinuation.

DRUG INTERACTION STUDIES

The effect of lebrikizumab-lbkz on the pharmacokinetics (PK) of co-administered medications has not been studied.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data on lebrikizumab-lbkz use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Transport of human IgG antibody across the placenta increases as pregnancy progresses and peaks during the third trimester; therefore, lebrikizumab-lbkz may be transmitted from the mother to the developing fetus. In animal reproduction studies, no effects on embryo-fetal development were observed after subcutaneous administration of lebrikizumab-lbkz to cynomolgus monkeys during organogenesis at doses up to 18 times the human exposure at the maximum recommended human dose (MRHD) (*see Data*). 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 to 4% and 15 to 20%, respectively. Report pregnancies to Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979).

Data

Animal Data

In an embryofetal development study, no malformations or embryofetal toxicity were observed in fetuses from pregnant cynomolgus monkeys administered lebrikizumab-lbkz during organogenesis at doses up to 150 mg/kg initial dose followed by 50 mg/kg per week by subcutaneous injection, which was associated with plasma exposure ($C_{avg,ss}$) approximately 18 times the human exposure at the MRHD. Lebrikizumab-lbkz crossed the placenta in monkeys.

In a prenatal and postnatal development study, pregnant cynomolgus monkeys were administered lebrikizumab-lbkz during organogenesis to parturition at doses up to 150 mg/kg initial dose followed by 50 mg/kg per week by subcutaneous injection, which was associated with plasma exposure ($C_{avg,ss}$) approximately 18 times the human exposure at the MRHD.

No embryofetal toxicity or malformations, or effects on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

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Lactation

Risk Summary

There are no data on the presence of lebrikizumab-lbkz in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to lebrikizumab-lbkz are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EBGLYSS and any potential adverse effects on the breastfed infant from EBGLYSS or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of EBGLYSS have been established in pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. A total of 372 pediatric subjects were exposed to EBGLYSS with 270 subjects exposed to EBGLYSS for at least one year. The safety and effectiveness were generally consistent between pediatric and adult subjects (*see Adverse Reactions*). The safety and effectiveness of EBGLYSS have not been established in pediatric patients younger than 12 years of age and pediatric patients 12 years and older who weigh less than 40 kg.

Geriatric Use

Of the 1348 adult subjects with moderate-to-severe atopic dermatitis exposed to EBGLYSS, a total of 123 were 65 years or older, and 29 subjects were 75 years or older. Clinical studies of EBGLYSS did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

DOSING

Recommended Dosage

The recommended dosage of EBGLYSS is an initial dose of 500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg every two weeks until Week 16 or later, when adequate clinical response is achieved. The maintenance dosage is 250 mg every four weeks.

OVERDOSAGE

In the event of overdosage, contact Poison Control (1-800-222-1222) for the latest recommendations and monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Administration Instructions: Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the prefilled pen and prefilled syringe correctly. Advise patients to follow sharps disposal recommendations (*see Instructions for Use*).

Hypersensitivity: Advise patients to discontinue EBGLYSS and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions (*see Warnings and Precautions*).

Conjunctivitis and Keratitis: Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop (*see Warnings and Precautions*).

Parasitic (Helminth) Infections: Advise patients to notify their healthcare provider if they present with clinical features consistent with helminthic infection (*see Warnings and Precautions*).

Vaccinations: Advise patients that EBGLYSS may increase the risk of infection following administration of live vaccines and that vaccination with live vaccines is not recommended during EBGLYSS treatment. Instruct patients to inform the healthcare provider that they are taking EBGLYSS prior to a potential vaccination (*see Warnings and Precautions*).

Pregnancy: Inform patients to report their pregnancy to Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) (*see Use in Specific Populations*).

Additional information can be found at www.ebglyss.lilly.com or by calling 1-800-LillyRx (1-800-545-5979).

See Instructions for Use accompanying the product device.

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injection for subcutaneous use

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JULY 2025

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is indexed in MEDLINE®/PubMed® and is published monthly by the
SanovaWorks, c/o WebMD
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Addressing the Root Causes of Female Hair Loss and Non-Pharmaceutical Interventions

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ABSTRACT

Female hair loss affects over 50% of postmenopausal women, with up to 40% of healthy women experiencing frontal/parietal hair loss, often beginning around reproductive age. Androgenetic alopecia is the most prevalent form of hair loss. Other types include alopecia areata, telogen effluvium, and scarring alopecias, such as lichen planopilaris and central centrifugal cicatricial alopecia. Hair loss can severely impact a woman's psychological well-being, yet treatments approved by the US Food and Drug Administration (FDA) remain limited to topical minoxidil and oral Janus kinase inhibitors. This manuscript reviews the multifaceted causes of female hair loss, hormonal imbalances, inflammation, nutrient deficiencies, aging, and oxidative stress, and explores non-pharmaceutical interventions. Saw palmetto, horsetail, and pumpkin seed oil, all of which inhibit 5 α -reductase, show promise in promoting hair density and reducing hair follicle miniaturization. Curcumin has demonstrated anti-inflammatory effects, contributing to improved hair and scalp health. Nutritional deficiencies, particularly in iron, vitamin D, and essential minerals, also play a significant role in hair loss, underscoring the importance of a balanced diet and conservative supplementation. Avoiding excessive supplementation, especially with biotin, is recommended due to potential diagnostic test interferences. With increasing demand for non-pharmaceutical options, identifying natural, safe, and effective treatments for female hair loss is imperative. Further studies are needed to validate the efficacy and safety of these interventions.

J Drugs Dermatol. 2025;24(7):658-661. doi:10.36849/JDD.8763

INTRODUCTION

Hair loss is a common problem that affects women. More than 50% of postmenopausal women, with up to 40% of healthy women, experience frontal/parietal hair loss, often beginning around reproductive age.¹ The most common type of female hair loss is called androgenetic alopecia (AGA) or female pattern hair loss (FPHL). Other forms of alopecia affecting women include alopecia areata (AA), telogen effluvium (TE), lichen planopilaris (LPP), central centrifugal cicatricial alopecia (CCCA), frontal fibrosing alopecia (FFA), and traction alopecia. Female hair loss can have a psychosocial impact, contributing to a lower self-image, anxiety, and depression.²

Currently, there are a limited number of medications approved by the US Food and Drug Administration (FDA) to address female hair loss. FDA-approved treatments include topical minoxidil

for FPHL and 3 oral Janus kinase inhibitors indicated for the treatment of AA.³ With the dearth of options, supplements and nonprescription therapies could play a beneficial role, filling a gap in the management of all females experiencing hair loss.

When discussing the pathophysiology of female hair loss disorders, it is helpful to consolidate etiologies into a few broad categories. These include hormone imbalance, systemic and localized inflammation, nutrient and vitamin deficiencies, aging and cellular senescence, and oxidative stress. Below, we discuss the origins of hair loss and review interventions that may serve as mediators impacting disease progression and reversal.

Hormone Imbalance and Sensitivities

Hair loss in women is often influenced by hormonal factors, such as the production of dihydrotestosterone (DHT), polycystic

ovary syndrome (PCOS), thyroid disorders, menopause, pregnancy, and hormone replacement therapy (HRT). While the role of DHT, a potent androgen, is established in male pattern baldness, DHT may also contribute to FPHL by miniaturizing hair follicles, particularly in genetically predisposed individuals.^{26,27} In PCOS, hormone dysregulation and elevated androgen levels lead to scalp hair thinning. Thyroid imbalances, both hyper- and hypothyroidism, can disrupt the hair growth cycle, leading to diffuse hair loss.²⁷ During menopause, estrogen levels decline, exacerbating hair thinning, while post-pregnancy hormonal shifts often trigger TE. HRT may alleviate or exacerbate hair loss depending on individual hormonal responses.^{26,27}

These insights highlight the complexity of managing hair loss in women, which requires individualized approaches and consideration of hormonal profiles and related endocrine disorders. While pharmacologic therapy remains the cornerstone of treatment, non-pharmacologic options are available as complementary and alternative treatments.

Saw palmetto (SP) is a natural treatment that has shown efficacy in addressing both FPHL and TE. Comprising primarily fatty acids and phytosterols, SP functions as a nonselective inhibitor of 5 α -reductase, reducing DHT binding to androgen receptors by nearly 50%.²⁸ Additionally, SP promotes the conversion of DHT to its weaker metabolite, androstanediol, further minimizing hair follicle damage.³¹ Studies show that SP can improve hair count, density, and overall quality in patients with FPHL and TE, with some reporting up to 83.3% improvement in hair density.³²

Horsetail (*Equisetum arvense*) has also demonstrated efficacy in inhibiting 5 α -reductase. In a recent study, the ethyl acetate extract (EA) of horsetail was the most effective among several *Equisetum debile* extracts, exhibiting inhibition of 5 α -reductase activity (approximately 35%), though it remains less potent than finasteride.²⁹ This inhibition is believed to be associated with the presence of palmitic acid, making horsetail a promising natural alternative for reducing DHT levels and promoting hair regrowth.³⁰

Pumpkin seed oil has anti-androgenic and anti-5 α -reductase activity. A randomized controlled trial of pumpkin seed oil capsules used among 76 patients with AGA demonstrated superior hair growth and patient-reported satisfaction among the intervention vs the control group.^{37, 38}

Systemic and Localized Inflammation

Systemic inflammatory diseases contribute to hair loss. Patients with connective tissue diseases, autoimmune disorders, and metabolic syndromes can experience cutaneous manifestations that often include alopecia.⁴ On a localized level, the role of inflammation in AGA, AA, and scarring alopecias is well documented. Historically, AGA was considered to be a

noninflammatory alopecia. However, biopsies of balding scalps in patients with AGA demonstrated an inflammatory infiltrate and perifollicular fibrosis.⁵⁻⁹ Studies have demonstrated that the extent of inflammation correlates with the most severe clinical forms of AGA, and the addition of anti-inflammatory therapies to AGA treatment has led to improved treatment outcomes.^{8,9}

The active constituent of turmeric, curcumin, shows promise as an ingredient to promote hair health. It has been shown to have a range of therapeutic effects, including antioxidant protection against free radicals, anti-inflammation by lowering histamine levels, and possibly by increasing the production of natural cortisone by the adrenal glands, and antimicrobial activity.⁴²

Pea sprout extract has been shown to improve hair density when applied topically through its anti-inflammatory and antioxidant properties. Results of a study from 2019 demonstrated that the supplementation of 100 mg of pea sprout extract daily decreased hair loss in individuals experiencing hair shedding.⁵⁷

Nutrient and Vitamin Deficiencies

Rapidly dividing hair matrix cells in the follicular bulb require micronutrients for cellular turnover. Nutrient and vitamin deficiencies can significantly impact hair health and contribute to hair loss. Iron deficiency is one of the most recognizable causes of TE due to its role in oxygen transport and cellular metabolism. Low serum ferritin levels are often associated with hair shedding.³⁶ Vitamin D plays a crucial role in hair follicle cycling, and low levels are linked to various hair disorders, primarily AA with weaker evidence for TE and AGA. Supplementation in cases of deficiency may improve these conditions.³⁶

Vitamin A is necessary for the growth and differentiation of hair follicles. Both vitamin A deficiency and toxicity may lead to hair loss. A deficiency can lead to dry, brittle hair and eventually hair loss. Excess vitamin A can disrupt the hair cycle, resulting in reduced hair density and fewer anagen-phase hairs.³⁶ Vitamins C and E, known for their antioxidant properties, support hair health by protecting follicles from oxidative stress and aiding in collagen synthesis, which is essential for hair structure.³⁶ Zinc, copper, and selenium deficiencies are known to manifest as alopecia. Excessive selenium intake may also contribute to hair loss.⁵⁵

Certain components of the vitamin B complex are associated with hair loss, including riboflavin, niacin, biotin, folate, and vitamin B12. Riboflavin deficiency is rare in the US. Biotin is the only B vitamin produced by the body; as such, healthy individuals do not require biotin supplementation. While adequate biotin supports hair growth and maintenance by promoting healthy keratin production, high doses can contribute to abnormalities in diagnostic tests for thyroid hormones and

troponins.³⁴ Niacin and folate are vital for cellular growth and hair follicle function, and deficiencies can lead to reduced hair growth and loss.³⁷ Groups at risk for folate deficiency include those suffering from alcoholism, poor diets, and malabsorption disorders. Otherwise, folate deficiency is uncommon.

While vitamins and minerals are essential for hair health, supraphysiologic doses of these nutrients can be harmful. Many supplements contain doses beyond the recommended daily amounts, which can lead to toxicity or other adverse effects. For most individuals, meeting the recommended daily intake of these nutrients through a balanced diet or conservative supplementation is sufficient to support hair health without risking the consequences of excessive supplementation.

Aging and Cellular Senescence

The scalp and hair follicles are subject to intrinsic, extrinsic, and natural aging, all of which contribute to hair loss.¹⁰⁻¹⁵ Intrinsic factors are related to genetic and epigenetic mechanisms, while extrinsic factors can be secondary to ultraviolet radiation, chemical treatments, pollution exposure, and other causes.¹⁶ Natural aging is phenotypically and histologically characterized by weathering of the hair shaft, a decrease in melanin and overall hair production, and development of increasingly dry, thin, dull, and brittle hair.¹⁷ Senescent alopecia has been described as a distinct process and is characterized histologically by a modest reduction in the size of otherwise normal hair.^{18,19}

Nicotinamide adenine dinucleotide (NAD⁺) is a fundamental molecule in human life and health as it participates in energy metabolism, cell signaling, mitochondrial homeostasis, and in dictating cell survival or death. This small molecule lies at the center of cell metabolism, mitochondrial function, and the biologic processes of aging by serving as a substrate for the electron transport chain.⁴³ Cellular NAD⁺ levels are strongly correlated with aging.⁴⁴

Nicotinamide Mononucleotide (NMN), a precursor to NAD⁺ in cells, has been studied for hair growth. A 2024 murine study by Chuntao Xu et al showed that NMN can promote hair health by significantly lowering inflammatory markers, which are expressed under states of high DHT activity, such as IL-6 and TNF-alpha, and by reducing oxidative stress. Furthermore, it can enhance VEGF expression in human dermal papilla cells equivalent to that achieved by minoxidil.⁵¹ In 2019, Khadka et al suggested that the modulation of NAD⁺ levels may be a novel therapeutic approach to prevent chemotherapy-associated hair loss.⁵²

Taurine is a naturally occurring amino acid. A growing number of studies have shown that taurine supplementation protects against pathologies associated with mitochondrial defects, such as aging, and serves as a major antioxidant, anti-inflammatory,

and anti-apoptotic factor in the body.⁴⁷ Taurine has been shown to promote hair survival and prevent hair growth inhibition in vitro. It can also prevent TGF-beta 1 from negatively affecting hair follicles.⁴⁸⁻⁵⁰

Oxidative Stress and Free Radicals

Oxidative stress has been linked to the pathogenesis of AGA, AA, and TE.³⁹⁻⁴¹ Oxidative stress can disrupt normal hair follicle maturation and growth cycles. Reactive oxygen species (ROS) are created during normal cellular function and have important physiologic functions, including maintenance of signaling pathways during hair follicle development.²⁰⁻²³ In vitro studies of AGA have shown increased markers of and increased sensitivity to oxidative stress in dermal papilla cells from balding scalp compared to non-balding scalp.^{24, 25}

Vitamins such as E and C have been shown to be potent antioxidants. Supplementation with these vitamins can affect hair loss. A randomized controlled trial (RCT)⁵⁶ of fish oil, black currant seed oil, vitamin E, vitamin C, and lycopene supplementation compared with no supplementation showed increased hair density and thickness in the intervention group.

Ashwagandha is a common ingredient in hair health products. It is a natural antioxidant and anti-inflammatory herb that has been shown to fight free radicals and strengthen hair follicles to promote hair growth.^{45, 46}

Biotin Free Matters

Biotin, often marketed for hair growth, can interfere with several lab values causing inaccurate results. Examples include cardiac markers such as troponin; sex hormones including estradiol, testosterone, and sex hormone binding globulin; other B vitamins such as folate and vitamin B12; parathyroid hormone; and hepatitis A and B antibodies/antigens.^{53,54} High doses of biotin can lead to falsely elevated freeT4 and T3 levels while lowering TSH, resulting in potential misdiagnosis of thyroid conditions.³³ The FDA has issued warnings about this interference, particularly in lab assays.³⁵ Additionally, biotin deficiency is rare in individuals with a balanced diet, and evidence supporting its role in hair growth is limited to cases of true deficiency.³⁴ Thus, choosing biotin-free supplements can be beneficial for avoiding diagnostic complications.

CONCLUSION

Given that more than half of postmenopausal women experience some form of hair loss, the lack of FDA-approved treatments contributes to a growing demand for non-pharmaceutical therapies. By considering the root causes, we can identify key ingredients and interventions that may benefit women experiencing hair loss. Evidence shows that while some nutritional deficiencies may cause or exacerbate alopecia, nutritional overdosing may also have deleterious

effects. Continued and additional studies should be performed to explore ingredient benefits and safety profiles.

DISCLOSURES

Dr Adam Leavitt reports involvement with Pfizer for abrocitinib. Dr Spencer D. Hawkins has no relevant disclosures.

Dr Chesahna Kindred is a founding advisor for Xtressé and serves as a speaker for Lilly (baricitinib), Aerolase (lasers), Regeneron (dupilumab), Sanofi (dupilumab), Arcutis (roflumilast), Pfizer (ritlecitinib), and Galderma (nemolizumab). She serves on advisory boards for Lilly, UCB, Novartis, Sun Pharmaceuticals, Janssen, AbbVie, Pfizer, Regeneron, Sanofi, and Arcutis. She is also a medical board member for Aerolase and Selphyl.

Dr Cheri Frey has affiliations with Galderma, Novartis, Sun Pharmaceuticals, Benev, L'Oréal, Nutrafol, Procter & Gamble, and Beiersdorf.

Dr Matt Leavitt is the Founder and CEO of Restore Biologics. Dr Madeliene Gainers and Dr Steven Grekin have no relevant disclosures.

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Photoprotection Efficacy of Sun Protection Factor and Iron Oxide Formulations in Diverse Skin With Melasma and Photodamage

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ABSTRACT

Visible light (400-700nm) comprises 45% of the sunlight spectrum and can induce both immediate and persistent skin darkening, as well as worsen dyschromia, especially in the skin of color population. In a recent mini-zone study, we demonstrated that iron oxide (FeO)-containing formulations could protect skin from visible light-induced pigmentation in Fitzpatrick skin type (FST) IV individuals, while ultraviolet (UV) protection sunscreen SPF 50+ (sun protection factor) could not. To assess the benefit of adding FeO-containing foundation into real-life daily sun care routine in improving the appearance of photodamage and melasma, we evaluated the efficacy of two sun protection regimens (SPF50 alone and SPF50+FeO) in healthy women of FST III to VI for 12 weeks. Clinical evaluation and colorimetric measurement showed that both regimens significantly improved skin quality and overall appearance over 12 weeks compared to baseline. At week 4, the photodamage subgroup using SPF50+FeO showed early improvement over baseline in skin roughness (visual and tactile). The melasma subgroup using SPF50+FeO showed early improvement in overall healthy appearance. At week 12, although both groups showed improvement in colorimetric measurements (L^*), the response was different: 36% of melasma participants in the SPF50+FeO group showed superior improvement in their skin radiance (L^*) vs 0% in the SPF50 group. A self-assessment questionnaire revealed that SPF50+FeO enhanced the quality of life in participants with melasma. This study demonstrated the importance of including visible light protection into a daily sun care routine, especially for melasma: masking and improving existing conditions indoors and outdoors at the same time.

J Drugs Dermatol. 2025;24(7):662-667. doi:10.36849/JDD.9240

INTRODUCTION

Globally, particularly in the United States (US), the skin of color population has been growing significantly, which requires tailored dermatological attention strategies due to the unique physiological conditions and clinical manifestations. Concerning photoaging, compared with Fitzpatrick skin types FST I, II and III, women of color with FST IV and above exhibit fewer visible signs of aging, such as wrinkles and fine lines. However, due to their melanin-rich skin, they are more susceptible to photo-mediated dyspigmentation, including photodamage and melasma, which may result in uneven skin tone, ashy skin, and blotchiness.¹ Those skin conditions could potentially impact the psychological state and quality of life of the individual.² Previously, studies on the cutaneous impact of sun damage have focused on ultraviolet B radiation (UVB) and ultraviolet A radiation (UVA)-mediated effects on lighter FST skin.³ Sunscreens have been demonstrated as effective photoprotection strategies to reduce harmful effects of UV radiation.³ The sun protection strategy against UVA and UVB was also found to be impactful in the skin of color population. In a one-year real-life multicenter study, we have shown that in Hispanic women with high FST (IV and V),

applying sunscreen every day could significantly improve their skin hyperpigmentation and aging signs.⁴

In the past decade, the sun protection strategy has extended into the visible light (VL) irradiation between 400 and 700 nm, which makes up 45% of sunlight spectrum, and has been recently demonstrated to induce both immediate and persistent pigment darkening, contributing to dyschromia in participants with Fitzpatrick skin phototype III and above.⁴⁻⁶ VL also darkens skin, additionally, when combined with long wavelength UVA.⁷ This overproduced pigmentation was induced by the Opsin3 receptor, which can sense visible sunlight and therefore activate the downstream melanogenesis.⁸ In the skin of color (SOC) population, the effect was more prominent and long-lasting.⁹ Those findings have created an urgent need to find full-spectrum photoprotection strategies beyond UV, particularly in individuals with Fitzpatrick skin phototypes III and higher.¹⁰

Iron oxides (FeO) as a topical ingredient have been proven to contribute to VL protection. Under real-life conditions, daily application of a tinted sunscreen was demonstrated to reduce the appearance of cutaneous hyperchromia after 60 days.¹¹

Additionally, broad-spectrum sunscreens containing oxide pigments were shown to improve melasma lesions after 8 weeks,¹² and to prevent relapses after 6 months.¹³ To better understand the VL protection efficacy of iron oxides in SOC, in a recent publication using a well-controlled minizone model, we showed that iron oxides containing makeup products alone protected the skin against visible light (wavelength 400 to 900 nm, with 88.2% visible light) induced skin pigmentation in participants with FST IV, while a mineral SPF50 against UVA/UVB was not sufficient to protect skin darkening induced by visible light.¹⁴ This could be potentially explained by the different mechanisms of action: mineral UVA/UVB protectants could reflect, absorb, and scatter UV light, but have poor VL absorption, while iron oxides absorb both UV (290-400nm) and VL (400-450nm) spectrum.^{14,15}

These recent findings indicate that topical products containing iron oxides, alone or in combination with SPF sunscreens, could extend photoprotection against UV and VL-induced dyschromia in higher skin phototypes. In this 12-week, monocenter, randomized, double-blinded, full-face study, we aimed to evaluate the efficacy of two home-care sun protection regimens under real-life conditions, on improving facial dyschromia of photodamage and melasma in healthy women with skin Fitzpatrick phototypes III to VI. We evaluated and compared two groups of treatment: one group with SPF50 only sunscreen, the other group with SPF50+FeO containing foundation. This new study finding has potential to bring awareness to consumers, particularly for SOC populations, that adding a FeO-containing product to their skincare routine can play a dual role: camouflaging existing skin concerns and reducing the development of pigmentation triggered by sun exposure, plus, advocate the importance for visible light photoprotection indoors and outdoors.

MATERIALS AND METHODS

Study Participants

The study was performed in accordance with the Good Clinical Practice and the principles of the Declaration of Helsinki.¹⁶ The procedures used in this study were approved by an independent Institutional Review Board. Before the study procedure, informed consent was obtained from all study participants before enrollment. Eligibility was determined by physical examination and confirmation of all inclusion/exclusion criteria.

Fifty-two healthy female participants between 29 and 65 years old with FST III to VI were enrolled in the study. The participants were qualified based on mild to moderate signs of facial dyschromia of photodamage (with 2-3 solar lentigine spots on the face) or mild to moderate facial melasma. Participants who have used within the last 6 weeks any whitening cosmetics and drugs, including retinoids and other skin rejuvenation procedures

were excluded from the study. The qualified participants were randomized into one of the following product regimen groups: SPF 50 alone (will be shortened to SPF50), or SPF 50 + iron-oxide-containing foundation (will be shortened to SPF50+FeO).

Study Design

This study was a monocenter, randomized, double-blinded, full-face study consisting of a 12-week treatment phase. All participants were randomized into one of the two treatment groups at week 0. Clinical gradings, instrumental measurements, full-face VISIA image, and self-assessment questionnaire were obtained at week 0 (baseline), week 4, week 8, and week 12. Participants in each group were additionally evaluated for the appearance of new and improvement of pre-existing melasma. At the end of 12 weeks, 21 participants in Group 1 and 21 participants in Group 2 completed the study.

Test Materials

All investigative and auxiliary products were dispensed for full-face topical application. All participants were provided with the investigational products according to their randomization and trained on the self-application of all test products. Participants assigned to the SPF50 group applied 2mg/cm² daily in the morning and 15 minutes before sun exposure for 12 weeks. Reapplication every 2 to 3 hours under sun exposure was recommended. The active ingredients in the sunscreen contain 3% avobenzene, 10% homosalate, 5% octisalate, and 7% octocrylene. Participants assigned to the combination regimen group applied the SPF50 followed by the iron oxides-containing foundation. Because the participants picked different shades to match their skin tone and shade, the content of iron oxides could vary (3-27% FeO). 1 to 4 drops of the foundation were applied on a brush and smoothed outward from the center of the face to build uniform coverage. Auxiliary products (cleanser and moisturizer) were distributed to use during the 12 week-treatment phases. All participants were provided diaries to daily record length, time, and type of outdoor activities, as well as frequency and time of test product application.

Clinical Evaluation

All clinical gradings were performed at baseline (week 0), week 4, week 8, and week 12 by a trained assessor. Clinical evaluations including skin dyschromia, overall hyperpigmentation, photodamage, skin-tone evenness, skin radiance/dullness, skin brightness, and visual and tactile skin roughness, were evaluated on all participants on the global face using a Modified Griffiths 10-point scale (0-9, 0 being best and 9 being worse score). For melasma participants only, the clinical assessment of melasma was done under standard daylight illumination by using the modified MASI scale by a certified dermatologist (Modified Melasma Area Severity Index (mMASI)).¹⁷ Change of grading from baseline was used for the evaluation of efficacy.

Instrumental Measurements for Skin Colorimetry

Instrumental measurements of skin colorimetry were performed with a Chromameter® (Konica Minolta CR400), using the L*a*b* color system (CIE lab, 1976). The individual typology angle (ITA°) was calculated from the L* and b* values using $ITA=[\arctangent(L^*-50)/b^*]180/\pi$, as an indication of skin pigmentation.

Digital imaging was captured using the VISIA CR digital imaging system (Canfield Scientific, Inc., Parsippany, NJ) using standard, cross-polarized, parallel polarized, and UV fluorescence light settings at each time point for each participant.

Statistical Analysis

The baseline values of the two treatment groups were first compared using ANOVA to make sure that there is no significant difference to cause baseline bias. All statistical analyses were calculated using the change from the baseline value. A linear mixed model was established to thoroughly evaluate the effect of different treatments, time, and their interaction effect at the same time. In cases of non-normality of data, comparisons were made by a Wilcoxon test. Benjamini-Hochberg’s adjustment procedure was used to adjust *P*-values for multiple comparisons. A comparison with *P*-value ≤0.05 was considered a statistically significant difference.

RESULTS

Fifty-two subjects were randomized, and 43 finished the study. Among the dropped-out participants, 3 were lost to follow up, 2 withdrew consent, and 4 were due to adverse events (AE). A total of 11 adverse events were observed in the study, including 2 cases of local intolerance where moderate erythema on the face was observed, other AEs included 2 cases of Covid-19, 2 cases of common cold, 1 oral herpes, 1 fever and cough, 1 lung infection, 1 face abrasion due to falling, and 1 case of hand-foot and mouth disease. The study finished with diverse demographics in ethnicity and even distribution between photodamage and

melasma (Table 1). This inclusive demography will provide important data for future study design as well.

Including Visible Light Protection into Daily Sun Care Routine Improves Skin Roughness and Overall Healthy Appearance as Early as 4 Weeks

Over the 12 weeks of study time, participants from both the SPF50 and SPF50+FeO groups showed significant improvement in skin hyperpigmentation, skin roughness, and skin quality (skin-tone evenness, skin radiance, skin brightness, visual, and tactile skin roughness) compared with baseline. The efficacy of SPF50 is consistent with previous reports that consistent usage of UV protection can improve skin quality over time.¹⁸ However, adding visible light protection to SPF50 manifested earlier improvement in skin quality. At week 4, photodamaged participants in the SPF50+FeO group showed significant improvement in skin roughness (both visual and tactile, Figure 1A shows improvement in visual roughness) compared with baseline, while photodamaged participants with SPF50 showed significant change only starting at week 8. At week 4, participants with melasma with SPF50+FeO regimen showed significant improvement in skin overall healthy appearance compared with baseline, while the SPF50 only group showed significant improvement only starting at week 8 (Figure 1B).

SPF50+FeO Sun Care Routine Improved Skin Luminance as Early as 4 Weeks

Skin colorimetric parameters are often used as an objective evaluation of skin pigmentation and photoaging. In this study, we included a chromameter to track how the two regimens improved the skin pigmentation on the pigmented and non-pigmented sites. The L* value and the individual typology angle (ITA°) were used to measure the luminescence and degree of constitutive pigmentation of the skin, respectively. ITA° changes have been proven to correlate with the UVA dose and DNA damage in melanocytes.¹⁹

TABLE 1.

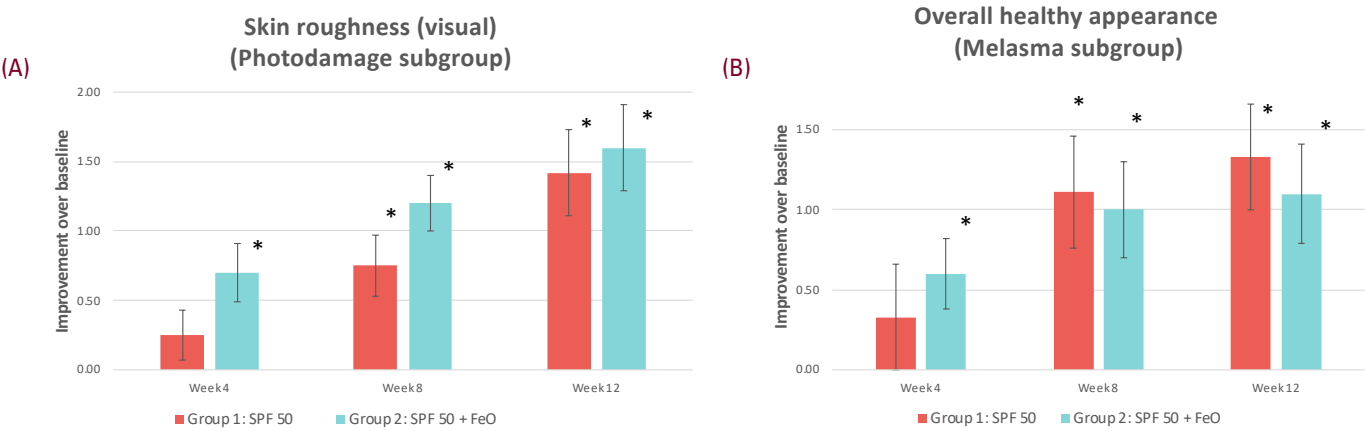
Diversity of Participants Completing the Study			
		Group 1-SPF50 (n)	Group 2- SPF50 + FeO (n) (FeO concentration in the product [%])
By Fitzpatrick Skin Type	III	7	6 (3.6-6.0)
	IV	9	3 (6.0)
	V	4	10 (6.0-14.6)
	VI	1	2 (14.6-26.8)
By Subgroup	Photodamage:	12	11
	Melasma	9	10
By Race/Ethnicity	Asian	11	14
	Black	1	2
	Hispanic/Latino	8	5
	Native Hawaiian or other Pacific Islanders	1	1

In our study, both routines showed statistically significant improvement in instrumental measurements over baseline (Table 2). SPF50+FeO combination showed statistically significant improvement in ITA° of pigmented skin starting at week 4, while the SPF50 only group showed significant improvement starting at week 8 (Figure 2A). In the melasma subgroup, although the ITA° of skin from the SPF50 group was not significantly lower compared to SPF50+FeO at week 12, only the SPF50+FeO group maintained the trend of ITA° improvement through week 12

(Figure 2B). A long-term efficacy test of SPF50+FeO could be tested in the future.

To identify not only the average changes over time but also demonstrate clinically meaningful improvements over time, we included responder analysis to identify which regimen can lead to a superior impact. Using the change of L* value that is related to skin luminescence, we found that at week 12, a higher percentage of melasma participants using SPF50+FeO

FIGURE 1. SPF50+FeO sun care routine improvement skin roughness in photodamage subgroup (A) and overall healthy improvements in melasma subgroup (B).



*P<0.05

TABLE 2.

Changes in L* and ITA° in the Two Sun Care Groups							
Parameters	Area	SPF50 (N=21)			SPF50+FeO (N=21)		
		Week 4	Week 8	Week 12	Week 4	Week 8	Week 12
L*	Pigmented area	--	*	*	--	*	*
	Non pigmented area	--	--	*	--	*	*
ITA°	Pigmented area	--	*	*	*	*	*
	Non pigmented area	--	--	*	--	*	*

Significant improvement compared to baseline: *P<0.05.

FIGURE 2. Both group 1 and group 2 show improvement in skin brightness in instrumental measurement. The lesional skin of all participants who used the Group 2 regimen (SPF50+FeO) showed statistically significant improvement in ITA starting at week 4 (A). Group 2 maintains the trend of improvement at week 12 in the melasma subgroup in ITA-skin brightness measurement (B).

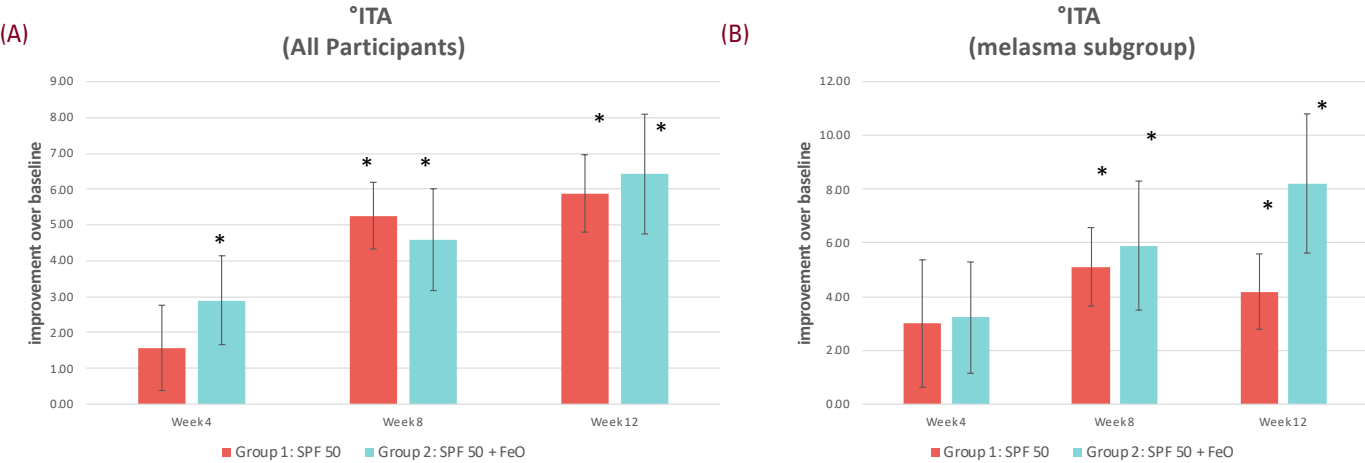
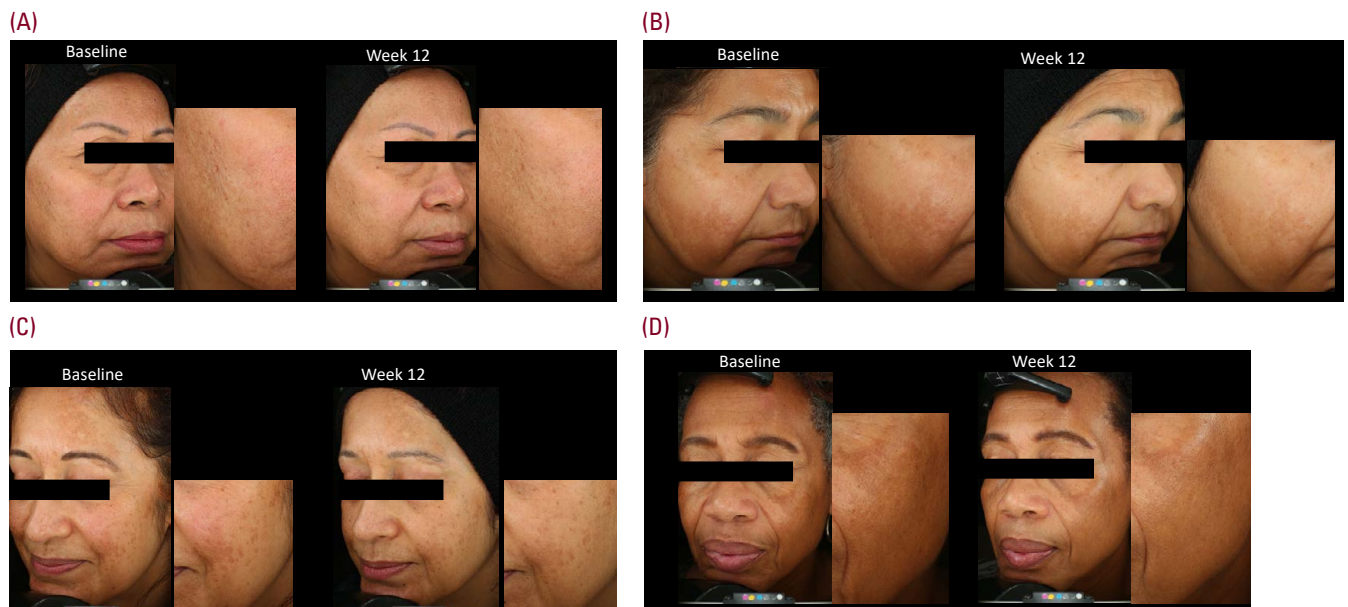


FIGURE 3. Representative VISIA images show improvement in skin conditions after 12 weeks of applying Group 1 regimen - SPF50 (A, B) or Group 2 regimen - SPF50+FeO (C, D).



showed superior response. In the responder analysis, we track the percentage of participants who achieve a certain level of improvement compared to baseline. For the melasma subgroup at week 8, we observed a statistically significant ($P=0.04$) higher percentage of participants with improvement of $\Delta L \geq 4$ in the melasma lesion in SPF50+FeO group (36.4%) compared with the SPF50 group (0%). This threshold was chosen because an earlier study found that the average difference between hyperpigmented lesions and normal skin of melasma patients was around 4.¹² The responder analysis (data not shown) indicates that the large variation could be the reason that we did not see the difference between the average change of L^* value in the 2 sun care regimen groups. The UV + visible light protection could achieve a higher magnitude of improvement in some melasma patients.

Quality of Life Questionnaire Results for Melasma Participants
In this study, we also included a quality of life self-assessment questionnaire to ask the participants to evaluate whether the skin condition could boost their self-confidence. We found that participants from both groups perceived improvement in skin pigmentation, skin clarity, radiance/brightness, youthful-looking skin, and smoother skin. Due to the psychological impacts of melasma,² we focused on the melasma participants to see how they responded to the two regimens. Although no statistically significant difference was observed between the two groups, most likely due to the smaller size (SPF50: $N=9$, SPF50+FeO: $N=11$). We were able to demonstrate that more participants in SPF50+FeO felt less troubled by their skin condition (Table 3). This observation highlighted the needs of FeO as both a visible light protectant and skin camouflage regimen for the melasma population.

TABLE 3.
Quality of Life Questionnaire for Melasma Participants.

	Increased Percentage of Participants in each group (week 12 vs day 0)	
	SPF 50 (n=9)	SPF 50 + FeO (n=11)
Not bothered by frustration due to skin condition	no change	36%
Not bothered by restricted sense of freedom	no change	27%
Not bothered by the feeling of unattractive due to skin conditions	11.1%	18.2
Not bothered by the reduced sense of importance/productivity	no change	27.2%
Not bothered by feeling the need to cover up or mask/camouflage skin condition	11%	36%
Less depressed by skin condition	no change	27%
Not bothered by skin appearance	no change	27%

No change: Indicates no percentage increase comparing with baseline+.

DISCUSSION

Hyperpigmentation disorders, such as postinflammatory hyperpigmentation and melasma, are common conditions affecting all skin types. Melasma is a frequent hyperpigmentary disorder that affects darker skin types, especially in women. This condition can significantly impact their quality of life. Biological differences in skin of color require additional consideration when deciding on treatment and management. Current treatment modalities include photoprotection, topical and systemic therapies, chemical peels, laser, and light-based therapies.²⁰ Although many treatment options exist, there is currently no cure for melasma. Incomplete response and relapse are very common. Although melasma can be induced by sun exposure, the triggering factors also include pregnancy, hormones, and inflammatory processes.²¹ Implementing a protective and concealing strategy that is simple and effective into everyday routine would help skin with more active melanocytes from sun damage. Relevant recent findings indicate that topical products containing pigments, alone or in combination with sunscreens, could extend photoprotection against UV and protect against visible light-induced dyschromia in higher skin phototypes.^{9,11} In our study, we chose a FeO-containing foundation product that matches the skin color and tone of our participants instead of compromising their needs for daily makeup, which brought extra challenges because the FeO contents are different for different participants (3-27%). Despite the difference, it has been shown that the participants who used SPF50+FeO responded as early as 4 weeks of application for improvement in skin roughness, healthy appearance, and luminance. This indicates that the sun protection strategy can be tailored to adapt to the needs of different FST and paves the road towards a customizable and personalized photoprotection strategy. Future studies can extend to larger population sizes, longer evaluation terms, and multiple sites with variable UV index to further evaluate how a skin tone-matching FeO product could benefit the populations with diverse skin melanin contents in real life. In conclusion, this study emphasizes the importance of sun protection for skin of color. In addition, visible light protection using FeO-containing products can bring some early benefits in improving skin quality and quality of life. Further confirmation of this study using longer-term real-life conditions, on photoprotection against both UV and VL, would be beneficial to advocate the importance of visible light photoprotection indoors and outdoors.

DISCLOSURES

Dr. Grimes has served as a clinical investigator and/or consultant for Galderma, Clinuvel, Board of Directors Clinuvel, L'Oreal, Johnson & Johnson, LaserOptek, Versicolor Technologies, MERCK, Dermbiont, VYNE Therapeutics, RAPT Therapeutics, Incyte, Pfizer, AbbVie/Allergan, SkinBetterScience, Klotho Skincare and Medscape, Beiersdorf. Stock Options – Versicolor Technologies.

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ACKNOWLEDGMENT

We thank the Center for Dermatology Clinical Research Inc., California team, for leading the clinical study; L'Oréal Data Management and Quality, plus Scientific Computing teams, for data processing and statistical analysis; Sharmila Gordon and Tara Pyle for providing the products.

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The Impact of Hyperpigmentation on the Lives of Patients

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ABSTRACT

Hyperpigmentation is a prevalent condition that disproportionately impacts individuals with skin of color, diminishing their quality of life and psychosocial well-being. There is a need to better understand the experiences, motivations, and expectations of patients seeking hyperpigmentation treatment. A cross-sectional survey was performed to analyze the perspectives and experiences of patients with hyperpigmentation. While over half (51.37%) of participants view their hyperpigmentation as “more bothersome than its initial cause,” there is a notable lack of routine dermatological care and sunscreen use. Of the respondents, 40.67% had never tried any treatments and among those who have, 34.67% were dissatisfied with the results. Expectations for treatment outcome timeframes varied, with 37.06% expecting results within 1 to 4 weeks. Of the participants, 52.67% reported being “not at all” or only “slightly” informed about current treatment options and only 16.32% feel “very” or “extremely” satisfied with current treatments. If their hyperpigmentation was successfully treated, 43.33% of respondents anticipated a very positive impact on their self-esteem. The current study highlights a critical need for improved patient education and tailored treatment approaches in hyperpigmentation practices. Enhancing patient knowledge about treatment options and setting realistic expectations may bridge the gap between patient experiences and treatment outcomes.

J Drugs Dermatol. 2025;24(7):668-674. doi:10.36849/JDD.8519

INTRODUCTION

Hyperpigmentation results from excessive deposition of melanin pigment in the epidermis and/or dermis layers following inflammation or injury.¹ The term hyperpigmentation encompasses numerous conditions causing discoloration, pigmentation, and darkening of the skin including melasma, post-inflammatory hyperpigmentation (PIH), ephelides, and lentigines.¹⁻³ Although a common skin condition prevalent among individuals across all demographics, hyperpigmentation disproportionately impacts individuals with skin of color in terms of both frequency and severity.⁴ The prevalence of PIH is as high as 9.99% in African American patients.⁴ Asian patients with darker skin also have a higher reported prevalence of PIH compared to Caucasian individuals.⁴

Hyperpigmentation is generally considered a benign condition, but it has a significant negative impact on patient quality of life and psychosocial well-being.⁵ One study found that among patients diagnosed with a pigmentary disorder, 47% felt self-conscious about their skin to some degree, 33% felt unattractive because of their skin, and 24% felt that their skin affected their daily activities.⁵ Another study found that 54% of patients express embarrassment due to their hyperpigmentation, with 22% experiencing a severe negative impact on their quality of life.⁶ Nearly half of those affected by hyperpigmentation report

applying makeup daily to conceal it, spending an average of 20.8 minutes each day on this routine.⁷

The hyperpigmentation treatment market has an estimated value of \$5.0 billion as of 2023, and is projected to reach \$9.5 billion by 2031.⁸ With some patients being willing to allocate up to 13.3% of their monthly income to address their symptoms, the projected growth of this market underscores its impact on patients and highlights the importance of addressing hyperpigmentation.⁷

There is a need to better understand the motivations, expectations, and experiences of patients seeking hyperpigmentation treatment. The aim of this study is to explore patients' perspectives on hyperpigmentation, including uncovering their treatment expectations, barriers to care, and satisfaction levels with current hyperpigmentation treatments. These insights can guide physicians to better align their practices with patients' diverse expectations and challenges.

MATERIALS AND METHODS

This study is a single-center, observational, cross-sectional, in-person questionnaire-based survey distributed to participants with a history of hyperpigmentation at SUNY Downstate Health Sciences University in Brooklyn, New York. A hard-copy

survey was distributed to participants following IRB approval. Participants were eligible if they were 18 years or older, spoke English, and had a history of hyperpigmentation. Data analysis was performed using Microsoft Excel.

RESULTS

A total of 150 individuals participated in the study between February 2024 and May 2024. Demographic data are provided in Table 1.

A high proportion of respondents (97.33%) reported they knew what hyperpigmentation is (Figure 1A). For those unfamiliar with hyperpigmentation, the medical terminology was explained to them, and participants proceeded with the survey if they reported a history of hyperpigmentation. The majority of respondents (59.06%) do not routinely wear sunscreen or see a dermatologist (78.67%) (Figure 1B and 1C). Approximately half of the participants (51.37%) perceive their hyperpigmentation as “more bothersome than its initial cause” (Figure 1D). The face was the most commonly affected area (80.67%), followed by the arms (28.00%), and legs (27.33%) (Figure 1E). The predominant triggers identified included “acne” (60.67%), “sun exposure” (51.33%), and skin trauma from “picking or scratching” (31.33%) (Figure 1F). Regarding information sources, participants primarily reported learning about hyperpigmentation through “the internet” (70.00%), “dermatologists” (43.33%), and “social media” (36.67%) (Figure 1G).

Treatment Experiences and Expectations

Of the respondents, 40.67% had never tried any hyperpigmentation treatments, 34.67% had tried treatments but were left unsatisfied with results, and 24.67% had tried treatments and were satisfied with results (Figure 2A). Participants most often tried “over the counter treatments” (59.33%), “prescription medications” (32.67%), and “professional treatments at a doctor's office or clinic” (20.00%). 10% of respondents have tried “alternative or home remedies,” including turmeric, carrots, lemon, cucumbers, a mix of baking powder and peroxide, and homemade sugar scrubs (Figure 2B). Participants' monthly spending on hyperpigmentation treatments ranged from “\$0” (42.67%), “less than \$50” (40.67%), “\$50-100” (8.67%), to “more than \$100” (8.00%) (Figure 2C).

Expectations regarding the time required to observe results from treatment ranged from “less than 1 day” (2.80%), “1-7 days” (13.29%), “1-4 weeks” (37.06%), “5-12 weeks” (31.47%), “4-12 months” (10.49%), and “over 1 year” (4.20%) (Figure 2D). When asked about their primary goal when treating their hyperpigmentation, 90.54% of participants indicated “lighter,” 5.41% indicated “the same,” 0.68% indicated “darker, and 3.38% indicated “other,” with fill in responses including “evening out skin tone” and “gone” (Figure 2E).

Treatment Satisfaction and Barriers

Many participants do not feel well informed about the different treatment options available for hyperpigmentation, with responses ranging from “not at all” (20.00%), “slightly” (32.67%), “moderately” (34.00%), “very” (8.00%), and “extremely” informed (5.33%) (Figure 3A). Satisfaction with current treatment options also varied, ranging between “not at all” (13.61%), “slightly” (34.01%), “moderately” (35.37%), “very” (12.24%), and “extremely” satisfied (4.08%) (Figure 3B).

TABLE 1.

Demographics (n=150)	
Characteristic	Respondents
Age, mean years (SD)	33.64 (12.07)
Age group (%)	
18-29	53.10%
30-39	22.07%
40-49	13.79%
50-59	4.83%
60-69	4.83%
70-79	1.38%
Gender (%)	
Female	81.88%
Male	18.12%
Race (%)	
White	22.00%
Black/African American	44.00%
Asian	23.33%
Native Hawaiian and other Pacific Islander	0.67%
American Indian/Alaskan Native	0.00%
Two or More Races	3.33%
Other	6.67%
Hispanic/Latino ethnicity (%)	10.74%
Education (%)	
Less than a high school diploma	1.33%
High school diploma or equivalent	11.33%
Associate degree	5.33%
Bachelor's degree	46.00%
Graduate degree	36.00%
Employment status (%)	
Full Time	52.67%
Part Time	5.33%
Student	38.67%
Self-employed	0.67%
Retired	2.67%

FIGURE 1. Respondents' experiences with hyperpigmentation. Respondents indicate their (A) awareness of hyperpigmentation, (B) sunscreen habits, (C) if they see a dermatologist, (D) perceptions of hyperpigmentation as more bothersome than its initial cause, (E) hyperpigmentation location, (F) triggers, and (G) information sources.

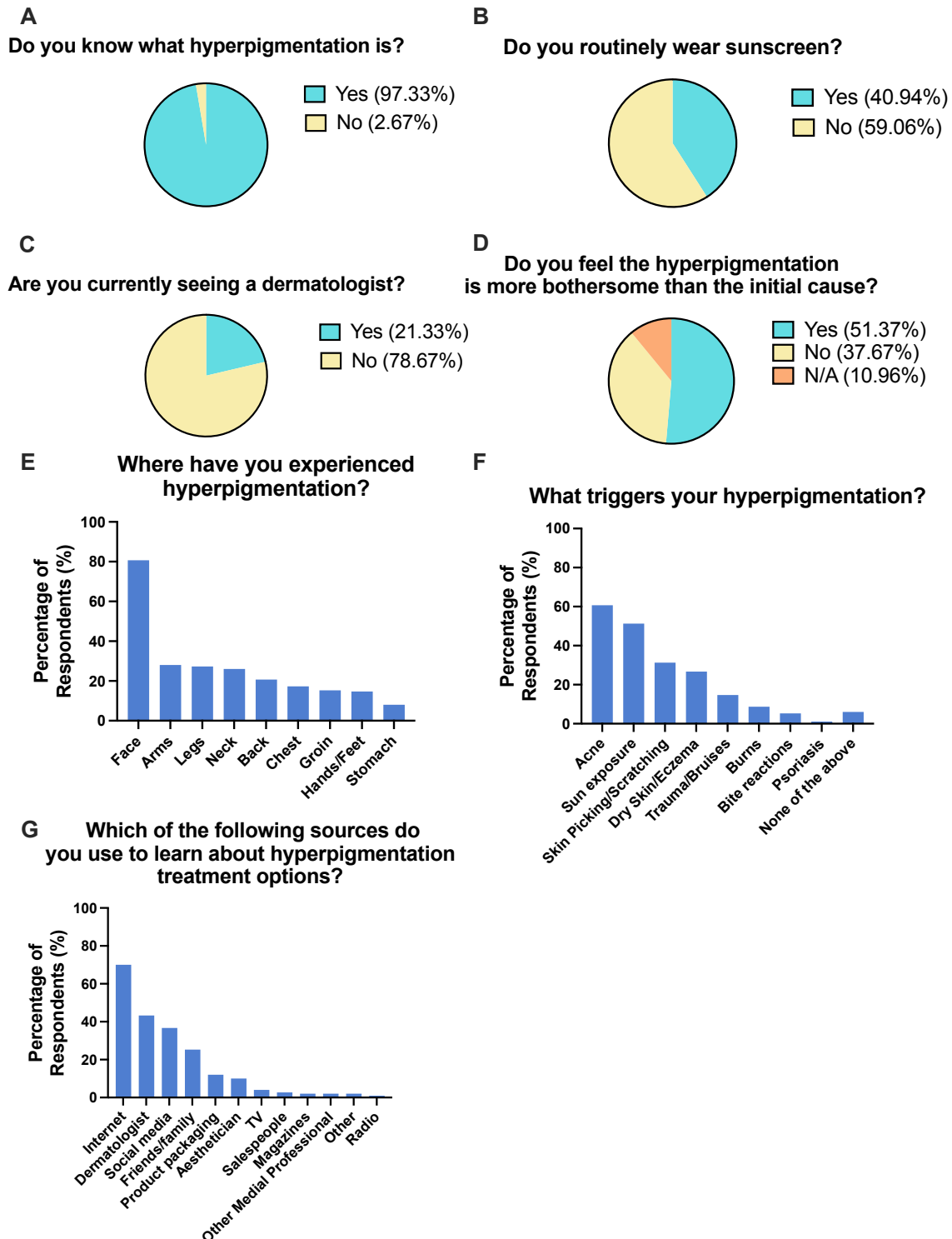


FIGURE 2. Respondents' hyperpigmentation treatment experiences and expectations. Respondents indicate their (A) previous treatment experience, (B) types of treatments tried, (C) expenditure on treatment, (D) expected timeframe for seeing results, and (E) primary treatment goal.

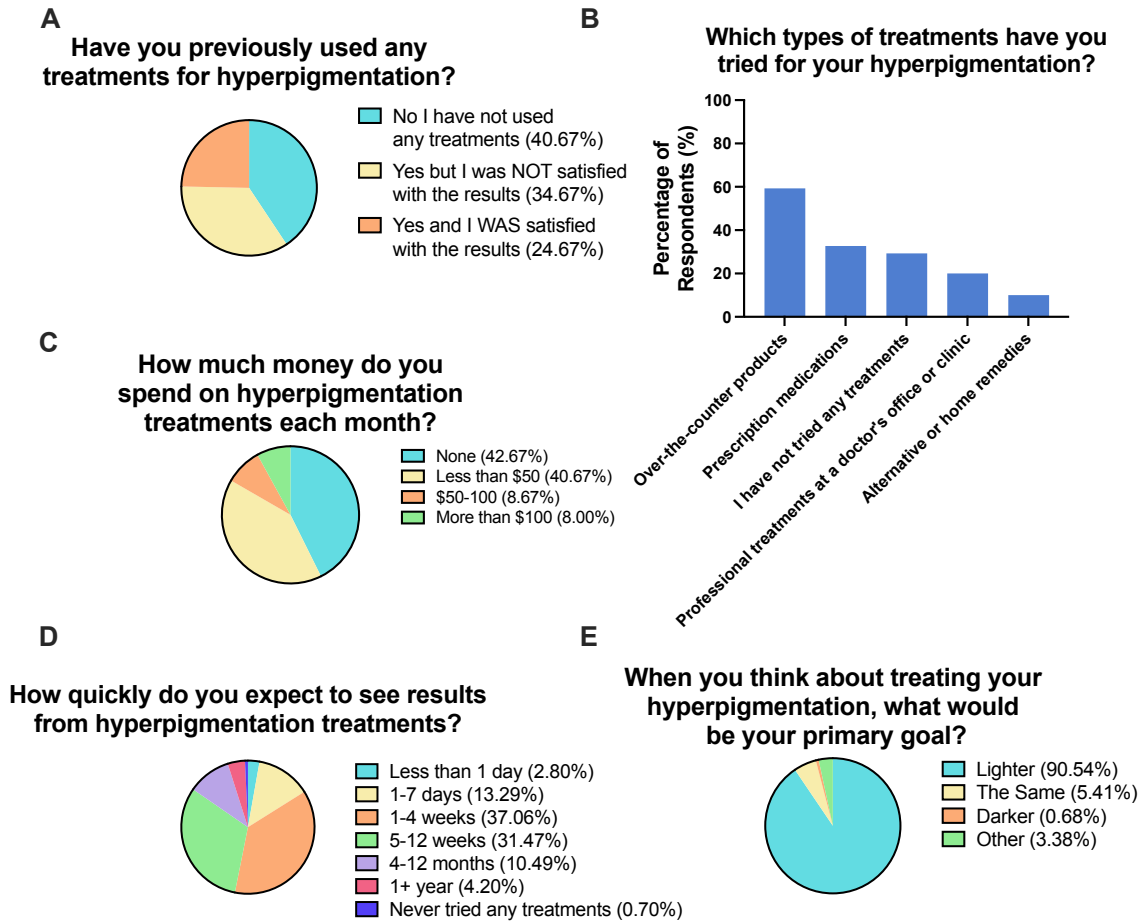


FIGURE 3. Respondents' perceptions regarding hyperpigmentation treatments. Respondents indicate their (A) perceived knowledge of treatments, (B) satisfaction with current treatments, (C) impact of hyperpigmentation on self-esteem, and (D) anticipated impact of successful treatment on self-esteem.

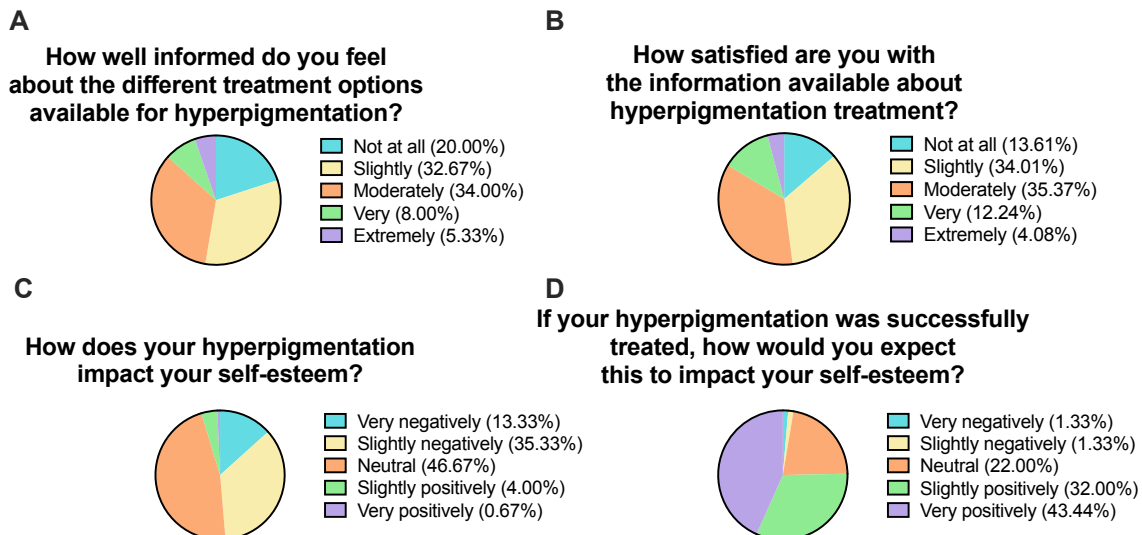
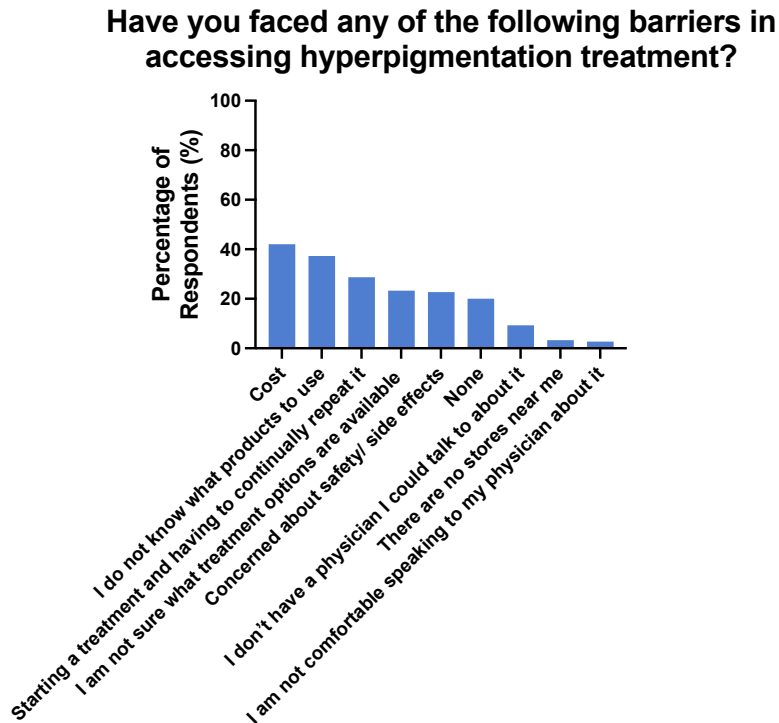


FIGURE 4. Barriers to accessing hyperpigmentation treatment. Respondents indicate their barriers to accessing hyperpigmentation treatment.



Participants frequently cited “cost” (42.00%), “uncertainty about which products to use” (37.33%), and “concerns about the need for ongoing treatment” (28.67%) as barriers to accessing hyperpigmentation treatments (Figure 4).

Impact on Self-Esteem

Respondents indicated their hyperpigmentation impacted their self-esteem “very negatively” (13.33%), “slightly negatively” (35.33%), “neutral” (46.67%), “slightly positively” (4.00%), and “very positively” (0.67%) (Figure 3C). If their hyperpigmentation were to be successfully treated, participants expected this to impact their self-esteem “very negatively” (1.33%), “slightly negatively” (1.33%), “neutral” (22.00%), “slightly positively” (32.00%), and “very positively” (43.33%) (Figure 3D).

DISCUSSION

Herein, we provide comprehensive insights into patients’ experiences and expectations regarding hyperpigmentation. To our knowledge, this is the first study to comprehensively analyze patients’ experiences with hyperpigmentation, encompassing disease perception, treatment experiences, barriers to care, knowledge gaps, and satisfaction with current treatments.

Approximately half (51.37%) of respondents endorsed their hyperpigmentation being more bothersome than the initial cause, consistent with a previous survey on acne-related PIH that found 50% of patients view their PIH as more bothersome than their initial acne.⁹ Despite patients’ high awareness

and self-reported knowledge about hyperpigmentation, there is a notable discrepancy in patients’ management of their hyperpigmentation. The majority of participants do not regularly use sunscreen or consult dermatologists, potentially exacerbating their condition. UV radiation is a known contributor to hyperpigmentation, and recent studies show that visible light also contributes to hyperpigmentation by acting synergistically with UV-A.⁹⁻¹¹ Physicians should recommend patients use a >30 SPF iron-oxide containing tinted sunscreen.⁹⁻¹¹ Patients with skin of color are less likely to wear sunscreen and are also more prone to hyperpigmentation, emphasizing the importance of educating these patients on sun protective practices.¹²⁻¹⁵

The primary source of information for most participants was the internet, consistent with previous research that demonstrated 82.4% of patients obtain dermatology information from the internet or social media, with 16.1% considering it their primary source for medical information.¹⁶ While the internet is a convenient, accessible, and inexpensive source of information, it also poses risks of misinformation.^{17,18} A cross-sectional analysis of 385 online dermatology websites found that 44.7% of online content was classified as “imprecise” and 20% as “confusing.”¹⁹ An analysis of psoriasis-related videos on YouTube found that only 28.1% of recommended treatments were consistent with Grade A recommendations by the American Academy of Dermatologists.²⁰ It is crucial to make patients aware of these potential sources of misinformation and actively correct any misconceptions they may have.

Nearly half of respondents have never tried any hyperpigmentation treatments. Despite the high prevalence of hyperpigmentation, over 50% of respondents in the current study feel “not at all” or only “slightly” informed about available treatment options and less than 20% of respondents feel “very” or “extremely” satisfied with current treatments, highlighting the need for dermatologists to better educate patients on available management strategies. Various treatment options are available for hyperpigmentation, including topical creams, lasers, light therapy, oral therapy, micro-needling, and chemical peels. Topical hydroquinone and triple combination cream (TCC) therapy (hydroquinone, retinoid, and corticosteroid) are currently recommended as first line-therapy.⁹⁻¹¹ However, these may be associated with the permanent unacceptable side effect of ochronosis.²¹ Several alternative treatments including tranexamic acid, cysteamine, azelaic acid, kojic acid, and ascorbic acid are more well-tolerated and not associated with ochronosis.^{9-11,22,23}

The dissatisfaction expressed by participants regarding treatment outcomes, with only 24.67% satisfied, underscores a critical gap in patient education and the importance of setting realistic patient expectations. Many patients expect quick results; however treatment for hyperpigmentation often involves a prolonged duration and may result in low patient adherence.^{10,24} One commonly used protocol requires 8 weeks of daily TCC application, followed by 6 months of twice weekly application for effective treatment and to prevent reoccurrence of melasma.²⁵ Depending on the depth of melanin deposition, treatment efficacy may vary.²⁴ Setting realistic treatment expectations may promote treatment adherence and improve both satisfaction and clinical outcomes. Notably, nearly 90% of patients indicated that their primary goal for treating hyperpigmentation was to make it “lighter.” However, in the authors’ clinical experience, what patients often mean by “lighter” is achieving an even skin tone that matches the surrounding areas. Both hyperpigmentation and hypopigmentation can significantly affect quality of life, with hypopigmentation sometimes having an even greater impact.^{26,27} One study demonstrated that patients with vitiligo have significantly worse quality of life compared to patients with melasma or lentigines.²⁷ The current study reveals that approximately 75% of patients expected a “slightly” or “very” positive impact on self-esteem with successful treatment of their hyperpigmentation, underscoring the profound psychological implications of hyperpigmentation. By effectively treating hyperpigmentation, dermatologists can not only improve the physical appearance but also the mental well-being of their patients.

Limitations of this study include a reliance on self-reported data and a single-center design, which may not reflect the broader hyperpigmentation patient population. The study’s strengths include a diverse racial and ethnic participant population and a comprehensive scope of the questions regarding participants’

experiences with hyperpigmentation. Additionally, our survey focused on individuals with a history of hyperpigmentation, providing valuable insights into the perspectives of those suffering from hyperpigmentation. Future research may include a multi-center design to enhance the representativeness and generalizability of the findings. Future studies could also examine quality of life measures, such as the Dermatology Life Quality Index (DLQI), to further understand the impact of hyperpigmentation on patients' lives.

CONCLUSION

Herein, we uncover the experiences and expectations of patients with hyperpigmentation, highlighting the importance of improved management strategies including increasing sunscreen use and enhancing patient education about available treatments. This study also underscores the impact of hyperpigmentation on patients’ self-esteem and identifies common barriers to treatment. These insights may enable dermatologists to better tailor their care, thereby improving patient satisfaction and outcomes.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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1. DATA ON FILE: CLINICAL FINAL RESULTS: JULY 2024. 2. 12-WEEK PROOF OF CONCEPT CLINICAL STUDY ON 54 MEN AND WOMEN AGED >65 WITH A HISTORY OF DERMATOPOROSIS AND SENSITIVE SKIN WITH TWICE-DAILY USAGE IN ARMS AND ONE LEG. 3. 12-WEEK IN USE CLINICAL STUDY ON 41 MEN AND WOMEN AGED 40-75 WITH VISIBLY AGED, SENSITIVE, UNEVEN SKIN TONE AND THIN, TRANSPARENT SKIN WITH TWICE-DAILY APPLICATION ON BODY. 4. INVESTIGATOR GRADED CREPINNESS SCORE. SUBJECT 13: LEFT ARM OF A 64-YEAR-OLD HISPANIC FEMALE, WITH FITZ III (AVERAGE CASE).

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Pyoderma Gangrenosum in Pregnancy: A Systematic Review of Clinical Characteristics, Treatment Outcomes, and Maternofetal Implications

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ABSTRACT

Background: Although cases of pyoderma gangrenosum (PG) during pregnancy have been reported, comprehensive data are limited. This review aims to (1) analyze the demographic and clinical characteristics of PG in pregnant and postpartum patients, (2) assess the frequency and effectiveness of treatments, and (3) explore the maternal and fetal implications of PG.

Methods: A systematic review was conducted following PRISMA guidelines, with searches in PubMed, Embase, and Web of Science up to September 27, 2023. Studies were included if they reported PG during pregnancy or within six weeks postpartum. Data extraction and screening were independently performed by 2 reviewers using Covidence.

Results: Sixty-two studies met the inclusion criteria, comprising 63 patient cases. Most cases (N=55, 87.3%) occurred without inflammatory bowel disease or rheumatologic disease. PG was frequently misdiagnosed (N=45), resulting in treatment delays and inappropriate interventions. Fifty-six cases (88.9%) were treated with systemic corticosteroids, while 21 (33.3%) were treated with cyclosporine. Emergency Cesarean section was the most common pregnancy complication (N=19).

Discussion: Increased awareness of PG in pregnant or postpartum patients could reduce misdiagnosis and improve outcomes. Immunological changes during pregnancy may trigger PG in susceptible patients, yet the safety and efficacy of treatment options are not well-established in this population, underscoring the need for research to guide management.

J Drugs Dermatol. 2025;24(7):676-682. doi:10.36849/JDD.8843R1

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by the sudden onset of painful, necrotic ulcers, most commonly affecting the lower extremities. PG is driven by abnormal accumulation and hyperactivation of neutrophils, leading to excessive infiltration that culminates in tissue destruction and ulceration.¹ Although clinical manifestations of PG are well recognized, its etiology remains largely elusive, with research implicating autoinflammatory mechanisms as a driving force.

A distinctive feature of PG is pathergy, seen in about one-third of patients, where minor skin trauma triggers an exaggerated inflammatory response and ulcerative lesions. PG is also commonly associated with systemic conditions, with about 50% of patients having diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis, or hematological malignancies, suggesting PG may reflect broader systemic inflammation.²

Pregnancy introduces additional complexity to the pathophysiology of PG due to the significant immunological and hormonal changes that occur during gestation and persist postpartum. While these changes are essential for fetal development, they also impact immune regulation and may exacerbate inflammatory conditions. Given the rarity of PG during pregnancy and the lack of consensus on optimal management, addressing gaps in the existing literature is critical. Current data on pregnant or postpartum patients with PG primarily stem from case reports and small-scale reviews. For example, Steele et al analyzed 26 cases and suggested that immune changes during pregnancy may play a role in the onset of PG.³ More recently, Wanberg et al reviewed 18 cases and proposed a treatment algorithm tailored to this population.⁴

Building on previous work, our review aims to broaden the scope with 3 key objectives: (1) analyzing the demographic and clinical features of PG in pregnant or postpartum patients,

(2) evaluating the frequency and effectiveness of treatment modalities, and (3) assessing the maternal and fetal implications of PG.

MATERIALS AND METHODS

Literature Review

A systematic literature review was carried out by a medical librarian (CDP) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁵This systematic review was registered with Prospero (CRD42023463805). We conducted searches in PubMed, Embase, and Web of Science through September 27, 2023 (Table 1). The searches were conducted without geographical or time restrictions and were limited to English-language only.

Study Selection and Eligibility

The search results were imported into Endnote 20 reference management software (Clarivate, Philadelphia, PA). They were then uploaded to Covidence (Veritas Health Innovation,

Melbourne, Australia), an online literature review management tool, where they were de-duplicated. The articles were screened against the eligibility criteria, first based on the title and abstract and then based on the full text. During both phases, each article was independently assessed by 2 reviewers who were blinded to each other’s decisions. Conflicts were resolved through consensus among the reviewers.

Studies were included in the systematic review if they met the following criteria: (1) original human research; (2) written in English; and (3) focused on patients who developed PG at any point during pregnancy or within 6 weeks postpartum. Exclusion criteria included: (1) papers without original data (eg, comments, editorials, or reviews); (2) articles in languages other than English; (3) references lacking full peer reviewed publication (eg, conference abstracts); and (4) studies of patients who were nulliparous or who developed PG prior to pregnancy or later than 6 weeks after delivery.

TABLE 1.

Full Literature Search Strategies	
Database	PubMed
Line #	Search Terms
1	"Pyoderma"[Mesh] OR "Pyoderma Gangrenosum"[Mesh] OR "pyoderma gangrenosum"[tiab] OR "pyoderma gangraenosum"[tiab]
2	"Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR "Pregnancy Complications"[Mesh] OR "pregnancy"[tiab] OR "pregnant"[tiab] OR "gravid*"[tiab] OR "Peripartum Period"[Mesh] OR "Postpartum Period"[Mesh] OR "perinatal"[tiab] OR "peri natal"[tiab] OR "postnatal"[tiab] OR "post natal"[tiab] OR "peripartum"[tiab] OR "peri partum"[tiab] OR "postpartum"[tiab] OR "post partum"[tiab] OR "puerperal"[tiab] OR "Cesarean Section"[Mesh] OR "c section"[tiab] OR "cesarean"[tiab] OR "caesarean"[tiab]
3	#1 AND #2
Filters	English-language only
Results	87
Database	Embase
Line #	Search Terms
1	'pyoderma gangrenosum'/exp OR "pyoderma gangrenosum":ti,ab OR "pyoderma gangraenosum":ti,ab
2	'pregnancy'/de OR 'pregnant woman'/exp OR 'pregnancy complication'/exp OR "pregnancy":ti,ab OR "pregnant":ti,ab OR "gravid*":ti,ab OR 'perinatal period'/exp OR 'puerperium'/de OR "perinatal":ti,ab OR "peri natal":ti,ab OR "postnatal":ti,ab OR "post natal":ti,ab OR "peripartum":ti,ab OR "peri partum":ti,ab OR "postpartum":ti,ab OR "post partum":ti,ab OR "puerperal":ti,ab OR 'cesarean section'/de OR "c section":ti,ab OR "cesarean":ti,ab OR "caesarean":ti,ab
3	#1 AND #2
Filters	English-language only
Results	221
Database	Web of Science
Line #	Search Terms
1	"pyoderma gangrenosum" OR "pyoderma gangraenosum"
2	"pregnancy" OR "pregnant" OR "gravid*" OR "perinatal" OR "peri natal" OR "postnatal" OR "post natal" OR "peripartum" OR "peri partum" OR "postpartum" OR "post partum" OR "puerperal" OR "c section" OR "cesarean" OR "caesarean"
3	#1 AND #2
Filters	English-language only
Results	47

Data Extraction

References that passed the screening underwent independent data extraction by 2 reviewers using a customized form in Covidence. The data extraction form collected information on the study and participant characteristics, including country, study design, age, race/ethnicity, past medical history, timing of diagnosis, and location, morphology, and size of pyoderma gangrenosum lesions. Data was also gathered on treatment methods and the implications of developing the disease for the pregnancy and for maternal and fetal health.

RESULTS

A total of 355 articles were imported into Covidence. After removing 105 duplicates, reviewers performed title and abstract screening for 250 studies and excluded 167 that did not meet the inclusion criteria. The full text was reviewed for 82 of the

remaining 83 studies. One paper could not be obtained in full-text form despite repeated attempts. Ultimately, 62 studies underwent data extraction. The PRISMA flow diagram is displayed in Figure 1.

Patient Demographics and Clinical Characteristics

From the 62 studies, 63 individual patient cases were extracted. Patient demographics and clinical characteristics are detailed in Table 2. Approximately 46% of patients (N=29) had no reported past medical history, and roughly 27.0% of patients (N=17) had a documented history of PG (N=6) or previous PG-like symptoms without an official diagnosis (N=11). Only 7.9% of patients (N=5) had a reported history of IBD, and 4.8% (N=3) had another systemic rheumatologic disease. Preceding trauma to the skin was reported in 45 cases (71.4%).

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

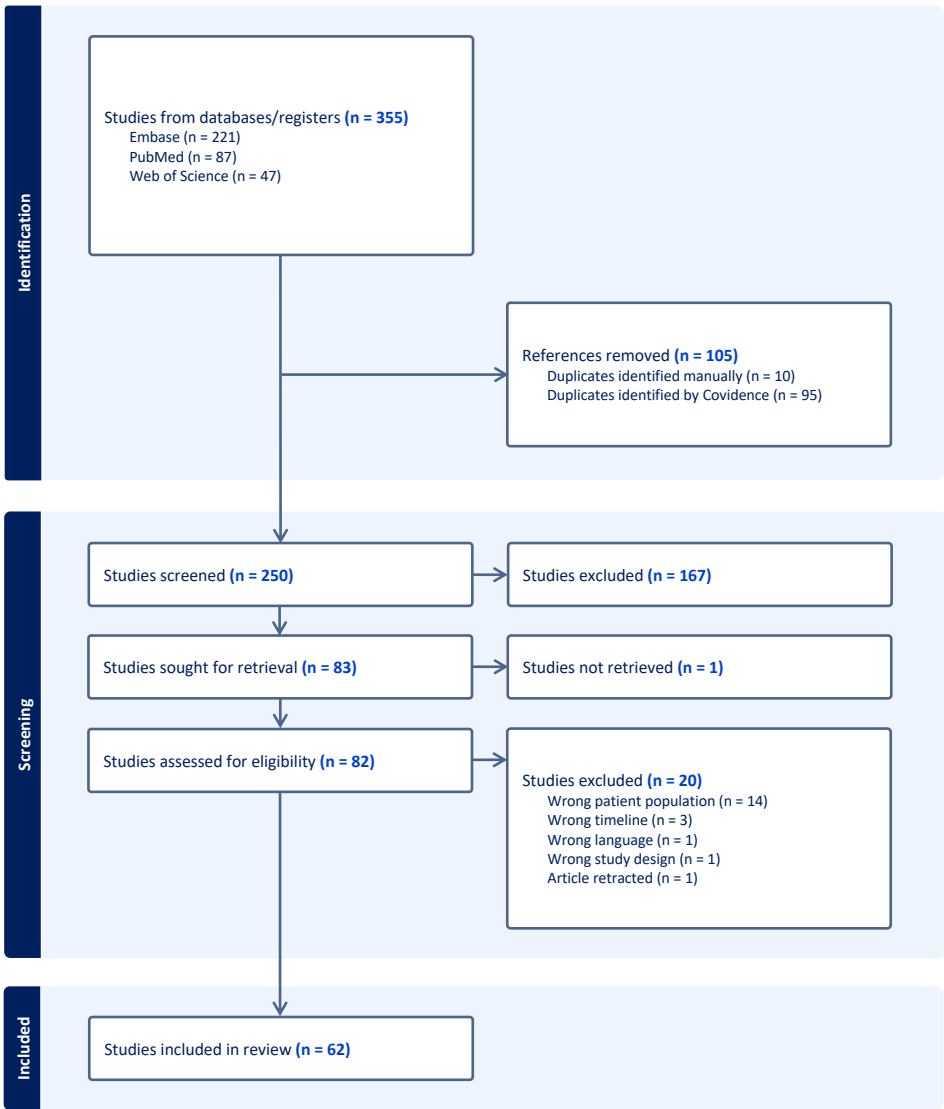


TABLE 2.

Demographic and Clinical Characteristics of Pregnant or Postpartum Patients With Pyoderma Gangrenosum	
Demographic/Clinical Characteristics	Patients (N=63)
Average age, years (range)	29.9 (20-43)
Age, N (%)	
≤29	33 (52.4)
30-34	17 (27.0)
35+	13 (20.6)
Past medical history, N	
Ulcerative colitis	5
PG	6
PG-like symptoms (without diagnosis)	11
Other rheumatologic disease	3
Systemic lupus erythematosus	1
Relapsing polychondritis	1
Antiphospholipid syndrome	1
Miscarriage/intrauterine fetal demise	3
Hepatitis C	2
Hidradenitis suppurativa	2
Leukocyte adhesion deficiency type 1	2
Preterm labor	2
Preeclampsia	1
None reported	29
Gestational age at PG onset, N (%)	
First trimester	10 (15.9)
Second trimester	7 (11.1)
Third trimester	5 (7.9)
Postpartum	41 (65.1)
Initial diagnosis, N	
Bacterial infection	34
Necrotizing fasciitis	6
PG	2
Other/multiple considerations	5
Not reported	16
Days to diagnosis, N	
0-7	6
8-14	10
15-21	6
22-28	1
≥29	3
Not reported	37
Location of PG, N (%)	
Cesarean section	35 (55.6)
Vulva	4 (6.3)
Lower extremity	14 (22.2)
Abdomen	1 (1.6)
Inguinal area	1 (1.6)
Scalp	1 (1.6)
Left breast	1 (1.6)
Multiple	6 (9.5)
Laboratory findings, N	
Elevated white blood cell count	27
Elevated CRP and/or ESR	24
Reported preceding trauma, N (%)	45 (71.4)
Reported positive microbial growth, N (%)	10 (15.9)

Abbreviations: pyoderma gangrenosum (PG); C-reactive protein (CRP); erythrocyte sedimentation rate (ESR)

Among the cases of PG that presented during pregnancy, the first trimester was the most common period of occurrence (N=10), followed by the second and third trimesters, respectively. Most cases (N=41) occurred postpartum; 35 occurred after a Cesarean section (C-section), with lesions developing within or around the surgical scar. In 1 of these cases, PG also developed at intramuscular gluteal injection sites.⁶

Only 6 postpartum PG cases did not occur after C-section. Three followed vaginal delivery: 2 at the site of an episiotomy, and 1 on the vulva secondary to an obstetric laceration.⁷⁻⁹ One case presented on the right foot 4 weeks post-abortion.¹⁰ Among the 2 cases of postpartum PG with unknown delivery method, 1 developed on the scalp, and the other presented at multiple sites, including the face, neck, upper arm, and thigh.^{11,12} Overall, the most common PG site was the C-section scar, followed by the lower extremities (N=14).

An initial diagnosis of PG was established in only 2 cases; most (N=34) were first diagnosed as non-specific bacterial infections.^{12,13} Where time to diagnosis was reported (N=26), 77.0% of cases (N=20) required more than 7 days for identification. Less than half of patients had documented elevated white blood cell counts (N=27) or inflammatory markers (N=24). Microbial growth was identified in 15.9% of cases (N=10).

Management strategies and treatment outcomes

Table 3 presents the management strategies and treatment outcomes. Before PG diagnosis, surgical wound intervention (N=46) and broad-spectrum antibiotics (N=43) were the most utilized treatments. After diagnosis, systemic corticosteroids (SCS) were the most used treatment (N=56), followed by cyclosporine (N=21), both typically in combination with other systemic medications. Complete resolution of PG lesions was achieved in at least 40 total instances. Notably, no cases were reported in which PG lesions failed to improve at least partially by follow-up. Among the 4 patients who experienced only partial resolution of PG lesions, 3 were treated with a combination of SCS and cyclosporine, and 1 was treated with SCS alone.¹⁴⁻¹⁷

PG recurrence was reported in 4 cases. Maier et al described a patient who developed PG on the abdomen during the second trimester, which recurred 12 months later alongside acute myeloid leukemia despite treatment with SCS, cyclosporine, dapsone, and surgery.¹⁸ Hilton et al described a patient with PG recurrence following steroid tapering, which was successfully managed by increasing the steroid dosage and reintroducing dapsone.¹⁹ Foessleitner et al reported a case of PG recurrence in 2 locations on a C-section scar after initial resolution with SCS and meropenem.²⁰ Cokan et al described recurrence on the breast in a patient with prior PG on a C-section scar, initially resolved with SCS.²¹

Pregnancy Outcomes

Methods of delivery were reported as follows: vaginal delivery (N=8), C-section (N=40), pregnancy termination or vaginal evacuation (N=3), and not reported (N=12). Among cases where delivery timing was reported (N=41), about half of

patients (N=22) delivered preterm (<37 weeks). Emergency C-sections (N=19) accounted for most pregnancy complication cases, followed by premature rupture of membranes (N=7) and placental abruption (N=6). Thirty-three patients (52.4%) had no reported pregnancy complications.

TABLE 3.

Management and Treatment Outcomes of Pregnant or Postpartum Patients With Pyoderma Gangrenosum	
Demographic/Clinical Characteristics	Patients (N=63)
Treatment before PG diagnosis, N	
Broad-spectrum antibiotics	43
Surgical intervention	46
Negative pressure therapy	6
SCS	3
Other	3
Treatment after PG diagnosis, N	
Systemic antibiotics	16
Dapsone	7
Surgical intervention	11
Negative pressure therapy	7
SCS	56
Intralesional corticosteroids	4
Cyclosporine	21
Intravenous immunoglobulin	4
Azathioprine	2
Mycophenolate mofetil	1
Mesalazine	2
Infliximab	1
Cyclophosphamide	1
Salicylazosulfapyridine	1
Isoniazid	1
Minimum weeks of treatment, N	
0-8	11
9-16	12
17-24	7
25-32	3
33-40	3
≥41	2
Not reported	25
Efficacy of treatment, N	
Complete resolution	40
Improvement, extent not specified	17
Partial resolution	4
Not reported	2
Treatments with reported adverse effects, N	
SCS	4
Cyclosporine	2
Surgical intervention	3
Systemic antibiotics	1
Salicylazosulfapyridine	1
Isoniazid	1
Reported recurrence, N (%)	4 (6.3)

Abbreviations: pyoderma gangrenosum (PG), systemic corticosteroids (SCS)

Of the 22 patients who developed PG during gestation, 15 (68.2%) had no reported pregnancy complications. Only 1 case in this group required an emergency C-section; all other emergency C-sections occurred in patients with postpartum PG.²²

DISCUSSION

Our systematic review highlights the frequent misdiagnosis and delays in the management of PG in pregnant and postpartum patients. Of the 47 cases in which the initial diagnosis was reported, 45 (95.7%) were initially suspected to be bacterial infections, necrotizing fasciitis, or other skin disorders. Additionally, as reported in the results, most cases took more than 7 days for PG identification. This delay is unsurprising, as PG is a diagnosis of exclusion and infrequently encountered by obstetricians and gynecologists.

Aggressive surgical interventions, generally discouraged in PG due to the risk of pathergy, were frequently performed during this diagnostic delay. In our study, 73.0% of patients underwent surgical wound interventions, all of which led to worsening conditions. Of particular concern, our review identified a case of intrauterine fetal demise after surgical debridement, highlighting the rare but serious risks associated with misdiagnosis and inappropriate treatment.²³

Research indicates that approximately 50% of PG cases are linked to systemic diseases, most commonly IBD, rheumatoid arthritis, and hematological malignancies; however, only 5 patients (7.9%) in our review had any of these associations.² This finding suggests that pregnancy may act as an independent trigger for PG. The immunological changes of pregnancy, such as altered humoral and cell-mediated immunity, reduced interleukin (IL)-2 or IL-1 activity, and decreased polymorphonuclear leukocyte chemotaxis and adherence, may promote PG development.²⁴ These immune changes persist into the postpartum period, where plasma markers of TNF ligand families and chemokine ligand (CCL)11/Eotaxin are upregulated, and increased cytotoxic natural killer and helper T cell activity create a proinflammatory state.^{25,26} Moreover, immune activity typically takes 3 to 4 months postpartum to return to baseline.²⁷ Thus, the immunological changes associated with pregnancy may play a significant role in PG pathogenesis.

PG is also a rare but recognized post-operative complication, and among the 41 patients who developed PG postpartum, most cases occurred after C-section. A systematic review of 220 postsurgical PG cases found that 16.8% had a history of PG, 8.6%

had hematologic disorders (eg, leukemia or lymphoma), 5.9% had IBD, and 3.6% had rheumatoid arthritis.²⁸ In our study, we observed that 9.5% of patients had a prior diagnosis of PG, 7.9% had IBD, and none had hematologic disorders or rheumatoid arthritis. These findings suggest that the immunological changes during pregnancy, combined with surgical intervention, may contribute to PG onset, even in the absence of common predisposing conditions.

Although the mainstay of treatment for PG is SCS and cyclosporine, SCS is associated with gestational diabetes, preeclampsia, preterm labor, and infant hypoadrenalism, while cyclosporine is associated with maternal hypertension and preterm labor.²⁹⁻³¹ No randomized controlled trials or cohort studies have been performed in pregnant patients with PG, presenting limitations in therapeutic recommendations. In our review, 88.9% of patients received SCS and 33.3% received cyclosporine after PG was diagnosed, with all patients experiencing improvement. Adverse effects of treatment were minimal, with only 6.3% and 3.2% of patients experiencing side effects secondary to SCS and cyclosporine, respectively.

A prior review suggested prioritizing topicals and TNF inhibitors in pregnant and breastfeeding patients with PG, as they may exhibit a more favorable side effect profile.⁴ In our study, 1 patient with a history of ulcerative colitis developed PG in the second trimester on the leg, which resolved completely with the TNF inhibitor infliximab and SCS.³²

Several other treatments for PG demonstrated efficacy but were infrequently reported in this review. Negative pressure wound therapy was used alongside other therapies in several cases and may have been helpful. Additionally, research supports the safety of intravenous immunoglobulins during pregnancy, which were used in 4 cases alongside other systemic medications.³³ Other cases reported improvement with dapsone, intralesional corticosteroids, and immunosuppressive agents such as azathioprine. However, determining the most effective treatments for this population remains difficult due to the frequent use of multiple therapies, underscoring the need for further research on their efficacy and safety.

As noted in the results, emergency C-sections were the most common complication in this cohort, often serving as a traumatic trigger for PG in postpartum patients. Premature rupture of membranes was reported in 7 cases (11.1%), consistent with the general population rate of 4 to 10%.³⁴ Placental abruption was reported in 6 cases (9.5%), higher than the typical 1%, though the small sample size limits definitive conclusions.³⁵

This study had several limitations, including a small sample size (N=63). As the review comprised case reports, inconsistencies in data reporting were common. In many instances, it was unclear

whether missing information was unreported or not assessed. Collecting data on pregnancy outcomes was particularly challenging due to the limited pregnancy details provided in dermatology journals.

CONCLUSION

Our systematic review analyzes the demographic data, clinical characteristics, treatment approaches, and pregnancy outcomes in patients who develop PG during pregnancy or postpartum. It highlights the frequent misdiagnosis of PG in this population, leading to treatment delays and inappropriate interventions that worsen the condition. Our findings, supported by immunological research, suggest that pregnancy may independently contribute to the development of PG. While SCS and cyclosporine are commonly used treatments, their safety during pregnancy and breastfeeding is not well-established, highlighting the need for further research on safe, effective treatment protocols.

DISCLOSURES

GDB, SR, ZL, JMB, GMH, and CDP have no conflicts of interest to disclose. ABG receives research/educational grants from Highlights Therapeutics, Bristol-Myers Squibb, Janssen, and UCB Pharma (all paid to Mount Sinai School of Medicine). ABG has received honoraria as an advisory board member and consultant for Amgen, AnaptysBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Eli Lilly, Highlights Therapeutics, Janssen, Novartis, Sanofi, Teva, UCB, and Xbiotech (stock options for a rheumatoid arthritis project).

Funding: This project was supported by the International Dermatology Outcome Measures (IDEOM) nonprofit group.

ACKNOWLEDGMENT

We would like to thank the International Dermatology Outcome Measures (IDEOM) non-profit organization for their support of this project.

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Socioeconomic Disparities in Gentle Skin Care Access for Atopic Dermatitis: Affordability and Pharmacy Deserts

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ABSTRACT

Background: Gentle skin care is key to atopic dermatitis (AD) treatment, yet products are often expensive. Pharmacy deserts may exacerbate socioeconomic disparities in AD.

Objective: To compare the price of dermatologist-recommended skin care to popularly purchased products, and to assess the prevalence and accessibility of pharmacy retailers selling these products in low- vs high-income zip codes.

Results: National Eczema Association (NEA)-recommended products were more expensive than popularly purchased products for moisturizing lotions (\$2.72/oz vs \$1.13/oz, $P < 0.0001$) and liquid body soaps (\$1.30/oz vs \$0.35/oz, $P < 0.0001$) across all retailers (Amazon, Walmart, Walgreens, CVS, Target, and Meijer). Lower-income zip codes had significantly lower densities of retail stores than higher-income zip codes in both Chicago (0.26 vs 3.20 stores/10,000 pop, $P = 0.0007$) and New York (0.26 vs 2.90 stores/10,000 pop, $P = 0.02$). Stores in low-income zip codes had fewer hours of operation in both Chicago (14.9 vs 19.2 hours/day, $P = 0.02$) and New York (13.3 vs 21.0 hour/day, $P = 0.0002$) and lower stock in both Chicago (2.0 vs 5.1 units, $P = 0.05$) and New York (1.4 vs 4.8 units, $P = 0.03$).

Conclusions: Recommended products are more expensive than popular products. Retail pharmacies selling these products are less prevalent in low-income neighborhoods, have fewer hours of operation, and have lower average stock, exacerbating AD disparities.

J Drugs Dermatol. 2025;24(7):683-686. doi:10.36849/JDD.8911

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory disease affecting up to 15% of children and 3% of adults.¹ Restoring barrier function with dermatologist-recommended gentle skin care is central to therapy. However, over-the-counter products are often expensive, exacerbating socioeconomic (SES) disparities in AD. Low SES patients are more likely to have poorer disease control and higher disease severity than their high SES counterparts.^{2,3} They are also more likely to live in low-income neighborhoods, raising concerns that geographic location and its impact on gentle skin care access may be an overlooked contributor to AD disparities.⁴

There is growing recognition of pharmacy deserts, or geographic areas where few or no pharmacies are accessible. Pharmacy desert studies, which extend findings from the food desert literature, indicate that they are most prevalent in low-income and minority neighborhoods.⁵ Pharmacy deserts may also limit access to gentle skin care products since this is where they are often purchased. However, the association between gentle skin care affordability, availability, and access across city zip codes has not been examined.

Here, we aimed (1) to assess the affordability of dermatologist-recommended AD skin care products compared to popularly purchased products; (2) to investigate whether pharmacy retailers that sell recommended gentle skin care were less prevalent in low-income neighborhoods in 2 cities: Chicago and New York; and (3) to examine how hours of operation, price, and stock levels vary between stores in high and low-income zip codes.⁶

MATERIALS AND METHODS

Data Collection

Prices of Skin Care Products

Products from the National Eczema Association (NEA) "Eczema Product Directory" were extracted as dermatologist-recommended gentle skin care products. For popularly purchased products, the top brand names were extracted from Statistica, a well-known provider of consumer data deriving from market research across industry and government.⁷ US surveys for 3 product types were used: moisturizing lotion,⁸ moisturizing cream,⁸ and liquid body soaps.⁹ Brand names with greater than 10% response rate were included. Brand names that were not descriptive, such as "Store Brand," or brands that could not be

TABLE 1.

Average Cost Per OZ of NEA-Recommended Versus Popularly Purchased Products by Retailer									
	Lotions		P-value	Creams		P-value	Liquid body soaps		P-value
	NEA-recommended products	Popular products		NEA-recommended products	Popular products		NEA-recommended products	Popular products	
Amazon	\$3.19/oz	\$1.22/oz	--	\$12.07/oz	\$3.96/oz	--	\$1.66/oz	\$0.37/oz	--
Walmart	\$2.20/oz	\$1.48/oz	--	\$4.87/oz	\$5.83/oz	--	\$1.01/oz	\$0.38/oz	--
Target	\$2.93/oz	\$1.42/oz	--	\$7.22/oz	\$3.93/oz	--	\$1.42/oz	\$0.30/oz	--
CVS	\$3.15/oz	\$0.95/oz	--	\$4.06/oz	\$5.12/oz	--	\$1.20/oz	\$0.44/oz	--
Walgreens	\$2.53/oz	\$0.90/oz	--	\$4.82/oz	\$4.83/oz	--	\$1.42/oz	\$0.35/oz	--
Meijer	\$2.37/oz	\$0.79/oz	--	\$2.70/oz	\$5.04/oz	--	\$1.05/oz	\$0.29/oz	--
Avg.	\$2.73/oz	\$1.12/oz	<0.0001	\$5.96/oz	\$4.79/oz	0.4201	\$1.29/oz	\$0.35/oz	<0.0001

found in multiple stores, such as “Bath & Body Works,” were excluded. To determine the most popularly purchased product from each brand, the brand name and product type were searched on Amazon.com.¹⁰ The product with the most reviews was chosen as the most popularly purchased. The cost per oz for both NEA-recommended products and most popularly purchased products was extracted from the following common pharmacy retailers: Amazon, Walmart, Walgreens, CVS, Target, and Meijer. If the product was not carried by the retailer, the cost/oz data was not extracted for that retailer.

Pharmacy Density

Zip codes, population, median household income from 2017 to 2021, and number of retailers (Target, CVS, and Walgreens) were extracted from the Chicago Health Atlas and the New York State Department of Health. Lower-income zip codes were defined as the bottom 10% by median household income, and higher-income zip codes were defined as the top 10% by median household income. The average numbers of retailers per 10,000 population were calculated in lower and higher income zip codes and compared.

In-Stock Availability, In-Store Prices, and Store Hours of Operation

In-store prices of Cerave body lotion 16 oz (a representative gentle skin care product), the number of units in stock, and the store’s hours of operation were collected via phone call to all retailers in the low- and high-income zip codes. Phone calls were conducted in 1 sitting to limit variability.

Data Analysis

Statistical analysis was performed using Stata statistical software (StataCorp, College Station, TX). Product and retailer characteristics, including cost per oz, store density, and stock availability, were compared using students’ t-tests. A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Prices of Skin Care Products

A total of 64 products were extracted as NEA-recommended: 12 moisturizing lotions, 22 creams, and 24 liquid body soaps, including the brands Cerave, Cetaphil, and SkinClinicals. Thirty-one (31) products were extracted as the most popularly purchased products: 10 moisturizing lotions, 10 creams, and 11 liquid body soaps, including the brands Aveeno, Nivea, and Jergins. NEA-recommended products were significantly more expensive than popularly purchased products for moisturizing lotions (\$2.73/oz vs 1.13/oz, $P<0.0001$) and liquid body soaps (\$1.29/oz vs \$0.35/oz, $P<0.0001$) across all retailers but not for moisturizing creams (\$5.96/oz vs \$4.79/oz, $P=0.4201$; Table 1). NEA-recommended products were more expensive at Amazon than at Target, CVS, or Walgreens (\$5.63/oz vs \$3.12/oz, $P=0.002$).

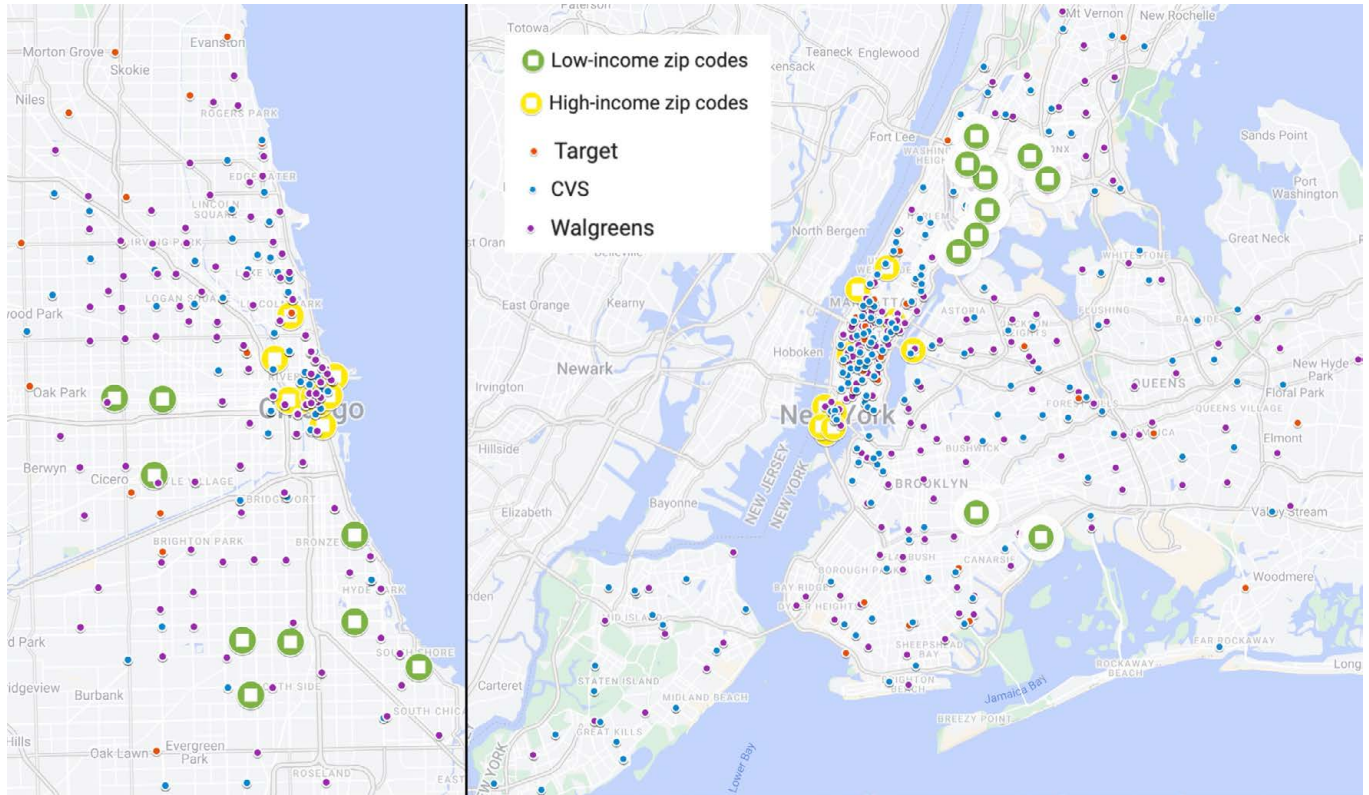
Pharmacy Density

Low-income zip codes had significantly lower densities of Target, CVS, and Walgreens stores compared to high-income zip codes in both Chicago (0.26 vs 3.20 stores/10,000 pop, $P=0.0007$; Figure 1) and New York (0.26 vs 2.90 stores/10,000 pop, $P=0.02$; Figure 2).

TABLE 2.

Store Hours, Stock, and Price of Cerave Lotion (16 oz) in High vs Low-Income Zip Codes			
	High-Income	Low-Income	P-value
Chicago			
Store Hours (hours)	19.20	14.9	0.02*
Store Stock (units)	5.10	2	0.05*
Store Price (\$)	\$19.59	\$19.66	0.93
New York City			
Store Hours (hours)	21.00	13.3	0.0002*
Store Stock (units)	4.80	1.4	0.03*
Store Price (\$)	\$21.49	\$20.44	0.32

FIGURE 1. Distribution of retail pharmacies compared to lowest- and highest-income zip codes in Chicago and New York City.



Low-income zip codes had significantly lower densities of pharmacy retail stores than high-income zip codes per 10,000 population in Chicago (left) and New York City (right).

In-Stock Availability, In-Store Prices, and Store Hours of Operation

Hours of operation were significantly more limited at stores in lower-income zip codes than higher-income zip codes in both Chicago (14.9 vs 19.2 hours operating/day, $P=0.02$) and in New York (13.3 vs 21.0 hours operating/day, $P=0.0002$; Table 2). Stores in lower-income zip codes also had significantly fewer units in stock of 16 oz Cerave lotion, a representative gentle skin care product, compared to the same stores in higher-income zip codes in both Chicago (2.0 vs 5.1 units in stock, $P=0.05$) and New York (1.4 vs 4.8 units in stock, $P=0.03$). There was no significant difference in the price of Cerave lotion 16 oz at the same retail chain between lower- and higher-income zip codes in either city.

DISCUSSION

We found that dermatologist-recommended gentle skin care products for AD were on average over twice the price of popularly purchased products, specifically lotions and liquid body soaps. Further, pharmacy retailers that sell recommended gentle skin care were less prevalent and had more limited hours in low-income neighborhoods in 2 major US cities. Lastly, for a given retailer, the same gentle skin care product was more likely to be out of stock in low-income compared to high-income store locations.

To our knowledge, this is the first study to compare prices of dermatologist-recommended products for AD with commonly purchased products and to identify existing disparities in access and availability of these products. Limitations include that popular products were inferred using online customer ratings, which may not directly represent consumer behavior. Further, stock was compared across stores by calling stores at 1 time-point, but this may not accurately measure the average supply of items across all opening hours of stores. Future studies should use centralized consumer demand data from the actual brands supplying these products. Further, future work should standardize stock estimates across stores by gathering centralized average stock data from the pharmacy retailers themselves.

This study highlights the impact of socioeconomic and geographic barriers on access to AD treatment, which can exacerbate existing disparities in AD. These findings are consistent with studies from the sociology literature on pharmacy deserts, which outline the triple impact on low-income patients: few pharmacies within walking distance, limited store hours, and low stock.⁶ This work underlines the critical need for interdisciplinary advocacy among dermatologists, policymakers, and business leaders to improve the affordability

of gentle skin care and to address pharmacy deserts for health equity.

DISCLOSURES

The authors declare that they have no potential perceived conflicts of interest and/or relevant financial relationships to disclose

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The Use of Biologic Therapeutic Regimens in Cutaneous and Systemic Mastocytosis: A Scoping Review

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ABSTRACT

Background: Mastocytoses, a category of diseases characterized by the clonal proliferation of mast cells and the release of their mediators, can be broadly classified as systemic mastocytosis (SM), cutaneous mastocytosis (CM), or mast cell sarcoma (MCS), with treatment options and prognoses varying based on subtype. Advancements in biologics and genetic testing have increased the variety of therapeutic options for mastocytoses. This paper characterizes the therapeutic landscape for mastocytoses with a focus on biologics and other novel medications.

Methods: A comprehensive literature search of PubMed and Scopus databases was conducted from the inception of the databases to January 31, 2024. Search terms included “[disease state] AND [biologic class]” or “[disease state] AND [biologic name]”.

Results: Of the 672 screened articles, 55 met the following inclusion criteria: (1) diagnosis of either CM, SM, or MCS, and (2) treatment with one of the following biologic regimens: tyrosine kinase inhibitor (TKI) (including a JAK/STAT inhibitor (JAK1/2i), or a monoclonal antibody). Treatment led to successful resolution of the disease or reduction of symptoms in 90% of the patients using TKIs (n=698), including all patients (n=4) using the JAK1/2i ruxolitinib alone, and 90.6% (n=125) using monoclonal antibodies.

Conclusion: Successful treatment or symptom improvement of SM, CM, and MCS has been demonstrated through the use of JAK1/2i, TKI, and monoclonal antibodies. More studies are needed to characterize JAK1/2i regimens as clinical trials are lacking.

J Drugs Dermatol. 2025;24(7):687-691. doi:10.36849/JDD.8437R1

INTRODUCTION

Mastocytosis refers to a group of disorders in which clonal mast cells proliferate and accumulate in various organs, triggering different physiologic responses. The disease is divided into 3 main categories: systemic mastocytosis (SM), cutaneous mastocytosis (CM), and mast cell sarcoma (MCS) (Table 1). The prevalence of mastocytosis is estimated to be 1 in 10,000, with the incidence being approximately 1 in 100,000 per year, with 65% of cases presenting in pediatric populations.¹ The disease is believed to be driven by a mutation in the *c-kit* proto-oncogene (KIT), which encodes the KIT protein. Proliferation of mast cells is driven by stem cell factor (SCF) protein binding to its receptor, KIT. With the *c-kit* mutation, there can be an activating mutation, ligand-independent activation, or suppression of protein apoptosis that drives the proliferation of mast cells we see in mastocytosis.² Interestingly, somatic gain of function mutation in the KIT gene, D816V exon 17, is found in over 80% of those with adult-onset mastocytosis, highlighting the role of KIT mutations in the pathogenesis of the disease. However, studies have shown that this is not the case for pediatric populations, as around 86% of children did not exhibit this mutation in 1

study.³ These genetic pathophysiologic differences illustrate the importance of correctly identifying the mutation present in order to help curate targeted therapeutic regimens.

TABLE 1.

Updated Classification of Mastocytosis From the World Health Organization in 2021¹⁴

Mastocytosis Classification

Cutaneous Mastocytosis	1. Urticaria Pigmentosa (UP), or Maculopapular Cutaneous Mastocytosis (MPCM) a. Monomorphic b. Polymorphic
	2. Diffuse Cutaneous Mastocytosis
	3. Cutaneous Mastocytoma a. Isolated mastocytoma b. Multi-localized mastocytoma
Systemic Mastocytosis	1. Bone marrow mastocytosis 2. Indolent systemic mastocytosis 3. Smoldering systemic mastocytosis 4. Aggressive systemic mastocytosis 5. Systemic mastocytosis with an associated hematologic neoplasm 6. Mast cell leukemia
Mast Cell Sarcoma	--

Currently, the treatment of mastocytosis varies depending on the classification of the disease. With the discovery of the genetic locus of mutation in this disease, targeted gene therapies have been used successfully to treat both SM and CM, such as with the tyrosine kinase inhibitors midostaurin and avapritinib. Janus kinase inhibitors (JAKi) selective for JAK1 and JAK2 offer prospective treatment benefits in mastocytosis, as they target a pathway crucial for the downstream effect of the activated KIT protein receptor. Monoclonal antibodies also offer prospective treatments, as they target immunoglobulin E (IgE) antibodies from binding to and activating mast cells, thus dampening the overall physiologic manifestations of mast cell degranulation.⁴ This review looks to characterize the therapeutic landscape for mastocytoses with a focus on biologics and other novel medications that can be recommended for future therapeutic use.

MATERIALS AND METHODS

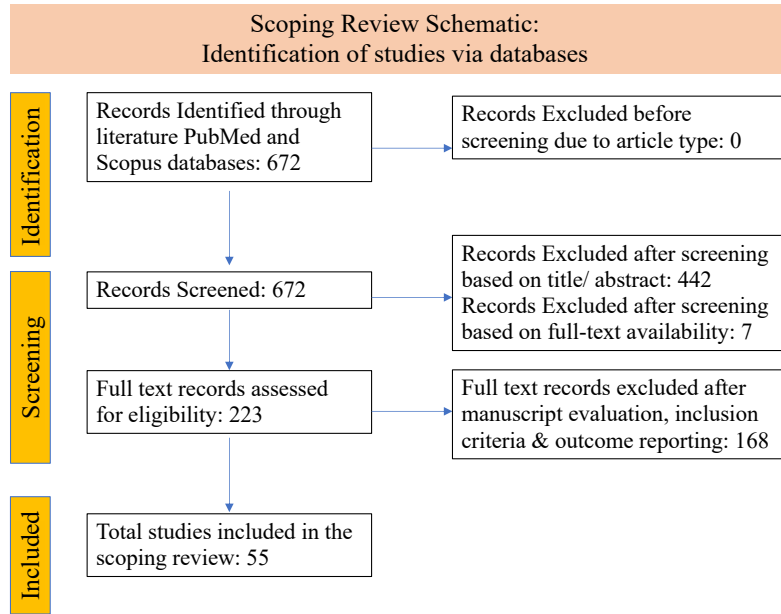
A scoping review was performed of the different studies outlining the use of tyrosine kinase inhibitors, JAK inhibitors, and monoclonal antibodies in the treatment of all types of mastocytosis. The search was conducted adhering to the updated 2020 standards of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement⁵ (Table 2; Figure 1).

A comprehensive literature search of PubMed and Scopus databases was conducted from the inception of the databases to January 31, 2024. Search terms included “[disease state] AND [biologic class]” or “[disease state] AND [biologic name]”. Disease states included “mastocytosis”, “systemic mastocytosis”, and cutaneous mastocytosis”. Biologic classes included “biologics”, “monoclonal antibody”, “JAK inhibitor”, and “tyrosine kinase

TABLE 2.
Mechanism of Action and Target of TKIs Used in the Management of Mastocytosis. Each “X” Represents the ATP-binding Catalytic Site of the Receptor That Each Biologic Competitively Inhibits^{15,16}

	JAK 1	JAK 2	BCR-ABL	KIT	PGFR	FLT3	VEGFR2
Ruxolitinib	X	X	--	--	--	--	--
Imatinib	--	--	X	X	X	--	--
Dasatinib	--	--	X	--	--	--	--
Midostaurin	--	--	--	--	--	X	--
Nilotinib	--	--	X	--	--	--	--
Avapritinib	--	--	--	X	X	--	--
Sunitinib	--	--	--	--	--	--	X

FIGURE 1. Percentage of biologic regimen used per classification of mastocytosis type.



(CM = cutaneous mastocytosis, SM = systemic mastocytosis, MCS = mast cell sarcoma, MA = monoclonal antibody).

inhibitor". Biologic names included "ruxolitinib", "imatinib", "dasatinib", "midostaurin", "sunitinib", "nilotinib", "avapritinib", "omalizumab", "dupilumab", "lirentelimab", "daclizumab", and "rituximab".

RESULTS

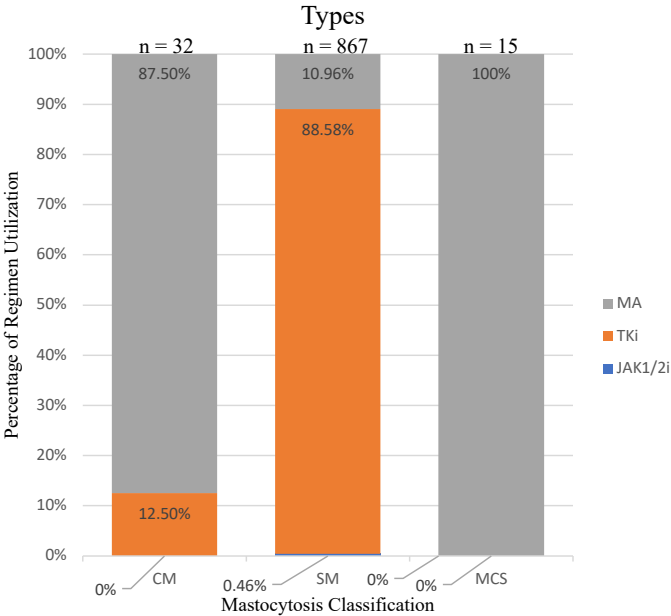
Of the 672 screened articles, 55 met the following inclusion criteria: (1) diagnosis of either CM or SM, and (2) treatment with one of the following biologic regimens: tyrosine kinase inhibitor (TKI) (including a JAK/STAT inhibitor (JAK1/2i), or a monoclonal antibody. The included articles consisted of 44 case studies, 7 clinical trials, 3 literature reviews, and 2 cohort studies (with some overlap in article types). Of the 925 included patients, a majority were treated with TKIs (84.5%), of which only 0.42% (n=4) were treated with a JAK1/2i alone, and 15.5% (n=138) were treated with monoclonal antibodies.

All JAKi and TKI regimens were administered orally, while all monoclonal antibody regimens were administered through subcutaneous injections, except for one administered intravenously (lirentelimab). TKI treatment regimens included either imatinib (n=87), dasatinib (n=60), midostaurin (n=452), nilotinib (n=105), avapritinib (n=71), and/or sunitinib (n=1). Four patients were treated with ruxolitinib (JAK1/2i). One hundred thirty-eight (138) patients were treated with monoclonal antibodies, consisting of omalizumab (n=112), lirentelimab (n=25), and/or daclizumab (n=1).

Eight hundred sixty-seven (867) patients were diagnosed with SM and were further classified with the following SM subtypes: general SM (n=324), SM with associated clonal hematological non-mast cell lineage disease (SM-AHNDM, n=210), aggressive SM (n=129), indolent SM (n=132), mast cell leukemia SM (n=43), bone marrow SM (n=28), and smoldering SM (n=1). The SM treatment regimens included TKIs (88.58%), monoclonal antibodies (10.96%), and JAK1/2is (0.46%; Figure 2). Thirty-two (32) patients were diagnosed with cutaneous mastocytosis (CM). The regimens included TKIs (12.5%) and monoclonal antibodies (87.5%). Fifteen (15) patients were diagnosed with MCS; 100% of these patients received a treatment of monoclonal antibodies (Figure 2).

Treatment led to successful resolution of the disease or reduction of symptoms in 90% of the patients using TKI's (n=698), including all patients (n=4) using the JAK1/2i ruxolitinib alone, and 90.6% (n=125) using monoclonal antibodies. The mean time until

FIGURE 2. Percentage of biologic regimen used per classification of mastocytosis type



(CM = cutaneous mastocytosis, SM = systemic mastocytosis, MCS = mast cell sarcoma, MA = monoclonal antibody).

treatment improvement in TKIs was approximately 2 months, and the mean duration of treatment was 17 months.

In those utilizing monoclonal antibodies, the mean time to see improvement in symptoms was around 4 months, and the mean treatment duration was 15 months. Adverse effects were more commonly reported in patients using TKI, with the most common being thrombocytopenia, anemia, and leukopenia, which were all seen in 40% of patients, as well as diarrhea and nausea, seen in 38% of patients.

Of the studies with available tryptase levels before and after treatment (18 TKI studies and 23 monoclonal antibody studies), both patients (n=2) treated with JAK1/2i had decreased levels and 89% of patients treated with TKI had decreased levels, with 40% (n=110) having a >20% decrease, and 48% (n=131) having a >50% decrease. Of those with a >50% decrease, 89 were on midostaurin and 42 on avapritinib. Only 2 individuals on TKI had increased tryptase levels, one each for imatinib and dasatinib. Thirty-four percent (n=46) of patients given monoclonal antibodies had improved tryptase levels.

TABLE 3.

Mechanism of Action of Monoclonal Antibodies Used in the Management of Mastocytosis ¹⁷⁻¹⁹	
Mechanism of action of monoclonal antibodies used in the management of mastocytosis	
Omalizumab	Binds to free IgE, causing downregulation of FcεRI receptors on mast cells and basophils
Lirentelimab	IgG1 antibody against Siglec-8 in mast cells and eosinophils
Daclizumab	Blocks CD25, an element of IL-2R, inhibiting effector T cell activation

DISCUSSION

The most common novel medications used in mastocytosis treatment regimens were TKI's (84.5%, n= 782), of which only 0.42% (n=4) used were JAK1/2is. Monoclonal antibodies represented a small but significant proportion of treatments (15.5%, n= 138). Of the TKIs, JAKs, and monoclonal antibodies used, the most common ones included imatinib, dasatinib, midostaurin, nilotinib, avapritinib, and sunitinib, with others used including ruxolitinib, omalizumab, liletelimab, and daclizumab (Table 3).

Drugs targeting tyrosine kinase signaling pathways have been trialed for the treatment of mastocytosis with increasing frequency in recent years.¹⁴ Imatinib was the first TKI developed for clinical use in humans with mastocytosis, followed by the second-generation TKIs: Nilotinib and Dasatinib.⁶ Before TKIs, the management of mastocytosis relied mostly on interferon-alpha, cladribine, and hydroxyurea treatments with limited disease improvement.⁶ The advent of more targeted JAK/STAT 1 and 2 inhibitors, such as Ruxolitinib for the treatment of mastocytosis, is a more recent therapeutic option. The first case of a patient with KIT-mutated systemic mastocytosis treated with a JAK inhibitor was published in 2013.⁷ Studies have shown that JAK1/2is like Ruxolitinib can inhibit mast cell activity and decrease symptoms of pruritus and fatigue, but there is a need for additional large clinical trials to elucidate the exact efficacy of JAK1/2is on the treatment of mastocytosis.⁸ This can explain why the majority of biologics used in mastocytosis treatments in the studies represented in this review were TKIs, despite the high rate of disease resolution seen in recent studies of patients who used JAK1/2is.

The review also found that most of the mastocytosis types treated with the biologics were mastocytosis type SM, specifically SM-AHNDM, followed by aggressive SM and indolent SM, with CM representing the smallest number of patients in this review. We predict that the prevalence rates we found in our study are similar to previous studies exploring treatments in those with mastocytosis.⁹

Tryptase can be a valuable marker for disease activity in mastocytosis due to its specificity for mast cell activation and burden.¹⁰ In studies with available tryptase levels before and after treatment initiation, 100% of those on JAK1/2i regimens had decreased tryptase levels after treatment. 89% of patients on TKIs had reduced tryptase levels after treatment, with 48% of those patients having as much as a greater than 50% reduction in tryptase levels. One study evaluating 273 patients with advanced systemic mastocytosis found similar findings; there was a more significant decrease in serum tryptase levels in the 135 patients treated with avapritinib compared to the patients treated with the best alternative therapy.¹¹ Other studies report that mastocytosis patients who experienced significant

reduction in symptom score, improvement in cutaneous and cardiovascular symptoms, and enhancement in quality of life after systemic therapies experienced concomitantly reduced tryptase levels.¹² Another clinical trial testing the response to imatinib showed normalization of tryptase levels in the patients who obtained a complete response of mast cell burden in the bone marrow.¹² Another study showed that reduced tryptase levels were associated with clinical improvement of mastocytosis symptoms and skin lesions in patients treated with masitinib, midostaurin, and BLU-285 treatments.⁹ Therefore, it can be deduced that the reduction of tryptase values can be used as a marker of symptom reduction and consequent improvement of mastocytosis disease management.

We also found that all patients (n=4) treated with JAK1/2is had either a resolution or reduction of disease. A total of 90.6% of the patients on monoclonal antibodies and 90% of those on TKIs had a resolution or reduction of their disease state. Though we see positive responses in all those utilizing JAK1/2i regimens, our study only included 4 patients on this regimen, highlighting the need for more studies utilizing JAK1/2is for mastocytosis.

Ruxolitinib, the first dual JAK1/2i approved for the treatment of myelofibrosis, has been shown to reduce splenomegaly and improve symptoms like pruritus. However, there is limited data on its ability to eliminate mutant clonal cell populations, like in TKI treatment.¹³ Some models have shown that the activation of alternate kinase pathways that aren't inhibited by Ruxolitinib can lead to the persistent growth of mutated cells in patients with myelofibrosis and mastocytosis.¹⁴ Additionally, interruption or abrupt discontinuation of Ruxolitinib treatment can worsen splenomegaly and cause 'discontinuation syndrome', a phenomenon in which drug withdrawal results in the sudden onset of new clinical symptoms such as acute respiratory distress syndrome.¹⁴ 'Discontinuation syndrome' was not known to be observed with type 1 JAK inhibitors.¹⁴ Regardless of these findings, one clinical trial in 89 patients with myelofibrosis showed that symptomatic improvement from JAK1 treatment was clinically comparable to the improvement seen with the dual JAK1/2 inhibitor, Ruxolitinib.¹⁸ This supports our finding that all patients (n=4) treated with JAK1/2is had either a resolution or reduction of disease. However, it is important to note that the vast majority of the current literature investigating JAK1/2is for the treatment of mastocytosis consists of case reports instead of clinical trials or large cohort studies. Hence, additional research is needed to better understand the effectiveness and response rates of JAK1/2is in comparison to TKIs and monoclonal antibodies in the treatment of mastocytosis.

Limitations of this review include tryptase levels being unavailable in the majority of included studies, and many studies used subjective endpoints such as self-reported side effects. Another limitation of this study is the small number

of patients (n=4) given JAK1/2 inhibitors. There is also limited data on MCS due to the rarity of the disease in humans, thus limiting the generalizability of the findings. Lastly, most studies reviewed were case reports or series, and only a small number of clinical trials have been conducted.

CONCLUSION

Successful treatment or symptom improvement of mast cell disorders has been demonstrated through the use of JAK1/2i, TKI, and monoclonal antibodies. Although JAK1/2is have proven to be highly successful in disease resolution and symptom reduction in small studies, additional studies are needed to characterize JAK1/2i regimens since very few clinical trials have currently been published on this topic.

DISCLOSURES

The authors have no disclosures or conflicts of interest.

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Poly-L-Lactic Acid (PLLA-SCA) as a Safe and Effective Method to Soften Transition Between Lower Eyelid and Midface

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ABSTRACT

Worsening depression around the lower eyelid and midface are seen over time with age. Skin thinning, fat atrophy, along with pigmentation, skin texture, and shadow changes contribute to the “tired” look of the area. Current minimally invasive treatments approved by the US Food and Drug Administration (FDA) include hyaluronic acid injections, but these come with limitations, such as patient selection and potential risks of Tyndall effect and swelling, which are dependent on injection technique and product selection. However, poly-L-lactic acid (PLLA-SCA) may be an alternative treatment option as it regenerates the patient’s own collagen and elastin and improves skin quality. The aim of this case series is to discuss the technique to improve maxilla/malar projection, pigmentation, texture, and volume after PLLA-SCA treatment.

This is a case series where healthy adults with lower eyelid- midface deficiency due to congenital or age-related soft or hard tissue atrophy were injected with 2 mL to 2.5 mL of PLLA-SCA collagen activator (PLLA-SCA, Sculptra) per injection site diluted to 8 mL to 9 mL of sterile water for injection (SWFI) and 1 cc lidocaine 2%. Patients returned typically for 3 sessions every 6 weeks.

Patients had improvement in maxilla/malar projection, pigmentation, texture, and volume. Clinical outcomes are seen as early as 6 weeks after last session (3 sessions average) with minimal to no touchup required 4 to 5 years post-initial treatment. No unanticipated adverse events were noted.

PLLA-SCA is a safe and possibly long-term effective treatment option for patients who require softening of the lower eyelid and midface transition.

J Drugs Dermatol. 2025;24(7):692-694. doi:10.36849/JDD.9003

INTRODUCTION

Lower eyelid and midface aging is characterized by worsening depression, skin thinning, fat atrophy, hyperpigmentation, and skin texture changes.¹ Extrinsic factors, like ultraviolet light exposure, cause photoaging through metabolic overreactivity. Rhytids form around the lateral canthus and lower eyelids as intrinsic, microscopic changes occur with degraded elastin and collagen.²

Other visible changes are seen with orbicularis rolls appearing in the pretarsal eyelids. The nasojugal groove, also known as the tear trough, forms below the lower eyelid. A contributing factor to tear trough deformity is fat loss at the inferior arcus marginalis. Whereas orbital septum attenuation can result in bulging of the lower eyelid fat pads. Changes in the centromedial cheek result in hollowing, also known as V deformity. The projection loss of the cheek occurs with festoons appearing in the mid-cheek.

Lower eyelid skin is thin, with minimal subcutaneous tissue.³ The orbicularis oculi muscle extends from the medial canthus

to the lateral canthus and orbits.⁴ The orbicularis oculi muscle separates the deep fat compartments: medial suborbicularis oculi fat (SOOF), lateral SOOF, and deep medial cheek. The transverse facial artery is a small vessel that lies along the lateral face, connecting with infraorbital arterials and ends at the buccal area. Above the pre-septal orbicularis oculi muscle, lies the superficial lymphatic system.⁴ In the pre-septal orbicularis oculi muscle, the deep lymphatic system and superficial lymphatic system connect.

Commonly used treatments to improve the area include hyaluronic acid filler injections (HA filler).⁴ However, patients with transparent skin, prominent skin laxity, history of fluid retention, or eye area edema are not ideal candidates. Potential risks with HA filler treatment in the periorbital region, which are due to product selection and injection technique, may include Tyndall effect, swelling, and filler migration.

Poly-L-lactic acid collagen activator (PLLA-SCA, Sculptra) is an injectable that regenerates the patient’s own collagen and

elastin and improves skin quality.⁶ PLLA-SCA is indicated by the US Food and Drug Administration (FDA) for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles, and for the correction of fine lines and wrinkles in the cheek region for immune-competent participants.⁸ PLLA-SCA works by the recruitment of fibroblasts, which deposit collagen and elastin to help restore the skin's structure and function.⁶⁻⁷ PLLA-SCA is reconstituted with sterile water and lidocaine for injection.⁸ Despite being a fluid, PLLA-SCA has decreased tissue spread both vertically and horizontally following massaging.⁹ The product is contained within the desired area by the orbital retaining ligament (ORL) and zygomaticus cutaneous ligament (ZML), delimiting this anatomical zone.

Patient Selection

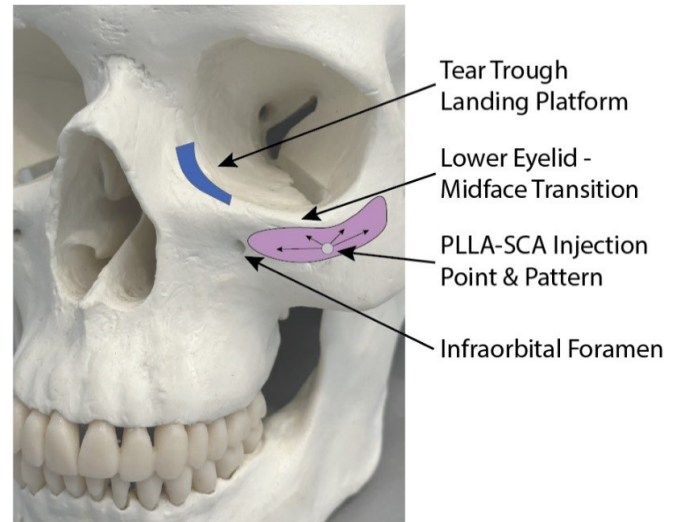
Patient selection for PLLA-SCA injection in the lower eyelid and midface differs from patients selection for HA fillers. Patients who may benefit from PLLA-SCA injections can be of any race/ethnicity/Fitzpatrick skin phototype; they can be men or women aged 18 or older; and should have a healthy immune system. The ideal patient includes those with lower eyelid/midface soft tissue collapse or atrophy, particularly those with thin skin. Patients with a negative vector, a cheek mass that lies posterior to the cornea, visible hollowness, and moderate-to-severe concavity medial to the mid-pupillary line are also candidates. Patients with shallow orbits giving the impression of having exophthalmos may also benefit from this procedure by obtaining increased maxillary projection. Patients with mild-to-moderate fat prolapse on the lower eyelid who are reluctant to or not candidates for surgery may benefit. Patients who may not be eligible for this treatment are those who are pregnant, have a history of allergy/hypersensitivity to the product, history of keloids, or have implants in the treatment area. If HA filler in the area is visible, it should be dissolved, and PLLA-SCA injected after.

Dilutions and Injections

PLLA-SCA is diluted with 8 mL to 9 mL of sterile water for injection (SWFI), with an additional 1 cc lidocaine 2% prior to injection. Topical anesthetic is optional.

Injections are performed with a needle. The entry point for the injection is aligned with the lateral corneal limbus. A retrograde injection using fanning vectors or a depot injection may be used due to the liquidity of the product. Injections are made deep with the needle directed toward the inferior orbital rim border (Figure 1). With the landing platform between the ORL and the ZML deep on bone, this technique, along with the liquidity of the product will target the suborbicularis fat pads. It is important to avoid injecting through the soft tissues of the malar mound, as this may increase the probability of malar edema.

FIGURE 1. Anatomy of the lower eyelid and mid face. Photograph outlining the junction. Bony structure diagram highlighting the underlying supporting structure and areas of retrusion. Injection entry point with markings of fanning pattern.



In addition, a lateral barricade, such as a nondominated finger, should be used to allow for movement of the product medially to flow around the inferomedial orbit, an area of safety concern due to infraorbital artery. A total of 2 to 2.5 mL is used per injection site, and each session should take on average 5 minutes for both sides. Depending on the degree of correction, 2 to 3 sessions may be needed every 6 weeks.

RESULTS

Improved maxilla/malar projection along with definite shadow improvement is seen due to the created topographical volume (Figure 2A-C). Younger patients may experience improvement after the first session. Older patients may need 3 sessions.

Patients should be advised to massage the injection site 5 times a day for 5 minutes for 5 days following each treatment session. Follow-up correction can be done 4 to 5 years after initial injection.

Safety

Potential treatment-related adverse events (AEs) include bruising and in a minority of patients, lower eyelid/malar edema lasting 2 to 3 days. Most AEs from PLLA-SCA injections are mild and transient and resolve without intervention. Potential vascular complications may occur due to the atrial branches in the periorbital and midface area. Vascular events with PLLA-SCA are rare but possible given that the molecule itself cannot

FIGURE 2A-C. Before and after images of participants treated with PLLA-SCA to soften the lower-eyelid-midface transition.

(2A) GM8122:62, Male, 3 treatment sessions, ½ vial PLLA-SCA per session



(2B) JRL 11129: 67, Male, 3 treatment sessions, ½ vial PLLA-SCA per session



(2C) ZCS17086 57, Female, 3 treatment sessions, 1/2 vial PLLA-SCA per session



be dissolved; however, given the product's liquid nature and particle size, the likelihood of vascular events are less than with HA fillers. The liquidity of the product allows an aspiration maneuver. Other concerns include nodule formation; however, there are not any current reports of nodule formation using this technique from the author after treating over 500 patients. This could be due to the described deep material deposition. Given the nature of the anatomic area, injection in the infraorbital artery is the highest risk. To help minimize this risk, it's important to align the entry point to the lateral corneal limbus and use a lateral barricade.

DISCUSSION

Treating the lower eyelid and midface area is important to improve overall facial aesthetics. PLLA-SCA may be a safe and effective long-term treatment option for those who require softening lower eyelid and midface transitioning. Other

alternative treatments to improve the area include HA fillers and surgery. HA fillers provide instant correction to the injection area, which may be ideal for candidates who prefer immediate results. Patients who may benefit from HA filler instead of PLLA-SCA injection, would be those with true hollowing and concavity of the region if they don't have hyperpigmentation, vascular dark circles, orbicularis oculi hypertrophy, and thin skin. HA fillers have the potential to cause the Tyndall effect and swelling, which could worsen the area when not used in the appropriate candidate.

Shallow orbits or negative vectors can be addressed via surgery and malar implants. However, this can also be addressed with the described PLLA-SCA injection technique without the potential complications of surgery. Overtime, age-related changes occur in the tissue, and malar implants risk looking unnatural with thin, aging skin. Given the lack of control groups and objective measurements, additional prospective randomized control trials should be conducted to further explore safety and efficacy in a broader population. Further research can help understand the mechanism of action of PLLA-SCA injections in correlation to the results in the lower eyelid. A current theory mentions soft-tissue injections may stimulate adipose stem cells to secrete growth factors, rejuvenate the injection area, and regenerate the tissue while working synergistically with collagen stimulation.¹⁰ In conclusion, the technique described here may be an option to soften the transition between the lower eyelid and midface and to improve maxilla/malar projection, pigmentation, texture, and volume with long-term effects.

DISCLOSURES

Dr Montes is a trainer and clinical trial investigator for Galderma. Dr Rohrich is a researcher, consultant, and/or receives royalties from MTF, Allergan, Merz, Galderma, InMode, Eriem Surgical, Thieve Publishers, and/or Medical Seminars of Texas, LLC. Dr Meckfessel and Dr Le are employees of Galderma.

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Podoconiosis: Review of This Unusual Cause of Lower Extremity Lymphedema and Its Global Health Burden

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ABSTRACT

Podoconiosis, or non-filarial elephantiasis, affects nearly 4 million people globally, primarily in regions with volcanic red clay soil. Characterized by lower extremity lymphedema from prolonged barefoot exposure to irritant soil particles, it causes significant economic losses, including \$200 million annually in Ethiopia. While its pathogenesis is unclear, genetic predisposition (HLA expression), inflammatory responses, and altered skin microbiota are implicated. Prevention focuses on footwear and hygiene, though these are costly. The stigma surrounding visible symptoms highlights the need for increased research, better diagnostics, effective treatment, and public health awareness.

J Drugs Dermatol. 2025;24(7):695-699. doi:10.36849/JDD.8748R1

INTRODUCTION

Podoconiosis, or non-filarial elephantiasis, is characterized by progressive lymphedema that affects the lower extremities of individuals with long-term exposure to alkalic volcanic red clay soil.¹ Affecting nearly 4 million individuals worldwide, it is known or suspected to be endemic in 32 countries across the globe, primarily in tropical regions within Africa, Asia, and Central America.²⁻⁴

Revalence data from Ethiopia alone estimate that approximately 1 million individuals are affected by podoconiosis, resulting in an estimated \$200 million in annual economic losses.⁵ Ethiopian patients incur an average annual cost of approximately USD 136, a substantial figure given the number of individuals living below the international poverty line (\$1.9 USD per capita per day). Additionally, the absence of podoconiosis cases within the United States contributes to limited awareness among US dermatologists, hindering international public health efforts, research, and recognition in recent immigrant populations.

While the pathogenesis of podoconiosis has not been entirely elucidated, it is thought to arise from cumulative barefoot exposure to mineral particles found in red clay soil, triggering inflammation in genetically susceptible individuals and leading to progressive lower extremity swelling.^{1,6} Without treatment, it severely impacts quality of life, daily activities, and social integration due to surrounding stigma.

Currently, no definitive diagnostic test for podoconiosis exists, leading to misdiagnosis, delayed treatment, and advanced lymphedema with fewer existing therapies.² In low-income countries, advanced lymphedema and limited therapies exacerbate the challenges of podoconiosis, including economic insecurity, reduced work capacity, psychological stress, and social stigma.⁷ This review aims to highlight the global health burden of podoconiosis and advocate for improved education, diagnostics, and treatment strategies.

MATERIALS AND METHODS

A narrative review was conducted using PubMed, OvidMedline, and the Cochrane Library with search terms including "podoconiosis," "non-filarial elephantiasis," and "endemic elephantiasis." Non-English, duplicate, and irrelevant studies were excluded. Titles and abstracts were screened for focus on podoconiosis epidemiology, etiology, diagnosis, treatment, prevention, and public health burden. Studies referencing elephantiasis, lymphedema, and other tropical diseases outside the scope of this review were excluded, as well as articles focusing on concurrent diagnoses or co-infection.

Historical Aspects

Dr. Eric J.T. Price, a British medical missionary, first documented podoconiosis in the 19th century, coining "mossy foot" to describe cases in Ethiopia and Cameroon.^{3,8-10} His findings highlighted a characteristic asymmetric swelling of the lower

limbs that progressed gradually among those working in agricultural roles. In the 1930s, Robles in Guatemala proposed a connection between soil exposure and clinical presentation.¹ Decades later, studies identified inorganic microparticles in lymphatic tissues of affected individuals, resembling those found in local red clay soil, thereby suggesting their role in pathogenesis. Though still unclear, this condition is thought to arise from greater absorption of irritants or tissue dysfunction impairing neutralization.^{11,12} Further lymphatic blockage from proliferation and hypertrophy of littoral cells (broadly classified as sinusoidal histiocytes and macrophages) was thought to occur in response to soil irritants penetrating through soft skin, especially in toe webs.¹³ Finally, familial clustering of cases suggested a genetic predisposition, though this remains to be fully elucidated.

Clinical Presentations

The hallmark presentation of podoconiosis involves gradual lower limb swelling accompanied by burning sensations, mild plantar edema, and increased skin markings.^{1,14} Initially affecting one limb with lymphedema that subsides overnight, it can progress to asymmetric involvement of both legs with irreversible edema. Symptoms often develop in the second or third decade of life, increasing with age.¹⁵ Podoconiosis is further categorized into 5 stages using a modified Dryer system, adapted from filarial lymphedema, due to differences in clinical progression.^{16,17}

Early-stage podoconiosis can often be reversed with proper footwear and foot hygiene. However, as the disease progresses, symptoms may intensify, leading to dermal changes referred to as mossy changes (Figures 1-4). This includes lichenification, hyperkeratosis, papillomata, and skin discoloration.¹⁸ Swelling spreads circumferentially to the knee, presenting bilaterally or asymmetrically with fibrosis, nodularity, or a boggy texture, eventually becoming irreversible.^{1,16,19,20} Advanced stages feature dermal nodules, ridges, nail changes, and maceration between digits. In stage 4, irreversible edema extends above the knee with hard nodules and papillomatous lesions.^{16,17,18,20} Finally, by stage 5, interdigital spaces may fuse and flexural creases of the ankle can become fibrotic, impairing movement.¹⁶

FIGURE 1. Left foot of a 46-year-old male farmer presenting to clinic for evaluation of progressive swelling in the lower extremities with dermal changes. Started around 1 year prior with wounds on the soles of the feet.



Patients may also experience acute inflammatory episodes known as acute dermatolymphangioadenitis (ADLA), a term unique to the presentation of podoconiosis and other lymphatic disorders.²¹⁻²³ These sudden, agonizing “attacks” are thought to be triggered by skin furrows and damaged tissue and are more colloquially referred to as cellulitis or lymphangitis. Moreover, poor lower extremity hygiene increases the risk of secondary bacterial or fungal infections, worsening outcomes.^{1,15,16,24} ADLA presents with a warm, erythematous, swollen extremity with palpable femoral lymphadenopathy, fever, chills, and malaise.^{1,2}

FIGURE 2. Left foot of a 46-year-old male farmer presenting to clinic for evaluation of progressive swelling in the lower extremities with dermal changes. Started around 1 year prior with wounds on the soles of the feet.



FIGURE 3. Left foot of a 46-year-old male farmer presenting to clinic for evaluation of progressive swelling in the lower extremities with dermal changes. Started around 1 year prior with wounds on the soles of the feet.



FIGURE 4. Left foot of a 46-year-old male farmer presenting to clinic for evaluation of progressive swelling in the lower extremities with dermal changes. Started around 1 year prior with wounds on the soles of the feet.



Studies in Ethiopia report an average of 5 ADLA episodes per year, with some cases involving exfoliative dermatitis.^{16,19,20}

Pathogenesis of Podoconiosis and the Role of Skin Microbiota

Research on podoconiosis pathogenesis is limited, but several risk factors have been identified, including high rainfall, altitude, volcanic soil composition, cumulative barefoot exposure, and poor foot hygiene.²⁵ Specifically, studies have shown associations between podoconiosis and phyllosilicate clays (smectite and kaolinite), gibbsite, mica, and quartz found in volcanic soil.^{6,26,27} Individuals who work in agricultural occupations without the use of footwear, such as subsistence farmers, potters, mine workers, and textile workers, and those with limited access to clean water and sanitation are most susceptible.^{8,9,15}

Genetic factors, particularly HLA class II variants (HLA-DQA1, HLA-DQB1, HLA-DRB1), are implicated in podoconiosis.^{25,28,29} Studies show T-cell activation with increased HLA-DR expression and decreased CD62L expression in CD4 and CD8 subsets, alongside upregulation of CD40 and CD86 on monocytes and dendritic cells.³⁰ These findings suggest podoconiosis arises from a combination of genetic, geographic, environmental, and socioeconomic factors. While red clay soil particles may predispose individuals to podoconiosis, their mechanism of entry and impact on lymphatic channels remains unclear. It is theorized that these particles breach the skin's barrier and are subsequently engulfed by macrophages.¹⁵ This triggers inflammation, vessel occlusion, and the release of free radicals, leading to fibrosis, scarring, and impaired lymphatic flow, ultimately causing lymphedema and elephantiasis via a recurring cycle.^{1,8}

A recent microbiome study examined 164 skin swabs from individuals with podoconiosis living in Cameroon and revealed a link between increased microbial diversity, higher anaerobic bacterial populations, and more frequent and prolonged ADLA episodes.³¹ Furthermore, anaerobic bacteria that are not typically found in normal skin flora were notably increased on the ankle and interdigital skin.³¹ Similarly, Nkwetta et al identified *Staphylococcus* as the predominant bacterial species and a potential ADLA trigger, with over 90% of isolates sensitive to doxycycline, gentamicin, and ofloxacin.³² Lastly, in patients with filarial lymphedema, Olszewski et al found a high prevalence of bacterial isolates, including *Bacilli*, from peripheral blood, skin wounds, and lymphatic tissues in those with acute or recent ADLA.³³ Bacterial strains of the same phenotype and antibiotic sensitivity were also noted on the toe web surface in tissue fluid, lymph, or lymph nodes.³⁴ While the role of these organisms in pathogenesis remains unclear, further research is needed to clarify bacterial contributions, improve infection control, and guide antibiotic treatments.

Histologic Features

Histologically, podoconiosis is characterized by distinct changes in the dermis and deep subcutaneous tissue. In the early stages, findings include mild epidermal hyperplasia, verrucous acanthosis, hyperkeratosis, and elongation of the rete ridges.¹⁸ In a study of 65 tissue specimens from affected patients, lymphocytic infiltrates were consistently present in the papillary or superficial reticular dermis. Late stages revealed mast cells, plasma cells, and lymphoplasmacytic infiltrates with perivascular involvement, distinguishing podoconiosis from filariasis. Moreover, the papillary dermis demonstrated thickening with signs of sclerosis and coarse collagen bundles.¹⁸ Changes in glandular structures, hyperplasia, and dilation of eccrine ducts are also typical, reflecting the chronic inflammatory response. While its pathogenesis and overall disease progression remain unclear, lymphatic and vascular compromise have been shown to contribute to vessel dilation, vascular sclerosis, and tissue dysfunction.^{18,20} In severe cases, adnexal structures are absent.

Management Options and Challenges in Less Favorable Health Systems

Podoconiosis management encompasses a multidimensional approach addressing both the chronic inflammatory process and the resulting disruption in the lymphatic system.³⁵ Management of podoconiosis in resource-limited healthcare settings is challenging.³⁶ Primary prevention relies on reducing contact with red clay soil through footwear or floor coverings, but access to durable footwear is often financially prohibitive.^{16,37} Additionally, moist soil may attach to and weigh down shoes, making farm work more challenging.³⁸ Those with a perception of low risk for acquiring podoconiosis were also less likely to don shoes.³⁸ Furthermore, strictly adhering to footwear may conflict with traditional customs within certain groups where walking barefoot holds a deeply ingrained cultural significance.³⁹

Secondary prevention of podoconiosis involves implementing proper foot hygiene practices, utilizing compression therapy, elevating the affected leg to maintain skin integrity, reduce lymphatic buildup, and improve drainage.¹⁶ Additionally, educating community members on daily foot washing, emollient use, and regular soaking with antiseptic agents can halt the progression of podoconiosis-related symptoms and secondary skin infections.¹⁶ However, clean water remains a valuable commodity and may be allocated to what are perceived as higher-priority needs.

In interviews of 1,319 patients with podoconiosis in Northern Ethiopia, 41.3% reported not knowing the cause of the disease, and roughly 20% to 40% believed it was unpreventable.⁴⁰ In addition, 21% believed podoconiosis was contagious and nearly 10% considered it a "family curse from God."⁴⁰ While imperative to dispel myths and misconceptions, disseminating accurate

educational resources is difficult in remote areas, regions with limited healthcare personnel, and low literacy populations. Increasing knowledge of this disease is vital for early, accurate diagnosis as well as effective community support and integration.^{7,41} Stigmatization of those living with this disease further hinders their pursuit of medical attention, exacerbating their debilitating condition, diminishing their internal locus of control, and fostering doubts regarding efficacy of preventative treatment.⁷ Advanced stages benefit from combining prevention with compression therapy, infection management, and surgical interventions like nodulectomy.⁴²

Challenges to the Global Health System and Impact on Individual Mental Health

Podoconiosis and lymphatic filariasis (LF) share clinical similarities, including lymphatic dysfunction and progressive edema, which complicates diagnostic accuracy and rapid treatment intervention. LF, caused by the parasitic worms *Wuchereria bancrofti* and *Brugia malayi* and transmitted via mosquitoes, typically manifests as unilateral lymphedema that may involve the groin and extend above the knee.^{18,43,44} Larvae of these parasites infiltrate the lymphatic system, inducing inflammation, fibrosis, and lymphatic obstruction.⁴³ LF is managed with vector control and community-wide mass drug administration programs using a dual drug combination of ivermectin and albendazole or diethylcarbamazine citrate and albendazole. In contrast, podoconiosis begins at the foot, progresses to bilateral, asymmetric lower-leg edema, rarely involves the groin, and does not respond to antiparasitic treatments due to its non-infectious etiology.^{18,44}

Although no validated diagnostic tool exists for podoconiosis, a 5-question algorithm has been proposed to improve identification.⁴⁵ These questions ascertain the presence of leg swelling, leprosy history, groin lymphadenopathy, chronic illness, mossy skin changes, and a family history of leg swelling.⁴⁵ This algorithm can aid in regions where LF is more commonly recognized and podoconiosis awareness is limited among providers.

Still, individuals with inadequate healthcare access often manage their disease alone or rely on caregiver assistance, particularly during acute attacks. This increases familial financial strain as both individuals may face prolonged work absences. Globally, affected individuals lose nearly 45% of working days annually, contributing to significant economic losses.^{46,47}

The social ramifications of podoconiosis are just as large due to negative sociocultural perceptions. Qualitative surveys reveal that individuals disfigured and disabled by podoconiosis express shame, embarrassment, mental and emotional suffering, negative self-image, and even thoughts of suicide.^{41,48,49} Interestingly, distress levels did not always correlate with illness severity. Promoting dialogue in affected communities is vital

to reducing stigma, correcting misconceptions, and enhancing self-efficacy in disease management.

Preventive measures like improved infrastructure, clean water, and adequate footwear have eradicated podoconiosis in parts of North Africa and Europe.²⁵ Yet, the multitude of social determinants of health thwarts similar progress in other regions. Sustainable solutions, including better diagnostics and personalized treatments, are needed to overcome these challenges.

Reappraisal and Suggestions for Enhanced Diagnosis and Management

Improving disease understanding and access to information is vital for addressing podoconiosis. Collaboration among healthcare systems, governments, and non-profit organizations is key to implementing effective solutions. Advances like near-infrared fluorescence (NIRF) imaging employing indocyanine green (ICG) offer a novel method for identifying potential lymphatic dysfunction.⁵⁰ Although quicker and more cost-effective than MR and PET, this technology requires significant financial support. Training healthcare professionals in endemic regions and investing in research on podoconiosis epidemiology, genetics, and the microbiome are essential for progress.

Empowering affected communities is crucial to reducing stigma and promoting education. Local support groups can share resources, strengthen social support, and encourage early detection and treatment adherence. Expanding funding for affordable footwear and wound care supplies enables better disease management.

Organizations like the Mossy Foot Treatment and Prevention Association (MFTPA), an Ethiopian non-governmental group established in 1998, and the global initiative “Footwork” offer support in endemic areas. MFTPA trains community podoconiosis agents (CPAs), former patients, and social workers to raise awareness, provide peer support, and serve as vital links to education and healthcare. While funded by the US-based Mossy Foot Project, broader support is needed for sustainability. Advocacy and policy engagement can improve treatment, promote disease control, and encourage environmental interventions like better infrastructure and flooring to reduce soil contact.

While comprehensive, this review has several limitations. Firstly, exclusion of non-English language articles may omit important primary literature from countries with a significant podoconiosis burden that were not historically under English influence. Secondly, the accessibility issues with some primary literature, due either to archival unavailability or restricted access, further limit the scope of included historical data. Additionally, the search terms may unintentionally constrain the breadth of this review and may miss studies predating the consistent use of

“podoconiosis.” Finally, the absence of definitive diagnostic testing for podoconiosis likely leads to underreporting. Despite these challenges, the findings emphasize the need for further research into pathogenesis and targeted interventions to improve quality of life and reduce the global burden.

CONCLUSION

Podoconiosis is a tropical disease causing debilitating lower extremity lymphedema, primarily affecting barefoot subsistence farmers exposed to volcanic red clay soil. Although the pathogenesis remains unclear, infiltration of soil particles is a suspected trigger, and the presence of anaerobic bacteria on affected skin has been associated with increased lymphedema severity. This disease disproportionately impacts laborers, causing economic instability, household financial strain, physical limitations, and mental distress exacerbated by limited awareness and access to treatment. Addressing podoconiosis requires advocacy, improved healthcare access, and targeted prevention and management strategies.

DISCLOSURES

There are no financial disclosures, commercial associations, or any other conditions posing a conflict of interest to report for any of the above authors.

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Pincer Nail Deformity in an African American Patient Corrected by Fractionated Carbon Dioxide Laser

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ABSTRACT

Pincer nail deformity is a painful nail condition characterized by excessive transverse curvature of the nail plate that pinches the surrounding tissue. Treatments such as nail braces and surgical interventions are commonly used; however, these approaches often fall short of providing consistent, long-term relief. Fractionated carbon dioxide laser therapy (fCO₂), which precisely targets the nail matrix, has emerged as a less invasive option to correct nail deformities. Treating patients with skin of color poses several challenges due to the higher risk of post-inflammatory hyperpigmentation (PIH) and scarring. Herein, we describe a case of a 78-year-old African American woman (Fitzpatrick V) with long-standing pincer nail deformity treated with fCO₂ laser therapy, with nail defect improvement. This case underscores fCO₂ laser therapy as an effective option for pincer nail deformity in skin of color, particularly notable due to its rare occurrence in the fingernails.

J Drugs Dermatol. 2025;24(7):700-701. doi:10.36849/JDD.8783

INTRODUCTION

Pincer nail deformity is a painful nail condition characterized by excessive transverse curvature of the nail plate that pinches the surrounding tissue.¹ This condition primarily involves the toenail of the hallux and is more frequently observed in older individuals.¹ Management of a pincer nail typically involves nail braces or surgical removal.¹ These managements usually fall short of providing long-term relief and satisfaction cosmetically.¹

Fractionated carbon dioxide (fCO₂) laser therapy offers an advanced option in treating severe cases. fCO₂ laser can precisely target the nail matrix without causing extensive damage to surrounding tissues.² However, laser treatment for skin of color patients presents with more complexity, including higher risks of post-inflammatory hyperpigmentation (PIH) and scarring.³ These complications are more common in individuals with darker skin tones. Risk of hyperpigmentation, particularly in skin of color patients, deters many clinicians and patients from utilizing fCO₂.⁴ Research indicates that up to 16% of individuals with skin of color may develop hyperpigmentation after laser procedures.⁴ In addition to other potential complications, such as scarring.⁴ Advances in laser technology have made it possible to minimize these risks if appropriate settings are used.⁵ Customized treatment protocols and proper post-treatment care have been shown to reduce the risks of adverse outcomes, highlighting the need to address specific concerns, especially in patients with skin of color, and empower them with confidence in their treatment options.⁵

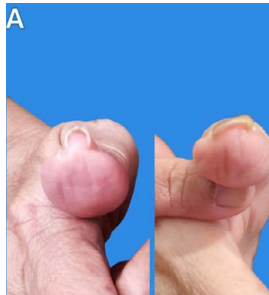
Case Description

A 78-year-old African American female (Fitzpatrick type V) presented with a painful right thumbnail deformity that had been present since September 2021. She reported significant pain that impaired her ability to perform daily activities. Prior treatments, including an incision and drainage (I&D) with matricectomy, and later trimming of the distal nail with application of a nail brace failed to provide relief. The patient's medical history included diabetes mellitus (DM), hypertension (HTN), and a history of tobacco use, contributing to the complexity of her case. Physical examination revealed a tender pincer nail deformity characterized by inward-curving lateral edges.

Prior to the procedure, an eutectic mixture of local anesthetics (EMLA) was applied under occlusion for 60 minutes from the distal interphalangeal (DIP) joint to the fingertip. The patient was treated with a fCO₂ laser (DEKA SmartXide DOT, Florence, Italy) in DOT mode. The laser settings included: a rectangular shape with a 60% size, a 4/10 ratio, and a power of 15 W. Spacing was set to 650 microns, with a dwell time of 500 microseconds and a stack of 1. The treatment area focused on the radial side of the lateral right thumb nail, including 1 to 2 mm of the lateral nail fold and 2 mm of the proximal nail fold, specifically targeting the nail matrix. The fCO₂ laser was pulsed 4 times on the lateral endpoint to ensure adequate coverage.

Post-treatment care consisted of applying triamcinolone 0.1% ointment to the treated finger to reduce inflammation, followed by covering the area with Telfa dressing, gauze, and a coband

FIGURE 1. Comparison of the patient's right thumbnail before (A) and after (B) treatment with a fCO₂ laser. Image A shows a pincer nail deformity, characterized by the excessive curvature of the nail plate, while image B demonstrates improvement of the nail defect.



wrap. The patient was prescribed cephalexin 500 mg to be taken 4 times daily for 14 days, and mupirocin ointment to be applied 3 times daily for 10 days to prevent infection.

Instructions were provided, and the patient was advised to keep the area clean and dry, avoid pressure on the finger, and monitor for signs of infection or complications.

The patient received a total of 5 treatments spaced over 18 months, with 3 to 4 months between each treatment. The progressive improvement was noted after each session, contributing to a gradual resolution of the nail defect.

Discussion and Future Directions

Herein, we present a case of pincer nail deformity in an African American patient. Pincer nail deformity is characterized by an excessive inward curvature of the nail plate.¹ This results in pain and discomfort leading to functional impairment and, at times, secondary infections.¹ Etiology of pincer nail is not well understood; however, contributing factors include systemic diseases.¹ In older patients with chronic diseases such as osteoarthritis, structural changes in the nail matrix and the surrounding tissues are more common, and other factors such as repetitive trauma, tight footwear, and even genetic predisposition are thought to be triggers.¹

While pincer nails most commonly involve the toenails, this patient's presentation is unique due to its occurrence in the fingernail.¹ In this case, her diabetes likely contributed to the exacerbation of the nail condition. Diabetic patients are 3 times more likely to develop onychomycosis, which is a well-documented risk factor for the development of pincer nails.^{6,7}

fCO₂ laser treatment for pincer nails is an effective non-surgical treatment option for managing pincer nail deformities. fCO₂ lasers can precisely ablate the nail matrix and facilitate reshaping the nail, allowing it to grow straighter over time.² The precision of lasers allows for the removal of diseased or overgrown tissue while minimizing damage to surrounding structures.² This approach is valuable for the elderly or those with co-morbidities like diabetes, where surgical risks are heightened.

Treating pincer nails in patients with skin of color, as in this case, introduces several challenges. Laser treatment poses a higher risk of PIH in darker skin tones, as heat generated by the laser can cause melanocytes to overproduce melanin.⁴ Proper patient selection and laser settings, such as lower energy levels and longer pulse durations, are essential to minimize these risks.⁵ Our patient demonstrated significant progress throughout the treatment course, highlighting the potential efficacy of fCO₂ laser therapy. The patient's satisfaction points underscore the importance of setting realistic expectations for patients undergoing laser treatment. Laser therapy may not yield immediate or dramatic results; however, instead it provides gradual improvement. As seen in this case, nail plate correction of nail curvature can enhance patient's comfort and quality of life.

Alternative treatment options for pincer nail deformity include nail braces, which apply gentle pressure to gradually straighten the nail over time.¹ However, this approach often requires long-term use and may be insufficient for correcting severe cases.¹ Surgical interventions, such as partial or total nail matrixectomy, may be necessary for refractory cases.¹ However, these procedures carry a higher risk of complications, especially in elderly patients or those with conditions that impair healing, such as diabetes.

To our knowledge, this is the first documented case of successful treatment of a pincer nail deformity of the thumb using fCO₂ laser in an African American patient (Fitzpatrick V). We propose that the fCO₂ laser may serve as a safe and effective treatment option for pincer nail deformity in patients with skin of color, offering an alternative approach for refractory cases. This case highlights a unique presentation of pincer nail deformity and contributes to the current understanding of dermatological manifestations in patients with skin of color, highlighting the necessity of patient-centered care. Further randomized control trials with fCO₂ laser are necessary to optimize fCO₂ laser settings and treatment protocols, thereby strengthening the recommendation of fCO₂ in pincer nail deformity in patients with Fitzpatrick skin types IV to VI.

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Treating Chronic Hand Eczema With Upadacitinib: Insights From Clinical Trials and Real-World Experience

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ABSTRACT

Background: Chronic hand eczema (CHE) is a chronic inflammatory skin condition that affects the hands and wrists causing itching, dryness, cracking, and pain. It often affects people with atopic dermatitis (AD) and can interfere with work and daily life. Topical therapies may have limited utility from ineffectiveness, poor adherence, or poor tolerability. Here, we evaluate oral upadacitinib (UPA) as a potential therapeutic alternative for patients with AD and refractory CHE.

Methods: This narrative review analyzed studies from PubMed, SCOPUS, and EMBASE evaluating CHE treatments. Eligible studies utilized the Hand Eczema Severity Index (HECSI), a validated clinician-reported outcome measure assessing CHE severity. HECSI-75 is the proportion of patients achieving at least a 75% improvement in clinical severity. Cases of three CHE patients from diverse demographics are presented.

Results: In two phase 3 randomized controlled trials of UPA for moderate-to-severe AD, 94.8% (803/847) and 92.6% (774/836) of patients had CHE with HECSI assessments at baseline. Rapid improvement in CHE was observed in patients who received either dose of UPA (15 mg or 30 mg) as early as week 1 ($P \leq 0.001$ vs placebo). By week 8, up to 83% of UPA-treated patients achieved a statistically significant improvement in CHE (HECSI 75; $P \leq 0.001$ vs placebo). These benefits were sustained through week 16. Real-world clinical cases showed CHE patients experienced marked symptom relief within days of initiating UPA.

Conclusion: UPA-treated patients experienced rapid and sustained relief from CHE lesions, making it a promising therapeutic option for CHE patients for whom topical therapies are ineffective.

J Drugs Dermatol. 2025;24(7):702-707. doi:10.36849/JDD.9156

INTRODUCTION

Chronic hand eczema (CHE) is a common and often relapsing, chronic inflammatory skin condition with an estimated prevalence of 4% and a lifetime prevalence of 14.5% in the general population.^{1,2} It typically presents with dry, scaly, and pruritic lesions on the palms, fingers, and backs of the hands, and also may be accompanied by vesicles, fissures, and edema.³ The etiology is often multifactorial, involving irritant or allergic contact dermatitis or representing a manifestation of atopic dermatitis (AD).⁴ Around one-third of patients with CHE had a history of AD. On the other hand, patients with AD

are significantly more likely to develop CHE, and up to 60% of patients with active AD report hand involvement.^{2,5}

CHE is defined as hand eczema that lasts for more than 3 months continuously or occurs at least twice within a 12-month period.¹ The physical symptoms of CHE can severely impact patients' quality of life, particularly when the condition interferes with work or daily activities. Individuals in occupations that involve frequent hand washing, exposure to chemicals, or use of gloves are especially vulnerable to

persistent or relapsing disease.⁶ In more severe cases, patients may face job loss or be forced to avoid entire fields of work due to the severity of symptoms. Despite this significant burden, treatment options remain limited. According to the American Academy of Dermatology (AAD) clinical guidelines for atopic dermatitis, current approaches to CHE rely heavily on topical therapies such as corticosteroids, emollients, and calcineurin inhibitors, with variable results.⁷ Oral immunosuppressants and retinoids are systemic therapies used in more resistant cases, though only oral alitretinoin is approved specifically for severe CHE unresponsive to potent topical corticosteroids in Europe but not the United States.⁸ A topical pan-JAK inhibitor cream, delgocitinib is currently approved in Europe for adults with moderate-to-severe CHE who are inadequately responsive to or inappropriate candidates for topical corticosteroids.⁹ A more selective topical JAK inhibitor (JAK1/2), ruxolitinib cream, has shown efficacy in patients with moderate-to-severe CHE in phase 2 clinical trials.^{10,11} Ruxolitinib is currently approved by the US Food and Drug Administration (FDA) for mild-to-moderate AD.¹²

Upadacitinib (UPA) is an oral, once-daily, selective JAK-1 inhibitor, FDA-approved for the treatment of moderate-to-severe AD and multiple chronic immune-mediated inflammatory conditions.¹³ In the Measure Up 1 and Measure Up 2 phase 3 clinical trials, UPA demonstrated rapid onset of action and long-term sustained efficacy and safety in patients with moderate-to-severe AD.¹⁴⁻¹⁶ Subgroup analyses from these trials support that UPA may also be highly effective in treating CHE in AD patients, which is a common and often treatment-resistant form of CHE.⁵

We reviewed the efficacy of UPA in CHE by evaluating published evidence from randomized controlled trials and real-world clinical experience provided by the authors. Our analysis focuses on Hand Eczema Severity Index (HECSI) outcomes from clinical trials in patients with AD and hand involvement. In addition, we summarized HECSI outcomes reported for topical JAK inhibitors and provided case reports that demonstrate real-world experience of UPA in the management of CHE in patients with diverse age and skin tone.

MATERIALS AND METHODS

A systematic literature review was conducted using PubMed, SCOPUS, and EMBASE databases to identify randomized controlled trials evaluating treatment efficacy in CHE. Search terms included “chronic hand eczema,” “upadacitinib,” “delgocitinib,” and “ruxolitinib.” Studies eligible for inclusion required clearly defined HECSI scoring for assessing CHE severity. HECSI is a validated composite outcome measure used to assess the severity and extent of CHE. It evaluates 6 clinical signs—erythema, infiltration/papulation, vesicles, fissures, scaling, and edema—across 5 regions of the hands (fingertips, fingers, palms, backs of hands, and wrists). Each sign is graded

by intensity (0–3), and the extent of involvement is scored based on the percentage of the area affected. The total HECSI score ranges from 0 to 360, with higher scores indicating more severe disease. Severity is categorized as almost clear (1–16), moderate (17–37), severe (38–116), and very severe (≥117). HECSI is used in clinical trials to evaluate treatment outcomes in CHE, with HECSI-75 (a 75% improvement from baseline) representing a clinically meaningful response (Figure 1).⁵ For inclusion, studies specifically required report of HECSI-75 responses. Only peer-reviewed articles published in English were included. Studies lacking clearly described trial methodology, such as those reporting outcomes based on observed cases alone, were excluded.

FIGURE 1. Overview of the rigorous HECSI scoring methodology used to assess CHE severity.

Clinical Signs	Fingertips	Fingers (except tips)	Palm of Hand	Back of Hand	Wrist
Erythema					
Infiltration/Papulation					
Vesicles					
Fissures					
Scaling					
Oedema					
Sum of Intensity Scores					
Extent					
HECSI scores					
Total HECSI Score (Sum of HECSI scores):					
Score of 0-360					
HECSI Score					
Severity					
0					
1 to 16					
17 to 37					
38 to 116					
≥ 117					
Clear					
Almost Clear					
Moderate					
Severe					
Very Severe					

RESULTS

Clinical Trials for Oral Upadacitinib: Once Daily Pill

A post hoc analysis of the randomized phase 3 monotherapy trials, Measure Up 1 and Measure Up 2 demonstrated consistently high and sustained efficacy of UPA 15 mg and 30 mg in treating patients with CHE and moderate-to-severe AD at all visits.⁵ In Measure Up 1, significant HECSI-75 responses were observed as early as week 1 in 16% and 23% of patients treated with UPA 15 mg and 30 mg, respectively, compared to 4% in the placebo group (*P* < 0.001). Response rates increased rapidly by week 4, with 71% (15 mg) and 75% (30 mg) of patients achieving HECSI-75, vs 13% with placebo (*P* < 0.001). By week 8, responses further improved to 76% and 83%, respectively,

compared to 12% with placebo ($P<0.001$). These improvements were sustained through week 16, with 71% (15 mg) and 79% (30 mg) maintaining HECSI-75 responses vs 14% in the placebo group ($P<0.001$).⁵ Non-responder imputation (NRI) was used to handle missing data (Figure 2; Table 1).

Clinical Trials for Topical Delgocitinib: Twice Daily Cream

DELTA 1 (n=487) and DELTA 2 (n=473), 2 randomized phase 3 trials evaluating twice-daily topical delgocitinib 20 mg/g, demonstrated efficacy in moderate-to-severe CHE, although response rates were notably lower than those observed in

UPA trials in AD patients with moderate-to-severe atopic hand eczema.^{17,18} At week 1, there was no significant difference in HECSI-75 vs vehicle in DELTA-1 ($P=0.36$).¹⁷ By week 4, approximately 39% of delgocitinib-treated patients achieved HECSI-75, compared with ~16% of patients receiving vehicle ($P<0.0001$). In contrast, 64% to 75% of patients treated with UPA 15 mg or 30 mg achieved HECSI-75 at the same timepoint. At week 8, HECSI-75 responses with delgocitinib rose to ~50%, vs ~19–26% with vehicle ($P<0.0001$), but remained lower than the >70% response seen with UPA 15 mg and >80% with UPA 30 mg. By week 16, HECSI-75 rates with delgocitinib plateaued at ~49%,

FIGURE 2. HECSI-75 response rates for oral UPA 15 mg (blue) once daily, oral UPA 30 mg (orange) once daily, and topical delgocitinib 20 mg/g (green) twice daily.

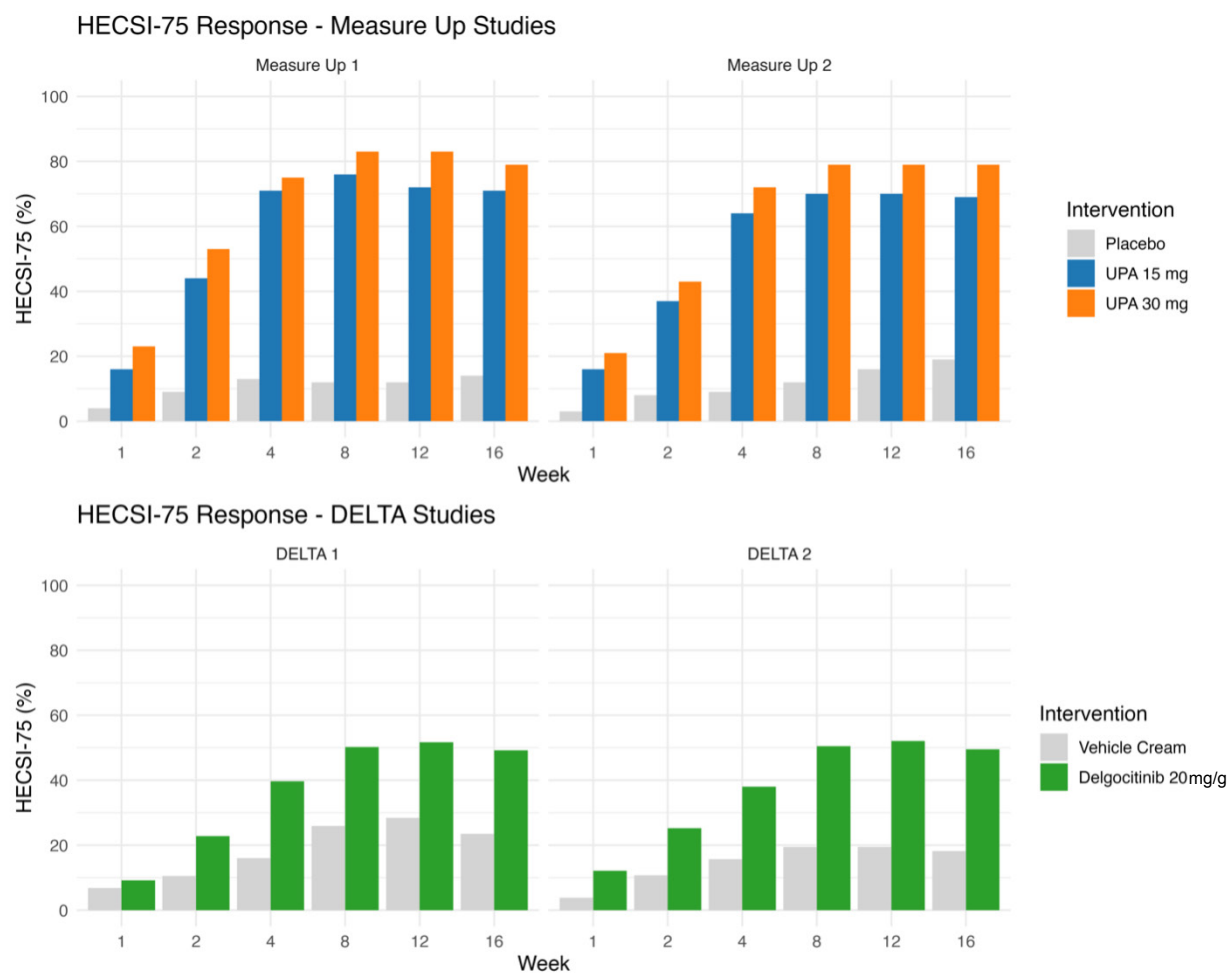


TABLE 1.

HECSI-75 response rates from Measure Up Phase-3 trials for UPA, and DELTA Phase-3 trials for delgocitinib. PBO, Placebo; P, P-value														
Timepoint	Measure Up 1				Measure Up 2				DELTA 1			DELTA 2		
	PBO	UPA 15 mg	UPA 30 mg	P	PBO	UPA 15 mg	UPA 30 mg	P	Vehicle Cream	Delgocitinib 20 mg/g	P	Vehicle Cream	Delgocitinib 20 mg/g	P
Week 1	4%	16%	23%	<0.001	3%	16%	21%	<0.001	6.8%	9.2%	0.36	3.8%	12.1%	0.003
Week 2	9%	44%	53%	<0.001	8%	37%	43%	<0.001	10.5%	22.8%	0.001	10.7%	25.2%	<0.001
Week 4	13%	71%	75%	<0.001	9%	64%	72%	<0.001	16%	39.7%	<0.001	15.7%	38%	<0.001
Week 8	12%	76%	83%	<0.001	12%	70%	79%	<0.001	25.9%	50.2%	<0.001	19.5%	50.5%	<0.001
Week 12	12%	72%	83%	<0.001	16%	70%	79%	<0.001	28.4%	51.7%	<0.001	19.5%	52.1%	<0.001
Week 16	14%	71%	79%	<0.001	19%	69%	79%	<0.001	23.5%	49.2%	<0.001	18.2%	49.5%	<0.001

significantly higher than vehicle (~18% to 23%; $P < 0.0001$), but below the 69% to 79% sustained responses reported with UPA in the Measure Up trials ($P < 0.001$).^{17,18} (Figure 2; Table 1). However, these are indirect comparisons across trials with differing indications, designs, patient populations, and endpoints, and no head-to-head study between UPA and delgocitinib has been conducted in CHE. Importantly, the UPA trials evaluated hand involvement as part of broader atopic dermatitis, likely capturing primarily atopic CHE, whereas the delgocitinib trials enrolled patients with multiple CHE subtypes, of which only approximately 35% were AD-related.

Real-World Experience with UPA in Treating CHE

Several published case reports demonstrated the effectiveness of UPA in treating CHE regardless of the etiology (irritant/allergic contact dermatitis or atopic dermatitis).^{19,20} A real-world study from the BioDay registry demonstrated that UPA effectively improved both AD and concomitant CHE, supporting its use in patients with CHE.²¹ Here we describe 3 case reports by the authors:

Case Report 1: 50-Year-Old White Male

A 50-year-old White male orthopedic surgeon with severe occupational-related CHE exhibited inadequate response to high-potency topical corticosteroids and 4 months of injectable dupilumab therapy (blockade of IL-4 and IL-13 signaling via binding IL-4R α). Patch testing identified multiple allergic contact dermatitis allergens, including carbamix, linalool, propolis, and methylisothiazolinone/methylchloroisothiazolinone, prompting targeted allergen avoidance. Despite these adjustments, minimal improvement was achieved (Figure 3A, 3B). Upon initiating UPA 15 mg monotherapy, the patient reported significant symptomatic relief within 48 hours. After 3 months, substantial clinical improvement was evident, and a marked reduction in CHE severity (Figure 3C). Although mild residual dermatitis persisted, functional impairment was completely resolved, allowing the patient to comfortably resume surgical activities.

FIGURE 3. Clinical improvement in CHE following treatment with UPA 15 mg daily in a 50-year old White male orthopedic surgeon. Panels A and B show the patient's hands prior to initiating UPA, with visible erythema, fissuring, and inflammation. Panel C shows marked improvement after 3 months of treatment. *Photos courtesy of Walter Liszewski MD.*



Case Report 2: 72-Year-Old Asian Male

A 72-year-old Asian male with a 20-year history of severe AD and extensive hand involvement showed limited response to prior biologic therapies (Figure 4A). After 6 months of dupilumab and 3 months of tralokinumab, he achieved only partial improvement in AD signs and symptoms. He was then transitioned to UPA 15 mg once daily. Within 2 weeks, the patient reported substantial reduction in pruritus and inflammation, with impressive improvement in hand eczema. After 1 year of continuous treatment, the patient achieved near-complete clearance of hand lesions, as evidenced by the attached photographs (Figure 4B), along with sustained, optimal outcomes in overall skin clearance and itch relief.

FIGURE 4. Clinical response to UPA 15 mg in a 72-year-old Asian male patient with severe AD and concomitant CHE, showing marked improvement. Panel A shows active CHE at baseline prior to treatment, characterized by erythema, lichenification, and scaling. Panel B shows near-complete clearance of hand lesions after 1 year of treatment. *Photos courtesy of Henry Yu PA-C.*



Case Report 3: 78-Year-Old African American Male

A 78-year-old African American male with a 6-year history of severe excoriated, cracked, fissured and eroded skin on the hands (Figure 5A) presented after receiving intramuscular kenalog every 2 to 4 months from his prior dermatologist requesting another dose. He had failed topical corticosteroids and calcineurin inhibitors and was informed that chronic systemic corticosteroids were a dangerous maintenance plan

FIGURE 5. Clinical resolution of CHE following treatment with UPA 15 mg once daily in 78-year-old African American patient. Panel A shows the patient's hands at baseline, with scaling, excoriations, fissures, and erosions. Panel B shows complete clearance of lesions and resolution of inflammation after 4 weeks of UPA treatment. *Photos courtesy of Diego Dasilva MD.*



and not recommended based on the most recent AAD guidelines. The patient declined biologic therapy given the frequency of injections. He was diagnosed with CHE and started on UPA 15 mg once daily, and at his 4-week follow-up, he had complete lesion clearance and resolution of pruritus/pain (Figure 5B). He has remained on UPA 15 mg for the last 2 years and denies any AEs or flares in that timeframe.

DISCUSSION

CHE presents significant management challenges, particularly in patients with refractory disease despite appropriate initial therapies, including topical JAK inhibitors. Ruxolitinib is a topical JAK1/JAK2 inhibitor that has shown promising efficacy for moderate-to-severe CHE in a phase-2 multicenter, randomized, double-blind study; however, additional evidence from larger-scale phase 3 studies is needed to substantiate its clinical benefit.^{10,11} Delgocitinib, a topical pan-JAK inhibitor, has shown efficacy in treating moderate-to-severe CHE in phase 3 clinical trials.¹⁸ However, while topical therapies – in general – remain the first-line treatment for isolated CHE, their long-term effectiveness is often limited by several factors. One key limitation is tachyphylaxis, a phenomenon in which the therapeutic effect of a topical agent diminishes rapidly with continuous or repeated use. This may result from local receptor desensitization, downregulation of inflammatory pathways, or altered skin barrier dynamics that impair drug penetration or responsiveness over time.²² Poor adherence is another major barrier, driven by the need for frequent application, concerns about local side effects, and treatment fatigue. In CHE specifically, the hands are subject to constant washing, friction, and exposure to irritants, which can physically remove or disrupt topical agents, reducing efficacy. Moreover, some formulations may be impractical for daytime use due to greasiness or interference with daily activities, especially in patients who rely on their hands for work or caregiving. These limitations highlight the challenges of achieving sustained disease control in moderate-to-severe CHE with topicals alone, underscoring the need for alternative or adjunctive systemic therapies in some patients. Several studies strongly suggest that patient adherence to oral dermatological drugs is better than adherence to topical drugs.²³⁻²⁵

UPA, an oral selective JAK1 inhibitor, represents a promising systemic agent in the management of CHE. Results from phase 3 clinical trials demonstrated rapid and sustained improvement in atopic hand eczema, a common subtype of CHE, through week 16 for both UPA 15 mg and 30 mg monotherapy.⁵ Similarly, a prospective observational study demonstrated that over 60% of patients with moderate-to-severe hand eczema achieved clear or almost clear skin within 4 weeks of initiating treatment with UPA.²⁶ Moreover, as illustrated by the presented 3 clinical cases, patients with refractory CHE may experience symptom relief as early as 48 hours after UPA initiation. These findings collectively suggest that UPA is an effective systemic treatment option for

patients with AD-associated CHE, including in patients with skin of color. Not only does UPA demonstrate high efficacy, but it also maintains a reassuring long-term safety profile. In the long-term extension clinical trial of patients with moderate-to-severe AD for up to 5 years of exposure, UPA was associated with low rates of adverse events of special interest, which is consistent with the short-term profile.^{14,16,27} These observations are strengthened by additional safety data spanning more than 15,000 patient-years across different indications, which confirm UPA's overall safety.²⁸ These findings indicate that with appropriate monitoring, UPA represents a safe and effective systemic therapy for patients with CHE when topical options are not viable.

Although no formal guidelines exist specifically for UPA use in CHE, treatment protocols can draw from established recommendations in AD. A starting dose of 15 mg once daily is generally recommended for most adults, with the option to increase to 30 mg for severe or refractory disease.²⁹

CONCLUSION

The selective JAK1 inhibitor upadacitinib demonstrates rapid, sustained efficacy in treating chronic hand eczema, supported by clinical trial data and real-world experience. Its once-daily oral dosing offers potential adherence advantages over topical treatments, which may be limited by treatment burden and application challenges.

DISCLOSURES

CGB has served as an investigator or consultant for AbbVie, Incyte, LEO Pharma, Regeneron, and Sanofi.

WL has served as an investigator and/or consultant for AbbVie, Regeneron, Sanofi, Novartis, Incyte, Arcutis, Lilly, and Galderma.

BS has served as a paid consultant for AbbVie, Arcutis, Castle Biosciences, Novartis, Ortho Dermatologics, Sanofi, and UCB; also a member of the speaker bureau for AbbVie, Sanofi, and UCB.

DD has served as a speaker or consultant for AbbVie, Pfizer, LEO Pharma, Regeneron, Sanofi, UCB, Dermavant, Arcutis, Lilly, Galderma, and Verrica.

AM has served as a speaker for Sanofi/Regeneron, AbbVie, Dermavant, Arcutis, Lilly, LEO Pharma, Bristol-Myers Squibb, Amgen, Pfizer, and Galderma.; as a consultant for Sanofi/Regeneron, AbbVie, Dermavant, Arcutis, Lilly, LEO Pharma, Bristol-Myers Squibb, Amgen, Pfizer, Incyte, Janssen, and Novartis; and participated in research or served as an investigator for AbbVie, Dermavant, Amgen, Lilly, Janssen, and Galderma.

FG has served as an investigator or consultant for AbbVie, Incyte, and LEO Pharma.

HY has served as a consultant, advisory board member, speaker, and/or researcher for AbbVie, Amgen, Arcutis, Boehringer-Ingelheim, Bristol-Myers Squibb, Dermavant, Ferndale, Galderma, Incyte, J&J, LEO Pharma, Ortho Dermatologics, Pfizer, Regeneron, Sun Pharma, and UCB.

OA, LS, ID, SW, and SO have no conflicts of interest to declare.

Patient Consent: At the time of article submission, the authors confirmed that all patients provided informed consent for the publication of their photographs and medical information, with the understanding that such materials may appear in both print and online formats and may be publicly accessible.

ACKNOWLEDGMENT

We thank Walter Liszewski MD, Henry Yu PA-C, and Diego Dasilva MD for generously providing the clinical case reports and photographs used in Figures 3, 4, and 5, respectively.

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Alopecia Areata in Skin of Color: Trichoscopic Analysis in Black/African American Patients

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ABSTRACT

Importance: Alopecia areata (AA) has a higher prevalence in populations with skin of color, yet the trichoscopic features in this population remain underexplored.

Objective: To identify trichoscopic findings present in a cohort of Black patients with a diagnosis of alopecia areata.

Evidence Review: The electronic medical records system was used to retrospectively analyze the trichoscopic images and medical records of 10 Black patients with a clinical diagnosis of AA who were seen and treated at an academic hair loss clinic between 2019 and 2024. Clinical and trichoscopic images of the scalp were reviewed independently by two board-certified dermatologists. Statistical analysis using the Mann-Whitney U Test highlighted significant trends in the occurrence of these features across varying severity levels as per the Severity of Alopecia Tool (SALT) scores.

Findings: Commonly reported features such as vellus hairs, black dots, and tapering hairs, alongside novel features including peripilar hyperpigmentation, follicular hypopigmentation, diffuse erythema, uninterrupted honeycomb patterns, and perifollicular scale were observed. No statistical significance was noted between the presence of trichoscopic features and the correlated SALT score.

Conclusions and Relevance: This study underscores the need for improved understanding and documentation of AA in Black individuals. Identification of trichoscopic features in AA will aid physicians with diagnosis and decrease the threshold for diagnosis of co-existing alopecias.

J Drugs Dermatol. 2025;24(7):708-712. doi:10.36849/JDD.9139

INTRODUCTION

Alopecia areata (AA) is a chronic autoimmune disease that results in non-scarring, patchy hair loss on the scalp and other parts of the body.¹ It affects individuals of all races; however, recent evidence suggests there is a higher prevalence in people with skin of color.² Despite this prevalence, trichoscopic features of AA in skin of color remain underexplored,³ especially amongst cases of Black patients.⁴ Although there is one case series examining trichoscopic features of AA in 116 Indian patients,² there are only two published cases of AA in the literature that include trichoscopy images of Black/African American patients.^{3,4} Both of these cases demonstrate normal findings of a diffuse honeycomb-pigmented network with pinpoint white dots. Considering the lack of consistent documentation of AA cases in Black patients, the variability in trichoscopic presentations makes it challenging to clinically differentiate AA from other types of alopecias.⁶ Thus, we analyze and document the trichoscopic features of AA in Black/African American patients to better characterize its presentation in this population.

MATERIALS AND METHODS

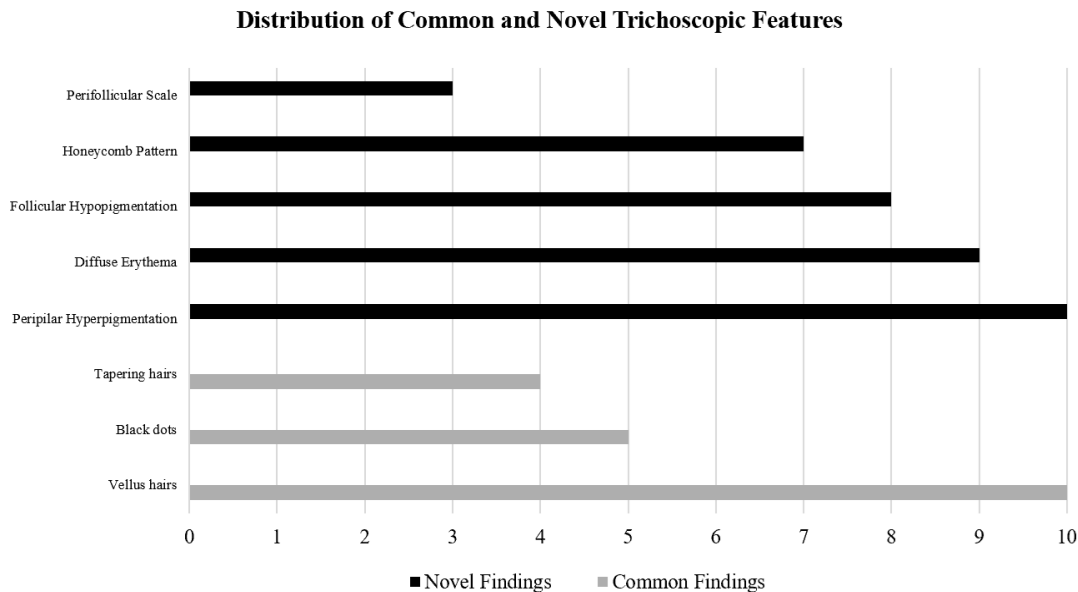
We retrospectively analyzed the clinical images, trichoscopic images, and medical records of 10 Black patients with a clinical diagnosis of AA who were treated at an academic hair loss clinic between 2019 and 2024. Trichoscopic features were categorized as either commonly reported features of AA (vellus hairs, black dots, tapering hairs, yellow dots) or novel features—those not typically seen in AA. The Mann-Whitney U Test was used to determine statistical significance. Baseline Severity of Alopecia Tool (SALT) scores were calculated using clinical images of the scalp.

RESULTS

Distribution of Common and Novel Trichoscopic Features:

Vellus hairs were present in all patients. Black dots and tapering hairs were also observed, appearing in 5 (50%) and 4 (40%) patients, respectively. No yellow dots were observed in this group (Figure 1).

FIGURE 1. Distribution of common trichoscopic features observed in 10 Black/African American patients with alopecia areata.



Novel trichoscopic features included peripilar hyperpigmentation (100%), follicular hypopigmentation (80%), diffuse erythema (90%), uninterrupted honeycomb pattern (70%), and perifollicular scale (30%) (Figure 1).

When trichoscopic features were evaluated by SALT score, vellus hairs, peripilar hyperpigmentation, and follicular

hypopigmentation were present in all SALT categories ($P>0.05$). Black dots and tapering hairs are present in all categories, with the greatest being in SALT>50. A homogenous honeycomb pattern was observed in all categories, whereas diffuse erythema was observed in moderate (SALT 21-49) and severe (SALT >50) disease. (Figures 2-3; Table 1).

FIGURE 2. Common and novel trichoscopic findings according to the SALT score.

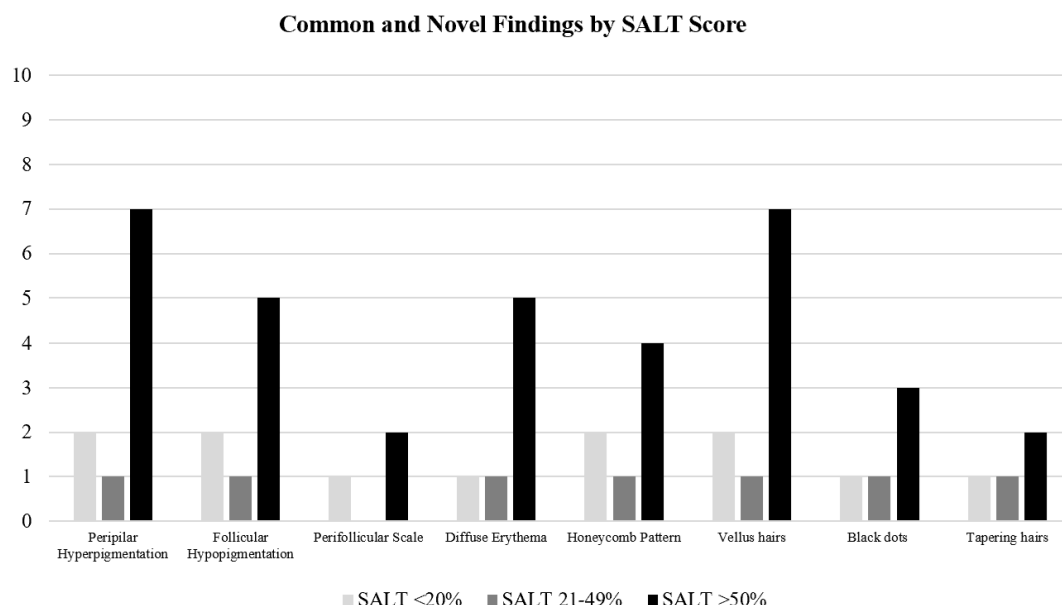


TABLE 1.

Demographics of Black/African American Patients With Alopecia Areata According to Severity of Alopecia Tool (SALT) Score							
Age	Sex	Length of Diagnosis (years)	Comorbidities	Medications for AA at Time of Study	Common Features	Novel Features	SALT Score
53	F	1	Acne vulgaris, seborrheic dermatitis, hand dermatitis, pseudofolliculitis barbae, HS, morbid obesity, GERD, depression, chronic back pain, HTN, DM	Ultra-high potency steroid, ILS	Vellus hairs, black dots, tapering hairs	Peripilar hyperpigmentation, follicular hypopigmentation, honeycomb pattern	<20
36	F	3+	Atopic dermatitis, acne vulgaris	Ultra-high potency steroid, ILS, topical JAKi to eyebrows, oral JAKi		Peripilar hyperpigmentation, follicular hypopigmentation, honeycomb pattern, Perifollicular scale	
14	M	8	N/A	Ultra-high potency steroid, pulse prednisone, ILS, topical minoxidil, oral minoxidil	Vellus hairs, black dots, tapering hairs	Peripilar hyperpigmentation, follicular hypopigmentation, diffuse erythema, honeycomb pattern	21-49
40	F	9	Nodulocystic acne, Nodular thyroid disease	Oral JAKi and oral minoxidil	Vellus hairs, black dots, tapering hairs	Peripilar hyperpigmentation, follicular hypopigmentation, diffuse erythema, honeycomb pattern, perifollicular scale	>50
17	M	6	N/A	Ultra-high potency steroid, ILS, topical minoxidil	Vellus hairs, tapering hairs	Peripilar hyperpigmentation, follicular hypopigmentation, diffuse erythema	
40	F	37	Acne vulgaris, hypothyroidism, HTN, depression	Oral JAKi and oral minoxidil	Vellus hairs, tapering hairs	Peripilar hyperpigmentation, follicular hypopigmentation, diffuse erythema, honeycomb pattern	
55	F	10+	N/A	Topical minoxidil, methotrexate, ultra-high potency steroid	Vellus hairs	Peripilar hyperpigmentation, diffuse erythema, honeycomb pattern	
21	F	12	N/A	Oral JAKi	Vellus hairs, black dots, tapering hairs	Peripilar hyperpigmentation, follicular hypopigmentation, diffuse erythema, honeycomb pattern	
16	M	6	Acne vulgaris				
10	F	1	Acne vulgaris, atopic dermatitis	Topical minoxidil, ultra-high potency steroid	Vellus hairs, black dots	Peripilar hyperpigmentation	

ILS= intralesional steroid; JAKi= Janus Kinase Inhibitor; HS= Hidradenitis Suppurativa; GERD= gastroesophageal reflux disease, HTN= hypertension, DM= Diabetes mellitus

This review is limited by a lack of trichoscopic correlation with histopathology. Additionally, the small sample size featured in this study may preclude the generalizability of the findings. However, the findings prompt a larger investigation into trichoscopic features on the scalps of different skin phenotypes.

DISCLOSURES

Dr Amy McMichael has received grants or research support from Concert, Procter & Gamble, Incyte, and Revian. She has served as a consultant for Lilly, Janssen, Pfizer, Arcutis, Almirall, AbbVie, CeraVe, Galderma, Bristol Myers Squibb, Kenvue, Sanofi Regeneron, Sun Pharma, UCB, Pelage, Procter & Gamble, Revian, Johnson & Johnson, L'Oréal, Leo, and Canfield. She also receives royalties from Informa/Taylor and Francis and McGraw-Hill. Authors Pyles, Palmer, Balding, and Larrondo report no conflicts of interest.

IRB Approval Status: Reviewed and approved by Wake Forest University Health Sciences; IRB approval # IRB00117708

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Dermatological Procedures as Gender-Affirming Care: Reframing “Cosmetic” Care Among Transgender Men and Women

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INTRODUCTION

Dermatological procedures such as Botox and injectable dermal fillers are commonly pursued by members of the LGBTQ+ community and are frequently depicted as being sought out only for “cosmetic” or aesthetic purposes.^{1,2} Studies have shown that these noninvasive procedures can function as crucial components of life-saving gender-affirming care among transgender patients. However, no studies to date have specifically evaluated reasons for dermatology procedure seeking among transgender patients. This study sought to evaluate which dermatological procedures are most pursued by transgender patients and their reasons for acquiring dermatological care.

An IRB-approved survey (NCR235235) was emailed via SurveyMonkey to participants in the platform’s Contribute and Rewards Panels. ANOVA and independent samples t-tests were used for statistical analysis and frequency distribution calculations. Respondents who received dermatological procedures, including Botulinum toxin (Botox), injectable

fillers, PRP injections, laser therapy, microdermabrasion, chemical peel, microneedling, silicone injection, sclerotherapy, radiofrequency, CoolSculpting, carboxytherapy, and surgical fat reduction, were included in the data analysis. The survey was sent to a total of 2,880 participants, and 2,275 responded, for a response rate of 79%. Of the remaining respondents, 516 reported receiving dermatological procedures, 138 identified as transgender, with a distribution of 86 transgender men and 52 transgender women.

Of the 138 transgender respondents, 81.9% stated that their personal experiences with gender dysphoria played a role in their decision to seek out dermatological procedures. Transgender men were significantly more likely than transgender women to seek out dermatological care due to gender dysphoria and for the purpose of gender-affirming care (Table 1). The most common individual factors influencing transgender patients’ decisions to seek out dermatological procedures include gender-affirming care, boosting self-esteem, and facial feminization or masculinization (Table 1).

TABLE 1.

Summary of Factors Influencing Transgender Men (N=86) and Transgender Women (N=52) in the Pursuit of Dermatological Procedures			
	Transgender Men	Transgender Women	P-value
Individual Factors			
Gender dysphoria	53.6% (74/138)	23.9% (33/138)	0.0041*
Gender-affirming care	24.6% (34/138)	9.4% (13/138)	0.019*
Facial feminization or masculinization	22.5% (31/138)	13.0% (18/138)	1.00
Boost self-esteem	40.6% (56/138)	16.7% (23/138)	0.00565*
Social Factors			
Social pressure	37.7% (52/138)	14.5% (20/138)	0.0442*
Fit in with others	15.2% (21/138)	6.52% (9/138)	0.0197*
Told by others	7.25% (10/138)	11.6% (16/138)	0.0104*
Appear youthful	36.2% (50/138)	13.0% (18/138)	0.0123*

*denotes P-value <0.05.

Transgender individuals also sought dermatological care for social reasons such as fitting in with others, social pressure, appearing youthful, and being told by others to receive the procedures (Table 1). When asked what is considered “beautiful” in the LGBTQ+ community, most transgender men answered muscular (54.7%, 47/86) while transgender women were more likely to choose thin (42.3%, 22/52) and youthful (30/52, 57.7%).

Our study found that both individual experiences with gender dysphoria and sociocultural factors play a role in transgender patients’ decisions to seek out dermatological procedures such as Botox and injectable fillers. Among transgender men, the increased rates of gender dysphoria and pressure to fit into traditionally masculine physical traits (ie, muscular) suggest that hypermasculine standards of beauty may exacerbate their gender dysphoria and consequently lead to increased rates of procedure seeking as a component of their gender-affirming care. Our study demonstrates that these unrealistic sociocultural standards may negatively impact self-esteem and the pursuit of dermatological procedures as components of gender-affirming care can function to boost mental health among transgender men and women. These results help redefine how dermatological procedures among transgender patients should not be considered solely “cosmetic,” but rather as powerful tools to help address both individual struggles with gender dysphoria and sociocultural stressors associated with transitioning.

DISCLOSURES

The authors have no financial or nonfinancial conflicts of interest to disclose.

IRB approval status: Reviewed and approved by GW IRB; approval #NCR235235.

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Utilization of a Heatmapping Python Program to Visualize Improvements of Skin Hydration After Use of a Moisturizing Lotion or Cream

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ABSTRACT

Dry skin is both extremely common and an important concern for those who suffer from it. In addition to uncomfortable signs and symptoms, dry skin can be associated with pigmentary changes in individuals with darker skin types. This small single-center study applied a split-body methodology to compare the hydrating effects of a gentle moisturizing lotion vs a gentle moisturizing cream on arms over a 4-week period. Corneometry and digital photography were used to compare changes in skin hydration, and heatmaps were generated to visualize changes and augment the visible results seen in photography. Both the lotion and cream effectively achieved a rapid and sustained improvement in skin hydration. The products were well tolerated, with no adverse events reported.

J Drugs Dermatol. 2025;24(7):715-720. doi:10.36849/JDD.9147

INTRODUCTION

Maintaining good hydration is an essential part of healthy skin. Skin hydration has been primarily assessed on facial skin; however, many individuals suffer from dry skin on additional areas of the body. Visually, this can be appreciated by roughness, flaking, or scaling (sometimes described as an “ashy” look in darker skin types). Sufferers may experience itchiness and even skin fissures. Symptoms and signs can vary based on age, health status, skin phototype, and environmental exposures. The American Academy of Dermatology (AAD) recommends applying moisturizers within a few minutes after cleansing, with the goal of trapping moisture.¹ Further, the AAD suggests using ointments, creams, or lotions with the caveat that ointments and creams may be more effective and less irritating than lotions.¹ Because patients have preferences for the type of formulation they wish to use (cream, ointment, or lotion), this study compares the moisturizing effects of a gentle lotion vs a cream to determine whether there may be differences in this particular product line’s formulation types.²

Additional formulation differences, including preferred ingredients, can be very important in managing dry skin. This study evaluates two products that contain glycerin, panthenol, and niacinamide. Glycerin, a natural substance that is one of the skin’s natural moisturizing factors (NMFs), acts as a humectant and attracts water into the skin’s stratum corneum.³ Glycerin also helps with retention of internal moisture within skin, which also enhances skin barrier function and overall skin health. It readily diffuses into skin and is a gentle, versatile ingredient

that provides beneficial effects across a wide range of skin types. In 2020, Proksch et al summarized a meeting of specialists in dry skin management, encouraging the incorporation of humectants into topical emollients for patients with dry skin to help boost the activity of enzymes and NMFs in skin.⁴ Panthenol (vitamin B₅) is a humectant that can enhance the production of cutaneous lipids and fibroblasts, translating to a stronger epidermal barrier.⁵ Panthenol can also mitigate skin irritation and has anti-inflammatory actions.⁵ Products that incorporate niacinamide can safely and effectively enhance skin brightness and overall skin appearance; niacinamide also helps smooth skin texture/roughness and restores the skin barrier.⁶

While hydration is important for all skin types, individuals with skin of color have a higher propensity for sequelae such as dyspigmentation.⁷ Indeed, when present, postinflammatory pigmentary changes may be more concerning to the patient than the dry skin itself.⁸ Therefore, the individual’s skin type should influence the management strategy in regards to moisturizing product timing of initiation, ingredients, and product formulation.

The goal of this study was to visualize skin hydration via heatmap (colormap) on extremities in a variety of skin types, as was shown in a prior study of heatmapping facial skin after use of skincare products.⁹ As with facial skin, understanding hydration on other bodily areas can be challenging due to environmental exposures (humidity, sunlight, and pollution) that affect water retention/loss.¹⁰ As discussed by Voegeli et al, single-point measurements of skin hydration may not provide

an accurate bio-instrumental evaluation.¹⁰ This has led to the implementation of heatmaps, a methodology that incorporates multiple data points into colorized images that correspond to corneometry readings and allow relatively simple visualization of differences.¹⁰

MATERIALS AND METHODS

In this 4-week split-body study, both moisturizing lotion or cream (Cetaphil® Moisturizing Lotion [ML] or Cetaphil® Moisturizing Cream [MC], Galderma LLP, Dallas, TX) were applied to each participant’s arms (each to one randomly assigned arm per product) at least once daily and reapplied as needed. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants provided written informed consent.

Assessments were performed at baseline, 30 minutes post-application, week 1, and week 4, with hydration measurements taken by Corneometer (Courage + Khazaka electronic GmbH, Germany) at 30 predefined points around the elbow (Figure 1). Additional assessments included standardized photography of the test area by VISIA-CR (Canfield Scientific, Inc, NJ), macroscopic imaging of the test area by Dino-Lite Microscope (AnMo Electronics Corporation, Taiwan), and standard safety assessments.

Pycharm, a Python programming software (JetBrains, Prague, Czech Republic), was used to interpolate hydration values to colors, along with Adobe® Illustrator® and Adobe® Photoshop® (Adobe Inc, San Jose, CA) to blend colors into a gradient heatmap. A rainbow color scale was applied in which colors trending toward green-blue indicated greater hydration, while those with more yellow-red tones indicated more dryness.

FIGURE 1. Points of measurement with the corneometer.



RESULTS

In this small imaging study, 7 participants with dry skin were enrolled, of which 5 participants completed the 4-week assessment period, with demographics shown in Table 1. Of note, the participant population was diverse in Fitzpatrick skin type, race/ethnicity, and age, and the majority of participants were female.

Figures 2 through 4 present clinical imaging results for participants in the study. Visible changes from dry skin to greater hydration were apparent in all images.

Both products were safe for application, and no adverse events were reported during the study.

TABLE 1.

Participant Demographics				
	Gender	Fitzpatrick Skin Type	Race/Ethnicity	Age
Participant 1	Female	V	African American	27
Participant 2	Female	IV	Middle Eastern	27
Participant 3	Female	VI	African American	39
Participant 4*	Female	I	Caucasian	N/A
Participant 5	Male	III	Asian	51
Participant 6	Female	II	White/Caucasian	25
Participant 7#	Female	II-III	Hispanic	47

*Participant 4 completed baseline and 1-week assessments; #Participant 7 only completed baseline and 3-week assessments.

FIGURE 2. Heatmap and macroscopic imaging of a participant with skin type V showing changes from baseline to week 4.

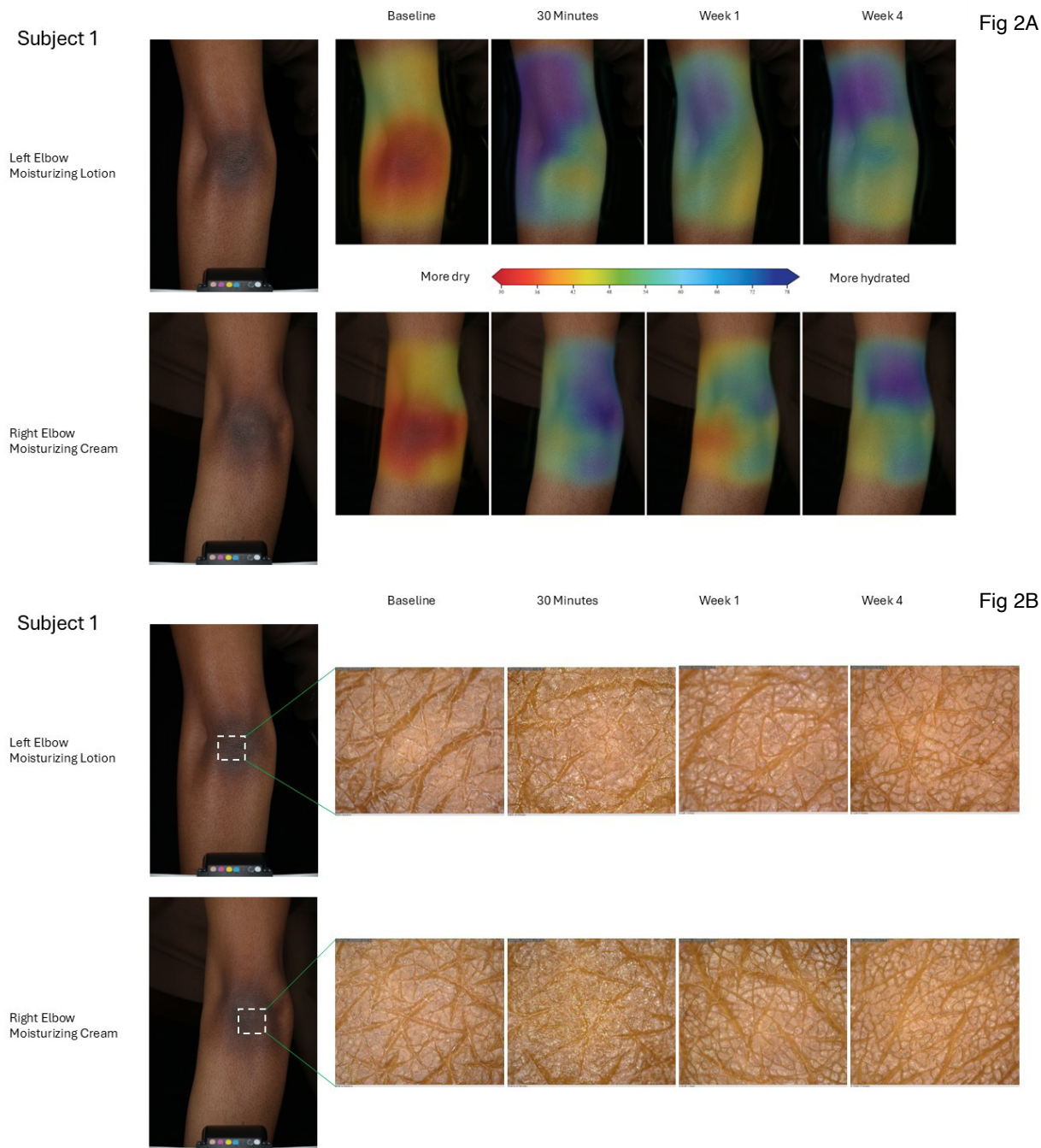


FIGURE 3. Heatmap and macroscopic imaging of participants with skin type III.

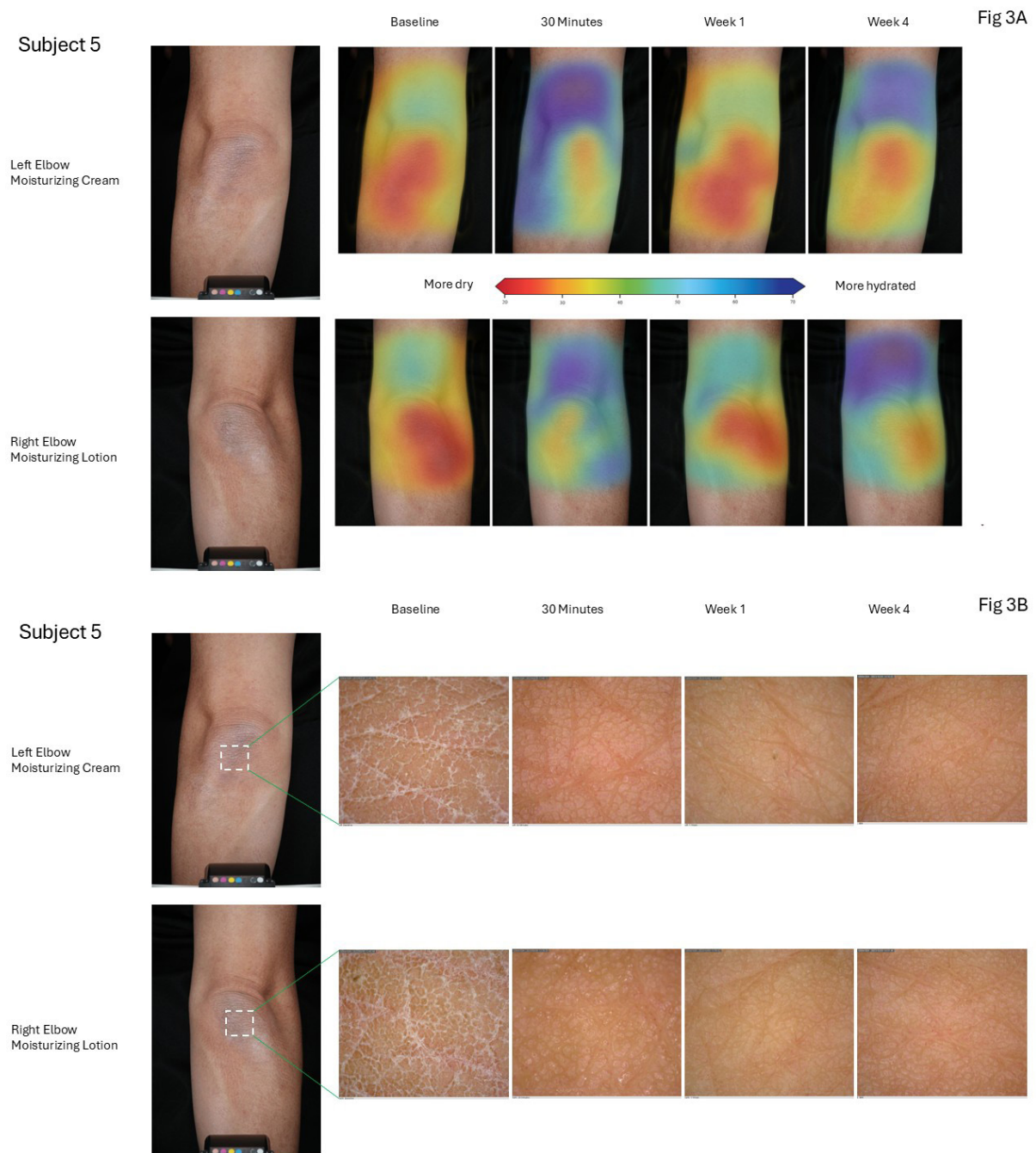
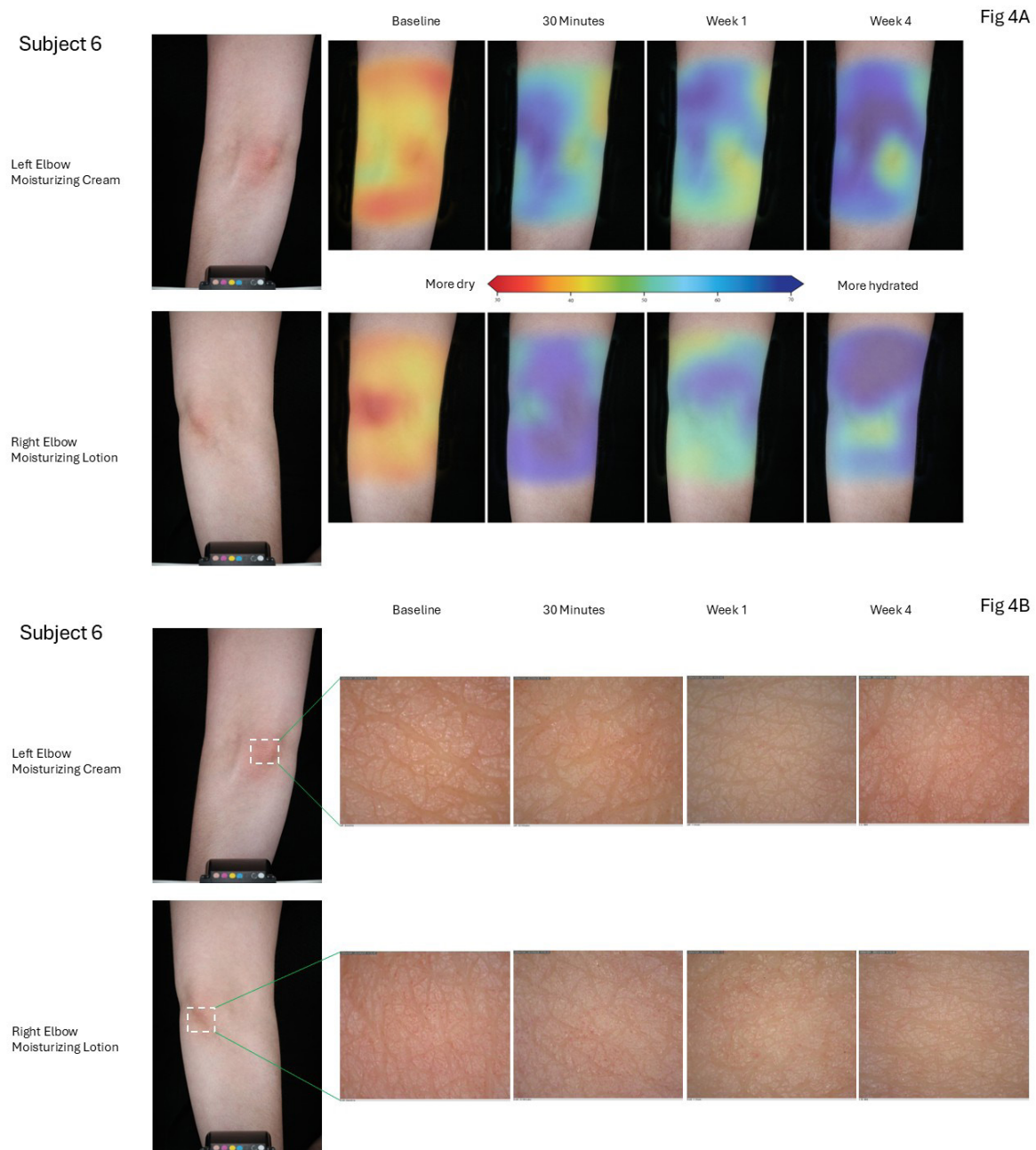


FIGURE 4. Heatmap and macroscopic imaging of a participant with skin type II.



DISCUSSION

As shown in the images, increases in hydration after product application were demonstrated at 30 minutes, 1 week, and 4 weeks of usage via clear color shifts from yellow-red to green-blue. Both ML and MC were associated with a rapid and long-term improvement in hydration in participants with a range of skin phototypes and ages. Notably, the skin of the elbow tends to be drier than surrounding areas, and the tested ML and MC both improved hydration in this area, which can be hard to treat.

Heatmaps are valuable to allow visualization of hydration results in a readily appreciable format, to incorporate data about larger skin areas, and facilitate interpretation of skin health. Heatmapping results have been reported for facial hydration, but less commonly hydration of skin on extremities.⁹ We feel the use of this technique adds an important facet to the understanding of both skin dryness and hydration that remains somewhat poorly understood. Improvements in skin hydration translate to improvements in skin texture. In our study, the skin around the elbow appeared smoother and healthier as demonstrated by macroscopic imaging.

While formulation differences can be important with moisturizers, this study showed that this product line’s lotion and cream, incorporating glycerin, panthenol, and niacinamide, both effectively improved hydration. This is useful for clinicians to be aware of, since individuals have varying preferences in the type of formulations they prefer to use. Further, these preferences may change somewhat throughout the year, along with the seasons.

DISCLOSURES

The authors are employees of Galderma Laboratories, LP.

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Current Use of Neoadjuvant Hedgehog Inhibitors Among Mohs Surgeons: Results of a Cross-Sectional Survey

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ABSTRACT

Recent studies have demonstrated functional and cosmetic benefits with the use of hedgehog pathway inhibitors in the neoadjuvant setting for basal cell carcinoma (BCC). This study investigated the current use of neoadjuvant therapy by Mohs surgeons for the treatment of BCC with an anonymous REDcap survey distributed to members of the American College of Mohs Surgery. In the study population, a considerable percentage (22%) of Mohs surgeons reported current use of neoadjuvant hedgehog inhibitors for BCC prior to Mohs surgery. Among this group, there is wide variation in BCC size, location, target tumor size reduction, and average length of therapy for their use of neoadjuvant hedgehog inhibitors prior to Mohs surgery. Concerns about adverse effects and creating a discontinuous tumor were the most cited reasons not to treat patients with neoadjuvant hedgehog inhibitors prior to Mohs surgery. Given there is better tolerability of hedgehog pathway inhibitors when used for shorter treatment duration, hedgehog pathway inhibitors may be most useful in the neoadjuvant setting to maximize clinical benefit and minimize toxicity.

J Drugs Dermatol. 2025;24(7):722-723. doi:10.36849/JDD.9105

INTRODUCTION

Recent studies have demonstrated functional and cosmetic benefits with the use of hedgehog pathway inhibitors in the neoadjuvant setting for basal cell carcinoma (BCC). In one open label study, investigators demonstrated a mean decrease in surgical defect size by 27% for locally advanced BCCs with 3 months of treatment with vismodegib.¹ In the VISMONEO neoadjuvant study, investigators found a 29% to 66% size reduction in high risk BCCs after treatment with vismodegib for 4 to 10 months.² And in the 27 patients who underwent surgery in the VISORB neoadjuvant trial for BCCs threatening the lacrimal drainage system, 67% of patients had no histologic evidence of disease during subsequent surgical intervention.³ Promising results in the literature have led Mohs surgeons to incorporate vismodegib as a neoadjuvant tumor modifying agent prior to definitive Mohs surgery. The purpose of this study is to investigate the current use of neoadjuvant therapy by Mohs surgeons for the treatment of BCC.

METHODS

An anonymous REDcap survey was approved by the American College of Mohs Surgery (ACMS) executive committee and distributed to its members via their seasonal ACMS newsletter. Participants who completed the survey and reported use of neoadjuvant hedgehog pathway inhibitors prior to Mohs surgery answered follow-up multiple choice and free-text questions about parameters for use. Participants who reported

not using neoadjuvant hedgehog pathway inhibitors prior to Mohs surgery answered yes/no questions about reasons they were hesitant to use hedgehog inhibitors. Differences between groups were analyzed with chi-square and t-tests with statistical significance defined as $P < 0.05$.

RESULTS

A total of 50 participants completed the survey (mean age 45±10, 30 [60%] male, 35 [70%] in private practice). A total of 11 (22%) participants reported current use of neoadjuvant hedgehog inhibitors prior to Mohs surgery. Regarding size, 4/11 (36%) reported initiating hedgehog pathway inhibitors for BCCs greater than 3.0 cm and 7/11 (64%) reported size was not a factor in decision to use hedgehog pathway inhibitors. Regarding location, 2/11 (18%) participants reported use for tumors in area H of the Mohs appropriate-use criteria, 5/11 (45%) reported use in tumors with periocular involvement, and 4/11 (36%) reported location was not a factor. For target reduction in tumor size prior to Mohs surgery, 1/11 (9%) participants reported 21-30%, 4/11 (36%) participants reported greater than 30%, and 6/11 (55%) reported reduction in size was not a factor. For average length of therapy prior to Mohs surgery, 1/11 (9%) participants reported 1 to 2 months, 6/11 (55%) participants reported 3 to 4 months, and 4/11 (36%) participants reported 4 to 6 months. All participants reported vismodegib was the hedgehog pathway inhibitor of choice. The average number of BCC cases treated with neoadjuvant hedgehog pathway inhibitors per year was 2.36.

A total of 39 (78%) participants reported not currently using neoadjuvant hedgehog inhibitors prior to Mohs surgery. Among these participants, 15/39 (38%) reported discomfort prescribing and managing hedgehog pathway inhibitors, 29/39 (75%) reported concerns about creating a discontinuous tumor, 23/39 (59%) reported concerns about cost, 34/39 (87%) reported concerns about medication adverse effects, 15/39 (38%) reported concerns about patient compliance, and 13/39 (33%) reported lack of experience with hedgehog pathway inhibitors.

There was no statistically significant difference in age, sex, years in practice, region in practice, and practice setting between those who prescribe neoadjuvant hedgehog inhibitors prior to Mohs surgery and those who do not.

DISCUSSION

In the study population, a considerable percentage (22%) of Mohs surgeons reported current use of neoadjuvant hedgehog inhibitors for BCC prior to Mohs surgery. Among this group, there is wide variation in BCC size, location, target tumor size reduction, and average length of therapy for their use of neoadjuvant hedgehog inhibitors prior to Mohs surgery. Concerns about adverse effects and creating a discontinuous tumor were the most cited reasons not to treat patients with neoadjuvant hedgehog inhibitors prior to Mohs surgery. It is well known that the adverse effects of hedgehog inhibitors (most commonly muscle cramps, dysgeusia, and alopecia) often preclude long term use, however, short term use in the neoadjuvant setting may be better tolerated. In the aforementioned studies, 4/14 (29%), 7/55 (13%), 2/34 (6%) of patients discontinued vismodegib due to treatment related adverse effects.¹⁻³ These rates of discontinuation are considerably lower than in trials analyzing long term treatment with hedgehog inhibitors alone.⁴ It is also notable that in Kahana et al, most adverse reactions were reported after tumors had already clinically responded to therapy.³ Therefore, hedgehog inhibitors may be most useful in the neoadjuvant setting to maximize clinical benefit and minimize toxicity.³ Although this survey demonstrated a high level of concern for discontinuous tumor formation with the use of neoadjuvant hedgehog inhibitors prior to Mohs surgery, at the date of publication, there is no evidence of this phenomenon in the current literature. Limitations of our study include small sample size.

CONCLUSION

This cross-sectional survey of Mohs surgeons demonstrates the current widespread use of neoadjuvant hedgehog inhibitors prior to Mohs surgery. Although beneficial use has been demonstrated in multiple settings, no current guidelines exist. We hope this study leads to future publications regarding treatment guidelines for use of neoadjuvant hedgehog inhibitors prior to Mohs surgery.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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Large Multiethnic Comparison Benchmark of the Fitzpatrick and Monk Skin Tone Scales

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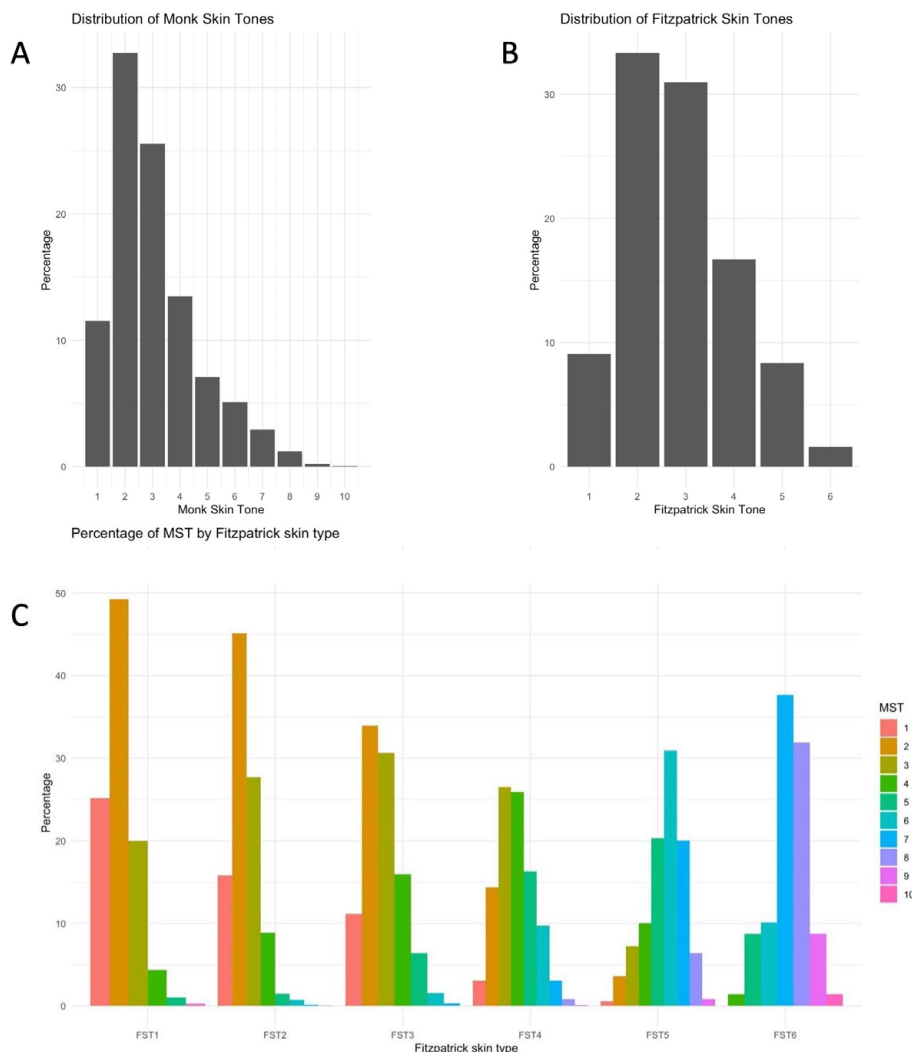
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To the Editor:

The Fitzpatrick scale (FST) was developed to classify skin types based on responses to ultraviolet light, but is now commonly used in dermatology as a surrogate for skin tone. The FST does not adequately account for the diversity in patients with skin of color (SOC), however, limiting its clinical utility.^{1,2,3} In response to these shortcomings, the Monk Skin Tone (MST) Scale, a 10-shade grading scale, was developed as a more inclusive skin tone assessment.⁴ However, the relationship between FST

and MST is not well known. While clinical validation of MST is limited, there are efforts by Google to use this scale to help train their artificial intelligence (AI) models. Recently, a partnership between Google and Stanford researchers generated the Skin Condition Image Network (SCIN) dataset, which includes extensive dermatological images from patients recruited from Google search advertisements.⁵ Our study utilizes this dataset to benchmark the relationship between FST and MST across different evaluators, ethnic backgrounds, and skin types.

FIGURE 1. (A) MST score distribution, (B) FST score distribution, (C) Percentage of MST by dermatologist-rated FST.



SCIN includes images with dermatologist-rated FST, patient self-reported FST, and MST assigned by 2 trained non-clinical annotators, 1 from the United States (US) and the other from India. We analyzed the 4292 patient images with all FST and MST scores available. Statistical analyses were performed using R software (Version 4.2.2).

The Spearman correlation between dermatologist-rated FST and US evaluator-rated MST scores was strong and significant ($\rho=0.541$, $P<0.001$); correlations between self-reported FST and US MST scores were significant but weaker ($\rho=0.299$, $P<0.001$). There was a moderate correlation between self-reported and dermatologist-assigned FST ($\rho=0.318$, $P<0.001$). Despite the strong correlation between dermatologist-rated FST and MST scores, there was a range of different MST scores for each FST score (Figure 1). For FST 1, the most common MST score was 2 (out of 10). For an FST 6, the most common MST score was 7 (out of 10). Within racial groups, the correlations between self-reported FST and US MST were only significant among white and Hispanic patients (Table 1). The internal consistency of MST scores between the U.S. and Indian trained evaluators was robust ($\rho=0.640$, $P<0.001$).

The results of this study provide insights into relationships between FST, a widely used skin tone assessment method, and the newly developed MST. Skin tone self-assessments using FST were less correlated to trained MST scores than dermatologist-assessed FST, with a relatively weak correlation between self-assessed and dermatologist FST, suggesting that the FST scale requires training and may be less intuitive for the general public. Corresponding data to compare dermatologist and self-reported MST are lacking, requiring additional research. Our study found a strong correlation between MST and dermatologist-assigned FST and internal consistency of MST amongst different reader ethnic backgrounds.

TABLE 1.

Correlations Between Self-Reported Fitzpatrick scores and US Trained Monk Scores by Race			
Self Reported Fitzpatrick scores and US Trained Monk Scores by Race			
Racial Groups	N	Rho	P-value
White	1582	0.208	$P<0.001$
American Indian	57	0.251	$P=0.091$
Asian	84	0.194	$P=0.137$
African American	264	0.105	$P=0.216$
Hispanic	263	0.207	$P=0.003$
Middle Eastern	6	-0.207	$P=0.695$
Other	13	0.362	$P=0.247$
Two or More	69	0.236	$P=0.077$

Although dermatologist-assigned FST scores are correlated with Monk Skin Tone MST scores, notable divergences exist between the two systems. Our study was limited by insufficient power to detect significant associations within several ethnic groups and did not include comparisons between self-reported and dermatologist-assigned MST scores. Additionally, participant recruitment via online advertisements may limit the generalizability of our findings. As MST is increasingly adopted in machine learning models, it is essential for dermatologists to serve as key stakeholders in the evaluation of skin tone classification systems. Identifying gaps in knowledge surrounding MST and its relationship to FST is critical for ensuring accurate, equitable applications in clinical and technological contexts.

DISCLOSURES

BU is an employee of Mount Sinai and has received research funds (grants paid to the institution) from: Bristol Myers Squibb, Incyte, Rapt Therapeutics, Pfizer, and Sanofi. He is also a consultant for AbbVie, Arcutis Biotherapeutics, Bristol Myers Squibb, Botanix Pharmaceuticals, Castle Biosciences, Ebla Holdco, Fresenius Kabi, Galderma, J&J, Leo Pharma, Lilly, Pfizer, Primus Pharmaceuticals, Sanofi, and UCB. The other authors have no conflicts of interest to disclose.

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The Impact of Increasing Skin of Color Representation in the Pre-Clerkship Dermatology Curriculum

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To the Editor:

The lack of representation of skin of color (SOC) in medical school dermatology curricula has been widely documented.¹ At Loma Linda University School of Medicine, the curriculum for the class of 2024 (CO24) was restructured by incorporating images from a wide range of skin tones and by adding lectures given by a dermatologist specializing in SOC. The classes of 2025 and 2026 (CO25, CO26) received the restructured curriculum. This study evaluates the impact of these curricular changes on students' diagnostic accuracy, perception, and confidence in treating dermatologic conditions in diverse populations.

The anonymous survey included 25 questions: 3 questions about demographics, 11 questions about the representation of SOC in the curriculum and personal confidence in treating SOC patients using a five-point Likert scale, 10 quiz questions involving photographs of common dermatologic conditions, and one free-response question to identify areas for improvement. All dermatology lecture presentations were analyzed by researchers (DK, LH, and AS), and photographs of skin were classified as light-skinned (Fitzpatrick skin types [FST] I-III) or SOC (FST IV-VI). A total of 124 students completed the survey (N = 124/539; 23% response rate). Lecture images were composed of 23% and 16% of SOC and 74% and 81% of light skin for CO25/26 and CO24, respectively, with no significant differences. However, CO25/26 reported that the curriculum was more diverse compared to

CO24 ($P<0.001$), and CO25/26 were less likely to think that more representation of SOC was needed ($P<0.001$; Table 1). Similarly, while both groups called for more SOC representation, many CO25/26 respondents commended the diversity of the added lectures and expressed satisfaction. CO25/26 scored higher on conditions presented on SOC than CO24 ($P=0.02$), but both classes did worse on photographs of SOC compared to light-skinned ($P<0.001$; Table 2). No relationships were found between diagnostic accuracy and perceptions of the importance of SOC representation, the impact of SOC representation, and confidence in making the correct diagnosis.

There are numerous reports of improved self-rated confidence and diagnostic accuracy regarding SOC after educational interventions.² To our knowledge, this is the first study to assess the impact of curriculum change on students' confidence and on their diagnostic accuracy while also investigating their perceptions of the importance of SOC representation. Although all students endorsed proper SOC representation as important and impactful, their diagnostic abilities differed; these results suggest that students' diagnostic performance depends more on the educational material than on their own beliefs. At this stage of medical education, learning primarily happens through direct transfer of information from professors to students, so it is paramount that professors judiciously analyze their lectures

TABLE 1.

Perception Results			
Question	Median rating 1 (least) – 5 (most)		P value
	CO24	CO25/26	
Thought the curriculum was diverse	2.0	3.0	<0.001
Thought the curriculum needed more representation of SOC ^a	3.0-4.0	2.0-3.0	<0.001
Importance of representation of diverse skin	5	4.0	0.1
Impact of representation of SOC on the ability to provide adequate care for future patients of color	4.0	4.0	0.7
Confidence in making correct diagnosis in patients of color	2.0	2.4	0.5
Confidence in making correct diagnosis in patients with lighter skin	3.0	3.0	0.1

^aSkin of Color

TABLE 2.

Quiz Results			
	Average score		P value
	CO24	CO25/26	
Diagnostic accuracy for SOC images	54%	64%	0.02
Diagnostic accuracy for light-skin images	80%	77%	0.4
P value	<0.001	<0.001	--

to prevent unintentional transmission of bias. Limitations of this study include low response rates, overrepresentation of White individuals in CO24, and self-selection bias, but the number of participants in each group and the demographics of CO25/26 were not different from the school population.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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Multidisciplinary Impact and Ethical Response to Skin Bleaching and Colorism

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To the Editor:

When encountering patients from diverse cultural backgrounds, dermatologists often face scenarios where individuals express concerns about skin issues linked to the use of skin bleaching products. Not uncommonly do we see women of African or Asian descent presenting with skin discoloration and irritation, as well as a history of use of skin bleaching products due to their common use in native communities. Although seeking assistance for their skin disease, may intend to continue using skin bleaching products due to having never experienced any issues with them in the past.

Given the cultural background and family practice of using skin bleaching products to maintain a "brighter skin" complexion, a multidisciplinary approach is warranted. This approach will allow us to address the complex interplay of the cultural, psychological, social, and ethical factors involved with this dilemma, utilizing the principle of beneficence. By engaging professionals from various fields, we can create a more comprehensive and effective strategy. This collaborative effort ensures that our interventions are culturally sensitive, socially responsible, and ethically sound, ultimately leading to more meaningful and sustainable outcomes for patients facing similar challenges.

Psychologists can offer significant contributions in addressing skin bleaching by focusing on the psychological and emotional aspects of this problem. Many individuals who engage in this practice suffer from body dysmorphic disorder and low self-esteem.¹ Cognitive-behavioral therapy (CBT) can help these patients develop a healthier self-image and cope with societal pressures. Dermatologists are also essential to achieving non-maleficence, providing safe skincare alternatives, and educating patients about the risks of bleaching. By working together, these professionals can create comprehensive treatment plans that address both the psychological and dermatological concerns related to skin bleaching.

Public health professionals and dermatologists can both address skin bleaching by combining their expertise in community health and medical care. They can develop guidelines for other

healthcare providers to recognize and address skin bleaching practices among their patients. This can include pamphlets on identifying signs of skin bleaching, understanding the cultural and psychological motivations behind it, and providing appropriate counseling and treatment options. By educating primary care physicians, nurses, and other healthcare workers, this initiative ensures a consistent and informed approach across different levels of healthcare. This comprehensive understanding enables providers to offer empathetic and culturally sensitive care that will guide patients towards both autonomous and safe skincare practices.

Religious leaders such as rabbis, imams, and priests can play a crucial role in addressing colorism, which is a driver of this skin bleaching. Colorism, the preference for lighter over darker skin, affects many communities and has a multitude of historical roots. Faith leaders have platforms in their communities that they can leverage to address these potentially harmful beliefs. Studies show that religious leaders can influence health behaviors not only on an individual level but also on the greater community.² Faith leaders can catalyze positive changes in skin health attitudes and practices within their communities by incorporating messages of justice that promote the acceptance of all the diverse skin tones.

CONCLUSION

The authors have no conflicts of interest to disclose.

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NEWS, VIEWS, AND REVIEWS

The Heat Is On: A Review of Heat-Induced Dermatoses

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INTRODUCTION

As the weather warms, both seasonally and longitudinally, the role of heat in eliciting or exacerbating various dermatoses becomes especially relevant. While much attention has been given to skin cancers and photodermatoses related to ultraviolet radiation, the broader dermatologic consequences of heat exposure remain underappreciated. Heat-induced dermatoses, ranging from benign but uncomfortable eruptions to severe inflammatory conditions, represent a spectrum of overlooked conditions that carry significant implications for diagnosis, management, and health equity, particularly among vulnerable populations. This review explores the diagnostic and therapeutic nuances of common dermatoses linked to heat, including miliaria, inducible urticarias, erythema ab igne, contact burns, and select heat-aggravated inflammatory conditions.

Miliaria

Miliaria is a benign condition caused by obstruction of eccrine sweat glands or ducts, often due to cutaneous debris or bacteria, resulting in sweat backflow into the epidermis or dermis.

It is characterized by the depth of ductal involvement, giving rise to three distinct clinical forms: miliaria crystallina, rubra, and profunda. Miliaria crystallina (MC) is the most superficial form, occurring within the stratum corneum, while miliaria rubra (MR) involves obstruction in the subcorneal epidermal layers, and miliaria profunda (MP) occurs at the dermal-epidermal junction.¹

Neonates are often affected by miliaria as their immature sweat duct systems are prone to dysfunction, manifesting as MC and MR. Other predisposing factors include febrile states and environmental contributors such as high humidity and occlusive clothing. Diagnosis of miliaria is primarily clinical, based on the characteristic morphology and distribution of lesions. Clinical presentation mirrors the location of involvement: MC presents as superficial vesicles; MR as larger erythematous papules or vesicles; and MP as firm, flesh-colored papules. Secondary bacterial infection should be suspected when pustular changes are present, referred to as miliaria pustulosa.¹

Management of miliaria emphasizes preventive measures, including maintaining a cool ambient environment, opting for breathable fabrics, gently exfoliating the skin, removing occlusive items like bandages or patches, and treating underlying fevers. Directed treatment of miliaria depends on the type. MC typically self-resolves within 24 hours, while MR can be managed with 0.1% triamcinolone

cream twice daily for 1 to 2 weeks. For MP, limited data suggest improvement with oral isotretinoin 40 mg daily for 2 months combined with topical anhydrous lanolin. If miliaria pustulosa occurs, topical clindamycin 1% can be utilized.¹

Cholinergic and Heat Urticaria

Inducible urticarias, particularly those triggered by heat, represent a challenging and often underrecognized subset of temperature-sensitive dermatologic conditions. Two subtypes, cholinergic urticaria (CholU) and heat urticaria (HU), occur in response to increases in temperature, though they are distinct entities.^{2,3} CholU is triggered by internal increases in core body temperature, such as those induced by exercise, emotional stress, or hot water exposure. Lesions are typically pinpoint papular wheals with a surrounding erythematous flare, often accompanied by intense sensations of itching or pain. HU, in contrast, is induced by direct application of heat, such as warm bath water (reported in 85% of HU cases), hot air, solar thermal energy, and hot objects like water bottles. HU manifests as larger, well-demarcated wheals typically confined to the area of contact.^{3,4} When sunlight is a trigger, care must be taken to distinguish HU from solar urticaria.⁴ HU may be accompanied by systemic symptoms in over half (53%) of patients, including headache, dizziness, abdominal cramps, and dyspnea. Mucosal involvement, angioedema, and syncope have rarely been reported.⁴ CholU has been associated with angioedema, respiratory symptoms, and anaphylaxis.²

The diagnostic work-up of HU includes heat provocation testing, though methods vary and often lack precise temperature thresholds, prompting the development of a novel Peltier-based energy device to standardize identification of the threshold for urticaria onset.³ In CholU, exercise or passive warming tests are employed to reproduce symptoms – the absence of symptoms during physical exertion testing supports a diagnosis of HU over CholU.²

First-line treatment for both HU and CholU consists of trigger avoidance and second-generation H1-antihistamines at up to fourfold the standard dose.^{2,4} However, complete symptom resolution is rare in HU with antihistamines alone (even at the highest doses). Omalizumab has shown success for refractory HU, with three patients achieving full remission in recent case reports using 300 to 450 mg biweekly or monthly.³ Additional management options for HU include indomethacin (25 mg QID), ketotifen (unspecified dose), and omalizumab ± antihistamines for CholU. Though not

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