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JOURNAL OF DRUGS IN DERMATOLOGY

JDD

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Ebglyss™
(lebrikizumab-lbkz)
250mg/2mL injection



NOW **APPROVED**

To treat moderate-to-severe atopic dermatitis (AD)[1]

Learn more about EBGLYSS by visiting:
www.ebglyss.lilly.com/hcp

Indication and Important Safety Information

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.

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.



Important Safety Information (cont.)

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 (≥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.

LK HCP ISI AD APP

Scan the QR code to see clinical data results for EBGLYSS.

Reference
1. EBGLYSS (lebrikizumab-lbkz). Prescribing Information. Lilly USA, LLC.

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Ebglyss™
(lebrikizumab-lbkz)
250mg/2mL injection

Lilly

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.

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

[a]Integrated analysis of ADvocate 1, ADvocate 2, and the phase 2 dose finding trial (KGAF)
[b]Analysis of TCS concomitant therapy trial ADhere
[c]EBGLYSS 500 mg at Week 0 and Week 2, followed by 250 mg every two weeks
[d]Conjunctivitis cluster includes conjunctivitis, conjunctivitis allergic, and conjunctivitis bacterial
[e]Injection 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.

EBGLYSS™ (lebrikizumab-lbkz) 250mg/2mL injection for subcutaneous use LK HCP BS AD APP

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.

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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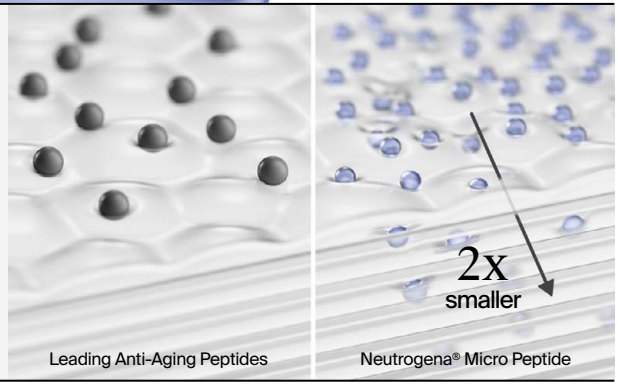
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EDITORIAL Journal of Drugs in Dermatology



Deborah S. Sarnoff MD
Editor-in-Chief
Journal of Drugs in Dermatology

Keeping You at the Forefront: A Message From the Editor-in-Chief

Dear Colleagues,

The March issue of the *Journal of Drugs in Dermatology* highlights a diverse range of topics that reflect our specialty's dynamic and evolving nature. From advancements in alopecia management to innovative therapeutic approaches for rare diseases, this issue underscores the importance of staying informed to optimize patient care.

The insights presented in this issue exemplify our field's unwavering commitment to innovation and patient-centered care. By embracing these advancements, we as dermatologists can refine our practices and improve patient outcomes, ensuring that our patients benefit from the latest in evidence-based research and emerging therapies.

As we continue to navigate the ever-changing landscape of dermatologic care, the *Journal of Drugs in Dermatology* remains committed to providing valuable clinical insights and supporting the advancement of our specialty. I encourage you to engage with this issue's research, share your perspectives, and contribute to the ongoing dialogue that propels our field forward.

Sincerely,

Deborah S. Sarnoff MD

Editor-in-Chief
Journal of Drugs in Dermatology

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Artificial Intelligence-Based Personalization of Treatment Regimen for Hair Loss: A 6-Month Clinical Trial

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ABSTRACT

Hair loss affects up to 50% of women and 80% of men. The high costs and wait times for professional consultations lead many to seek one-size-fits-all solutions that are frequently ineffective. This study tested an artificial intelligence (AI) model for customizing non-medicated hair loss treatments. In a 24-week trial, 38 women with self-reported hair thinning received personalized product kits based on AI analysis of scalp images and questionnaires. Treatments included various combinations of topical serums, shampoos, oral supplements, and marine collagen peptides. Of the 27 participants who completed the study, significant improvements were observed in hair growth, coverage, and thickness ($P<0.001$ for all). Hair shedding decreased by 37.3% at 12 weeks and 32.4% at 24 weeks. Scalp transepidermal water loss was reduced by 61.5% at 12 weeks and 69% at 24 weeks. Scanning electron microscopy showed improved hair texture. Participants reported overall hair improvement (88.9%), better scalp health (85.2%), and less hair brittleness (92.6%) ($P<0.001$ for all). No adverse events were reported. The AI-driven platform effectively delivered personalized hair loss treatments, suggesting a data-driven, customized, and accessible self-served alternative for hair loss management.

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INTRODUCTION

Hair loss is a prevalent health condition affecting up to 50% of women and 80% of men during their lifetime.[1] Many refrain from professional dermatological consultations and procedures due to their high cost and long appointment wait time, turning instead to generic one-size-fits-all solutions that can be irritating and ineffective. Hair loss treatment is a long process; therefore, ease of use is essential for treatment compliance.[2] Combining accessible skin or hair assessment and a large arsenal of topical and oral nutraceuticals personalized to the individual's needs can further improve the benefits of non-medicated hair growth research and offer a more affordable and easily accessible alternative or addition to current medicated alternatives. A retrospective cohort study found better outcomes from combination therapy (topical minoxidil and oral nutraceutical) than topical minoxidil alone to treat chemotherapy-induced alopecia.[3] Combination therapy induced higher improvement in hair density and thickness compared to monotherapy with minoxidil.

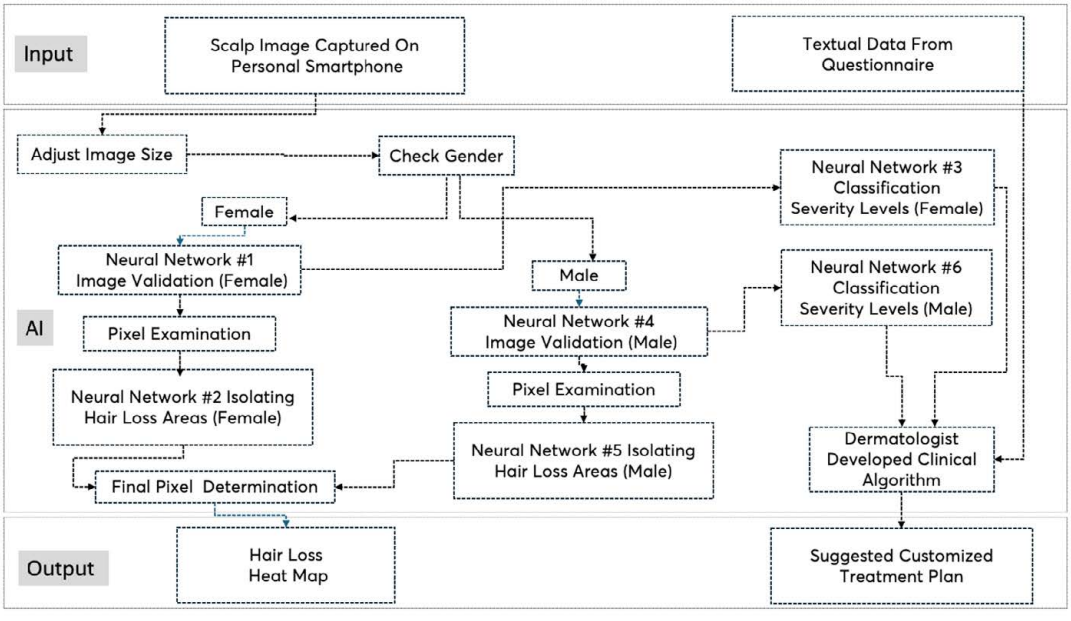
Advancements in smartphone camera technology, computer vision, and deep learning artificial intelligence (AI) have facilitated the development of AI-driven platforms that offer personalized dermatological assessments via personal devices, thereby democratizing access to specialized care. Skin and hair conditions, due to their visual nature, are particularly amenable to AI exploration.[4,5] Moreover, increasing evidence supports the benefits of nutraceuticals for individuals with hair loss. While previous research has primarily focused on the impact of single topical or oral products, this study aims to employ AI-driven assessments to curate a personalized set of topical and oral products targeting multiple mechanisms of hair loss to maximize efficacy. In a pilot study,[6] data from 30 women with androgenetic alopecia demonstrated that AI-based assessments aligned with human dermatologist evaluations in 28 out of 30 cases, resulting in a 94% accuracy rate. This current study investigates the potential of a proprietary AI platform developed by MDalgorithms, Inc.[7] to deliver customized over-the-counter sets of topical and oral products tailored to individual needs and characteristics.

The AI model tested in this study was trained on tens of thousands of scalp images to evaluate hair loss pattern and severity, providing grading and visual heatmap of hair loss. This assessment allows the AI to customize a treatment plan for each individual, which includes a personalized set of topical serums, shampoos, and oral supplements.

PATIENTS AND METHODS

This study employed a prospective single-center, single-blind clinical trial design to assess the effectiveness of an AI-based personalized hair loss treatment. Thirty-eight women aged 34 to 65 with self-reported hair thinning were recruited for the trial. The study consisted of three clinic visits at baseline, week 12, and week 24, along with two self-assessment evaluations at week 4 and week 8.

FIGURE 1. Schematic showing the development and training of a deep learning model for hair loss analysis to customize treatment regimens/products.



AI Development

Figure 1 shows the schematic of the AI training. The AI model was trained on 47,000 images of people with hair loss (27,000 female and 20,000 male). The dataset included a broad spectrum of ethnicities, ages, hair loss severities, and hair types. The input to the model included the answers to a questionnaire and an image of the top of the scalp captured on the participant's smartphone. To assess the image, we used a combination of six different neural networks, three of which were trained on female images and three on male images. The output of these neural networks was used to produce a heat map of hair loss and to determine the hair severity and content of the suggested customized kit.

AI-Based Customization of Treatment Kits

To customize the kits, we used proprietary software developed by MDalgorithms Inc., San Francisco, as explained in the previous section. Each participant answered an online questionnaire (www.mdhair.co/quiz) and uploaded a captured selfie image on the web (Figure 2A). The questionnaire and images (Figure 2B)

FIGURE 2. (A) Participant uses MDhair's mobile web app on her smartphone to take a scalp picture. (B) Backend image processing by AI shows images with and without an automated AI heatmap (bald areas marked in white). (C) Procedure of Shed Hair Count. (D) Tewameter measurements.

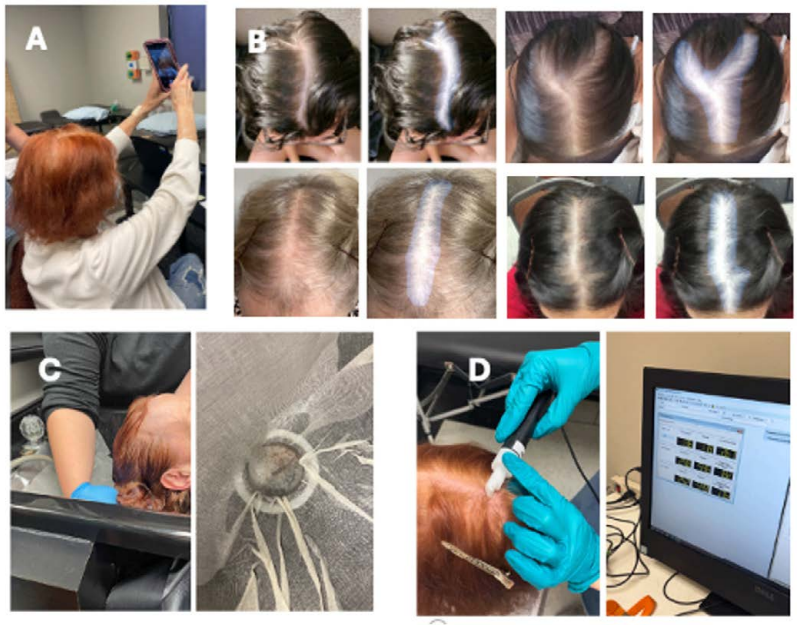


TABLE 1.

List of Active Ingredients and Their Mode of Action		
Ingredient	**Benefit**	**Delivery Method**
Saw Palmetto Extract	DHT Blocker	Shampoo, Serum, Supplements
Green Tea Extract	Antioxidant, DHT Blocker	Shampoo, Serum, Supplements
Glycerin, Hyaluronic Acid	Hydrating	Shampoo, Serum
Lactobacillus Ferment	Balance Scalp Bacterial Flora	Shampoo
Caffeine, Ginger Extract	Stimulating Scalp Blood Flow	Shampoo, Serum
Biotin, Vitamins (E, D), Minerals (Zinc, Selenium, Copper)	Providing Vitamins and Minerals	Shampoo, Serum, Supplements
Hydrolyzed Wheat Protein, Hydrolyzed Keratin	Hydrating Scalp and Hair	Shampoo, Serum
Amino Acids, Hyaluronic Acid Vitamin C	Building Blocks of Collagen	Oral Collagen Powder

were automatically analyzed, and the recommended treatment regimen/products appeared on the participant's mobile phone screen within seconds. The clinic staff then provided the personalized kits/products along with instructions for at-home use.

Tested Products

Based on AI recommendations, the MDhair kit was personalized for each participant. Each one was provided with a specific topical serum, shampoo, and oral supplement, which varied based on real-time AI analysis of the questionnaire and images together with one kind of marine collagen peptide hydrolysate. Products included dermatologist-formulated cosmeceuticals and nutraceuticals containing popular and well-understood active ingredients (Table 1).

Digital Imaging Procedures

Photography was performed by clinical staff using the Canfield Hair Rig Imaging System (Canfield Imaging Systems, Fairfield, New Jersey) with a Canon EOS 7D DSLR camera (Canon Inc, Tokyo, Japan) under visible lighting using the Canfield IntelliFlash lighting system affixed to the photo station. A color standard was attached to the forehead rest and was included in each photograph. At each photography visit, a color standard (CasMatch Color Mire chip from Bear Medic Corporation) was photographed before beginning each day's photography. Digital images were taken of each subject's superior scalp and right and left temple areas (3 images total) at baseline and weeks 12 and 24. Before photography, each subject's hair was parted and combed to show the hair thinning conditions. The subject's head was positioned on a headstand (with chin and forehead rest) at an appropriate angle to capture the hair condition with the scalp toward the camera at a fixed distance. Images were taken of the superior scalp view (center) at 60° and the left and right temples at 60°. Positioning was replicated at each post-baseline time point.

Objective Grader Assessment

Photograph grading was performed by an expert grader using standardized global photographs from baseline and weeks 12 and 24. Grading was performed after week 12 for photographs taken at baseline and week 12 and after the study for photographs taken at week 24. The investigator or designee rated the improvement from baseline for the indicated parameters using the 7-point Likert scale for hair growth,[8] appearance of coverage, overall volume/thickness/fullness, and overall perception of treatment benefit.

Shed Hair Count

Figure 2C shows hair wash and shed hair count procedures at baseline and weeks 12 and 24, using a cheesecloth in a salon sink to collect shed hairs. With gloved hands, clinic staff applied conditioner and washed the subjects' hair, followed by a comb-out over the sink. After drying and styling their hair, the captured hairs on the cheesecloth were counted and recorded. The same comb and procedure were consistently used to ensure accuracy across all subjects. Once counted, the hairs and cheesecloth were discarded.

Tewameter Measurement

Figure 2D shows Tewameter measurements performed at baseline and weeks 12 and 24. Single Tewameter measurements were taken at the center of the hair part on top of the crown of each subject's scalp. The Tewameter TM Nano (Courage + Khazaka electronic GmbH, Cologne, Germany) measured the passive transfer of water through the stratum corneum (transepidermal water loss [TEWL]). This water evaporation measurement was based on the diffusion principle in an open chamber, and the density gradient was measured indirectly by 2 pairs of sensors located inside the hollow cylindrical probe. Data were analyzed by a microprocessor and reported in $g/m^2/h$. A decrease in TEWL values reflected an improvement in the skin's barrier properties.

Scanning Electron Microscopy

Hair strands were collected from 3 study participants at baseline and 24 weeks. Segments of three individual hairs from each sample were attached to cylindrical aluminum mounts and sputter-coated with a conductive layer of gold. Images were obtained with a JEOL JSM-6490LV scanning electron microscope (NDSU Electron Microscopy Core, supported by the National Science Foundation under Grant No. 0619098). The

damage to the hair shaft under scanning electron microscopy (SEM) was graded into 5 grades, described previously[9]: Grade 0: Virgin intact hair with a regular overlay of the cuticle. Grade 1: Irregular overlay of the cuticle without cracks or holes. Grade 2: Severe lift of the cuticle with cracks or holes but without cortex exposure. Grade 3: Partial exposure of cortex, and Grade 4: Complete disappearance of cortex.

Self-Assessment Questionnaires

Self-assessment questionnaires using 5- and 7-point scales (Strongly Disagree to Strongly Agree) were performed at weeks 4, 8, 12, and 24 to rate hair growth, quality, and improvements in skin and nails. Hair satisfaction and lifestyle factors, such as mood and confidence, were also evaluated.

Ethics

This study was approved by the IntegReview IRB and conducted in accordance with Good Clinical Practices. Informed consent and photo release forms were obtained from all participants.

Statistical Analysis

Descriptive statistics were conducted for the per-protocol population, defined as participants who completed the study as per the protocol. Investigator ratings and self-assessment questionnaire results were analyzed using the Wilcoxon signed-rank test. All statistical tests were two-sided, with alpha=0.05.

RESULTS

Twenty-seven participants completed the 6-month treatment; the median age was 60. Ethnicities included 16 White or Caucasian, 7 Asian, and 4 Black or African American. The Fitzpatrick Skin Types were primarily Type III (11), followed by Type II (9), Type V (4), and Type IV (3). Hair texture varied, with wavy hair being the most prevalent (12), followed by straight (11), coily (3), and curly (1).

Objective expert grading demonstrated statistically significant improvements in hair growth, coverage, and overall hair volume/thickness/fullness at weeks 12 and 24 (7-point Likert scale, Sign Test *P*-value, $P<0.001$). At 24 weeks, improvements in hair growth were found in 77.7% of participants, hair coverage in 62.9%, and overall hair volume/thickness/fullness in 74%. Digital images of 4 representative cases show visual improvement in hair loss before and after 24 weeks of treatment.

Hair shed counts decreased in 84% of participants at 12 weeks and 63% at week 24, with an average reduction in hair shed count of 37.3% (Signed Rank Test *P* Value, $P<0.001$) at week 12 and 32.4% at week 24 (Signed Rank Test *P*-value, $P<0.05$). Measurements of transepidermal water loss (TEWL) on the scalp at 12 weeks were reduced in 61.5% of participants (Paired T Test *P*-value, $P=0.017$) and 69% (not statistically significant) at 24 weeks, indicating improved scalp health.

SEM images of hair strands showed normalization of cuticle structure and reduced hair shaft damage after 24 weeks of treatment (Figure 4). The same observation was made in all 3 examined sample sets, implying stronger hair post-treatment. According to accepted SEM hair health grading, the reduction of hair damage recorded was one grade for 2 participants and 2 grades for the third participant.

FIGURE 3. Digital photography using Canfield Hair Rig Imaging System showing images of the four representative cases before (baseline) after 12 weeks and 24 weeks of treatment.

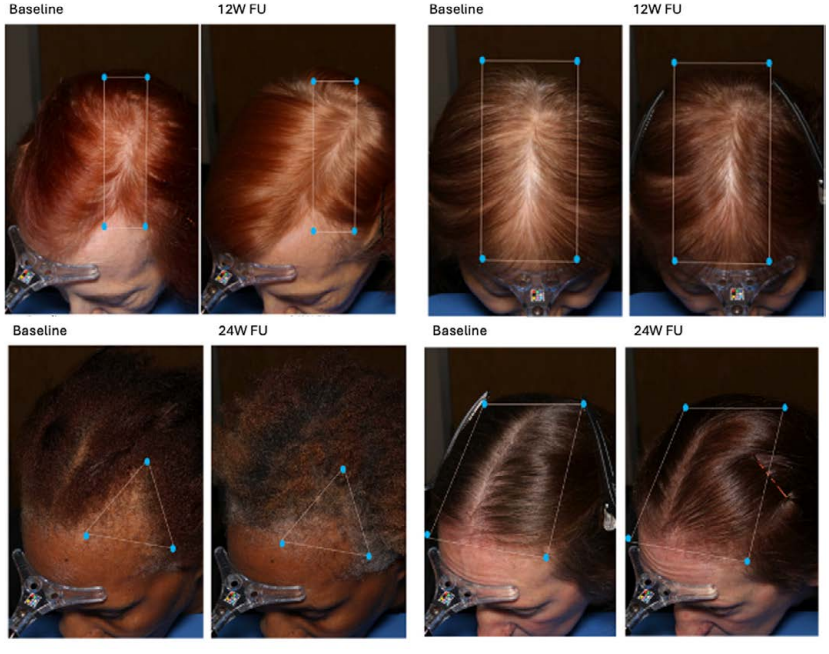


FIGURE 4. SEM images of hair strands showing improvement in hair texture and damage before (baseline) and after 24 weeks of treatment. Subject 015, (A) baseline (Grade 1)–lift-up of the cuticle without cracks, holes, or exposure to the cortex and 24 weeks after treatment (Grade 0) showing a regular overlay of the cuticle that was otherwise lifted at the baseline. Subject 017, (C) baseline (Grade 2), and (D): after 24 weeks of treatment, showing drastic improvement in hair morphology that otherwise had rough and damaged cuticle at baseline.

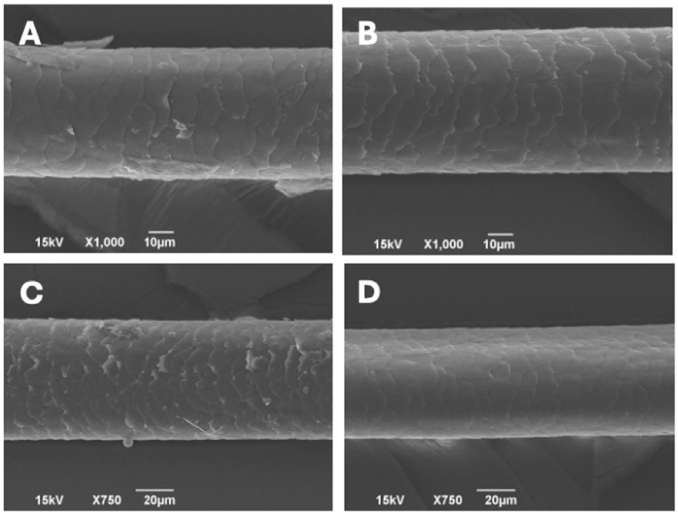


TABLE 2.

Results of Self-Assessment Questionnaires		
After 24 Weeks	%	*P*-Value
Saw an overall improvement in their hair	88.9%	<0.001
Noticed increased thickness of their hair	88.9%	<0.001
Noticed decreased shedding of their hair	88.9%	<0.001
Saw decreased brittleness of their hair	92.6%	<0.001
Reported that their hair felt fuller	88.9%	<0.001
Saw increased shine of their hair	77.8%	<0.01
Felt improvement in the health of their scalp	85.2%	<0.001
Saw increased density of their hair	81.5%	<0.01
Saw decreased frizz of their hair	81.5%	<0.01

In self-assessment questionnaires, 88.9% of participants noted hair improvement, 85.2% reported better scalp health, and 92.6% observed less hair brittleness, all with significant binomial test results (P<0.001; Table 2). There were no product or treatment regimen-related adverse events (AEs).

DISCUSSION

Hair loss remains a challenging condition for both patients and dermatologists. While androgenetic alopecia is the most common cause, there are multiple triggers, severities, and treatment preferences. As the number of dermatologists workforce in the United States declines,[10] clinical accessibility to in-office consultations decreases, and costs increase. The current array of over-the-counter medicated and non-medicated products can be confusing, making it difficult and frustrating to choose the right products.

A growing body of evidence suggests that AI systems can perform at the standard we require from physicians. Recent work showed that GPT-4 performance is comparable to that of physicians on official medical board residency examinations[11] and somewhat better than the diagnosis performance of non-expert physicians in some fields of medicine.[12] A few studies have looked at the use of high-end cameras and image analysis as tools for laboratory and in-office assessments of hair growth,[4,5] but to our knowledge, the images were not captured on personal smartphone cameras, were not analyzed by deep learning AI models, or used for automatic fulfillment of customized treatment kits or products.

To evaluate hair loss, we utilized a unique combination of AI and computer vision tools, including a deep learning model trained on over 47,000 distinct hair loss images, computer vision image preprocessing, and AI decision tree analysis of textual input.

At present, the only 2 FDA-approved medications for the treatment of female androgenetic alopecia are minoxidil 2% topical solution and minoxidil 5% topical foam preparation. A study[16] using a 7-point scale showed objective investigators' improvements in hair volume from baseline through week 24 in 67.7% of participants in the 5% minoxidil foam arm compared with 56.1% of participants in the 2% minoxidil solution arm. The results of our nutraceuticals topical and oral combination therapy investigated in this study are superior to the aforementioned 5% minoxidil foam study, with combination therapy showing an increase in hair volume in 74% of participants.

The treatment results of the investigational personalized combination regimen were also superior to the results of previous studies using non-customized nutraceuticals for hair loss.[17] In the current study, the objective graded Likert score showed an improvement in hair regrowth of 1.44 versus 0.5 at 90 days and 1.22 vs 1.08 at 180 days, compared to studies using non-customized nutraceuticals for a similar group of women with hair loss. Additionally, the improvement in hair quality was 1.185 vs 0.4 at 90 days and 1.63 vs 1.1 at 180 days.

The wash test is a valuable technique to quantify the changes in hair shedding. In a previous study,[18] mean hair counts were 27.9 for women with normal hair, 52.2 for women with androgenetic alopecia, and 125.5 for women. In our study, we found an average shed hair count of 61.3 that was reduced to 41.4 at 24 weeks, indicating a significant reduction in hair shedding (Signed Rank Test P<0.05).

Trans-epidermal water loss (TEWL) measurements provide valuable insights into the biophysical properties of the scalp in individuals with androgenetic alopecia (AGA). Comparative

studies between males with AGA and healthy controls have been conducted, revealing that AGA patients exhibit significantly elevated TEWL values, particularly in the vertex and occipital regions of the scalp. These heightened TEWL values suggest a compromised skin barrier in AGA patients, potentially linked to alterations in skin surface lipids and hydration levels of the stratum corneum.[19] We believe the superior results observed in this study are because of a synergistic approach that combined topical and oral products to target hair loss, and these products were customized as per individual needs.

To our knowledge, very few studies used TEWL to assess stratum corneum barrier. Scalp skin is distinct from the skin on the face and other body areas, with the skin barrier being relatively weak (higher TEWL values) than other sites.[21] One study showed that dandruff and hair loss impair the skin barrier,[21] and in another study, hair density and thickness decreased with age. In our research findings, we observed a statistically significant reduction in TEWL values, which highlights the beneficial impact of the customized treatment kit on improving the skin's barrier function and overall scalp health.

Previous scanning electron microscopy studies in patients with AGA have shown that the surface of the cuticle on the hair shafts was irregular, with a poorly defined scale surface and contour, commonly giving a "melted candle" appearance. Over the years, these features can be worsened by using harsh chemicals for hairstyling and environmental ultraviolet (UV) and air pollution.[22] SEM, used in this study, provided visualization of changes in hair strand texture, showing a significant improvement in hair strand surface texture.

The active ingredients used in the products provided to study participants included phytoactives with DHT-blocking, antioxidative, and anti-inflammatory effects, as well as vitamins, minerals, and amino acids believed to support healthier scalp and hair growth. Unlike previous nutraceutical treatments,[17] the customized kit offered in this study included both topical and oral products and was personalized using AI to assess individual needs.

Our results demonstrate that an AI-based customized topical and oral kit can safely and effectively improve hair growth and scalp health in an ethnically diverse group of women with self-perceived thinning. This approach offers a multi-targeted therapeutic strategy for hair loss that is effective, affordable, and easy to use. While it is not intended to replace expert dermatologists for complex conditions requiring prescription medication, it provides a superior alternative to generic over-the-counter products often chosen without expert advice.

The limitations of this study include its single-arm design and the relatively small sample size, necessitating randomized controlled studies on larger cohorts and randomized controlled studies. We also believe that combining large language models (LLMs) with the tested AI technology will further improve assessment and treatment recommendations.

DISCLOSURES

Vinay Bhardwaj PhD and Nancy Rodgers PhD conducted the clinical study for SGS, supported by a research grant from MDalgorithms Inc. Dr Yoram Harth and Oded Harth are part of the MDalgorithms Inc. team and hold stock in the company.

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FOR THE TREATMENT OF ACNE VULGARIS IN PATIENTS 12 YEARS OF AGE AND OLDER[1]

CABTREO®
(clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%

ONE SCRIPT ONE PUMP ONCE A DAY



Not actual patients.

The *first and only* FDA-approved, fixed-dose triple-combination topical prescription for the treatment of acne[2]

HELP SIMPLIFY YOUR PATIENTS' TREATMENT REGIMEN WITH CABTREO[3]

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INDICATION

CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1% is indicated for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

CABTREO is contraindicated in patients with:

- known hypersensitivity to clindamycin, adapalene, benzoyl peroxide, any components of the formulation, or lincomycin.
- history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported. If a serious hypersensitivity reaction occurs, discontinue CABTREO immediately and initiate appropriate therapy.

Colitis: Clindamycin can cause severe colitis, which may result in death. Discontinue CABTREO if diarrhea occurs.

Photosensitivity: CABTREO may increase sensitivity to ultraviolet light. Avoid or minimize exposure to sunlight and sunlamps. Wear sunscreen and protective clothing when sun exposure cannot be avoided.

Skin Irritation and Allergic Contact Dermatitis: Stinging/burning/pain, erythema, dryness, irritation, exfoliation, and dermatitis may occur with use of CABTREO and may necessitate discontinuation. Weather extremes, such as wind or cold, may be irritating to patients under treatment with CABTREO. Depending upon severity, patients can use a moisturizer, reduce frequency of application, or discontinue use. Avoid applying CABTREO to areas of broken, eczematous, or sunburned skin, and concomitant use with other potentially irritating topical products. Avoid use of "waxing" as a depilatory method on skin treated with CABTREO.

Use of CABTREO with concomitant topical acne therapy has not been evaluated.

ADVERSE REACTIONS

The most common adverse reactions (occurring in >1% of the CABTREO group and greater than the vehicle group) were application site reactions, pain, erythema, dryness, irritation, exfoliation, and dermatitis.

DRUG INTERACTIONS

Use CABTREO with caution in patients receiving neuromuscular blocking agents.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on adjacent pages.

References: 1. CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1% [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Stein Gold L, Baldwin H, Kircik LH, et al. Efficacy and safety of a fixed-dose clindamycin phosphate 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% gel for moderate-to-severe acne: a randomized phase II study of the first triple-combination drug. *Am J Clin Dermatol.* 2022;23(1):93-104. **3.** Stein Gold L, Lain E, Del Rosso JQ, et al. Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel for moderate-to-severe acne: Efficacy and safety results from two randomized phase 3 trials. *J Am Acad Dermatol.* 2023;89(5):927-935.

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CABTREO®
(clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%

Summary does not include all the information needed to use CABTREO safely and effectively. See full prescribing information for CABTREO.

CABTREO™ (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%
Initial U.S. Approval: 2023

INDICATION

CABTREO (clindamycin phosphate/adapalene/benzoyl peroxide) Topical Gel, 1.2%/0.15%/3.1% is indicated for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
CABTREO is contraindicated in patients with:

- Known hypersensitivity to clindamycin, adapalene, benzoyl peroxide, any other components of CABTREO, or lincomycin.
- A history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Hypersensitivity
Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported with use of clindamycin phosphate, benzoyl peroxide, and adapalene. If a serious hypersensitivity reaction occurs, discontinue CABTREO immediately and initiate appropriate therapy.

Colitis
Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical and systemic clindamycin. Severe colitis has occurred with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death. Discontinue CABTREO if diarrhea occurs.

Photosensitivity
CABTREO may increase sensitivity to ultraviolet light. Avoid or minimize sun exposure (including use of tanning beds, and sun lamps) following CABTREO application. Instruct patients to use sunscreen products and wear protective apparel (e.g., hat) when exposure to sun cannot be avoided.

Skin Irritation and Allergic Contact Dermatitis
Stinging/burning/pain, erythema, dryness, irritation, exfoliation, and dermatitis have been reported with use of CABTREO. These application site adverse reactions occurred at a greater frequency in CABTREO-treated subjects than in vehicle-treated subjects. These adverse reactions are most likely to occur during the first four weeks of treatment. Irritant and allergic contact dermatitis have been reported with use of CABTREO. Weather extremes, such as wind or cold, may be irritating to patients under treatment with CABTREO. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of CABTREO, or discontinue use. Avoid applying CABTREO to areas of broken, eczematous, or sunburned skin. Avoid use of "waxing" as a depilatory method on skin treated with CABTREO. Avoid concomitant use of other potentially irritating topical products such as peeling, desquamating, or abrasive agents and products with high concentrations of alcohol, astringents, spices, or limes. Use of CABTREO with concomitant topical acne therapy has not been evaluated.

ADVERSE REACTIONS
The most common adverse reactions (occurring in >1% of the CABTREO group and greater than the vehicle group) were application site reactions, pain, erythema, dryness, irritation, exfoliation, and dermatitis.

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
In two multicenter, randomized, double-blind, vehicle-controlled clinical trials (Trial 1 and Trial 2), 363 adult and pediatric subjects 10 years of age and older with facial acne vulgaris were treated with CABTREO or vehicle topically once daily for 12 weeks Adverse reactions reported by >1% of subjects treated with CABTREO and more frequently than subjects treated with vehicle are summarized in Table 1. These adverse reactions were mild (59%), moderate (36.4%), and severe (4.5%). Overall, 2.5% (6/242) of subjects discontinued CABTREO because of local skin reactions.

Table 1: Adverse Reactions Reported by >1% of Subjects with Facial Acne Vulgaris Treated with CABTREO (and More Frequently than Vehicle) in Trials 1 and 2

Adverse Reactions N (%)		
	CABTREO N=242	**Vehicle N=121**
Application site pain[1]	33 (13.6)	1 (0.8)
Application site erythema[2]	11 (4.5)	0
Application site dryness[3]	10 (4.1)	1 (0.8)
Application site irritation	5 (2.1)	0
Application site exfoliation	4 (1.7)	0
Application site dermatitis	3 (1.2)	0

[1]Application site pain also includes application site stinging and burning

[2]Application site erythema also includes erythema

[3]Application site dryness also includes xerosis

Local tolerability evaluations were conducted at each study visit by assessment of erythema, scaling, itching, burning, and stinging. Table 2 presents the signs and symptoms of local facial tolerability at Week 12 in subjects treated with CABTREO.

Table 2: Facial Cutaneous Tolerability Assessment during 12 week treatment period in Subjects with Acne Vulgaris Treated with CABTREO in Trials 1 and 2

	Maximum During Treatment*			**Week 12 (End of Treatment)****		
	Mild n (%)	**Mod n (%)**	**Severe n (%)**	**Mild n (%)**	**Mod n (%)**	**Severe n (%)**
CABTREO (N = 242)						
Erythema	34.2	19.7	2.1	22.4	6.5	0.5
Burning	29.6	10.7	3.0	4.2	1.4	0.9
Scaling	26.7	3.4	0	7.0	0.9	0
Itching	24.3	3.4	0.4	6.0	0.9	0
Stinging	20.5	5.1	2.6	2.3	0.9	0.5
Vehicle (N = 121)						
Erythema	22.5	21.7	1.7	25.5	5.5	0
Burning	2.5	0.8	0.8	0.9	0	0
Scaling	12.5	0	0	4.5	0	0
Itching	11.6	0.8	0	1.8	0	0
Stinging	3.3	0.8	0	1.8	0	0

*The denominators for calculating the percentages were the number of subjects with at least one post-baseline cutaneous tolerability assessment.

**The denominators for calculating the percentages were the number of subjects with Week 12 assessment.

Local tolerability scores for erythema, scaling, itching, burning, and stinging increased during the first two weeks of treatment and decreased thereafter.

BRIEF SUMMARY OF PRESCRIBING INFORMATION This Brief Summary does not include all the information needed to use CABTREO safely and effectively. See full prescribing information for CABTREO.

CABTREO™ (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%
Initial U.S. Approval: 2023

DRUG INTERACTIONS

Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use CABTREO with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Available data with CABTREO use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with CABTREO.

Clindamycin
In published clinical trials and observational studies with pregnant women, oral or IV administration of clindamycin has not been associated with an increased frequency of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, clindamycin phosphate did not cause malformations or embryofetal development toxicity in pregnant rats and mice when administered during the period of organogenesis as systemic doses up to 192 times the maximum recommended human dose (MRHD) of 2.5 g CABTREO, based on a body surface area (mg/m2) comparison.

Adapalene
Available data from clinical trials with adapalene topical gel use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of adapalene to pregnant rats and rabbits during organogenesis at dose exposures 64 and 128 times, respectively, the MRHD resulted in fetal skeletal and visceral malformations.

Benzoyl peroxide
The systemic exposure of topical benzoyl peroxide is unknown. Based on published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure of the drug.
The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
Animal reproductive/developmental toxicity studies have not been conducted with CABTREO or benzoyl peroxide. Clindamycin phosphate administration during the period of organogenesis in pregnant rats and mice at oral doses of up to 600 mg/kg/day (192 and 96 times the MRHD), respectively, based on a mg/m2 comparison) or subcutaneous doses of up to 200 mg/kg/day 64 and 32 times the MRHD, respectively, based on a mg/m2 comparison) did not cause fetal malformations or fetotoxicity.
No malformations were observed in rats treated with oral adapalene doses of 0.15 to 5.0 mg/kg/day adapalene (up to 13 times the MRHD based on a mg/m2 comparison). However, malformations were observed in rats and rabbits when treated with oral doses of ≥ 25 mg/kg/day adapalene (64 and 128 times the MRHD, respectively, based on a mg/m2 comparison). Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits. Dermal adapalene embryofetal development studies in rats and rabbits at doses up to 6.0 mg/kg/day adapalene (up to 15 and 30 times the MRHD, respectively, based on a mg/m2 comparison) exhibited no fetotoxicity and only minimal increases in skeletal variations (supernumerary ribs in both species and delayed ossification in rabbits).

Lactation

Risk Summary

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

Clindamycin
There are no data on the presence of clindamycin in human milk, the effects on the breastfed child, or the effects on milk production following topical administration. However, clindamycin has been reported to be present in human milk in small amounts following oral and parenteral administration.

Adapalene
There are no data on the presence of topical adapalene gel or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, adapalene is present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topical administration of large amounts of adapalene could result in sufficient systemic absorption to produce detectable quantities in human milk (see Clinical Considerations).

Benzoyl peroxide
There are no data on the presence of topical benzoyl peroxide in human milk, its effects on the breastfed infant, or its effects on milk production. The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Any amount of benzoyl peroxide excreted into human milk by a nursing mother would be expected to be rapidly metabolized by tissue and stomach esterases.

Clinical Considerations
To minimize potential exposure to the breastfed infant via breastmilk, use CABTREO on the smallest area of skin and for the shortest duration possible while breastfeeding. To avoid direct infant exposure, advise patients who are breastfeeding not to apply CABTREO directly to the nipple and areola. If applied to the patient's chest, care should be taken to avoid infant exposure via direct contact with the infant skin.

Pediatric Use
The safety and effectiveness of CABTREO for the topical treatment of acne vulgaris have been established in pediatric patients 12 years of age and older. Use of CABTREO for this indication is supported by data from two randomized, double-blind, vehicle-controlled trials.

The safety and effectiveness of CABTREO have not been established in pediatric patients younger than 12 years of age.

Geriatric Use
Clinical studies of CABTREO did not include any subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Spesolimab for the Treatment of Generalized Pustular Psoriasis Flares

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ABSTRACT

Background: Generalized pustular psoriasis (GPP) is a rare, life-threatening neutrophilic skin condition characterized by widespread sterile eruptions. Treatment approaches vary due to a lack of standardized guidelines. Interleukin-36 signaling is involved in GPP activation and disease progression. An interleukin-36 receptor monoclonal antibody, spesolimab, is a new treatment option for GPP flares. The Effisayil 1 clinical trial investigated the efficacy and safety of spesolimab, a remarkable task due to the unpredictable nature of GPP flares coupled with intrinsic trial challenges.

Methods: We searched PubMed using the terms: generalized pustular psoriasis, spesolimab, and Effisayil 1. Clinicaltrials.gov was used to identify clinical trial data including efficacy, safety, and tolerability.

Results: In Effisayil 1, a phase II study, 53 patients with a GPP flare were enrolled: 35 patients were randomized to spesolimab and 18 to placebo. At baseline, 46% of the patients in the spesolimab group and 39% of the patients in the placebo group had a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 3; 37% and 33% of patients in each group, respectively, had a pustulation subscore 4. At the end of week 1, 19 of the patients in the spesolimab group, (54.3%) had a pustulation subscore of 0 compared to 1 patient in the placebo group (5.6%) (-49%, $P<0.001$).

Conclusions: The Effisayil 1 trial faced many difficulties affecting trial completion, but the results of this study provided encouraging results. Spesolimab was effective in treating GPP flares after just one week. Patient demographics and baseline characteristics did not affect the efficacy or safety profile of spesolimab.

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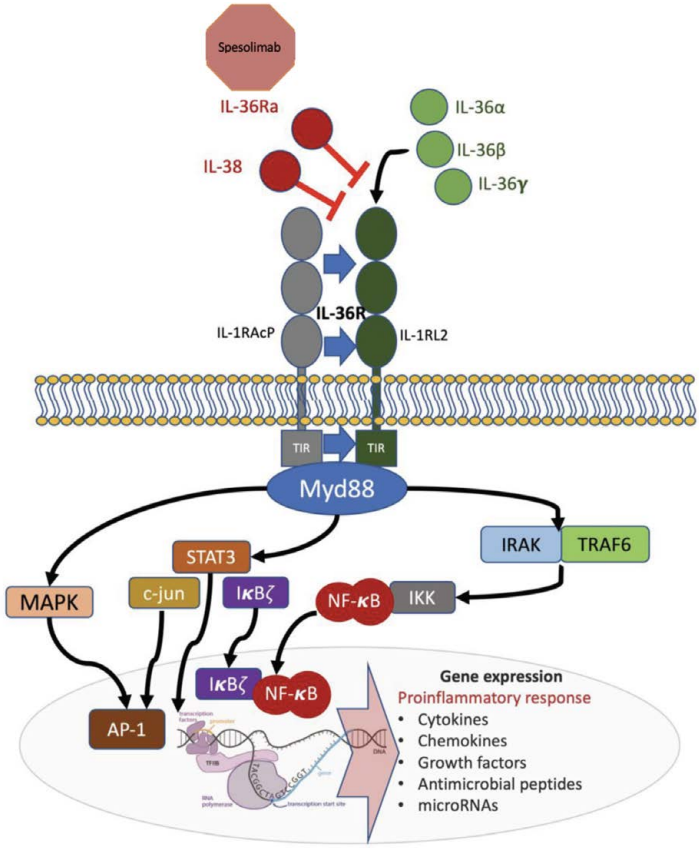
INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare skin condition with prevalence rates ranging from 2 to 124 cases per million persons characterized by potentially disfiguring and painful erythematous, exudate-filled lesions.[1,2] Interleukin 36 (IL-36) plays a key role in GPP; some patients with GPP have a recessive mutation in the interleukin 36 receptor antagonist (IL-36RN) gene. The IL-36RN gene antagonizes IL-1F6, IL-1F8, and IL-1F9, cytokines that activate pro-inflammatory pathways. Various substitution, frameshift, and splicing defect mutations have been implicated in the pathophysiology of GPP, including an autosomal recessive homozygous missense mutation causing the substitution of proline for leucine at amino acid 27 in multiple families.[3] Families who lack IL-36RA have unrelenting disease.[1]

The IL-36 pathway plays a role in acute generalized exanthematous pustulosis (AGEP), too. AGEP presents as erythematous, painful pustules that appear as a reaction to infection or medication.[4] In contrast, psoriasis vulgaris is associated with over 100 genetic loci and HLA genes with the IL-23/TYK2/IL-17 inflammatory pathway playing the key role.[6]

Treatment of GPP is vital to address the severity of symptoms and mortality risk, but because it is so rare, it is seldom a focus of research. With a better understanding of the pathophysiology of GPP, spesolimab was developed to inhibit the IL-36R, replacing the role of the IL-36RA (Figure 1). While it is challenging to do a controlled clinical trial for such a rare, severe disease, the Effisayil trial was established to test the efficacy and safety of spesolimab for GPP.

FIGURE 1. Spesolimab IL-36Ra inhibition and pathways involved in the IL-36 axis. IL-36R is a heterodimeric complex composed of an IL-1RL2 subunit and IL-1RAcP co-receptor. Agonist binding (IL-36α, IL-36β, or IL-36γ) to IL-1RL2 results in IL-1RAcP recruitment and the activation of intracellular pathways. The MyD88/IRAK1/IRAK2/TRAF6 platform with corresponding intracellular signaling results in pro-inflammatory gene expression. Antagonism by IL-36Ra (Spesolimab) and IL-38 inhibits IL-36R signaling (shown in red).



TIR: Toll/interleukin-1 receptor; MyD88: Myeloid differentiation primary response (88); NF-kB: nuclear factor kB; IRAK: Interleukin 1 receptor-associated kinase; TRAF: TNF receptor-associated factor; STAT3: Signal transducer and activator of transcription 3.
Note: Reprinted with permission from "Exploring the Role of IL-36 Cytokines as a New Target in Psoriatic Disease" by Iznardo H and Puig L. 2021. *MDPI.* 22:4344. https://doi.org/10.3390/ijms22094344. CC BY.

MATERIALS AND METHODS

We searched PubMed for: generalized pustular psoriasis, spesolimab, and Effisayil 1. This search returned 11 articles. The titles and abstracts were then reviewed to screen articles for relevance. English-language articles published between 2000 and 2023 were included. Full texts of qualifying articles were downloaded and reviewed. Additional articles were identified using the reference lists of relevant articles and then cited by function on PubMed as well as through additional searches on specific topics. Clinicaltrials.gov was also used to identify clinical trial data for spesolimab including efficacy, safety, and tolerability.

Effisayil 1 Study Design

A controlled clinical trial to assess the efficacy of a treatment for GPP would face many challenges. GPP is a rare condition that manifests acutely and severely. Recruiting enough participants to make statistically significant conclusions would be daunting. Getting systemically ill patients in pain, and their physicians, to risk assignment to placebo for some prolonged period would further complicate recruitment. The tendency for GPP to improve with supportive care in the hospital might make it even harder to show a drug was more effective than a placebo.

Despite all these challenges, the Effisayil study recruited enough patients to collect meaningful data on spesolimab. Researchers overcame the challenges by: enrolling patients across numerous sites, greatly increasing their potential participant pool, with 37 out of 52 participating sites recruiting patients, spanning 12 countries[8]; having families with multiple members affected by GPP aided the achievement of overall recruitment goals; by keeping the placebo period to 8 days, researchers were able to limit the risks associated with delayed treatment; and allowing those assigned to the placebo group to cross over to active drug after 8 days further encouraged enrollment. Despite the small sample size, statistically significant results were seen

as spesolimab was highly effective in treating GPP flares. The improvement in GPP associated with the specific blockade of IL-36 confirmed the critical role IL-36 plays in the pathogenesis of GPP.

Effisayil 1 Study Outcomes

Spesolimab, an anti-IL-36RN monoclonal antibody was tested in the Effisayil 1 study: a multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of spesolimab in GPP flares.[9,10] Patients (*n = 53*) experiencing a GPP flare were randomly assigned to either receive one 900 mg intravenous dose of spesolimab (*n = 35*) or placebo (*n = 18*) and results were assessed after one week.[9,10] Eight days after the initial treatment, 12 of the 34 that completed the experimental group treatment received a second dose of spesolimab. Eight days after the initial treatment, 12 of the 34 who completed the experimental group treatment received a second dose of spesolimab. After this, four additional participants received a second dose. At 12 weeks, 32 experimental participants were reassessed.[10] Additionally, 15 of the original placebo patients received a dose of spesolimab after the first assessment period. Pain, itching, burning, redness, quality of life, and fatigue were evaluated via multiple-choice self-report surveys. Physician-reported outcomes were measured by the GPPGA pustulation subscore and total score.[10]

Even just one week after treatment, physician-reported outcomes improved in the experimental group compared to the placebo group. A GPPGA total score of zero was achieved by 42.9% of the experimental group, but only 11.1% of the placebo group, and a GPPGA pustulation subscore of zero was achieved by 54.3% of the experimental group compared to 5.6% of the placebo group (Table 1, 2).[8] The placebo group had similar improvement after crossover to active treatment.[10] Outcomes improved consistently over the 12-week study.[8] Additionally, spesolimab improved self-reported pain, itching, burning, redness, quality of life, and fatigue.[10] Despite a small sample size, spesolimab enhanced quantitative and qualitative patient outcomes. Throughout the first week of the trial, 66.7% of placebo group participants and 77.1% of experimental group participants experienced adverse effects ranging in severity (Table 3).[8] However, only 33.3% of placebo group patients and 34.3% of experimental group patients' adverse effects were defined as "drug related." Most experiences were mild, though some severe reactions did occur.[8] The frequency of skin disorders, general disorders, infections, and nervous system disorders were similar between the 2 groups. The dropout rates were 5.56% and 8.57% for the placebo and treatment groups, respectively (Table 4). Of those remaining in the study, 11.12% of the placebo group received spesolimab rescue treatment after the first week while 11.42% of the treatment group received rescue treatment.[8]

Pustular psoriasis was the most common adverse effect reported.[8] With such severe symptoms and potential consequences, the ability of spesolimab to improve generalized pustular psori-

TABLE 1.

Demographics and Efficacy Parameters		
	Placebo	Spesolimab
Demographics		
Mean Age	43.2	42.6
Female	83.3%	60.0%
White	27.8%	54.3%
Asian	72.2%	45.7%
Original GPPGA Efficacy Parameters		
GPPASI Total	24.1	27.8
Pain VAS	64.6	76.4
PSS	10.3	10.4
FACIT-Fatigue	19.0	18.1
CRP	72.2%	57.1%

TABLE 2.

Efficacy and Clinical Pharmacology Results			
	Placebo	Spesolimab	Significance
	n	n	*P*
Week 1			
GPPGA Pustulation Subscore = 0	5.6	54.3	0.0004
GPPGA Total	11.1	42.9	0.0118
Week 4			
GPPASI 75	11.1	45.7	0.0081

TABLE 3.

Adverse Effects		
	Placebo	Spesolimab
	n	n
Patients with adverse effect reports	12	27
Severe (RCTC grade 3 or 4)	2	6
Serious adverse event reported	3	5
Investigator-defined drug-related	6	12

TABLE 4.

Study Flow		
	Placebo	Spesolimab
Patients with adverse effect reports	12	27
Participants at study start	18	35
Spesolimab treatment: week 1, day 8	15	12
Spesolimab treatment: after week 1 (rescue treatment)	2	4
Participants at study completion	17	32

asis symptoms in only 8 days is a remarkable accomplishment. The drug should be further studied for periods longer than 12 weeks to determine long-term results and use as maintenance treatment in the future.

CONCLUSION

GPP is a rare and often life-threatening skin condition characterized by painful pustulation. Due to how rare the disease is, the Effisayil 1 study had many challenges to overcome in order to complete a pharmaceutical trial. By enrolling patients from multiple study centers, including families experiencing GPP, and limiting the placebo period, this study was able to collect enough data to change the way GPP treatment is considered. Spesolimab has opened a new target of treatment for GPP by interacting directly with IL-36 receptors, a mutation that affects many individuals. The IL-36RN mutation, however, was not a requirement for spesolimab efficacy as patients with the mutation and without had improvement in symptoms. Encouraging results were seen in recent open-label Phase II clinical trials. When compared with placebo subgroups with GPP flares, spesolimab efficacy and safety profiles had clearance of skin and pustule development within just one week, and similar improvements in inflammation. The success of this trial defines a model for identifying key pathophysiology of a rare disease and developing a uniquely challenged-focused protocol to trial pharmaceutical intervention.

While spesolimab was effective for GPP flares, more needs to be known about its use in long-term GPP control. Recurrence of flares is a concern for patients afflicted with GPP. As such, developing treatment strategies to prevent future flares may facilitate disease management. Future research directives could build on knowledge of spesolimab's efficacy in reducing flares in the long term. Effisayil 2, a Phase II clinical trial of spesolimab, focused on sustained control of GPP. In this trial, subcutaneous spesolimab was effective in GPP flare prevention for up to 48 weeks. Effisayil ON trial, an extended study focused on long-term safety and outcomes, is ongoing.[11] Spesolimab safety data were consistent with previous trials. Spesolimab remains the most successful trial in GPP treatments thus far. IL17 inhibitors were approved for use in Japan, but do not have enough data to support their efficacy in comparison to spesolimab.[12]

Finally, there is an overlap in GPP and plaque psoriasis in the patient populations observed in the study. Further treatment development requires a better understanding of the pathophysiology behind GPP and the signaling pathways in common with other dermatologic conditions. Additionally, addressing patient adherence to other anti-inflammatory therapy options, such as TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors, may still play a role in long-term GPP control. Optimizing such treatments may help minimize the need for treating GPP flares. Spesolimab, a targeted IL-36R inhibitor, is an efficacious treatment option for GPP flares and may play a role in flare prevention in the future. Its pharmaceutical trial faced several obstacles but was ultimately a successful undertaking that will hopefully improve patients' lives.

DISCLOSURES

Feldman has received research, speaking and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, Eurofins, Informa, UpToDate and the National Psoriasis Foundation. He is the founder and part owner of Causa Research and holds stock in Sensal Health. Abukhadra and Parraga have no conflicts to disclose.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Frequency of Non-Scarring Alopecia in Autoimmune Connective Tissue Diseases

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ABSTRACT

Background: Autoimmune connective tissue diseases (ACTDs) are relatively rare systemic diseases featured by immune dysregulation and often have prominent cutaneous manifestations. The most common is systemic lupus erythematosus (SLE), dermatomyositis (DM), systemic sclerosis (SSc), Sjogren syndrome (SJO), undifferentiated connective tissue disease (UCTD), and mixed connective tissue disease (MCTD). Alopecia is one of the most common symptoms of these diseases, with significant impact on the quality of life of these patients.

Objective: Our aim is to better characterize non-scarring alopecia in ACTDs.

Methods: A retrospective chart review study of patients seen at the Autoimmune Connective Tissue Diseases clinic at Massachusetts General Hospital, Boston, MA, was conducted from November 2012 to January 2018. The study was reviewed and approved by Partners IRB.

Results: A total number of 1486 visits where 734 were new patients, and 241 patients with ACTDs included in our analysis. Of the new patients, 80% were female and 20% were male, with an average age of 51 years. Of patients with MCTD, 46.6% presented with non-scarring alopecia at their initial evaluation. Of patients with SLE, 36% presented with non-scarring alopecia. Of the 32 patients with SJO, 28% reported diffuse non-scarring alopecia. Of patients with UCTD, 22% presented with diffuse non-scarring alopecia. Only 9.5% of our patients with DM and 9% of our patients with SSc presented with diffuse non-scarring alopecia.

Conclusion: Alopecia is common in all ACTDs and often under evaluated. Treatment of alopecia in ACTDs can be challenging, and oftentimes patients require joint management and work-up.

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INTRODUCTION

Alopecia is a common troubling symptom in dermatology. It can be divided into various categories and is usually classified clinically and histopathologically into scarring and non-scarring alopecia.[1] It can also be subdivided based on etiology such as genetic, nutritional deficiency, endocrine, infectious, and autoimmune. There is an overlap between these categories, eg, scarring alopecia can be autoimmune, but not all autoimmune alopecias are scarring.[1] The human hair follicles are immune-privileged structures, and under normal circumstances, they are protected from immune damage.[2] Autoimmune-associated hair loss results whenever there is a collapse in this immune privilege. Autoimmune alopecia refers to hair loss secondary to an underlying autoimmune skin disease. This includes alopecia from lichen planopilaris (LPP), bullous diseases, and connective tissue diseases. In this paper, we focused on autoimmune connective tissue disease (ACTD)-related hair loss, and in particular non-scarring alopecia. ACTDs are a relatively rare group of multisystem diseases characterized by immune dysregulation and autoantibodies. The most common include systemic lupus erythematosus (SLE), dermatomyo¬sitis (DM), systemic sclerosis (SSc), Sjogren syndrome (SJO), undifferentiated connective tissue disease (UCTD), and mixed connective tissue disease (MCTD). They usually present with characteristic signs and symptoms. Cutaneous manifestations and hair loss are common in ACTDs. There are few studies of alopecia in ACTDs, and most of them focus on SLE and discoid lupus erythematosus (DLE). However very little is known about alopecia in other less common ACTDs. We performed this study to better understand the frequency and characteristics of non-scarring alopecia in different ACTDs.

MATERIALS AND METHODS

This study was performed to characterize non-scarring alopecia, timing relative to disease onset of hair loss in different ACTDs, to identify if these characteristics can be related to potentially different etiologies of non-scarring alopecia, and to examine the frequency with which non-scarring alopecia is evaluated and treated in ACTDs in standard vs specialty dermatology-rheumatology clinical care.

TABLE 1.

Autoimmune Patients
Showing the number of patients with autoimmune connective tissue diseases (ACTDs) who presented with alopecia at our clinic.

ACTDs	Total number of patients	With Alopecia	Without Alopecia
SLE	95	40	55
DM	42	4	38
SJO	32	9	23
SSc	32	5	27
MCTD	15	7	8
UCTD	14	4	10
Recalcitrant scalp DLE without SLE	11	11	0

SLE, Systemic lupus erythematosus; DM, Dermatomyositis; SJO, Sjogren syndrome; SSc, Systemic sclerosis; MCTD, Mixed connective tissue disease; UCTD, Undifferentiated connective tissue disease; DLE, Discoid lupus erythematosus.

We performed a retrospective chart review of all patients seen at the Rheum-Derm clinic, currently known as autoimmune connective tissue disease clinic, at Massachusetts General Hospital, Boston, MA, between November 2012 and January 2018. The study was reviewed and approved by Partners IRB (protocol # 2014P001562). The chart review was performed by the author.

Presence and frequency of hair loss were extracted from patient history of the present illness and physical examination, and underlying cause of alopecia from the assessment and plan. Patients included in the study were those with a confirmed diagnosis of SLE, DM, SJO, SSc, MCTD, UCTD, or recalcitrant scalp DLE by independent board-certified rheumatologists in consultation with board-certified dermatologists specifically trained in this area. Gender pattern hair loss, alopecia areata, scarring alopecia, and telogen effluvium were excluded. Scalp biopsy was performed only in a few selected cases where histopathology was needed to confirm the diagnosis.

Patients with a different diagnosis, such as localized scleroderma, generalized morphea, vasculitis, sarcoid, psoriasis, psoriatic arthritis, etc., were not included in our analysis. We also reviewed the evaluation and treatment for alopecia for this patient set in the visit-documentation of dermatology, rheumatology, or referring physicians, preceding their visit to Derm-Rheum clinic.

RESULTS

Of the total 1486 visits, 734 patients were evaluated, of whom 241 patients with ACTDs fit our criteria. The sample age ranges from 16 years to 94 years with a mean age of 51 years, and 80% of the sample was female. Of the 241 patients with ACTDs, 42.2% complained of hair loss during our initial clinic evaluation (Table 1). Rheumatologists documented alopecia in only 16% of the patients they referred; whereas, dermatologists documented alopecia in 89% of the patients they referred.

Of the 95 patients with SLE, 6% presented with scarring alopecia secondary to concomitant scalp DLE; whereas, 36% presented with non-scarring alopecia, not attributable to other causes. The most common pattern and location of SLE-associated non-scarring alopecia was multiple patches all over scalp in 48%, patchy pattern of posterior scalp in 20%, patchy pattern of temporal scalp in 16%, and patchy pattern of central scalp in 12% of patients. Forty-two patients with DM were evaluated, of whom only 4 patients (9.5%) presented with hair loss at the initial visit.

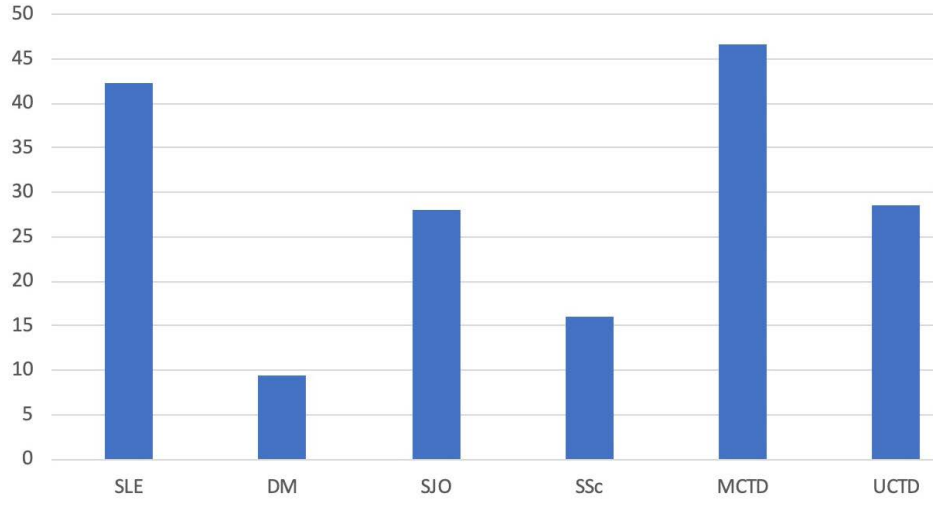
In 32 patients with SJO, only 9 patients (28%) reported hair loss. The duration of hair loss was reported as >6 months in 86%, and <6 months in 14% of patients. Thirty-two patients with SSc were evaluated at our clinic of whom only 9% had diffuse non-scarring alopecia. Of our 15 patients with MCTD, 7 patients (46.6%) had diffuse non-scarring alopecia at their initial visit. We evaluated 14 patients with UCTD, of whom 21.4% presented with diffuse non-scarring alopecia. Eleven patients with recalcitrant scalp DLE were referred to our clinic for further management. Four patients developed hair loss from treatment of their ACTDs.

DISCUSSION

Most of the cases were referred by rheumatologists (52.7%) and dermatologists (26.5%). Primary care physicians referred 17% of the cases, and 3.5% of the cases were referred by other specialties including allergy, nephrology, neurology, cardiology, pulmonology, surgery, and oncology. The most common condition was SLE, but a significant number of other ACTDs were also seen (Figure 1). Alopecia was documented in 100% of the Derm-Rheum clinic notes, while 89% of dermatology notes and 16% of rheumatology notes prior to Derm-Rheum clinic visit documented alopecia.

The most well-described form of alopecia in ACTDs is scalp DLE or chronic cutaneous lupus erythematosus (CCLE), which

FIGURE 1. Showing the percentage of patients with autoimmune connective tissue diseases (ACTDs) who presented with alopecia at our clinic.



SLE, Systemic lupus erythematosus; DM, Dermatomyositis; SJO, Sjogren syndrome; SSc, Systemic sclerosis; MCTD, Mixed connective tissue disease; UCTD, Undifferentiated connective tissue disease; DLE, Discoid lupus erythematosus.

can occur in isolated DLE or as a manifestation of SLE. We evaluated 95 patients with SLE, of whom 6% presented with scarring alopecia secondary to concomitant scalp DLE, and 36% presented with non-scarring alopecia not attributable to other causes. Although DLE alopecia is the most recognized and most serious form, given its scarring and disfiguring nature, it is not the most common form of SLE-associated alopecia. A cross-sectional study of alopecia patterns in 122 Korean patients with SLE found diffuse non-scarring alopecia to be the most common form of SLE-associated alopecia among that cohort.[3] Non-scarring alopecia is now part of the Lupus International Collaborating Clinics classification criteria 2012 (SLICC'12).[4] The duration of alopecia in our patients with SLE ranged from 2 months to 30 years, and 38% of our patients with alopecia had SLE <2 years, 36% for 3 to 10 years, and 26% >10 years. This suggests that alopecia is associated with SLE at all stages regardless of the disease duration. However, clinically, alopecia increased during flares of underlying SLE with 20% of patients reporting alopecia as significant. On the other hand, some patients with SLE >10 years had prior episodes of alopecia, while others noted no such history, suggesting that alopecia may not be a consistent feature of any individual disease.

Scalp pruritus and erythema are well-known in DM; however, data about hair loss is limited. Kasteler et al, in 1994, described scalp involvement in 14 of 17 patients with DM, and 6 of the 14 patients (43%) had severe non-scarring alopecia.[5] More recently, in 2011, Fiorentino et al reported diffuse non-scarring alopecia in 22 of 77 patients with DM.[6] We evaluated 42 patients with DM patients, of whom 41 had a disease duration <2 years at initial presentation, and 34% patients had scalp itching since the time of diagnosis. Only 4 patients (9.5%) presented with diffuse non-scarring alopecia at the initial visit. In our study, alopecia was less frequently reported than in the above studies. The explanation may be because most of the patients were referred to our specialty Derm-Rheum clinic for diagnosis and or controlling severe disease, and all of our patients with DM had disease <2 years. Once they are in remission, they return for follow-up with their primary referring physician. If we follow patients with DM for longer period and collect data over the next decade, the frequency of hair loss most likely will be higher. A longitudinal larger study is needed to characterize alopecia in DM.

To our knowledge, there are no studies that specifically described non-scarring alopecia in SJO. Of our 32 patients with SJO, 9 patients (28%) reported diffuse non-scarring alopecia. Scalp itching was reported in 16% of patients. In contradistinction with DM, hair loss was more bothersome than scalp itching in patients with SJO. The disease duration in our patients with SJO was >1 year in 21%, 3 to 5 years in 37%, and >10 years in 42% of patients. Of the patients with alopecia, 86% reported that their alopecia was equivalent to their disease chronicity; whereas, 14% reported their alopecia is recent and not related to their disease duration.

Similar to SJO, studies of non-scarring alopecia in SSc are lacking. Thirty-two SSc patients (10 with diffuse SSc, 22 with limited SSc) were evaluated at our Derm-Rheum clinic. Only 3 patients (9%) had diffuse non-scarring alopecia (2 with diffuse SSc and 1 with limited SSc), all reported chronic hair loss related to their chronic disease.

MCTD is a connective tissue disorder characterized by the presence of high titers of ribonucleoprotein autoantibody and clinical features of SLE, systemic sclerosis, rheumatoid

arthritis, and polymyositis.[7] Gilliam et al, in 1977, reported focal and diffuse non-scarring alopecia in 10 of 15 patients with MCTD.[8] In 2008, a cross-sectional study of patients with MCTD found alopecia in 16 of 21 patients (76%).[9] The first study was done by a dermatologist, while the second study was done by rheumatologists. We evaluated and followed 15 patients with MCTD, of whom 7 (46.6%) presented with non-scarring alopecia at their initial evaluation. They reported that their hair loss duration was related to the chronicity of their disease. All improved with topical treatment and controlling their underlying MCTD.

Patients who have characteristic features of systemic ACTD, but do not meet the criteria for classification of a particular ACTD are often considered to have UCTD. About 34% of the patients with UCTD eventually develop a well-defined ACTD.[7] We evaluated 14 patients with true UCTD, of which 3 patients (22%) presented with diffuse non-scarring alopecia. One patient had scarring alopecia, and the scalp biopsy confirmed LPP. An Italian study of 79 patients with true UCTD with mean follow-up period of 3 years reported alopecia in 22% of patients. Although they did not report what type of alopecia and whether it was related to the underlying disease. The frequency of alopecia in their patients is similar to ours.[10]

Eleven patients with recalcitrant scalp DLE, without systemic lupus, were referred to our Derm-Rheum clinic for management. Currently, there are no medications approved specifically for DLE. First-line treatment for DLE includes photoprotection with topical, intra-lesional, or oral corticosteroids, topical calcineurin inhibitors, and systemic antimalarial medications.[11] All 11 patients failed conventional first-line treatment. All complained of scarring alopecia, itching, and pain. We managed and followed 6 patients, For the remaining 5 patients, we sent our recommendations to their primary referring physician. We were able to control the disease with mycophenolate mofetil in 2 patients. Two patients were stable on combination hydroxychloroquine and methotrexate. We were able to control the disease with methotrexate and quinacrine in 1 patient and with methotrexate and chloroquine in 1 patient. DLE can be severe, and aggressive treatment is warranted to control the condition to prevent scarring and alleviate pain.

Finally, in some patients, the medications used to treat their underlying ACTD, such as hydroxychloroquine or methotrexate, can cause hair loss and should be always carefully reviewed.[12,13] We had 4 patients who developed non-scarring alopecia secondary to treatment of their ACTDs. Two patients had hair loss secondary to methotrexate and their alopecia resolved completely after discontinuing methotrexate. The other 2 patients had diffuse non-scarring alopecia secondary to hydroxychloroquine, which improved after switching to another immunosuppressant.

CONCLUSION

Hair loss is a common problem in dermatology, however data about alopecia in ACTDs are sparse. Non-scarring alopecia is the most common form of alopecia in SLE. Non-scarring alopecia is also common in other rare ACTDs and often under-evaluated. With this study, we intended to increase the awareness of non-dermatologists and dermatologists alike in identifying this type of alopecia in all ACTDs. Finally, the medications used to treat ACTDs can cause hair loss and should be carefully reviewed.

Limitations of our study include that our data on alopecia history and duration of the episode is mainly based on patient reports, and patients may not accurately note onset, or differentiate causes of alopecia (ACTD-related vs androgenetic). Larger longitudinal studies as we accumulate data over decades in our Derm-Rheum clinic may help answer this question more definitively.

DISCLOSURES

The author has no conflict to disclose.

IRB approval status: Reviewed and approved by Partners IRB; approval # 2014P001562

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The most common adverse reactions (≥1%) for ZORYVE cream 0.15% for atopic dermatitis include headache (2.9%), nausea (1.9%), application site pain (1.5%), diarrhea (1.5%), and vomiting (1.5%).

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The most common adverse reactions (≥1%) for ZORYVE cream 0.3% for plaque psoriasis include diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain (1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%).

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INDICATIONS

ZORYVE cream, 0.15%, is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.

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*Two Phase 3 multicenter, randomized, double-blind, vehicle-controlled studies (INTEGUMENT-1 & INTEGUMENT-2) evaluated 1337 participants with mild to moderate atopic dermatitis ages 6 years and older. Participants applied ZORYVE or vehicle once daily. Primary endpoint was vIGA-AD Success at Week 4; ZORYVE cream = 884, vehicle = 453. WI-NRS Success at Week 4 was a key secondary endpoint; ZORYVE cream = 542, vehicle = 271.[1]

†Two multicenter, randomized, double-blind, vehicle-controlled studies (STRATUM and Trial 203) evaluated 683 participants with moderate to severe seborrheic dermatitis treated with ZORYVE or vehicle once daily for 8 weeks. STRATUM: ZORYVE foam = 304, vehicle = 153. Trial 203: ZORYVE foam = 154, vehicle = 72. Primary endpoint was IGA Success at Week 8.[2]

‡Two Phase 3 randomized, parallel, double-blind, vehicle-controlled, multicenter studies (DERMIS-1 and DERMIS-2) evaluated 881 participants with plaque psoriasis treated with ZORYVE or vehicle once daily for 8 weeks. ZORYVE = 576, vehicle = 305. Primary endpoint was IGA Success at Week 8.[1]

IGA Success/vIGA-AD Success = Achievement of Clear (0)/Almost Clear (1) and a ≥2-grade improvement from baseline.
IGA = Investigator Global Assessment. vIGA-AD = Validated Investigator Global Assessment—Atopic Dermatitis.
WI-NRS Success defined as a ≥4-point improvement for patients with a baseline score ≥4. WI-NRS: 0 (no itch) to 10 (worst imaginable itch).
WI-NRS = Worst Itch Numeric Rating Scale.

References: 1. ZORYVE® cream. Prescribing information. Arcutis Biotherapeutics, Inc; 2024. **2.** ZORYVE® foam. Prescribing information. Arcutis Biotherapeutics, Inc; 2023. **3.** Data on File. Arcutis Biotherapeutics, Inc. **4.** Pickett K, Loveman E, Kalita N, Frampton GK, Jones J. Educational interventions to improve quality of life in people with chronic inflammatory skin diseases: systematic reviews of clinical effectiveness and cost-effectiveness. *Health Technol Assess.* 2015;19(86). **5.** Hessler-Waning M, Heinecke G. Diagnosis and management of common inflammatory skin diseases in older adults. *Clin Geriatr Med.* 2024;40:11-23. **6.** Harvard Health Publishing. Special Health Reports – Inflammatory skin conditions: eczema, seborrheic dermatitis, and psoriasis. *Harvard Medical School Guide*; 2023. Accessed Feburary 3, 2025. https://www.health.harvard.edu/diseases-and-conditions/inflammatory-skin-conditions-eczema-seborrheic-dermatitis-and-psoriasis. **7.** Simpson E, Boguniewicz M, Eichenfield L, et al. Pooled efficacy, patient-reported outcomes, and safety of roflumilast cream 0.15% from the INTEGUMENT-1 and INTEGUMENT-2 Phase 3 clinical trials of adults and children with atopic dermatitis. Poster presented at: American Academy of Dermatology Annual Meeting; March 8-12, 2024; San Diego, CA. **8.** Lebwohl M, Gooderham MJ, Guenthner ST, et al. Pooled efficacy and safety results from the DERMIS-1 and DERMIS-2 Phase 3 trials of once-daily roflumilast cream 0.3% for the treatment of plaque psoriasis. Poster presented at: American Academy of Dermatology Annual Meeting; March 25-29, 2022; Boston, MA.

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US-COM-PTF-00190 v2.0 01/2025

ZORYVE® (roflumilast)

Brief Summary of Prescribing Information for ZORYVE® (roflumilast) cream, 0.15%, ZORYVE® (roflumilast) cream, 0.3%, and ZORYVE® (roflumilast) foam, 0.3%, for topical use. See package insert for full Prescribing Information.

INDICATIONS AND USAGE

ZORYVE cream, 0.3%, is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in adult and pediatric patients 6 years of age and older.

ZORYVE cream, 0.15%, is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.

ZORYVE foam, 0.3%, is indicated for the treatment of seborrheic dermatitis in adult and pediatric patients 9 years of age and older.

DOSAGE AND ADMINISTRATION

Use ZORYVE cream, 0.3%, for the treatment of plaque psoriasis.

Use ZORYVE cream, 0.15%, for the treatment of mild to moderate atopic dermatitis.

Apply ZORYVE cream to affected areas once daily and rub in completely. Wash hands after application, unless ZORYVE cream is for treatment of the hands.

Use ZORYVE foam, 0.3%, for the treatment of seborrheic dermatitis.

Shake can prior to each use. Apply a thin layer of ZORYVE foam, 0.3%, once daily to affected areas on skin and/or scalp when they are not wet. Rub in completely.

Wash hands after application.

Avoid fire, flame, and smoking during and immediately following application.

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use.

CONTRAINDICATIONS

ZORYVE is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

Plaque Psoriasis

In two multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 and DERMIS-2), 881 adult and pediatric subjects 6 years of age or older with plaque psoriasis were treated with ZORYVE cream, 0.3%, or vehicle cream once daily for 8 weeks.

The median age was 47 years (range 6 to 88). The majority of the subjects were male (64%) and White (82%). The median body surface area (BSA) affected was 5.5% (range 2% to 20%). The proportion of subjects who discontinued treatment due to an adverse reaction was 1.0% for subjects treated with ZORYVE cream, 0.3%, and 1.3% for subjects treated with vehicle cream. The most common adverse reaction that led to discontinuation of ZORYVE cream, 0.3%, was application site urticaria (0.3%).

Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE cream, 0.3%, and for which the rate exceeded the rate for vehicle cream.

Table 1: Adverse Reactions Reported in ≥1% of Subjects with Plaque Psoriasis Treated with ZORYVE Cream, 0.3%, (and More Frequently than Vehicle Cream) for 8 Weeks in Trials DERMIS-1 and DERMIS-2

Adverse Reaction	ZORYVE Cream, 0.3% (N=576) n (%)	Vehicle Cream (N=305) n (%)
Diarrhea	18 (3.1)	0 (0.0)
Headache	14 (2.4)	3 (1.0)
Insomnia	8 (1.4)	2 (0.7)
Nausea	7 (1.2)	1 (0.3)
Application site pain	6 (1.0)	1 (0.3)
Upper respiratory tract infection	6 (1.0)	1 (0.3)
Urinary tract infection	6 (1.0)	2 (0.7)

In 594 subjects with plaque psoriasis who continued treatment with ZORYVE cream, 0.3%, for up to 64 weeks in open-label extension trials, the adverse reaction profile was consistent with that observed in vehicle-controlled trials.

Atopic Dermatitis

In two multicenter, randomized, double-blind, vehicle-controlled trials (INTEGUMENT-1 and INTEGUMENT-2), 1336 adult and pediatric subjects 6 years of age or older with mild to moderate atopic dermatitis were treated with ZORYVE cream, 0.15%, or vehicle cream once daily for 4 weeks.

The median age was 20 years (range 6 to 91). The majority of the subjects were female (57%) and White (60%). The median body surface area (BSA) affected was 10% (range 3% to 88%).

The proportion of subjects who discontinued treatment due to an adverse reaction was 1.6% for subjects treated with ZORYVE cream, 0.15%, and 1.1% for subjects treated with vehicle cream.

Table 2 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE cream, 0.15%, and for which the rate exceeded the rate for vehicle cream.

Table 2: Adverse Reactions Reported in ≥1% of Subjects with Atopic Dermatitis Treated with ZORYVE Cream, 0.15%, (and More Frequently than Vehicle Cream) for 4 Weeks in Trials INTEGUMENT-1 and INTEGUMENT-2

Adverse Reaction	ZORYVE Cream, 0.15% (N=885) n (%)	Vehicle Cream (N=451) n (%)
Headache	26 (2.9)	4 (0.9)
Nausea	17 (1.9)	2 (0.4)
Application site pain	13 (1.5)	3 (0.7)
Diarrhea	13 (1.5)	2 (0.4)
Vomiting	13 (1.5)	2 (0.4)

The adverse reaction of insomnia was reported in fewer than 1% of subjects treated with ZORYVE cream, 0.15%.

Seborrheic Dermatitis

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 203 and STRATUM), 683 adult and pediatric subjects 9 years of age or older with seborrheic dermatitis were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks.

The combined trial population was 79% White, 11% Black, and 5% Asian; for ethnicity, 79% identified as non-Hispanic/Latino and 21% identified as Hispanic/Latino. Fifty percent (50%) were male and 50% were female. The median age was 41 years (range 9 to 87 years). The median body surface area (BSA) affected was 2.5%.

Table 3 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE foam, 0.3%.

Table 3: Adverse Reactions Reported in ≥1% of Subjects with Seborrheic Dermatitis Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 203 and Trial STRATUM

Adverse Reaction	ZORYVE foam, 0.3% (N=458) n (%)	Vehicle foam (N=225) n (%)
Nasopharyngitis	7 (1.5)	1 (0.4)
Nausea	6 (1.3)	0 (0)
Headache	5 (1.1)	0 (0)

The following additional adverse reactions were reported in fewer than 1% of subjects treated with ZORYVE foam, 0.3%: diarrhea and insomnia.

In 408 subjects who continued treatment with ZORYVE foam, 0.3%, for up to 24 to 52 weeks in an open-label, long-term trial, the adverse reaction profile was consistent with that observed in vehicle-controlled trials.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are insufficient data available on the use of ZORYVE in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 36 and 31 times the maximum recommended human dose (MRHD), respectively, for ZORYVE cream and up to 30 and 26 times the MRHD, respectively, for ZORYVE foam. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 12 times the MRHD for ZORYVE cream and 10 times the MRHD for ZORYVE foam. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 19 and 59 times the MRHD, respectively, for ZORYVE cream and 16 and 49 times the MRHD, respectively, for ZORYVE foam. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 59 times the MRHD for ZORYVE cream and 49 times the MRHD for ZORYVE foam during pregnancy and lactation periods in mice.

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.

Clinical Considerations

Labor and delivery

Avoid using ZORYVE during labor and delivery. There are no human studies that have investigated effects of ZORYVE on preterm labor or labor at term; however, animal studies showed that oral roflumilast disrupted the labor and delivery process in mice.

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (36 times the MRHD for ZORYVE cream and 30 times the MRHD for ZORYVE foam on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (4 times the MRHD for ZORYVE cream and 3 times the MRHD for ZORYVE foam on a mg/m^2 basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (12 times the MRHD for ZORYVE cream and 10 times the MRHD for ZORYVE foam on a mg/m^2 basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (35 times the MRHD for ZORYVE cream and 29 times the MRHD for ZORYVE foam on a mg/m^2 basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (31 times the MRHD for ZORYVE cream and 26 times the MRHD for ZORYVE foam on a mg/m^2 basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (19 and 59 times the MRHD, respectively, for ZORYVE cream and 16 and 49 times the MRHD, respectively, for ZORYVE foam on a mg/m^2 basis). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (19 times the MRHD for ZORYVE cream and 16 times the MRHD for ZORYVE foam on a mg/m^2 basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (59 times the MRHD for ZORYVE cream and 49 times the MRHD for ZORYVE foam on a mg/m^2 basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (116 times the MRHD for ZORYVE cream and 97 times the MRHD for ZORYVE foam on a mg/m^2 basis).

Lactation

Risk Summary

There are no data on the presence of roflumilast or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production.

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZORYVE and any potential adverse effects on the breastfed infant from ZORYVE or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use ZORYVE on the smallest area of skin and for the shortest duration possible while breastfeeding. To avoid direct infant exposure, advise breastfeeding women not to apply ZORYVE directly to the nipple or areola. If applied to the patient's chest, avoid exposure via direct contact with the infant's skin.

Data

Animal data

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.

Pediatric Use

Plaque Psoriasis

The safety and effectiveness of ZORYVE cream, 0.3%, for the topical treatment of plaque psoriasis, including intertriginous areas, have been established in pediatric patients 6 years of age and older. Use of ZORYVE cream, 0.3%, in pediatric patients 6 years of age and older is supported by data from two 8-week, vehicle-controlled, safety and efficacy trials which included 18 subjects 6 to 17 years of age, of whom 11 received ZORYVE cream, 0.3%. Use of ZORYVE cream, 0.3%, in pediatric patients 12 years of age and older is also supported by data from open-label trials of 2 and 24 weeks duration which included 18 subjects 12 to 17 years of age treated with ZORYVE cream, 0.3%. Use of ZORYVE cream, 0.3%, in pediatric patients 6 to less than 12 years of age is also supported by data from one 4-week, open-label, safety and pharmacokinetic (PK) study which included 20 pediatric subjects 6 to less than 12 years of age.

The safety and effectiveness of ZORYVE cream, 0.3%, have not been established in pediatric patients younger than 6 years of age.

Atopic Dermatitis

The safety and effectiveness of ZORYVE cream, 0.15%, for the topical treatment of mild to moderate atopic dermatitis have been established in pediatric patients 6 years of age and older. Use of ZORYVE cream, 0.15%, in this age group is supported by data from two 4-week, vehicle-controlled, safety and efficacy trials which included 615 subjects 6 to 17 years of age, of whom 406 received ZORYVE cream, 0.15%. Use of ZORYVE cream, 0.15%, in pediatric patients 6 years of age and older is also supported by data from 481 pediatric subjects treated with ZORYVE cream, 0.15%, in open-label trials, of which 104 were treated for 52 weeks.

The safety and effectiveness of ZORYVE cream, 0.15%, have not been established in pediatric patients younger than 6 years of age.

Seborrheic Dermatitis

The safety and effectiveness of ZORYVE foam, 0.3%, for the treatment of seborrheic dermatitis have been established in pediatric patients 9 years of age and older. Use of ZORYVE foam, 0.3%, in this age group is supported by data from two 8-week, vehicle-controlled trials which included 32 pediatric subjects 9 to 17 years of age, of whom 17 received ZORYVE foam, 0.3%, and from open-label trials of up to 52 weeks which included 23 pediatric subjects treated with ZORYVE foam, 0.3%. The adverse reaction profile was consistent with that observed in adults.

The safety and effectiveness of ZORYVE foam, 0.3%, in pediatric patients below the age of 9 years have not been established.

Geriatric Use

There were 184 patients 65 years of age and older in clinical studies for plaque psoriasis and atopic dermatitis.

Plaque Psoriasis

Of the 576 patients treated with ZORYVE cream, 0.3%, in the 2 controlled clinical studies for plaque psoriasis, 56 (9.7%) were 65 to 74 years of age and 21 (3.7%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Atopic Dermatitis

Of the 885 subjects patients treated with ZORYVE cream, 0.15%, in the 2 controlled clinical studies for atopic dermatitis, 36 (4.1%) were 65 to 74 years of age and 8 (0.9%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Seborrheic Dermatitis

Of the 683 subjects with seborrheic dermatitis exposed to ZORYVE foam, 0.3%, or vehicle for up to 8 weeks in the controlled clinical trials, 98 (14%) were 65 years of age or older, and 33 (5%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The systemic exposure of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C). No dosage adjustment is needed in patients with mild (Child-Pugh A) hepatic impairment.

PATIENT COUNSELING INFORMATION

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

Flammability

Because the propellants in ZORYVE foam, 0.3%, are flammable, instruct the patient to avoid fire, flame, and smoking during and immediately following application.

Lactation

Advise patients to use ZORYVE on the smallest area of skin and for the shortest duration possible while breastfeeding. Instruct patients who are breastfeeding not to apply ZORYVE directly to the nipple or areola to avoid direct infant exposure. Instruct patients to avoid inadvertent contact of treated areas with infant skin.

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SKIN OF COLOR UPDATE

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Alopecia as an Adverse Event of Immune Checkpoint Inhibitor Therapies: Clinical Evidence and Outcomes

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ABSTRACT

Immunotherapy utilizing immune checkpoint inhibitors (ICIs) such as PD-1, PD-L1, and CTLA-4 inhibitors has revolutionized cancer therapy by enhancing T cell recognition and attack against cancer cells.[1] Immune-related adverse events (irAEs) are a limitation of ICI therapy, encompassing various manifestations such as colitis and cutaneous adverse events such as dermatitis, alopecia, and vitiligo.[2] Hair loss is a common concern of cancer patients as they embark on their therapeutic paths. The evidence on alopecia from isolated clinical trials with ICI therapies is limited and largely lacks diagnostic and prognostic details to help guide patients.[3,4] In this systematic review, we examined the types of alopecia as part of the irAEs of ICI therapy, timing of onset, prognosis, and treatment approaches. Our analysis includes 19 studies describing new-onset non-scarring or scarring alopecia following ICI treatment. Alopecia was a rare adverse event in the setting of ICIs (n=26) with the onset of alopecia occurring within one year of initiating treatment. Slightly over half of the affected patients reported some degree of hair regrowth after attempted alopecia-directed treatments. We discuss available data to increase awareness of this rare but potentially permanent side effect of ICI therapy. Further research is warranted to enhance our understanding of alopecia as an irAE and to optimize patient management strategies.

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INTRODUCTION

Immune checkpoints are inhibitory pathways within the immune system that maintain self-tolerance and regulate the duration and strength of immune responses.[1] Tumors can exploit this mechanism to evade immune surveillance by upregulating the expression of checkpoint molecules, downregulating major histocompatibility complex (MHC) molecules, producing immunosuppressive factors, and altering the tumor microenvironment.[1]

To combat this mechanism, immunotherapy with immune checkpoint inhibitors (ICIs) has emerged as a revolutionary therapy for cancers such as metastatic malignant melanoma, non-small cell lung cancer, and urethral carcinoma.[5] ICIs work by blocking the interaction between checkpoint proteins with their partner proteins, thereby suppressing the inhibitory signaling and allowing the T cells to recognize and attack cancer cells.[6]

Currently, the most widely used ICIs target the programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptors.[6] PD-1 inhibitors bind to the receptor on T cells to block the PD-1/PD-L1 immune-suppressing interaction.[7,8] Examples of these agents include pembrolizumab, nivolumab, and cemiplimab. PD-L1 inhibitors target the ligand portion of the PD-1/PD-L1 interaction and include agents such as atezolizumab, avelumab, and durvalumab.[7,8] CTLA-4 inhibitors such as ipilimumab indirectly regulate CD28/B7 interaction to promote T-cell activation.[9,10]

Despite their therapeutic impact, ICIs are not without limitations. Many studies have shown irAEs due to their modulation of the immune system. These irAEs include skin rash, hypothyroidism, and GI toxicity.[2,11,12] Recently, alopecia has been reported as a rare side effect in patients, however, details to guide patients while on therapy are lacking.[3] The evidence concerning the causal relationship between ICI therapy and alopecia is limited, necessitating further studies to better understand this potential adverse effect. Given the significant physiological stress alopecia can cause, early diagnosis and timely treatment are crucial.[13] Here, we aim to summarize the data on alopecia, both non-scarring and scarring, following ICI therapy, to gain insights into onset, prognosis, and potential treatments.

MATERIALS AND METHODS

A PubMed literature search following the PRISMA guidelines was conducted on April 2023 with the following keywords: "(immune checkpoint OR nivolumab OR pembrolizumab OR cemiplimab OR dostarlimab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR PD-1 OR PD1 OR PD-L1 OR PDL1 OR CTLA4 OR CTLA-4) AND (alopecia OR hair loss)" and "(immune checkpoint OR nivolumab OR pembrolizumab OR cemiplimab OR dostarlimab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR PD-1 OR PD1 OR PD-L1 OR PDL1 OR CTLA4 OR CTLA-4) AND (scarring OR cicatricial OR lichen OR frontal OR lupus OR chronic cutaneous lupus OR graham-little OR mucinosa OR central centrifugal OR folliculitis OR dermatosis)". Inclusion criteria included clinical trials, case reports, case series, and retrospective studies that discuss the onset of both non-scarring and scarring alopecia as a side effect of immunotherapy. Exclusion criteria included articles that discuss mixed use of immunotherapy (Figure 1). Data from relevant studies included study type, patient demographics, diagnosis, type of ICI, number and intervals of ICI treatments, onset of alopecia after first/initial ICI treatment, alopecia diagnosis, treatment of alopecia, and hair regrowth outcome.

RESULTS

A total of 19 articles were identified after screening: 17 case reports, 1 randomized controlled trial, and 1 retrospective case study (Figure 1, Table 1). Twenty-seven patients who experienced hair loss following ICI therapy were identified among these records. Among 26 patients, 14 received treatment with PD-1 inhibitors, 2 with PD-L1 inhibitors, and 3 with CTLA-4 inhibitors. Seven patients received a PD-1 and CTLA-4 inhibitor combination therapy. Alopecia onset occurred 2 to 9 months after the initiation of immune checkpoint inhibitor (ICI) therapy. Of 20 patients who received treatment for hair loss, 12 (60%) reported hair regrowth.

PD-1 Inhibitor (Nivolumab, Pembrolizumab)

PD-1 inhibitors were the most commonly listed ICI in patients who experienced hair loss. It is unclear if this is due to PD-1 inhibitors being most commonly prescribed. Fourteen patients in this study have solely used PD-1 inhibitors (nivolumab n=7, pembrolizumab n=7).[14-25] Alopecia areata (AA), lichen planoplanus (LPP), eosinophilic folliculitis, and erosive pustular dermatosis of the scalp (EPDS) were noted as an irAE. Patients were being treated for malignancies such as melanoma,

FIGURE 1. PRISMA Diagram. Process of inclusion of studies.

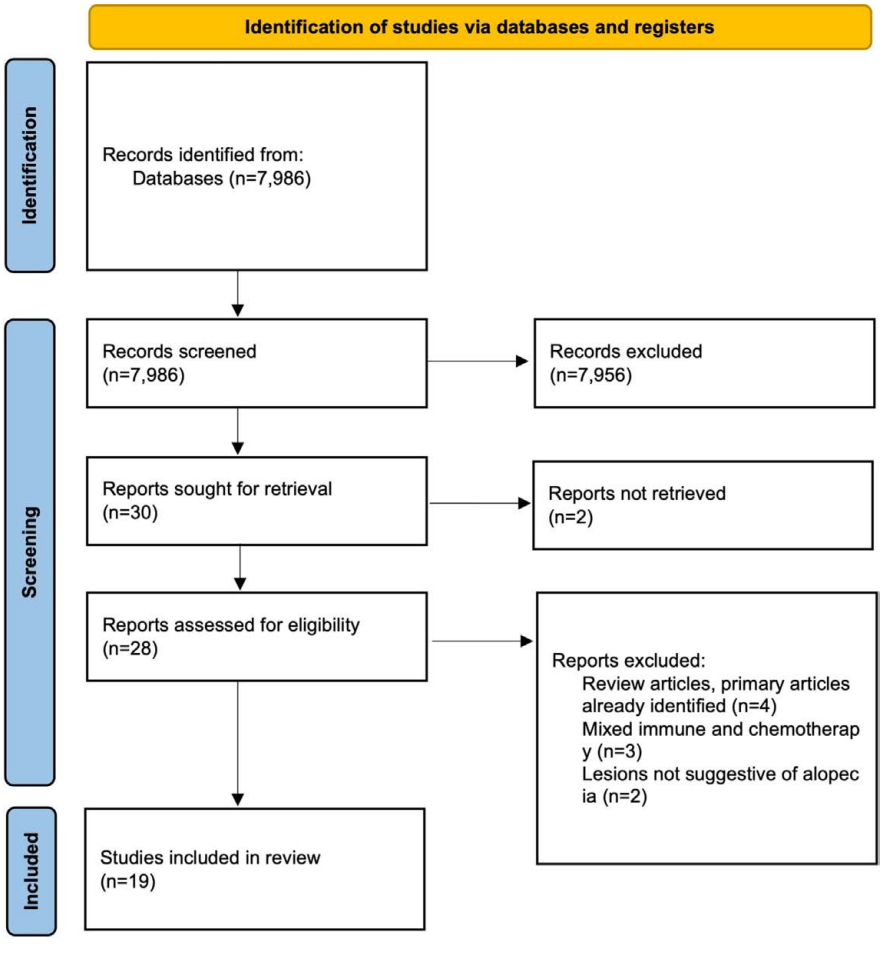


TABLE 1.

Summary of Current Literature on Alopecia as a Side-Effect of Immune Checkpoint Inhibitor Therapy

Authors (Year)	Study Type	Patient Age, Gender	ICI Type	ICI treatment duration	Alopecia Onset (time after first treatment, unless specified)	Alopecia Diagnosis	Treatment for Hair Loss	Regrowth after Treatment?
PD-1 Inhibitors								
Guidry et al (2018)	CR	64, F	Pembrolizumab	Unknown	9 months	AA	Treatment declined	Y
Kim et al (2021)	CR	55, M	Nivolumab	6 months	5 months	AA	Triamcinolone intralesional injections, topical steroids, minoxidil	N
Uthayakumar et al (2021)	CR	62, F	Pembrolizumab	2 years	9 months	LPP	Clobetasol lotion, 0.1% topical tacrolimus, oral doxycycline started, hydroxychloroquine 200 mg, prednisolone, triamcinolone scalp injection, 5% minoxidil topical, 0.1% tacrolimus topical	N
Rossi et al (2020)	CR	65, M	Nivolumab	Unknown	2 months	Eosinophilic folliculitis	Clobetasol propionate cream, topical lotion (2.4% minoxidil, 0.08% hydrocortisone butyrate)	N
Braasch et al (2022)	CR	76, F	Pembrolizumab	2.5 years	2 years	LPP	Topical clobetasol 0.5 mg/g solution	Unknown
	CR	63, F	Nivolumab	Unknown	16 weeks	LPP	Topical clobetasol 0.5mg/g	Unknown
Elshimy et al (2019)	CR	59, M	Pembrolizumab	Unknown	21 months	AA	Unknown	Unknown
Galli et al (2019)	CR	58, M	Nivolumab	Unknown	23 months	AA (universalis)	Topical steroids	N
Lakhmiri et al (2018)	CR	54, F	Nivolumab	26 months	6 months	AA (universalis)	Clobetasol gel and foam, intralesional triamcinolone	N
	CR	64, F	Nivolumab	30 months	15 months	AA	Foam and shampoo corticosteroid	Y
Magile et al (2020)	CR	72, M	Nivolumab	Unknown	2 months	EPDS	None	Y
Garcia-Melendo et al (2022)	CR	62, M	Pembrolizumab	Unknown	16 weeks	LPP	Clobetasol propionate 0.05% lotion once daily	Y
Hara et al (2022)	CR	73, M	Pembrolizumab	Unknown	6 months	AA	Topical steroids and phototherapy for 2 months	Y
Shen et al (2018)	RCS	67, M	Pembrolizumab	Unknown	18 weeks	AA	Unknown	Unknown
PD-L1 Inhibitors								
Kinoshita-Ise et al (2019)	CR	79, F	Atezolizumab	Unknown	4 weeks	AA	clobetasol lotion, minoxidil 5% foam on scalp	Y
Domingues-Santas et al (2021)	CR	61, M	Avelumab	Unknown	6 months	LPP	Clobetasol propionate 0.05% solution QD. 2 weeks, then twice a week for maintenance Doxycycline 100 mg QD for 3 months	Y
CTLA-4 Inhibitors								
Assi et al (2013)	CR	54, M	Ipilimumab	1-2 months for induction, 34 months for maintenance	1-2 months	AA (universalis)	Unknown	Unknown
Pearson et al (2019)	CR	88, M	Ipilimumab	12 weeks	17 months after last treatment	AA	Unknown	Unknown
Jaber et al (2006)	RCT	35, M	CTLA-4 inhibitor	Unknown	7 weeks	AA (universalis)	Bland emollients (no topical steroids)	N
Combined ICI Therapy								
Zarbo et al (2017)	CR	67, F	CTLA-4 and PD-1 inhibitors (Unspecified)	Unknown	6 months after last treatment	AA	Clobetasol foam, biotin, and orthosilicic acid	Y
		65, F	CTLA-4 and PD-1 inhibitors (Unspecified)	Unknown	3 months after last treatment	AA	Unknown	Y
		62, M	CTLA-4 and PD-1 inhibitors (Unspecified)	Unknown	After 3 cycles	AA (universalis)	Unknown	N
Cogen et al (2018)	CR	47, M	Pembrolizumab + Ipilimumab	Unknown	2 months	LPP	Prednisone, systemic minocycline and topical clobetasol	Y
Lakhmiri et al (2018)	CR	29, F	Ipilimumab + Nivolumab (2 months), Maintenance Nivolumab (15 months)	2 months; maintenance 15 months	4 months	AA	Topical corticosteroid cream and sham-poo, intralesional injections of triamcinolone	Y
	CR	33, F	Ipilimumab + Nivolumab / 4 infu-sions / 3 weeks	8 months	After 3 cycles	AA	Topical corticosteroid cream	Y
Braasch et al (2022)	CR	62, F	Nivolumab + Ipili-mumab, Nivolumab monotherapy after	1.5 years	2.5 months	FFA	Topical clobetasol 0.5 mg/g solution	N

CR = Case Report, RCT = Randomized Controlled Trial, AA = Alopecia areata, LPP = Lichen Planopilaris, EPDS = Erosive pustular dermatosis of the scalp, FFA = Frontal fibrosing alopecia

hepatocellular carcinoma, and renal cell carcinoma. Median age was 63.5 and 6 women were identified among the 14 patients. The median onset of alopecia after treatment initiation was 30 weeks (7.5 months). Prognosis of alopecia varied, where 5 patients experienced reversal of hair loss and other 5 patients experienced no regrowth or worsening of alopecia. 2 patients of the 10 discontinued ICI therapy after hair loss. Outcomes of 4 patients were not reported.

Clinical presentation of alopecia varied widely among patients. A 64-year-old female was diagnosed with AA 9 months after starting treatment with pembrolizumab for superficial spreading melanoma.[14] Despite not receiving any alopecia-directed treatment, the patient experienced achieved complete hair regrowth after 5 months while continuing ICI therapy. In contrast, a 55-year-old male diagnosed with AA 5 months after starting treatment with nivolumab for hepatocellular carcinoma progressed to alopecia totalis despite treatment with topical steroids and topical minoxidil.[15]

The use of ICIs has been associated with the development of cicatricial alopecia in 6 patients.[16-18,22,23,27] Scarring alopecias are driven by an inflammatory process that can cause irreversible damage to hair follicles.[26] LPP was diagnosed in 4 patients; one with eosinophilic folliculitis, and another with EPDS. Patient ages ranged from 62 to 76 with an equal gender distribution. The median onset of alopecia was 16 weeks after therapy initiation.

A 62-year-old female diagnosed with LPP 9 months after starting pembrolizumab therapy for stage IV metastatic melanoma.[16] Despite treatment with clobetasol lotion, 0.1% topical tacrolimus, oral doxycycline, and a multitude of other treatments, there was no improvement in hair regrowth while staying on ICI treatment.

In addition, a 65-year-old male was diagnosed with eosinophilic folliculitis 5 months after starting treatment with nivolumab for metastatic clear cell renal carcinoma, but there was no improvement despite alopecia treatment.[17]

A unique case of EPDS was reported in a 72-year-old male after nivolumab treatment for metastatic squamous non-small cell lung cancer.[27] 2 months after treatment initiation, confluent hyperkeratotic plaques in frontal and parietal area were noted. Due to tumor progression, the patient discontinued ICI therapy, which markedly improved scalp lesions without any alopecia-directed treatment.

PD-L1 Inhibitors (Atezolizumab, Avelumab)

Two cases of alopecia, non-scarring AA and scarring LPP, have been reported as irAEs of PD-L1 therapy.[28,29] Both patients responded positively to alopecia-specific treatment and reported hair growth with decreased pruritus.

AA as a side effect of PD-L1 inhibitors was reported in a 79-year-old female.[28] After 4 weeks of starting atezolizumab for ureteral cancer, ICI therapy was halted immediately, but no growth of hair was noted. The patient demonstrated significant hair regrowth after treatment with clobetasol lotion and topical minoxidil.

LPP was described in a 61-year-old male 24 weeks after starting avelumab.[29] The patient had a prior history of androgenic alopecia (AGA) but developed diffusely erythematous scalp with perifollicular hyperkeratosis after starting PD-L1 treatment. Hair regrowth was achieved with clobetasol propionate 0.05% solution with maintenance doxycycline 100 mg for 2 months even with continuation of ICI therapy.

CTLA-4 Inhibitors (Ipilimumab)

Two case reports and one randomized control trial identified three patients who developed alopecia areata between 4 weeks and 1.5 years after starting treatment.[30-32] One patient reported no growth of hair after minimal treatment, while the remaining two patients have no mention of alopecia prognosis.

An 88-year-old male with metastatic melanoma experienced patchy scalp hair loss after ipilimumab treatment over 12 weeks, but was not diagnosed with AA until 1.5 years after completing his treatment.[31] While a weak and delayed link between ipilimumab therapy and AA can be presumed, the treatment and prognosis of the hair loss were not discussed.

A randomized controlled trial of 63 patients reported a 35-year-old male who experienced hair loss 49 days after starting a CTLA-4 inhibitor.[32] The patient was treated with bland emollients and oral diphenhydramine hydrochloride, but no hair growth was observed two months after completing the ICI treatment.

Combined Treatments

Seven patients were reported to develop varying forms of alopecia such as AA, LPP, and frontal fibrosing alopecia (FFA) after treatment with a combination of a PD-1 inhibitor and a CTLA-4 inhibitor in four case reports.[4,18,21,33] Of the 7 patients, 5 patients (71%) reported hair regrowth. 4 of these 5 patients were treated with a mix of topical clobetasol, systemic minocycline, or systemic prednisone. There was no mention of treatment regimen for the other patient with hair regrowth. The remaining 2 patients (29%) did not show hair regrowth, either with or without treatment. The general time of onset for alopecia ranged from 2 months after initiating treatment to 6 months after completing treatment.

DISCUSSION

Our in-depth search of the current literature on ICIs reports both non-scarring and scarring alopecia as potential side effects, found with low incidence of 1 to 2% of patients treated with ICI

as reported in a previous randomized clinical trial.[32] It is difficult to extrapolate and speculate from the available data on the prognosis of hair loss. Alopecia areata was the most common type of alopecia diagnosed among patients in this review (n=18). The onset of alopecia appears to typically occur between 2 to 9 months after starting treatment, with rare cases reported with onset greater than 12 months.

The mechanism behind immune checkpoint inhibitor therapy leading to alopecia areata alludes to the immune milieu created by ICI therapy, where T-cells activate against common antigens in normal tissues.[34] This general mechanism, when applied to hair follicles specifically, indicates that ICIs can disrupt the hair follicle immune privilege (HF-IP).[35] PD-1 pathway dysregulation has been suggested to contribute to hair follicles autoantigens, such as melanogenesis-associated proteins.[35,36] In addition, PD-L1 is significantly upregulated in the dermal papilla and dermal sheath cup cells in hair follicles.[37] Combined with the disruption of the cytotoxic T cell balance and HF-IP, ICI can allow cytotoxic T cells to react with the hair follicle autoantigens, causing T-cell mediated destruction implicated in scarring alopecias such as LPP.[38] Undiagnosed primary immunodeficiency syndromes such as CTLA-4 haploinsufficiency can also be a cause of these immune reactions.[39] Although rare, patients on ICI therapy should be thoroughly checked for immunodeficiency syndromes with further worsening of AA and unrelated comorbidities.

Treatment of ICI-induced alopecia should focus on addressing the immune disruption caused by ICIs to facilitate hair protection and regrowth. Data indicate that in both non-scarring and scarring alopecia, topical corticosteroids (n=17) were most commonly used treatment with topical clobetasol (n=11). Triamcinolone intralesional injections (n=4) were also used either alone or as an adjunct therapy. Other therapies included topical minoxidil (n=4) or oral antibiotics such as doxycycline or minocycline (n=3). These treatments are in line with the current mainstay treatment of both non-scarring and scarring alopecia.[3,40,41]

There are limitations to evaluating the occurrence of non-scarring or scarring alopecia after ICI usage in the published isolated reports and clinical studies. The absence of standardization in medication dose and intervals poses a challenge in evaluating any trends. Furthermore, there is potential for misdiagnosis due to the lack of dermatological assessment of alopecia. For instance, scarring alopecia leads to irreversible damage to the hair follicles, which may result in permanent hair loss. Albeit, some of the articles report near-complete hair regrowth in patients diagnosed with subtypes of scarring alopecia, raising concerns about the accuracy of the diagnosis and highlighting the need for more precise diagnostic approaches.[33]

To date, there are increasing reports of individuals presenting with different types of alopecia after ICI treatments. It is noteworthy that all the patients in the review presented only when there were overt symptoms (eg, severe pruritus, erythema). This raises the question of whether milder cases with slight erythema and inflammation are being underdiagnosed. Thus, surveillance of initial signs of scalp erythema and inflammation can allow early management of alopecia to reduce the number of patients who develop worsening alopecia. The impact of discontinuing ICI therapy on hair regrowth is unclear. Among 3 patients who discontinued ICI therapy while on alopecia-direct treatment, only 1 patient experienced regrowth. In contrast, 11 out of 17 patients who continued ICI therapy reported hair regrowth with alopecia-directed treatment. These findings suggest discontinuation may not affect hair regrowth, but a further study with larger sample is needed. Alopecia treatment should be started before considering the discontinuation of ICI therapy.

CONCLUSION

Both non-scarring and scarring alopecia following ICI treatment have primarily been discussed in case reports. The onset of alopecia typically occurs between 2 to 9 months after starting ICI therapy, but there have been reports of immediate onset and onset occurring 1.5 years after therapy completion. Hair regrowth was observed approximately 2 to 6 months after alopecia treatment in patients who responded well. The lack of standardized assessment among patients can impact the quality of the review. Although alopecia is not the most common irAE of ICIs, it warrants routine surveillance and monitoring to identify signs of scalp inflammation and erythema for early intervention and management.

DISCLOSURES

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ORIGINAL ARTICLE

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Latin America Cutaneous Oncology Management (LACOM) I: The Role of Skin Care in Oncology Patients and Survivors

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ABSTRACT

Background: Cancer-treatment-related cutaneous adverse events (cAEs) are common and may severely impact quality of life (QoL) and decrease treatment outcomes. The Latin American Cutaneous Oncology Management (LACOM) project provides clinical insights into cancer-treatment-related cAEs, offering tools for preventing and managing cAEs.

Methods: LACOM I focuses on integrating education, prophylactic measures, and skincare in cancer treatment to improve treatment adherence, outcomes, and patients' and survivors' QoL.

Results: The LACOM panel provides evidence and opinion-based best practice recommendations for oncology skincare programs to support all stakeholders in the Latin American healthcare setting (Argentina, Chili, Colombia, Ecuador, Panama, Peru, and Mexico) working with oncology patients throughout the entire continuum of care to achieve optimal outcomes, improving cancer patients and survivors' QoL. Oncology skincare programs comprise hygiene, moisturization, and sun protection with products that should be safe and help to minimize cAEs and improve skin conditions.

Conclusions: Integrating education, general measures, and skincare programs into cancer treatment should encourage the adoption of a proactive role of skincare from the beginning of treatment and ongoing, supporting optimal outcomes and improving cancer patients' and survivors' QoL.

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INTRODUCTION

Socioeconomic development is associated with cancer's prevalence and distribution. According to the GLOBOCAN Estimates of Incidence and Mortality Worldwide, the estimated incidence rate (ASR) for males and females in South America and the Caribbean in 2020 was 199.1 and 178.8, respectively, and 186.5 combined. The age-standardized mortality rate was 98.1, 78.2, and 86.5 for males, females, and both sexes combined.[1] The 5 most common types of cancers, excluding Non-melanoma skin cancer, for women were breast, colorectal, cervical, thyroid, and lung, and prostate, colorectal, lung, stomach, and bladder for men.[1] For females in Argentina, Chile, Colombia, Panama, and Mexico, breast cancer was the most common type, whereas for Peru and Ecuador, cervical cancer leads.[1] Argentina's estimated ASR is 215 cases per 100,000 people, 211 for Chile, 153 for Colombia, 125 for Ecuador, 135 for Panama, 126 for Peru, and 139 for Mexico.[1] Cultural differences in diet, smoking, obesity, behavior and lifestyle, and socioeconomic factors have all been reported to differ by ethnicity and have significant effects on cancer incidence and mortality rates.[1] Although incidence continues to increase, advancements in therapy have contributed to an increase in survival and prevalence; now, more than ever, patients are living with cancer.[1] The increase in survival has led to a rise in patients living with cutaneous adverse events (cAEs) or sequelae of cancer treatments.[2-10] Several treatment

options are available depending on the disease type and stage, including surgery, radiation, transplantation, chemotherapy, immunotherapy, hormonal therapy, or combinations. Many cancer treatments can be related to cAEs, including pruritus, xerosis, papulopustular eruptions, paronychia, periungual inflammation, palmoplantar lesions, changes in tactile exchange, and alopecia.[2-10] Almost 70% of patients report that cAEs are worse than their initial beliefs.[7] Cancer treatment-related cAEs can alter a patient's self-image, affect interpersonal relationships, and be disfiguring.[2-10] Some cAEs are severe enough to warrant temporary or permanent discontinuation of cancer treatment.[2-10] Despite high prevalence, cAEs often do not get the medical attention needed to prevent their recurrence, as physicians may focus on the tumor's clinical response and life-threatening AEs.[3,4]

Attention to prevention, and early and correct diagnosis ruling out life-threatening cAEs can improve patients' QoL, cancer treatment adherence, and outcomes.[2-10] Studies have shown that early education on preventive measures and using skincare products benefits patients and significantly reduces cAEs.[5,6]

Why This Project?

The LACOM project provides clinical insights into cancer-treatment-related cAEs. The LACOM panel aims to provide evidence and opinion-based best practice recommendations for oncology skincare programs to support all stakeholders in LATAM healthcare settings (Argentina, Chili, Columbia, Ecuador, Panama, Peru, and Mexico) working with oncology patients throughout the entire continuum of care to achieve optimal outcomes, improving cancer patients and survivors' QoL. The LACOM project is supported by a member of the US Cutaneous Oncodermatology Management (USCOM) project to share experience.

MATERIALS AND METHODS

The LACOM project used a modified Delphi technique for interactive decision-making. The LACOM panel of 9 dermatologists/ clinicians who treat cAEs developed, discussed, and reached a consensus on evidence and opinion-based best practice recommendations for oncology skincare programs aiming to support all stakeholders in the LATAM healthcare setting working with oncology patients and cancer survivors such as Medical oncologists, Radiation Oncologists, Family practice/internal medicine specialists, Dermatologists, Oncology nurses, Advanced Practice Providers (Nurse Practitioners/ Physician Assistants), Pharmacists.

The process entailed preparing the project, selecting the panel, and conducting scoping literature searches. The panel met on December 16, 2023, in Mexico City to discuss the literature review results addressing non-prescription skincare for prevention, treatment, and maintenance of cAEs and discussed, adopted, and agreed on 5 statements using evidence coupled with the expert opinion and experience of the panel. Online, the panel finetuned, prepared, and reviewed the publication.

Literature Review

The LACOM panel explored clinical insights in addressing cAEs in oncology patients focusing on skincare regimens involving hygiene, moisturization, sun protection, and camouflage products. AA searched PubMed and Google Scholar (secondary source) for articles in the English and Spanish languages published from 2010 to November 2023 describing current best practices for cAEs using skincare in LATAM countries. We included clinical studies, reviews, consensus papers, guidelines, algorithms, and reviewed titles and abstracts, followed by the complete publication. Publications not dealing with skin care for cAEs or published in a language other than English or Spanish were excluded; for search terms, see Table 1. First, we searched the LATAM population (group 1), which resulted in little information on cAEs; followed by searches expanded beyond the LATAM population (Group 2). N=120 papers were included (Group 1: n=12 LATAM* epidemiology papers) and (Group 2: n=108 papers). The n=39 clinical studies included case series from LATAM countries that did not include skincare (Figure 1).

Clinical Evidence and Opinion-Based Recommendations

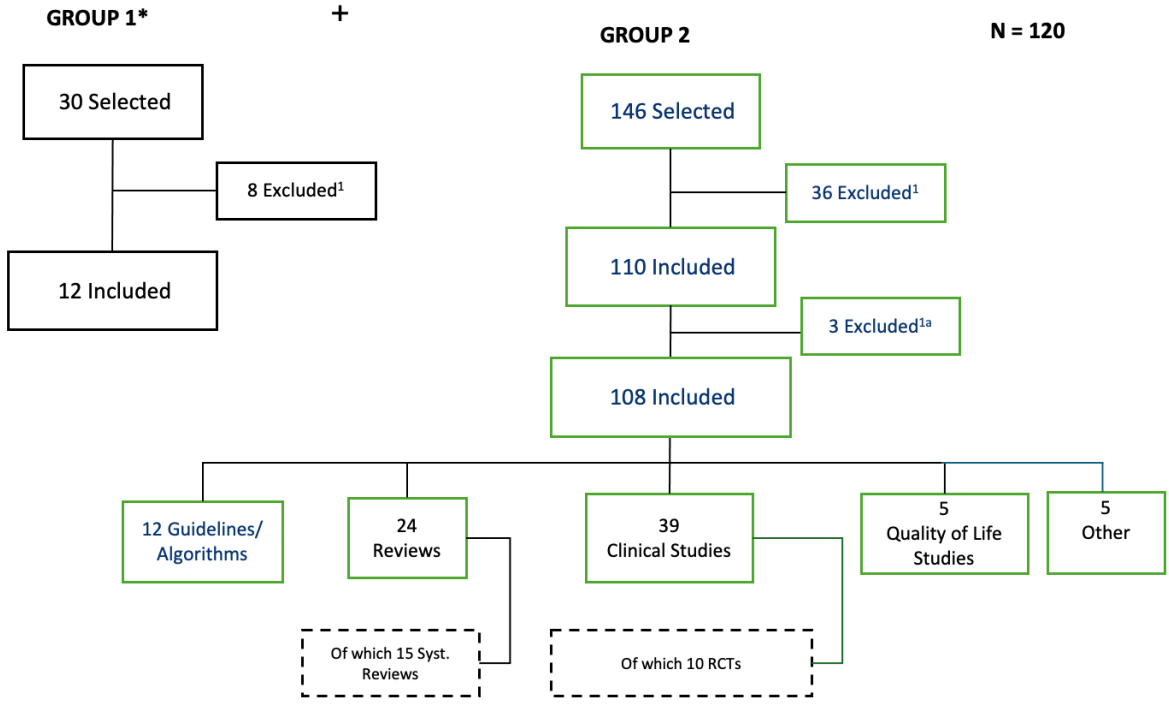
The literature review results informed fifteen statements drafted by AA and MLC before the meeting. During the meeting, the LACOM advisors set and finetuned 5 statements to explain to their peers the importance of detecting cAEs early and using

TABLE 1.

Terms Used for the Literature Searches	
Group 1	**Group 2**
Incidence of cancer in the Latin American population* Types of cancer and their treatment (radiotherapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy) Cancer-treatment-related cutaneous adverse events (cAEs) Mortality rates and 5-year survival.	cAEs* AND Radiation treatment; OR* chemotherapy; OR* targeted therapy; OR* immunotherapy; OR* Hormonal treatment; OR* Health-related quality of life; OR* skincare and prevention; OR* skincare and treatment; OR* adjunctive skincare; OR* non-prescription skincare; OR* skincare adherence, concordance; OR* skincare efficacy, safety, tolerability, skin irritation OR* staff and patient education.

*Argentina, Chili, Columbia, Ecuador, Panama, Peru, and Mexico
Cutaneous adverse events (cAEs)

FIGURE 1. Literature search results.



*Group 1:LATAM population, Group 2: General population. Systematic reviews (Syst reviews), Randomized controlled trials (RCTs).

a skincare regime to improve patient outcomes through the prevention and management of cancer treatment-related cAEs.

Statement 1: *An increasing number of patients are living with cancer and are suffering from skin changes or sequela of cancer treatments, which can severely impact patients' QoL and interfere with cancer treatment outcomes.*

With the increase in survival rates over the past decades for breast and prostate cancer due to early diagnosis, effective treatment, and enhanced preventative measures, not only are more patients living with cancer, but also surviving the treatment AEs, which can be disabling.[11-15] The cAEs depend on the cancer and treatment type, with xerosis and pruritus commonly reported in all oncology treatments.[2-10] Radiation therapy causes direct damage (acute radiation dermatitis [ARD]) to the area where it is administered, affecting 1 in 4 patients and depending on the dose administered and the schedule.[3] Mild ARD presents with desquamation, erythema, and pruritus; moderate ARD has more intense erythema with desquamation, particularly in skin folds and creases, easy bleeding, and pruritus (Figure 2); severe ARD shows spontaneous bleeding, with severe pain and ulceration.[10] Chronic RD presents severe dermatitis, altered pigmentation, telangiectasia, and necrosis.

FIGURE 2. Patient with head and neck cancer presenting with acute radiation dermatitis.



Chemotherapy disrupts cell cycle phases in the rapidly dividing cancer cells; AEs are systemic and are not limited to the area treated but occur on uninvolved organs.[7] The most common chemotherapy-related cAEs are reversible or permanent alopecia (Figure 3).[7] A study found that 58% of patients considered chemotherapy-induced hair loss to be the most distressing side effect, and 8% of patients would refuse chemotherapy due to

FIGURE 3. Patient with head and neck cancer presenting with targeted therapy-related seborrheic dermatitis.



their fear of losing their hair.[7] Other chemotherapy-related cAEs are hand and foot syndrome (HFS), onycholysis, periarticular thenar erythema, oychomelanosis, and phototoxicity.[3] These reactions can take a toll on the patient's well-being due to physical and emotional discomfort, especially the loss of hair and the appearance of the nails.[7]

Targeted therapies interfere with regulatory molecules involved in cancer cell growth; these include trametinib, cobimetinib, vemurafenib, and dabrafenib.[3-5,7,12] Those that target BCR-ABL can cause edema, hypopigmentation, morbilliform rashes, and dermatitis, whereas those that target VEGF/PDGF cause HFS, stomatitis, hair changes, seborrheic dermatitis, splinter hemorrhages and for sorafenib, squamous cell carcinomas.[3-5,7,12] EGFR/MEK targeted immunotherapy causes papulopustular eruptions, paronychia, pruritus, and xerosis, Hedgehog targeted therapy causes alopecia, muscle spasms, and dysgeusia, and RAF targeted therapies can cause keratinocytes or melanocytes proliferation, HSF, KP-like eruptions, and photosensitivity (Figure 3).[3-5,7,12] HFS can be categorized into 3 grades: grade 1 comprises erythematous palms, especially around finger pads, or yellow hyperkeratotic plaques on pressure-bearing areas of the soles; grade 2 involves erythematous palms with desquamation and tense bullae; finally, grade 3 shows painful and severe skin abnormalities with significant limitations in self-care and daily activities. HFS and hyperkeratosis may be treated with vaseline and betamethasone ointment in the evening, and moisturizers and skin-repairing balms should be prioritized.[3-5,7,12]

Papulopustular eruptions caused by EGFR/MEK targeted therapy can occur in up to 45-100% of patients. It usually occurs on the scalp, face, and upper trunk, characterized by follicular-based papules and pustules that become crusted, with an onset at 8-10 days and a resolution after 8-10 weeks post-treatment.[3-5,7,12] Cancer treatment may be stopped by 32% of oncologists due to rash alone interfering with treatment efficacy.[12] Papulopustular eruptions should be treated with corticosteroids in the absence

FIGURE 4. Patient with head and neck cancer presenting with targeted therapy-related seborrheic dermatitis.



of bacterial infection; tetracyclines may be warranted, and non-occlusive moisturizers are encouraged.[3-7,9,12]

Immunotherapy activates the patient's immune mechanism by blocking immune suppressing pathways; these include Anti PD1, PD-L1, LAG-3 and Anti CTLA-4.[13-15] Common immunotherapy-related cAEs include eczematoid, lichenoid, psoriasiform, eruptions, vitiligo, and bullous pemphigoid.[13-15] Several other conditions like pyoderma gangrenous diseases, non-specific rashes, Grover's disease, dermatitis herpetiformis, prurigo nodularis, vasculitis, dermatomyositis, sarcoidosis, sweet's syndrome keratoacanthomas, squamous cell carcinomas, erythema nodosum like panniculitis, urticaria, AGEP, DRESS, SJS and TEN have also been reported (Figure 4).[13,14]

Hormonal therapy, ie, for breast and prostate cancer, may cause flushing, xerosis, vulvovaginal dryness, atrophy, and alopecia.[3] Xerosis and pruritus are frequently occurring cAEs, and can be devastating for patients and potentially lead to secondary infection; treatment with second-generation antihistamines and non-occlusive moisturizers and photoprotection is encouraged. Avoiding corticosteroids and focusing on moisturizers and ethyl-cyanoacrylate adhesives for cracks on soles is recommended. Clinicians may minimize cAEs by using adequate skincare to maintain a healthy skin barrier.

Statement 2: *Effective management of cAEs is a multidisciplinary effort involving medical oncologists, radiation oncologists, dermatologists, and oncology nurses. It should also include the patient, family, and palliative care teams.*

Providing a multispecialty approach to treatment, including dermatologic care, is effective, but despite this knowledge, up to 84% of cancer survivors with cAEs are not referred to dermatologists.[15] Timely intervention by a dermatologist trained in treating cAEs for cancer patients is critical to prevent cancer treatment interruptions.[3] Tools that can facilitate this include telemedicine or virtual consultations, which connect patients in need with trained dermatologists through portals, remote monitoring, and patient education, particularly useful for LATAM, where access to a specialized dermatologist is scarce.

Statement 3: *Evidence and opinion-based best practice recommendations about education and proper skin care may help optimize skin health and quality of life in patients undergoing active cancer treatment and cancer survivors.*

Evidence supports that optimizing skin health in conjunction with cancer treatment improves QoL and adherence to treatment.[4,6,9,16-18,21] Non-adherence to treatment leads to suboptimal results and prognosis.[4,6,9,16-18,21] Skincare products comprise ingredients that improve skin condition beyond the vehicle effects by restoring barrier function and alleviating symptoms.[16] A study evaluated the use of skincare regimens in preventing and treating cAEs during chemotherapy in 147 patients, in which cAEs were statistically significantly more frequent in those who did not use the regimen daily.[17] The literature shows that soap-free cleansers and moisturizing help restore skin barrier function.[18] Sun exposure can worsen associated conditions, so photoprotection is always recommended.[19] The daily use of a mobile application for reminders on skincare use was associated with reduced radiation dermatitis.[20] Skincare should be started before oncology treatment and continued after that.[18]

Statement 4: *Skin cleansing, skin hydration, and photoprotection that is safe, effective, and free of additives and fragrances should be considered to prevent and manage cutaneous side effects before, during, and after cancer therapy.*

In addition to dermatologic treatment of cAEs, skincare tested on reactive skin, avoiding perfumes, allergens, preservatives, scents, and herbal extracts is recommended to improve adherence to cancer treatment, reducing side effects.[18] Elevated skin pH can trigger inflammation and dysbiosis of the skin microbiome; soaps, surfactants, and detergents with an alkaline pH (>7) should be avoided.[21]

Statement 5: *Supportive care includes:*

a. *Provide detailed patient education on cancer-treatment-related cAEs that may occur due to the treatment.*
b. *Give patient contact information and explain whom to contact, when, and why.*
c. *Explain to the patients that they should always report their skin changes regardless of severity.*
d. *The verbal information should be supported by printed or digital material to allow the patient to clarify and process the information.*
e. *Multidisciplinary management.*

The LATAM panel agrees that early education of patients on their cancer treatment and treatment-related cAEs, preventative measures using skincare, is crucial. It is highly encouraged that oncologic patients are cared for by a multidisciplinary team focusing on a skin care regimen tailored to cancer therapy, starting before treatment. The team should address the treatment protocol and elucidate possible cAEs prevention and management. The skincare regimen should always include a gentle cleanser (pH<7), moisturizer products, sunscreen (SPF >50), and skin repair balms.[2-10] Patients should be encouraged to report skin changes regardless of severity to enable prompt management and avoid suboptimal cancer treatment results.[2-10] Some patients wait until cAEs appear to start moisturizing; clinicians should educate patients on proactive and prophylactic moisturization. Verbal information should be supported by printed material for patients to reference when at home (Table 2).[3]

Call to Action

Clinicians are committed to better managing cancer treatment-related cAEs by spreading awareness through publications, congresses, webinars, media, and companies that manufacture products aiding these conditions. In LATAM, nurses can aid in wound care and assist in oncology patient care but cannot prescribe medications. Appropriate knowledge of non-prescription products such as skincare that are a part of a preventative skin care regimen is critical. Although data is scarce to support the prevention of cAEs for cancer patients and survivors, the LACOM panel agreed that early education on preventive measures using skincare is beneficial to patients. Given the lack of insurance coverage, sunscreen, cleansers, and moisturizers are often an out-of-pocket cost to patients. These products should be provided or made more readily available through sampling to patients undergoing cancer treatment. Providing algorithms on cAEs for LATAM will help improve access of physicians to information on the prevention and treatment of cAEs.

Limitations

More data are needed regarding cAEs in LATAM. LATAM patients should be included in US trials to improve diversity and access to care, considering the epidemiological differences between LATAM and North American patients.

CONCLUSION

The impact on QoL of cAEs related to cancer treatments is significant and can be directly proportional to prognosis. By educating, prophylactic measures, and integrating skincare into cancer treatment, patient QoL, treatment adherence and outcomes may improve.

TABLE 2.

Common Terminology Criteria for Cutaneous Adverse Events (CTCAE)				
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Hair loss of <50% of normal, visible on close inspection	Hair loss of >50% of normall, visible to others	--	--
Bullous Dermatitis	Asymptomatic; blisters <10% BSA	Blisters 10 - 30% BSA; painful; limiting instrumental AD	Blisters >30% BSA; limiting self-care ADL	Blisters >30% BSA; fluid or electrolyte abnormalities; ICU care or burn unit indicated
Dry Skin	30% BSA and pruritus	10 - 30% BSA and erythema or pruritus; limiting instrumental ADL	>30% BSA and pruritus; limiting self-care ADL	--
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not life-threatening; IV intervention indicated	--
Erythema Multi-forme	Target lesions <10% BSA and no skin tenderness	Target lesions 10 - 30% BSA and skin tenderness	Target lesions >30% BSA and oral or genital erosions	Target lesions >30% BSA; fluid or electrolyte abnormalities; ICU care or burn unit indicated
Erythroderma	--	Erythema >90% BSA without symptoms; limiting instrumental ADL	Erythema >90% BSA with symptoms (eg, pruritus or tenderness); limiting self-care ADL	Erythema >90% BSA, fluid or electrolyte abnormalities; ICU care or burn unit indicated
Hyperhidrosis	Limited to 1 site (palms, soles, or axillae); self-care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Electrolyte/hemodynamic imbalance	--
Hyperkeratosis	Present	--	Limiting self-care ADLs	--
Nail Changes	Present	--	--	--
Nail Discoloration	Asymptomatic; clinical or diagnostic observations only	--	--	--
Nail Loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	--	--
Pain of Skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	--
Palmar-plantar Erythrodysesthesia Syndrome	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain	Skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL	--
Photosensitivity	Painless erythema and erythema <10% BSA	Tender erythema 10 - 30% BSA	Erythema >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (eg, narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	--
Purpura	Combined area of lesions <10% BSA	Combined area of lesions 10 - 30% BSA; bleeding with trauma	Combined area of lesions >30% BSA; spontaneous bleeding	--
Rash Acneiform	Papules and/or pustules <10% BSA which may or may not present pruritus or tenderness	Papules and/or pustules 10 - 30% BSA, which may or may not present pruritus or tenderness; psychosocial impact; limiting instrumental ADL; papules and/or pustules > 30% BSA with or without mild symptoms	Papules and/or pustules >30% BSA with moderate or severe symptoms; limiting self-care ADL; local superinfection with oral antibiotics indicated	Life-threatening; papules and/or pustules covering any % BSA, which may or may not present pruritus or tenderness, extensive superinfection with IV antibiotics indicated

TABLE 2. (CONTINUED)

Common Terminology Criteria for Cutaneous Adverse Events (CTCAE)				
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Rash Maculopapular	Macules/papules <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules 10 - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; rash > 30% BSA with or without mild symptoms	Macules/papules >30% BSA with moderate or severe symptoms; limiting self-care ADL	--
Skin Ulceration	Combined area of ulcers <1cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full-thickness skin loss
Telangiectasia	Telangiectasias covering	Telangiectasias covering >=10% BSA; associated with psychosocial impact	--	--
Urticaria	Urticarial lesions covering <10% BSA topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	--

Table adapted with permission from Lacouture et al. 20213
Grade 1: Mild, Grade 2: Moderate, minimal, local or noninvasive intervention indicated, Grade 3: Severe, medically significant, not life-threatening, Grade 4: Life-threatening, urgent intervention indicated.[3]
Adverse Event (AE) unfavorable, unintended sign or disease temporally associated with medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Activities of Daily Living (ADL) *Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refers to bathing, dressing, undressing, feeding self, using the toilet, taking medications, and not being bedridden.[3]

DISCLOSURES

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Healing of Mohs Surgery Wounds on the Vermilion and Cutaneous Lip With Bovine Collagen Dressings

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ABSTRACT

Background: Surgical wounds confined to the vermilion lip and superficial orbicularis musculature can be allowed to heal by second intention with good aesthetic and functional results. Historically, defects extending onto the cutaneous lip or into the deeper orbicularis musculature have generally required more extensive repairs with local flaps to avoid cosmetic distortion or functional issues. We aim to demonstrate the utility of bovine collagen xenografts to augment second intention healing of surgical defects on the lip, including those defects extending into the cutaneous lip and musculature.

Type of Study: Retrospective observational study with historical control.

Results: Twenty-nine patients with 31 tumors underwent Mohs surgery on the lip, with most wounds extending into the orbicularis oris musculature (65%) and onto the cutaneous lip (65%). The average defect size was 2.8 cm^2 (range, 0.7-6.3 cm^2). The average time to re-epithelialization was 29.7 days, with a rate of 10.2 days per cm^2 of defect size, which was faster than historical controls of second-intention healing. Cosmetic outcomes were rated as acceptable to outstanding in 92% of cases.

Conclusion: For wounds on the vermilion lip, including those extending onto the cutaneous lip and into the orbicularis musculature, bovine collagen xenografts are an effective adjunct to second-intention healing with good cosmetic and functional outcomes.

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INTRODUCTION

Cancers of the lip are the second most frequently encountered skin cancer in the head and neck region, accounting for approximately 0.6% of all malignancies overall in the United States. The majority of these skin cancers are diagnosed in male patients, with some studies reporting a male-to-female ratio of 5-8:1, potentially owing to trends in sun exposure with various occupations and trends in alcohol and tobacco use. In addition to the known carcinogenic effect of ultraviolet radiation, other potential pathologic factors contributing to the incidence of lip cancer include pathogens such as human papillomavirus and Epstein-Barr virus, arsenic exposure or occupational exposures, and immunosuppression. Squamous cell carcinoma (SCC) is the most frequently diagnosed cancer of the lip, making up greater than 90% of cancers in this location, and generally occurs at a greater frequency on the lower lip compared to the upper lip.[1] Skin cancers involving the lip additionally confer a greater risk of recurrence, deep invasion, and metastasis than skin cancers on other sun-exposed surfaces.[2]

Owing to the sensitive location and necessity to preserve as much normal tissue as possible while achieving negative surgical margins, skin cancers on the lip are encountered with some frequency in the Mohs surgery clinic, with the surgical defects created from these operations presenting a significant reconstructive challenge. Reconstructive surgeons must account chiefly for the critical functional role of the lips in vocal articulation, nonverbal communication, and full closure of the mouth when eating and drinking to avoid loss of oral contents. As the dominant cosmetic feature of the lower face, the importance of the aesthetic outcome of any reconstruction undertaken on the lips cannot be overstated. Several studies published on results of second intention healing (SIH) on the lips have reported good cosmetic and functional outcomes in wounds mainly confined to the vermilion lip and into the superficial portion of the orbicularis muscle.[3,4] Others have cautioned against utilizing SIH on wounds extending beyond the vermilion to the cutaneous lip, or those that extend into the orbicularis oris muscle given the risk of formation of a depressed scar or distortion of the vermilion border.[5,6]

Some have begun utilizing biologic wound dressings, either packed or sewn into place, as an adjunctive product to enhance the second intention healing of vermillion-only wounds, anecdotally noting superior results compared to more morbid reconstructive procedures such as mucosal advancement flaps and wedge repairs.[7] Several biologic dressings including collagen wound matrices have been utilized for wounds following Mohs micrographic surgery (MMS). They have been found to decrease postoperative pain and healing time in surgical wounds on the scalp, legs, ear helix, conchal bowl, nose, and large defects of the temple.[8,9] In a study involving the use of a bovine collagen matrix dressing in MMS wounds compared to site-matched wounds that were left to heal by second intention, Kolenik et al reported that the collagen matrix sped average time to complete re-epithelialization of surgical wounds on the face, scalp, back, and legs (6.1 weeks vs 9.4 weeks) without any post-surgical wound infections.[10]

In the author's experience, a bovine-derived collagen wound dressing (BCWD) provides a superior wound healing experience to SIH without significant additional cost. Puracol® Plus (Medline Industries, Inc; Mundelein, IL) is a bovine-derived collagen wound dressing (BCWD) composed of a pure native collagen matrix that preserves the triple helix structure of collagen.[11] Puracol® Plus, in comparison to traditional Puracol®, is purported to consist of 100% collagen, while the collagen content of traditional Puracol® has been found to be 88.4%.[12] Most studies on this collagen xenograft have been in the setting of chronic wounds where it has demonstrated some success in speeding healing over standard wound care. It is currently indicated for use in full and partial-thickness wounds of various etiologies, trauma wounds healing by second intention, surgical wounds, and dehisced surgical wounds. It is not intended for use in wounds with active vasculitis or in patients with sensitivity to bovine collagen or other collagen products. It is available in 2 x 2.5 in and 4.25 x 4.5 in fenestrated or non-fenestrated sheets without adhesive or impregnated antimicrobial. It is sterile, stored at room temperature, and rehydrated in the course of application to the wound.[13]

The purpose of this study was to evaluate an augmented second intention wound healing strategy for surgical defects of the lip vermilion and mucosa utilizing a BCWD, including those defects extending onto the cutaneous lip and into the orbicularis oris musculature. Here, we present a single-center, observational study on the surgical defects on the lip that healed with the addition of a bovine collagen matrix material.

MATERIALS AND METHODS

A retrospective chart review was undertaken to identify patients who underwent MMS on the vermilion lip with subsequent application of a BCWD between November 2021 and January 2024 at the Laser and Skin Surgery Center of Indiana in Indianapolis, IN. Patients who did not have follow up at our practice after MMS, or those who underwent a different wound closure such as primary closure, flap, or graft were excluded.

Surgical defects were created by excision of basal and squamous cell carcinomas by MMS technique. The sterile collagen xenograft was stored at room temperature. For repair, a single layer of the collagen xenograft was cut to a size slightly larger than the defect, applied directly to the wound, rehydrated with sterile saline, and secured to the epithelial edge of the wound with a running suture around the periphery of the wound with 5-0 Chromic gut. Post-operative wounds were treated similarly to a skin graft, with patients instructed to apply only petroleum jelly for 1 week, followed by gentle cleansing and petroleum jelly with a nonstick dressing until complete healing. Patients were scheduled for follow-up approximately every 3 to 6 weeks, as is standard practice in our office for post-operative visits after application of collagen xenografts on any site. Long-term follow-up data and photographs were also available for many established patients. Photographs of the surgical defect were taken immediately postoperatively, after application of the collagen xenograft, and at both short-term and long-term follow-up.

Data collected included demographics, skin cancer type, defect location, and size, involvement of the cutaneous lip and/or orbicularis muscle, time to healing, and any surgical complications or concerns on follow up including bleeding, pain, and surgical site infections. In addition, photographs of the wounds at patient's most recent follow-up visits were analyzed and rated on cosmetic appearance of the final scar as "poor", "acceptable", or "outstanding". "Poor" outcomes were noted if there was unacceptable atrophy, hypertrophy, or significant notching or if intralesional injection, surgical revision, or resurfacing procedures were required. "Acceptable" outcomes were noted if there was minimal or slight atrophy or hypertrophy or minor notching not requiring further intervention. "Outstanding" outcomes were noted if the scar was nearly imperceptible.

For those patients who had a follow-up appointment between 3 to 6 weeks after initial application of BCWD, whether or not the wound was fully healed at the time of follow up was noted, and time in days to that follow up was used as a surrogate for time to healing. Patients who did not have follow-up within the 3- to 6-week period but had more remote follow-up were excluded from the analysis of time to re-epithelialization but were included in the cosmetic outcome ratings. The primary outcome analyzed was time to complete re-epithelialization, which was compared to previously published historical controls of time to re-epithelialization of second intention healing on the lip.

RESULTS

A total of 29 patients were identified, with a total of 31 tumors. The surgeries and subsequent follow up encompassed 26 months from November 2021 to January 2024. Five patients were excluded due to lack of follow up to healing completion. Of the 24 patients who did have follow up, 2 patients had 2 sites treated on the lip. One patient underwent treatment of 2 separate sites on the vermilion lip on the same day and 1 patient underwent treatment of a cancer of the same type adjacent to their initial Mohs site 13 months following their first procedure. It is unclear whether this singular patient represents a recurrence or is a consequence of field cancerization. The total number of lip defects treated with BCWD included in this analysis was 26. Patient demographics are presented in Table 1.

All surgical defects were located on the upper or lower vermilion lip and the majority extended into the underlying orbicularis oris muscle (65%) and onto the cutaneous lip (65%). The average defect was 2.8 cm^2 after an average 1.8 stages to tumor clearance. All patients were prescribed prophylactic antibiotics for 7 days, and no patients required an additional course. Only 1 patient reported pain after surgery, and no patients required prescription pain medications. Detailed procedure and defect characteristics are listed in Table 2.

Three patients with 3 surgical defects did not have follow up between 3 to 6 weeks after application of BCWD but had more remote follow up, so data from 21 patients with 23 surgical wounds were included in the analysis of time to re-epithelialization. The average number of days to follow up at which complete healing was noted was 29.7 days, with a range of 25 to 44 days. In only 1 patient did the BCWD not incorporate into the wound. This patient required removal of the initial BCWD due to continuous bleeding and hematoma at day 9, at which time the BCWD was replaced. This patient was noted to have complete re-epithelialization of their surgical wound at 30 days following their Mohs surgery, or 21 days after BCWD replacement despite this complication.

Clinical photographs were taken as standard practice at each follow-up visit for the majority of patients (23 patients, 24 defects), which were used to determine physician-rated cosmetic outcomes. One patient did not have follow-up beyond 14 days, and another patient did not have follow-up photographs; therefore, they were excluded from the analysis of cosmetic outcomes. The majority of patients (92%) had acceptable to outstanding results, as shown in Table 3, which also includes further descriptive analysis of outcomes.

The mean post-excision wound area for defects included in the analysis of time to re-epithelialization was 2.9 cm^2, with a mean time to re-epithelialization of 29.7 days. The rate of healing was 10.2 days per cm^2 of defect size (29.7 days/2.9 cm^2). Although days to follow-up were used as a surrogate for days to complete healing, it is likely that defects were fully re-epithelialized several days prior to follow-up in some patients who were seen between 3 and 6 weeks. The majority of patients experienced little to no pain throughout the healing process. One patient noted a bleeding complication as above despite 33% of patients

TABLE 1.

Patient Demographics	
	N=24
Age in years, mean (SD)	68 (14.0)
Male gender, n (%)	14 (56)
Smoking, n (%)	
Current	2 (8)
Former	7 (29)
Never	15 (63)
Anticoagulants, n (%)	
Yes	8 (33)
No	16 (67)
Diabetes, n (%)	
Yes	4 (17)
No	20 (83)
>1 site treated	
Yes	2 (8)

TABLE 2.

Procedure Characteristics		
	N=26	
Cancer type, n (%)		
Basal cell carcinoma	9 (35)	
Squamous cell carcinoma	17 (65)	
Lip Location, n (%)		
Upper lip	7 (27)	
Lower lip	19 (73)	
Involves cutaneous lip, n (%)		
Yes	17 (65)	
No	9 (35)	
Involves orbicularis muscle, n (%)		
Yes	18 (69)	
No	8 (30)	
Defect Size (mean cm2)	2.8	Range (0.7 - 6.3)
Treatment Course		
Antibiotics		
Prophylactic	26	100%
>1 course	0	0%
Pain medication	0	0%

TABLE 3.

Outcomes		
	Follow-up (N=26)	
Duration of follow up (mean days)	133.3	Range (14 - 370)
Time to re-epithelialization (N=23), mean days	29.7	Range (25 - 44)
Post-excision wound area in cm2 (N=23), mean	2.9	Range (0.7-6.3)
Rate of healing per wound area (N=23) (days/cm^2)	10.2	
Incorporation of collagen	25	96%
Complications, n (%) (N=26)		
Bleeding	1 (4)	
Pain	1 (4)	
Infection	0 (0)	
Hypertrophic scar	3 (12)	
Notching of lip	5 (19)	
Physician rating of cosmetic outcome, n (%) (N=24)		
Poor	2 (8)	
Acceptable	11 (46)	
Outstanding	11 (46)	

reporting concurrent use of anticoagulants. None of the patients experienced an infectious complication though all patients were started on prophylactic antibiotics after application of the collagen matrix.

DISCUSSION

The use of collagen xenograft biologic dressings as an adjunct to second intention healing in acute wounds formed during Mohs surgery continues to expand as more evidence supports a comfortable wound healing experience for the patient without greater risk for complications such as bleeding or infection. Additionally, a reported benefit in wounds treated with BCWD in comparison to wounds left to heal by second intention is an increased rate of healing.[10,14,15] In the author's experience, patients report reduced anxiety and psychological distress in the early healing period with BCWD compared to SIH as the collagen dressing provides a cover that slightly obscures and conceals the granulating wound.

Previous studies have published results of SIH on the lip, including time to complete healing. In 2002, Gloster reported on SIH of lip defects of the vermilion and mucosa in 13 patients with an average wound area of 2.1 cm^2. Only 1 of these patients had a defect that extended to the cutaneous lip, and those who had defects involving greater than a superficial portion of the orbicularis were excluded. Time to healing was noted to be between 3 to 5 weeks (average 28.5 days) and 12 of 13 patients had good to excellent cosmetic results, with only the defect involving part of the cutaneous lip developing a deformity of the vermilion border. In this cohort, the rate of healing equates to 13.6 days per cm^2.[3] Leonard and Hanke in 2007 demonstrated that excellent cosmetic and functional results could be achieved with SIH of even large defects of the vermillion lip, up to 3.2 cm in diameter, including defects extending onto the cutaneous lip and into underlying superficial orbicularis muscle. These wounds healed in an average of 25 days with only mild, short-lived functional complications. The average wound area in this cohort was 2.0 cm^2, equating to a rate of healing of 12.5 days per cm^2.[4] In our cohort of patients treated with BCWD, the rate of healing was 10.2 days per cm^2, demonstrating a faster rate of wound healing with the addition of BCWD.

In the author's experience, BCWD enhances the cosmetic outcome of wounds on the lip. Avoidance of notching of the lip is not only necessary cosmetically, but it is also of functional importance to maintain competence of the oral aperture. Additionally, authors of previous studies have recommended avoiding SIH in wounds crossing the vermilion due to the potential distortion of the vermilion border, which is cosmetically displeasing.[5,6] In our case series, only the minority of patients had wounds that were confined to the vermilion lip and did not extend into the muscle. In spite of this, 22 patients (92%) had an acceptable to outstanding cosmetic outcome (Figures 1 and 2)

FIGURE 1. Surgical defect involving a large portion of the lower vermilion lip (left), immediately following application of BCWD TM (center), 31 days post-surgery (right).



FIGURE 2. Surgical defect involving the central lower vermilion lip and a large portion of the cutaneous lip (left), immediately following application of BCWD (center), 28 days post-surgery (right).

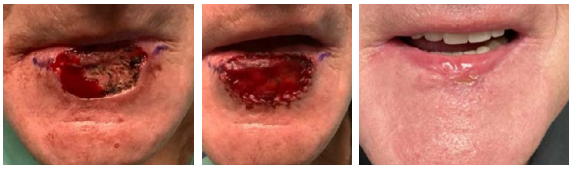
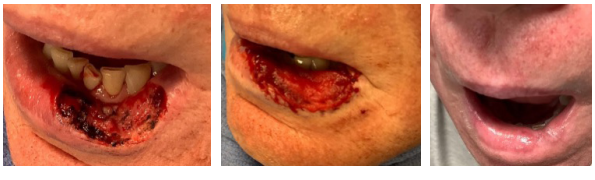


FIGURE 3. Surgical defect on the L lower vermilion lip extending to the cutaneous lip and deep into the orbicularis musculature (left), immediately following application of BCWD (center), and 28 days post-surgery with notching and patient-reported loss of oral competence (right).



The 2 patients who experienced a poor surgical outcome had wide defects extending along the vermilion, 2.5 cm to 4 cm in largest diameter, and which extended deep into the orbicularis oris muscle, leading to notching (Figure 3).

CONCLUSION

In conclusion, for wounds on the vermilion lip, including those extending onto the cutaneous lip and into the orbicularis oris musculature, we observed that collagen xenografts as an adjunct to second intention healing provide an acceptable wound healing experience without pain, good cosmetic and functional outcomes even for larger wounds, and shortened healing times compared to second intention healing of similar wounds.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Effects on the Skin Microbiome by a Moisturizer Formulated for Eczema-Prone and Sensitive Skin

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ABSTRACT

Background: Cutaneous dysbiosis contributes to the pathophysiology of atopic dermatitis and potentially that of sensitive skin; regulation of the bacterial communities through skincare products is an emerging management strategy. Previous studies have highlighted the utility of ingredients that function as prebiotics, are anti-inflammatory, and have barrier-repairing properties to help shift species richness and composition toward more eubiotic states.

Methods: In a single-site open-label study, a moisturizer containing colloidal oatmeal, *Ophiopogon japonicus* root extract (AD-Resyl®, SILAB, France), and a patented filaggrin protein byproduct was evaluated for its effect on the bacterial communities of eczema-prone and sensitive skin (n=12). Skin swab samples from participants' cheeks were collected before and after applying the moisturizer twice daily for 21 days. Measures of alpha diversity (richness, Shannon diversity index) and beta diversity were calculated using paired, comparative analyses of sampled bacterial loads.

Results: Bacterial species richness was significantly increased in 10 participants ($P<0.05$) without dysbiotic shifts in overall microbial composition.

Conclusion: These results support the use of a moisturizer containing anti-inflammatory and skin barrier-repairing ingredients for managing atopic dermatitis and add to our knowledge of the skin microbiome in sensitive skin.

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INTRODUCTION

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease for which cutaneous dysbiosis is a core component of disease pathophysiology.[1,2] AD-associated dysbiotic changes in the skin microbiome composition include an increased abundance of *Staphylococcus aureus* (*S. aureus*), *S. epidermidis*, and *S. haemolyticus*, decreased bacterial species diversity, and reduced colonization of the fungal genus *Malassezia*.[3] Regulation of the skin microbiota is an emerging strategy for managing AD, and monitoring could be a biomarker for disease activity and treatment success.[4-6] Cosmetic skin care products may be tools for microbial manipulation through barrier restoration and foundational support for diverse cutaneous flora. Even simpler, anti-inflammatory ingredients could theoretically augment the microbiota through this mechanism alone and enhance AD treatment and management.

Colloidal oatmeal is an often used ingredient in skin care products for AD for its anti-inflammatory, anti-pruritic, and barrier repair properties and is listed in the US Food and Administration monograph as a skin barrier protectant and irritation-relieving ingredient for skin irritation due to eczema; notably, colloidal oat also acts as a prebiotic, encouraging the balanced growth of commensal bacteria.[7-10] Additionally, extracts from the plant *Ophiopogon japonicus* have demonstrated immunoregulatory activity in an AD mouse model[11] and clinically improved AD symptoms and patient's quality of life compared to placebo.[12] Finally, filaggrin, an essential protein for maintenance of the epidermal barrier, is reduced in atopic skin.[13] Reduced levels of filaggrin metabolic byproducts such as pyrrolidone carboxylic acid (PCA) correlate with disease severity,[14] thus topical replenishment of PCA may improve the defective skin barrier in AD. Despite these findings, the impact of these combined ingredients on improving dysbiosis has not been well elucidated to date.

Sensitive skin syndrome (SSS) is a condition of increased skin reactivity to innocuous exposures and is associated with an impaired skin barrier like AD. Although the skin microbiome of sensitive skin is not well understood, it is suspected that this impaired skin barrier contributes to the abnormal neurosensory responses of this condition.[15–17]

Therefore, the authors sought to investigate the activity of a moisturizer containing colloidal oatmeal, *O. japonicus* root extract (AD-Resyl®, SILAB, France), and a patented filaggrin technology (Restoraderm Technology™, sodium PCA, and arginine) on the skin microbiome of eczema-prone and sensitive skin.

MATERIALS AND METHODS

An open-label, in-use study (SPR.205147) was conducted at a single site to investigate a moisturizer (Restoraderm Cream Fla#1808) containing 2% colloidal oatmeal, Ad-Resyl, and the filaggrin technology for its effects on the skin microbiome composition of eczema-prone and sensitive skin. Study participants (n=12) were 18 to 60 years old with eczema-prone (self-perceived mild to moderate persistent dry, pruritic, and flaky skin) and sensitive skin (identified as a score >13 using a clinical questionnaire, Table 1). Subjects underwent the following washout period before starting the study: no new

TABLE 1.

Questionnaire for Selection of Subjects With Sensitive Skin to be Completed by a Dermatologist				
1. Do you regularly use cosmetic products dedicated to sensitive skin?				
The answer "yes" is not mandatory. *Yes * No				
2. Inclusion Questionnaire				
Severity: from 1 to 3: mild, from 4 to 7: moderate, and from 8 to 10: severe 0=0 none				
3. When you do NOT use your usual products", do you have discomfort sensations triggered by cosmetic products?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Cosmetic CARE products (1)	Do you have or did you have abnormal and repeated discomfort* sensations on your face/body skin linked to SKIN CARE PRODUCTS (cream, serum, essence, lotion…)?	--	--	I _ _ I
Toiletries products (2)	Do you have or did you have abnormal and repeated discomfort* sensations on your face/body skin linked to TOILETRIES (cleanser, soap, make up remover…)?	--	--	I _ _ I
4. Do you have discomfort sensations triggered by Environmental/External conditions?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Temperature change (3)		--	--	I _ _ I
Cold (4)		--	--	I _ _ I
Wind (5)		--	--	I _ _ I
Pollution (6)		--	--	I _ _ I
Limestone/Chlorine (7)		--	--	I _ _ I
5. Are these sensations regularly associated to?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Redness (8)		--	--	I _ _ I
Dryness (9)		--	--	I _ _ I
Redness (8)		--	--	I _ _ I
4. Do you have discomfort sensations triggered by Environmental/External conditions?		**Yes**	**No**	**If yes, severity rated on a scale from 1 (Not severe) to 10 (very severe)**
Temperature change (3)		--	--	I _ _ I
Cold (4)		--	--	I _ _ I
Others (precise) (10): _____ _____		--	--	I _ _ I
5. To be included as a subject with a sensitive skin a positive answer should be given for:				
CARE products with a minimum score of 2 or TOILETRIES products with a Minimum score of 4		*Yes	* No	--
AND AT LEAST 2 OF THE LISTED ENVIRONMENTAL CONDITIONS with a minimum score of 3		*Yes	* No	--
CONCLUSION: INCLUSION OF THE SUBJECT (11)		*Yes	* No	--

*Discomfort sensations: prickling, tightness, itching, stinging, burning sensation, heat sensation, pain of skin.
( ): numbers referring to template data entra- specific excel file

skincare product application 3 days before D0 and no application of any skincare products on day 0 (D0). Skin swab samples were collected from the cheeks of study participants before (D0) and after (D21) the 3-week intervention in which all participants applied the cream to their face and body twice daily. In total, 24 skin swab samples were collected, and samples were analyzed by V3V4 16S rDNA PCR sequencing for bacterial microbiome assessments. Using amplicon sequence variants (ASVs) data, bacterial taxonomic profiles to, at minimum, the genus level were created for each sample. To assess changes in the skin microbiome before and after the intervention, measures of the alpha diversity – richness (number of different taxa) and Shannon diversity index (abundance evenness of different taxa) – and beta diversity (overall microbiome composition) were calculated.

Statistical Analysis

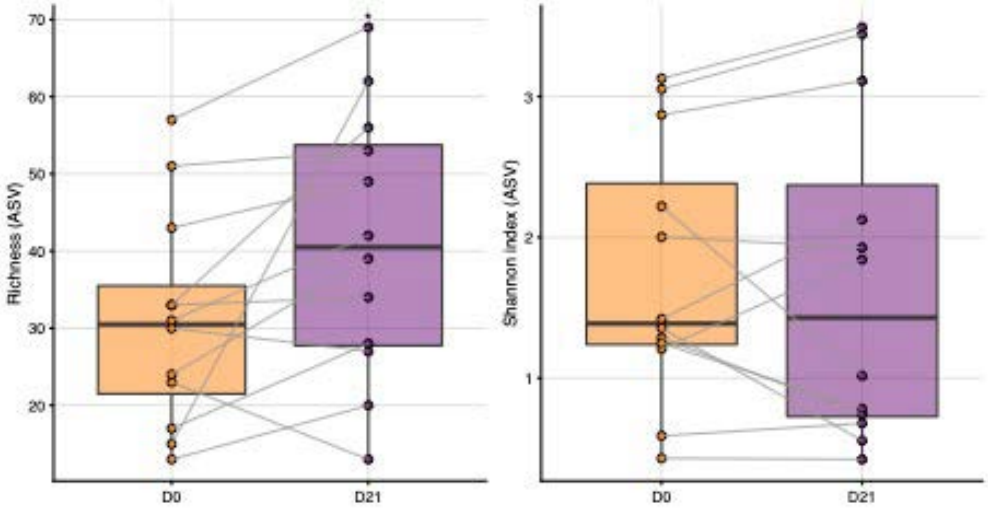
For the in-use skin microbiome analysis, the Benjamini-Hochberg (BH) method was used to control the false discovery rate (FDR) at 10%. Statistical analyses for the visit and subject variable effects were performed using permutational multivariate analysis of variance (PERMANOVA) tests; for changes in taxa abundance and prevalence, Mann-Whitney U tests (Wilcoxon signed rank tests) and exact McNemar's tests were performed, respectively.

RESULTS

Bacterial Analysis

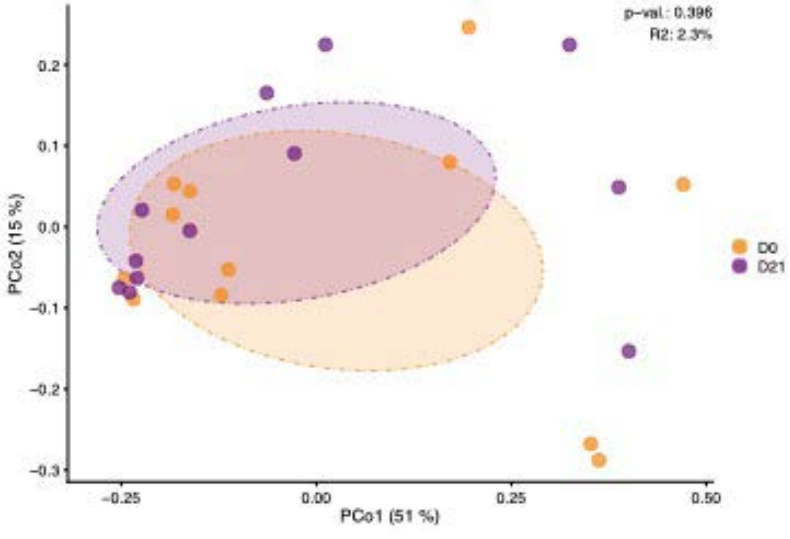
16S sequencing data was obtained for all 24 samples (average 104750 high-quality read pairs per sample, median 65342, minimum 8963), and ASVs of expected, commensal bacteria species were observed (eg, *S. epidermidis* and *Cutibacterium acnes*). A comparison of the phylum, genus, and species taxonomic profiles showed that intra-subject profiles were similar from D0 to D21, and inter-subject profile variation was greater than that of intra-subject profiles. Paired comparisons of alpha diversity measurements showed a significant increase in richness from D0 to D21 in 10 of 12 subjects (*P*-value < 0.05) but no significant effect on the Shannon diversity index (Figure 1). Dissimilarity measurements (Bray Curtis, weighted UniFrac, and unweighted UniFrac) calculated to assess the overall microbiome composition (beta diversity) showed that the participant variable (*P*-value=0.002) but not the visit variable (*P*-value=0.396) had a significant effect. Thus, participants maintained overall similar microbiome compositions before and after the intervention (Figure 2). Moreover, paired abundance/prevalence tests showed no taxon was significantly different between D0 and D21 samples. Sub-analysis of *Staphylococci* species found no significant changes in the abundance of four species (*S. epidermidis*, *S. capitis*, *S. hominis*, and *S. aureus*), consistent with other results. Of note, *S. aureus* was only detected in low abundances in two D0 samples. Overall, the intervention significantly increased bacterial species richness but did not impact the species evenness and overall microbiome composition.

FIGURE 1. Alpha diversity measures calculated from ASV relative abundances (paired data, same participant connected by gray line). Richness values increased significantly. No significant changes were detected for the Shannon index.



Asterisks refer to *P*-values of paired Mann-Whitney U tests (*: *P*-value < 0.05).

FIGURE 2. A PCoA plot is shown based on weighted UniFrac dissimilarities calculated from ASV relative abundances (N=24; grouped by visits D0 vs D21).



The ellipses cover one standard deviation of the mean of the group centroids. The x- and y-axis labels indicate the variance explained by the first two principal coordinates. The visit variable had no significant effect on the overall microbiome composition of the samples (*P*-value of PERMANOVA test after adjustment for subject variable = 0.396; effect of participant variable was highly significant with a *P*-value of 0.002 and a R2 of 70.3%).

DISCUSSION

The clear link between AD and dysbiosis requires understanding how topical products and their ingredients impact the skin microbiome. Herein, a moisturizing cream including ingredients beneficial for AD was investigated for its effect on the skin microbiota to provide further insight into the mechanism of clinical impact.[7,9,12-14,18]

Compared to that of AD, the skin microbiome of adults without skin disease has overall stable and established microbial communities over time, regardless of changes in the external environment.[19-21] The composition of bacterial communities is largely determined by the unique microenvironments created by the cutaneous physiologic features of skin sites.[19,21] Sebaceous, moist, and dry are the 3 main cutaneous biogeographic habitats, and each varies in their respective microbial diversity and biomass.[22] In comparison to bacterial communities, the composition of fungal communities is largely determined by body location as a function of environmental exposure (ie, high fungal diversity on feet and toenails) rather than biogeographic habitats, and across most sites fungi of the genus *Malassezia* predominate.[19,23] Furthermore, for both bacterial and fungal community composition, intrapersonal variation is smaller than interpersonal variation.[21,23]

The bacterial species identified and the variation of the taxonomic profiles were consistent with the expected skin microbiome patterns discussed above. Firstly, *S. epidermidis* and *C. acnes* were collected from the cheeks of participants, which are 2 species commensal to this sebaceous skin site.[19,22]

Also, as expected, intra-participant taxonomic profiles were more similar than inter-participant profiles. Together, these results increase confidence in the study's ability to detect true significant differences before and after the intervention. Our results showed increased bacterial species richness following application of the moisturizer, a potentially beneficial effect since AD skin is associated with decreased bacterial diversity.[24,25]

Throughout this study, *S. aureus* was infrequently detected, and its presence was not significantly affected post-intervention. The presence of *S. aureus* detected on D0 for 2 participants suggests they were currently experiencing an AD flare since exacerbation of disease is correlated with increased abundance of *S. aureus*.[24] Overall, a study limitation was the absence of clinical scoring of AD severity and activity in participants; future studies investigating this moisturizer could be improved by documenting current AD activity as the relative abundance of *S. aureus* is increased during a flare and associated with worse disease.[2,24]

Multiple factors underlie the complex pathogenesis of AD, namely skin barrier defects, aberrant immune system regulation, environmental exposures, and dysbiosis.[26] Certain ingredients in skin care products may impact the skin microbiome and simultaneously the aforementioned factors as they are closely interrelated. The studied moisturizer was formulated with several ingredients that could have led to the observed effects on the skin microbiome, specifically the significantly increased bacterial species richness and decreased *S. aureus* colonization.

A proprietary form of PCA was a key ingredient in the moisturizer studied. PCA is a filaggrin byproduct and major component of natural moisturizing factor (NMF), an essential humectant found in the stratum corneum. Loss-of-function mutations in the gene encoding filaggrin (FLG) are a well-established predisposing factor of intrinsic skin barrier dysfunction in some, but not all, patients with AD.[27] Those without FLG mutations are also found to have defective epidermal barrier function, reduced filaggrin levels, and altered ceramide levels in the stratum corneum.[13,27] Filaggrin deficiency in AD skin regardless of FLG genotype may be due to the downregulation of filaggrin expression by T2 cytokines or decreased activity or protein expression of proteases that sequentially process profilaggrin to NMF.[27] Notably, evidence supports the defective stratum corneum caused by filaggrin deficiency alters the skin microbiome and may lead to AD-associated dysbiosis.[28] It is thus plausible topical delivery of PCA contributed to the improved bacterial diversity seen in this study by reinstating a normal stratum corneum barrier and improving its physiologic function. By improving moisture retention, keratinocyte maturation, and maintenance of an acidic pH, epidermal homeostasis is restored and hospitable to eubiosis.[27] Finally, regarding the decreased detection of *S. aureus* at conclusion of the study, although non-significant this may have been due to the addition of the proprietary PCA technology. PCA and urocanic acid (UCA), another filaggrin byproduct and major component of NMF, are antimicrobial and, importantly, low levels of NMF in the skin strengthen *S. aureus* binding to corneocytes.[27]

The natural active ingredient, *O. japonicus* root extract, was also included in the studied moisturizer formulation. This extract is rich in immunomodulating polysaccharides, which decreased T2 inflammatory cytokines in an AD-mouse model.[18,29] In AD, increased T2 cytokines inhibit the expression and function of a key antimicrobial peptide against *S. aureus* thus, this anti-inflammatory effect of *O. japonicus* may impact the skin microbiome.[30] Additionally, cosmetic products rich in polysaccharides like those found in *O. japonicus* increase alpha- and beta-diversity of bacterial communities on the skin, possibly due to prebiotic properties.[31] Taken together, the significantly increased bacterial diversity and reduction in *S. aureus* colonization following application of the moisturizer possibly resulted from the anti-inflammatory and prebiotic properties of O. japonicus root extract.

Colloidal oatmeal has many properties beneficial to AD skin, including richness in barrier-repairing lipids and fatty acids, plus anti-inflammatory, anti-pruritic, and anti-oxidant activities.[8] Most notable for this study, colloidal oatmeal is a known prebiotic that is metabolized by commensal bacteria and subsequently promotes their growth. Previous studies found increased microbial diversity and promotion of *S. epidermidis* growth compared to *S. aureus*; these effects are thought to result from colloidal oat's prebiotic properties encouraging commensal bacteria growth and restoration of the epidermal barrier through increased hydration and maintenance of an acidic pH deterring pathogenic colonization.[7,9] Our study found a similar increase in bacterial diversity, and this could result from the colloidal oat properties discussed above; however, a significant differential impact on *Staphylococcal* species growth was not observed, perhaps due to the rare presence of pathogenic *S. aureus* throughout the study.

Notably, this moisturizer was studied in eczema-prone individuals with concomitant sensitive skin. Sensitive skin syndrome (SSS) is a condition of increased skin reactivity to innocuous exposures – such as temperature changes, stress, or cosmetic products – and is characterized by abnormal stinging, pruritus, burning, pain, dryness, and often erythema; notably, SSS is not attributable to another skin condition.[17] A direct link between sensitive skin and the skin microbiome has yet to be elucidated.[16] Despite this, it is theorized the skin microbiome impacts the aberrant activity of the cutaneous nervous system underpinning the pathophysiology of SSS. Commensal or pathogenic bacteria interact with the epidermis and dermis and can directly stimulate cutaneous nociceptors, transducing sensations of pain, itch, and temperature.[32,33] Antimicrobial peptides produced upon pathogenic bacteria detection may also stimulate mast cell degranulation and promote the release of interleukin 31, the pruritus-mediating cytokine.[34] Moreover, substance *P* and calcitonin gene-related peptide, two key neuroinflammatory peptides expressed in the skin and involved in SSS, also impact the skin microbiome.[35,36] Finally, SSS is linked to an impaired skin barrier, including lower PCA levels and bleomycin hydrolase activity, two components of filaggrin metabolism also dysregulated in AD.[15] Considering these relationships, the skin microbiome of SSS may be distinct from non-sensitive skin, yet few studies have investigated this with conflicting results.[37,38] This study adds to our knowledge of the skin microbiome in SSS and how a moisturizer containing anti-inflammatory and skin barrier-repairing ingredients may impact it.

This study was limited by its uncontrolled design and small number of participants. It is also unknown if participants were experiencing active eczema flares before or during the study, which may have impacted the skin microbiome composition. Finally, this study sampled microorganisms from a single body site; thus, alterations in the microbiome at other sites were undetermined. Future investigations would be improved by analyzing changes in fungal species and sampling multiple body sites of lesional and non-lesional skin across time, as this would provide greater insight into lesion-associated, temporal, and regional changes in the skin microbiome and mycobiome.

CONCLUSION

In conclusion, an in-use, open-label study found a moisturizing cream formulated with AD-beneficial ingredients positively affects the skin microbiome of eczema-prone and sensitive skin by increasing bacterial species richness and not causing dysbiotic shifts in the overall microbial composition. These results support its use as part of a topical product regimen for managing AD with concomitant sensitive skin.

DISCLOSURES

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ORIGINAL ARTICLE

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The Use of Acneceuticals to Improve Acne Care: Introduction of a New Term and Review of the Literature

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ABSTRACT

Background: Acne is a multifactorial inflammatory skin condition that commonly presents to the dermatology clinic. Treatment generally involves the use of pharmaceutical agents and procedural techniques. Recently, the importance of over-the-counter skin care in acne has been recognized in many studies. This paper introduces the term acneceuticals to encompass a wide range of FDA monographed, yet non-prescription ingredients proven to alter the structure and function of acneic skin.

Methods: A panel of 8 dermatologists with an interest in acne and skin care performed a literature review of active skin care in acne. The role of acneceuticals in the treatment of acne — as monotherapy, adjunctive, and maintenance therapy — was evaluated using a modified Delphi approach. Studies were limited to in vivo human trials involving acne. Individual actives were assessed separately.

Results: The quality of evidence was moderate-to-low for many of the ingredients. Most of the actives included in the final assessment had been studied in vehicle-controlled, blinded, often comparative studies but enrolled a small number of subjects. In these studies, the acneceuticals were found to reduce lesion count, reduce sebum production, and improve efficacy of existing pharmacologic therapies.

Conclusion: Acneceuticals have demonstrated benefits in treating acne, alone or in conjunction with established pharmaceutical agents. These data allow us to make quality recommendations for our patients that should be a part of every patient encounter. The recommendations also serve as a guide for patients searching the internet for beneficial self-care products.

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INTRODUCTION

Acne is the most common cutaneous disease worldwide and the most frequent disorder to present to the dermatology practice. Although efficacious treatments exist, clinicians continue to search for better regimens with improved safety for our patients. Our patients search, too – with or without our guidance. Many patients are looking for more "natural" approaches to skin care. Selecting skincare products gives patients a satisfying sense of control that can help attenuate the psychological sequelae of acne. Unfortunately, the media and the internet abound with alternatives to prescription medications; many without efficacy and some with harmful consequences. Since delay in acne therapy is associated with an increased risk of scarring, uneducated postings can lead to permanent disfigurement. As a result, it is incumbent upon clinicians to be well-versed in routine skin care as well as active ingredients in over the counter (OTC) products that may augment care. Many clinicians fail to discuss skin care, missing an opportunity to enhance patient outcome.

Clinicians in the United States are far behind our European colleagues who have embraced the concept of what they have termed "dermocosmetics".[1-3] Dermocosmetics are defined as products with both cosmetic and active ingredients that improve cutaneous disorders. The term "acneceuticals" is thus introduced to encompass formulations with active ingredients

that have a potential role in acne therapy, whether as first-line or adjunctive therapy. Like cosmeceuticals for anti-aging, acneceuticals fall short of being drugs; yet they contain FDA-monographed ingredients that alter the structure and function of acneic skin and have many clinical studies to substantiate their efficacy.

The most recent publication on the topic, an international consensus recommendation for the use of dermocosmetics in acne, is a comprehensive review of the topic.[4] After a thorough literature search and endeavoring to review actives with only the highest quality of in vitro and in vivo data, the authors evaluated dermocosmetics by class rather than by individual agents. They noted that studies of individual ingredients often had few, low quality studies, which made their goal of an evidence-based review unattainable.

However, patients often inquire about acneceuticals by ingredient name and a review of existing data for individual actives is worthy of assessment, even if less rigorous. Combination products are not given consideration herein, particularly proprietary formulas that are unobtainable by our patients. This review is limited to in vivo human trials in patients with acne. Benzoyl peroxide (BP) and adapalene are not included given that these are drugs, not acneceuticals. The goal of this compilation is to simplify the OTC acne landscape for prescribers as well as for patients looking to self-treat with effective and safe products.

MATERIALS AND METHODS

A scoping literature review was conducted in August 2023 on PubMed and Google Scholar and evaluated by 2 reviewers (HB, HB). Search terms were Acne AND adjunctive skincare or cosmeceuticals or dermocosmetics or barrier repair. Once the list of acneceuticals of interest was generated (see Table 1), a search was done for each active AND acne. Included studies were limited to in vitro, human and participants with acne. In September 2023, a panel of 7 dermatologists convened, and using the modified Delphi method, reviewed the data and came to consensus on which acneceuticals had sufficient data for inclusion. The goal was to provide specific evidenced-based skincare recommendations for acne therapy.

The clinician's choice of which active ingredients to review was based on knowledge of acne pathophysiology. Four central factors are thought to be most important: hyperkeratinization, hyperseborrhea and dysseborrhea, *Cutibacterium acnes* (*C. acnes*) colonization, and inflammation.[5,6] Additional studies implicate skin barrier dysfunction as a material contributor to the pathophysiology of acne. In 1995, Yamamoto and co-workers demonstrated that acne should be considered a barrier deficiency disorder alongside atopic dermatitis and psoriasis.[7] The authors found an increase in transepidermal water loss (TEWL) as well as a statistically significant reduction in ceramides, both hallmarks of barrier deficiency. Barrier dysfunction is known to be accompanied by hyperkeratosis of the follicular epithelium and therefore, Yamamoto et al postulated that barrier dysfunction could be partially responsible for comedone formation.

TABLE 1.

Proposed Mechanism of Action of Acneceuticals in Acne	
Mechanism of action	**Actives**
Keratolytic	Alpha and beta hydroxyacids Azelaic acid Retinol derivatives Bakuchiol Silymarin Sulfur
Antibacterial	Azelaic acid Niacinamide Zinc Green Tea Resveratrol Silymarin Bakuchiol Soy Probiotics Retinaldehyde Sodium hypochlorite Tea tree oil
Anti-inflammatory	Niacinamide Bakuchiol Salicylic acid Azelaic acid Linoleic acid Lactobacillus Aloe vera Green tea Cannabidiol Zinc Resveratrol Silymarin Sodium hypochlorite Tea tree oil
Sebum reduction	Niacinamide Zinc Green tea Silymarin Bakuchiol Linoleic acid Clay Soy Resveratrol
Barrier repair	Hyaluronic acid Alpha and beta hydroxy acids Glycerin Colloidal oatmeal Niacinamide Panthenol Ceramides Shea butter

Based on these tenets of acne pathophysiology, potential therapeutic targets focus on keratolysis, inhibition of sebum production, and antibacterial and anti-inflammatory agents. More recently, the importance of barrier repair in acne care has gained traction in the literature.

Mechanism of Action

Active ingredients meeting initial consensus were divided into 5 mechanisms of action: keratolytic, anti-inflammatory, sebum control, antibacterial (preferably specifically *C. acnes*), and skin barrier repair in acne studies (see Table 1). Studies were further divided into those with data supporting use of the active as monotherapy, adjunctive therapy with established prescription agents and maintenance therapy after prescription drug discontinuation (see Tables 2-4).

Many actives had data demonstrating efficacy in acne as standalone treatments. However, it is likely that in clinical practice, combination treatment will be necessary for maximum effectiveness, selecting agents from several categories to approach acne from different directions simultaneously. Studies looking at adjunctive therapy were of 2 types: the addition of an acneceutical to prescription care to augment effectiveness and the addition of a barrier repair acneceutical to improve prescription drug tolerability and therefore adherence and efficacy. Acne medications often need to be discontinued, whether due to achievement of adequate clearance, side effects, cost, or concerns about antibiotic resistance. Maintenance or treatment transition is necessary and several acneceuticals are uniquely suited to this role — continuing improvement attained with the prescription drugs or in some cases improving outcome. Choosing an acneceutical from the list of agents having the same mechanism of action as the drug itself is expected to be the most effective: switching prescription antibiotic to an acneceutical with antibacterial activity, or retinoid to OTC keratolytic.

Keratolytics

Keratolytics are thought to work in acne by decreasing adhesion of keratinocytes in the stratum corneum, helping to remove the superficial portions of follicular plugging, reducing further occlusion. Additionally, the disruption of the stratum corneum allows other actives to penetrate more effectively, increasing their efficacy.

Acneceuticals with data supporting keratolytic activity included azelaic acid (AzA), Alpha- and Beta-hydroxy acids (AHA, BHA), retinol derivatives, bakuchiol, and sulfur.

Sebum Control

The inflammatory state of acne may be partly driven by hyperseborrhea and dysseborrhea. Decreased levels of linoleic acid, total ceramides, free sphingosine, and higher levels of inflammatory free fatty acids have been noted. This dysseborrhea has been clinically correlated with epidermal barrier dysfunction.[8,9]

Acneceuticals with data supporting sebum control include niacinamide, clay, zinc, green tea, resveratrol, silymarin, and bakuchiol. Consideration was purposely limited to those actives with data indicating reduced sebum production (sebumeter, tape stripping) as opposed to those that reduce the appearance of oiliness (eg, mattifying agents such as perlite, kaolin, calcium carbonate, bentonite, methacrylate copolymer).

TABLE 2.

Actives With Monotherapy Data	
Active	**Reference**
Azelaic acid	22-24
Bakuchiol	25
Beta hydroxy acids	16-19
Cannabidiol	27
Clay	28,29
Green Tea	32-34
Niacinamide	37-40
Probiotics	43-37
Resveratrol	48
Retinol derivatives	49-50
Silymarin	51,52
Sodium hypochlorite	55
Soy	56
Tea tree oil	57,58
Zinc	60-62

TABLE 3.

Actives as Adjunctive Therapy to Prescription Medications	
Active	**Reference**
Aloe vera and tretinoin	13
Azelaic acid and erythromycin	23
Azelaic acid and clindamycin	24
Ceramide/niacinamide with BP/clindamycin	42`
Lipohydroxy acid and BP	19
Niacinamide and BP	41,42
Salicylic acid and BP	20
Silymarin and Salicylic acid peels	53
Tea tree oil and adapalene	59
Zinc and erythromycin	63,64

TABLE 4.

Actives With Maintenance Data	
Active	**Reference**
Lipohydroxy acid	20
Hydroxy acid complex	21
Retinol derivatives	24
Salicylic acid	20,21

Antibacterial Agents

C. acnes has an important role in the pathogenesis of acne. Although antibiotics, both topical and oral, are highly effective in the treatment of acne, eventual discontinuation results in rapid bacterial repopulation. Antibiotics also cause collateral damage on the skin and the gut, altering the normal healthy microbiome in both locations. Acneceuticals with antibacterial activity may not only be effective, but preferable to prescription antibiotics, allowing us to be good stewards of antibiotics by reducing the development of resistant microbes.

Acneceuticals with data supporting antibacterial activity include zinc, hypochlorous acid, tea tree oil (TTO), resveratrol, AzA, aloe vera, green tea, *Lactobacillus spp*, Enterococcus faecalis, and cannabidiol.

Anti-inflammatory Agents

Acne is a chronic inflammatory condition, and anti-inflammatory agents can reduce lesion number, size, and erythema. Acneceuticals with anti-inflammatory activity and demonstrated efficacy in acne include niacinamide, bakuchiol, salicyclic acid (SA), AzA, linoleic acid, zinc, soy, aloe vera, silymarin, Lactobacillus spp., green tea, and cannabidiol.

Skin Barrier Repair

Skin barrier repair in acne serves 2 distinct purposes. First is the possibility that improving the inherent barrier dysfunction in acne affects improvement in the disease. Data suggests that good quality skin care alone can result in acne improvement. We frequently see this when faced with unexpectedly good results in the vehicle arms of acne studies. Small studies have demonstrated that daily use of a facial cleanser and moisturizer can reduce acne lesions without aggravating epidermal barrier dysfunction, thereby reducing TEWL, mitigating aberrations of cutaneous pH, and fostering the growth of a diverse microbiome.[8]

Second is the ability of quality skin care to improve pharmaceutical tolerability. The acne management paradigm is built on topical retinoids and BP. In addition to having documented efficacy for acne, these ingredients can also increase cell turnover, induce stratum corneum thinning, and increase TEWL, often leading to xerosis, irritation, and even inflammation.[2,8,10] When combined with acne treatment regimens, the use of gentle cleansers, quality moisturizers, and sunscreen can improve patient comfort and patient-centered goals, including minimizing the adverse effects of dryness, irritation, and photosensitivity. Although there are many factors leading to poor compliance, skin irritation is a prominent factor.[11,12] A double-blinded, randomized study compared the outcome of an acne treatment regimen consisting of a twice-daily skincare routine in addition to a nightly combination topical agent (adapalene 0.3%/BP 2.5%).[13] Use of a ceramide-containing cleanser and moisturizer during the 12-week treatment period resulted in a statistically significant improvement in both primary endpoints: markers of skin barrier function and acne severity.

Acneceuticals that have specifically been shown to improve the ability of patients to tolerate acne pharmaceuticals include hyaluronic acid, alpha hydroxy acids, glycerin, panthenol, niacinamide, colloidal oatmeal, ceramides, shea butter, aloe vera, and petrolatum.

Acneceutical Data

Aloe Vera

Aloe vera as an anti-inflammatory and hydrating agent was evaluated as adjunctive therapy in a double blind, randomized, 8-week study of 60 participants with mild and moderate acne. Tretinoin 0.5% cream combined with a 50% aloe vera formulation resulted in better lesion reduction compared to tretinoin 0.5% alone.[14]

Alpha and Beta Hydroxy Acids

Hydroxy acids act as keratolytics and hydrating agents in the treatment of acne, reducing follicular obstruction and increasing absorption of coapplied ingredients. Data are most rigorous for the beta hydroxy acids, including SA and lipohydroxy (LHA). The most used alpha hydroxy acid is glycolic acid; although, in topical preparations, it is most often used in combination with other active ingredients.

Zander and Weisman reported that pads containing 0.5% and 2% SA resulted in lesion resolution in 3 small placebo-controlled studies.[15] A comparison study of 2% SA vs 10% BP cleansers in 30 participants showed superiority of the SA cleanser after 4 weeks.[16] A combination of SA-based products was effective in reducing inflammatory acne over 8 weeks without side effects.[17] LHA was as effective as 5% BP in 80 patients with mild-moderate disease.[18] LHA twice daily was also as effective as 2.5% tretinoin cream in 85 mild-moderate patients after 3 months with fewer side effects.[19]

Hydroxy acids have been evaluated extensively as ideal maintenance products after discontinuation of prescription medications. One hundred participants who improved on BP were randomized to receive either a SA/niacinamide combination cream or vehicle. Continued improvement was seen with the SA cream over 12 weeks.[20] Continued improvement was also seen with a tri-acid complex serum (glycolic acid, SA, and LHA) in 30 participants once daily for 2 months after discontinuation of prescription medications.[21]

Azelaic Acid in OTC Concentrations

AzA, in its prescription concentration of 15% and 20%, is thought to be effective in acne due to its anti-inflammatory activities, its ability to inhibit growth of *C. acnes*, and its mild keratolytic

effects. This product is available OTC in lower concentrations with limited data supporting its use.

As monotherapy, in a small uncontrolled, 8-week study of patients with mild-to-moderate acne, once-daily application of a 10% AzA gel resulted in significant reduction in inflammatory lesions and non-inflammatory lesions.[22]

As adjunctive therapy, use of AzA 5% with erythromycin 2% was more effective than monotherapy with erythromycin 2% or 20% AzA in a randomized, double-blind, 12- week study of 147 patients with mild-to-moderate acne.[23] The combination product was better tolerated than the 20% AzA. In a similar double-blind, randomized, 12-week trial of 150 patients with mild-to-moderate disease, the combination of azelaic acid 5% and clindamycin 2% was significantly more effective than either monotherapy arm in reducing both inflammatory lesions and non-inflammatory lesions.[24]

Bakuchiol

Bakuchiol has been touted as a more tolerable retinol alternative. Although it is not structurally similar to retinoids, it does demonstrate retinol-like regulation of gene expression. Its use in acne has been based on in vitro data demonstrating anti-inflammatory, antibacterial and keratolytic activity.

As monotherapy, a small study of 13 patients with mild-to-moderate acne used a 5% formulation twice daily for 12 weeks with a significant reduction of inflammatory lesions.2[5]

As adjunctive therapy, a combination dermocosmetic containing bakuchiol was shown to improve the efficacy of adapalene 1% in a 2-month study of 111 patients.[26] An improvement in seborrhea was also noted.

Cannabidiol

Cannabidiol has been proposed for the treatment of acne due to its anti-inflammatory activity. It has also been shown to inhibit *C. acnes* growth in vitro. A small pilot study of 30 participants showed a decrease in inflammatory lesions.[27]

Clay

There are limited studies for clay masks in acne. Clay has hydrating and anti-inflammatory activity as well as data demonstrating reduced sebum production. As monotherapy, a mask used twice weekly for 4 weeks resulted in reduced acne lesion counts, decreased sebumeter values, and improved subjective oiliness in 75 adults with oily skin.[28] An open label study of 194 patients with mild acne demonstrated a 54% reduction in total lesion count after utilizing a mask 2 to 3 times/week for 6 weeks.[29]

Green Tea

Green tea has been evaluated for the treatment of acne due to its antimicrobial and anti-inflammatory activity, as well as evidence that it can reduce sebum production.

In 2 uncontrolled studies, green tea extract was shown to decrease sebum production: a split-face study of 11 men found a 27% reduction in sebumeter values after 60 days of daily use[30]; a 3% extract showed similar results in 10 participants after 8 weeks of use.[31]

As monotherapy, green tea extract was evaluated in several studies. In an uncontrolled study of 20 patients, a 2% extract resulted in a statistically significant reduction in lesion counts after 6 weeks of daily use.[32] A 1% or 5% extract was utilized in a split-face study vs vehicle in 35 patients with acne: at 8 weeks there was a significant decrease in both inflammatory and non-inflammatory lesions.[33] A comparison of 2% extract to vehicle in 60 patients resulted in a statistically significant reduction in inflammatory lesions at 8 weeks and high patient satisfaction.[34]

Linoleic Acid

A decrease in linoleic acid in surface lipids has been found in patients with acne compared to healthy controls. This is thought to be related to an alteration in the quality of sebum produced by acne patients. Linolenic acid is a potent inhibitor of 5-alpha reductase and is an anti-inflammatory that has been used in combination with many other agents in numerous studies. Recently, it has been reported that a combination cream containing linoleic acid, linolenic, and lecithin was effective in 4 patients in a case series.[35]

Niacinamide/Nicotinamide

The best studied of the acneceuticals is niacinamide. This anti-inflammatory and antimicrobial (including activity against *C. acnes*) is hydrating and has sebum-reducing activity. Niacinamide/nicotinamide has been extensively studied as monotherapy and as adjunctive therapy.

As monotherapy, Draelos et al evaluated the ability of 2% niacinamide to reduce facial sebum production in 100 participants vs vehicle for 4 weeks and in 30 split-face participants for 6 weeks.[36] In both studies there was a statistically significant reduction in sebum excretion rate by sebumeter. Three studies evaluated niacinamide 4% and 5% in comparison to clindamycin 1% or 2% with similar success at study conclusion.[37,38,39] It was also found to be comparable to 1% green tea extract.[40]

As adjunctive therapy, Kaewsanit et al evaluated the use of niacinamide 5% in a split-face study of 21 participants with mild-to-moderate acne who were treated with 2.5% BP.[41] The entire

face was treated with BP, and niacinamide was applied once daily to 1 side of the face and cream base was applied to the other. The niacinamide-treated side showed superior reduction of non-inflammatory lesions at 12 weeks and a significant decrease in sebum at 6 weeks. Another split-face study evaluated the addition of a niacinamide/ceramide cream to 1 side of the face that had been treated with 5% BP/.1% Clindamycin. The niacinamide/ceramide-treated side showed superior reduction of inflammatory and non-inflammatory lesions and sebum production, as well as superior tolerability.[42]

Probiotics

Acne lesions create an environment that facilitates the excess growth of *C. acnes*. In vitro studies have shown the ability of some bacteria to directly inhibit *C. acnes* growth. *Lactobacillus spp*, *Enterococcus faecalis*, and *Nitrosomonas eutropha* have the most data behind them.

Lactobacillus was shown in 10 participants with mild-to-moderate acne to reduce *C. acnes* and Staphylococcal taxa after 8 weeks of twice-daily application.[43] In a vehicle-controlled study of 79 patients, there was a 34% decrease of inflammatory lesions (vs control 1.7%).[43] In a randomized controlled trial vs 2.5% BP in 104 participants, reduction of total lesion count was comparable with fewer side effects in the participants treated with *Lactobacillus*.[44] Results were also similar in comparison to salicyclic acid 1% in 10 patients.[45]

A lotion containing *Enterococcus faecalis* was shown to be effective in reducing inflammatory lesions in 70 participants with mild-to-moderate disease after 8 weeks.[46]

Nitrosomonas eutropha is an ammonium oxidizing bacterium that converts ammonium into nitric oxide, known to be antimicrobial and anti-inflammatory. This probiotic was studied in a phase 2b study of 358 patients with mild-to-moderate acne for 4 weeks resulting in a 2-grade (5-point scale) improvement in investigator global assessment.[47]

Resveratrol

Resveratrol has antimicrobial and anti-inflammatory activities and some evidence suggesting it decreases sebum production. In a single-blind, vehicle controlled, split-face pilot study of 20 participants, resveratrol demonstrated a 54% (vs 6% vehicle) reduction in global improvement after 2 months.[48]

Retinol Derivatives

Retinoids such as retinol, retinal, and retinaldehyde abound in the OTC space and are used widely for anti-aging indication. Compared to prescription retinoids, OTC retinoids are far less effective in the treatment of acne. However, in their ability to act as keratolytics, they may help mild disease. Retinaldehyde has been shown to differ from the other OTC retinoids in its significant in vitro antibacterial activity and may be the most effective.[49]

A combination cream of hydrocypinocolone retinoate and retinol glycospheres was evaluated for its ability to prevent disease recurrence post-isotretinoin use. The need for additional acne treatment was only 15.38% at 12 months, but there was no control group.[50]

Silymarin

Silymarin has keratolytic, anti-inflammatory, and antioxidant activities and may also reduce sebum production.

As monotherapy, it was evaluated in 56 patients demonstrating a 45% reduction in inflammatory lesions and 43% reduction in non-inflammatory lesions after 12 weeks of use.[51] In a split-face comparison study, 1.4% silymarin cream twice daily was compared to SA 30% peels twice monthly for 3 months.[52] Treatments were equally effective.

Two studies evaluated the addition of silymarin to existing acne therapy of various types. Forty patients noted improvement in existing inflammatory and non-inflammatory lesions, as well as a reduction in sebumeter values.[51] An open label study evaluated 22 patients with mild-to-moderate acne already on therapy, in whom the addition of 0.5% serum twice daily reduced lesion count and sebum secretion after 4 weeks.[53]

Sodium Hypochlorite

Sodium hypochlorite has anti-inflammatory activity and is bacteriocidal against *C. acnes*. A study of 40 participants utilized 0.005% 3 times daily for 1 month resulting in a significant resolution of papules without irritation.[54] It was shown to be as effective in the treatment of mild-to-moderate disease as BP 5%.[55]

Soy

Soy has anti-inflammatory, antioxidant, and antimicrobial activities as well as hydrating and antiandrogenic activity. However, as monotherapy there are few studies. Ghyczy et al reported on 7 small open-label trials totaling 77 patients in whom split-face use daily for 20 days to 2 months resulted in a reduction in inflammatory lesions.[56]

Sulfur

Sulfur has been used for decades in the treatment of acne and is thought to act by keratolytic activity. This topical agent has been extensively studied in combination with resorcinol, zinc, salicyclic acid, and sodium sulfacetamide but there are no human studies of sulfur alone in the treatment of acne.

Tea Tree Oil
TTO has anti-inflammatory and anti-bacterial activity.

Five percent TTO formulations have been studied in single- and double-blind studies in comparison to BP 5%. In a study of 119 and another of 60 participants with mild-to-moderate acne , the 2 arms showed similar improvement with more side effects in the BP 5% arm.[57,58]

As an adjunctive, a randomized comparison trial evaluated the use of 6% TTO in addition to adapalene 0.1%. A total of 100 patients were randomized to be treated with either 6% TTO or adapalene 0.1% plus 6% TTO. After 12 weeks, the patients treated with the combination had a better outcome in both inflammatory and non-inflammatory lesions.[59]

Zinc
Zinc has anti-inflammatory activities, is bacteriostatic against *C. acnes* and has been shown to decrease sebum production. It has been used both orally and topically in the treatment of acne with mixed results. The following is limited to topical alone.

As monotherapy, it was evaluated in a placebo-controlled trial of 60 patients for 8 weeks with superior outcome compared to vehicle.[60] Compared to BP 5% in 28 patients for 8 weeks, results were comparable.[61] It was found inferior to 2% TTO in an 8-week comparison trial of 40 patients.[62]

As adjunctive therapy, addition of zinc to erythromycin 4% in 60 patients for 12 weeks and erythromycin 2% for 3 weeks resulted in minimal improvement compared to erythromycin alone.[63,64]

CONCLUSION

There is a strong need for both clinician and patient education regarding skincare selection and ingredients suitable for acne care. Acneceuticals play an important supportive role in acne management. They can be used to increase the efficacy of prescription products, increase the tolerability of prescription products, and maintain or repair the skin barrier. Although beyond the scope of this paper, acne sequelae such as dyschromias may also respond to acneceuticals.

For the dermatologist to optimize outcomes, it is vital to dedicate time during initial and follow-up encounters to patient education regarding the importance of a sound skincare regimen. When combined with prescription therapy, gentle cleansers, quality moisturizers, and acne actives are capable of mitigating irritation, erythema, dryness, pruritus, and other symptoms common during the initiation phase of topical regimens. They may also have additive or synergistic effects in achieving treatment outcomes aside from maximizing adherence.

The symptoms of epidermal barrier dysfunction – erythema, pruritus, peeling, dryness – are common adverse effects of first-line acne treatment options. Without appropriate counseling and management, these symptoms may lead to regimen nonadherence, negative patient experience, and poor outcomes. Patient education regarding acneceuticals may give patients a greater sense of involvement and buy-in to their care. Given the expansive selection of commercial cleansers and moisturizers, dermatologists may be able to combat patient's choice-paralysis by providing specific recommendations as well as instruction on when and in what order to apply their skincare and prescription products.

Current limitations include the lack of robust, long-term clinical trial data especially within diverse populations. Despite the lack of rigor, data exist that support the recommendation of acneceuticals within dermatology practices. Perhaps more importantly, this provides patients with a roadmap for self-treatment and the ability to obtain efficacious and safe acne care regardless of insurance coverage.

While challenging to execute within the confines of a high-volume practice, improving patient knowledge of comprehensive acne treatments may be an effective way to maximize regimen efficacy and provide patients with the necessary tools for personalized and successful acne treatments.

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ORIGINAL ARTICLE

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Management of Acute Hematomas and Methods to Mitigate Risk

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ABSTRACT

One of the most common complications in dermatologic surgery is postoperative bleeding, which can result in hematoma formation and suboptimal healing outcomes. Identifying preoperative, intraoperative, and postoperative risk factors can reduce the risk of bleeding complications. However, despite best risk mitigation practices, hematomas remain a possible outcome of cutaneous surgery. Expanding hematomas causing functional pain and compromise to the surrounding neurovasculature should be evacuated. The authors herein discuss the risks associated with bleeding complications, methods to manage these risks, and a protocol to follow if an acute hematoma were to occur.

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INTRODUCTION

Postoperative bleeding is one of the most frequent complications seen in dermatologic surgery, of which hematoma formation is a known consequence.[1] A hematoma is defined as a collection of blood outside of a vessel as a result of damage to the surrounding vasculature. While the incidence of hematoma formation in dermatologic surgery is less than 3%, this complication can result in unintended outcomes such as surgical site infection, wound dehiscence, tissue necrosis, and permanent damage to vital structures if located in peri-orbital or cervical regions.[2–5] Consequently, sub-optimal healing outcomes may occur, such as prolonged healing time, scarring, and poor cosmesis.[5] Although a seemingly rare complication, multiple studies have reported difficulties with hemostasis being the most common adverse event following cutaneous surgery in both the setting of basic standard excision and Mohs micrographic surgery (MMS).[3,4,6] Recognition of risk factors associated with hematoma formation is vital in determining appropriate risk mitigation practices in order to decrease the incidence of bleeding complications and promote proper wound healing. These risks are summarized in Table 1.

Preoperative Risk Mitigation

Many factors that increase the risk of hemorrhage expectedly play a role in the formation of hematomas. These factors can be identified and addressed preoperatively by noting the patient's medication list, medical history, and social history. One prospective cohort study involving 20,821 MMS cases reported 149 adverse events, 15.1% of which were related to bleeding and hematoma formation, most of which comprised patients on anticoagulation medications.[7] The use of anticoagulant medications, appreciated in approximately 25% to 46% of patients undergoing dermatologic surgery, may place the patient up to 7 times more likely to experience a moderate to severe hematoma.[2,8,9] Interestingly, up to 50% of patients undergoing a dermatologic surgery may use over the counter (OTC) supplements involved in the coagulation cascade. Patients with a history of myocardial infarction, stent placement, cerebrovascular accidents (CVA), deep venous thrombosis, pulmonary embolism, and atrial fibrillation are often on anticoagulant agents.[9] Anticoagulant medications are categorized by mechanism of action, and include platelet inhibitors, direct oral anticoagulants (DOACs), vitamin K antagonists, and over the counter products. Antiplatelet agents include aspirin, clopidogrel, ticagrelor, prasugrel, and nonsteroidal anti-inflammatory agents (NSAIDs). Direct oral anticoagulants include apixaban, rivaroxaban, dabigatran, edoxaban, and betrixaban. The most common vitamin K antagonist to date is warfarin. Additionally, certain herbal supplements and vitamins may increase the risk of postoperative bleeding, such as ginkgo biloba, ginseng, ginger, saw palmetto, feverfew, St. John's wort, garlic, fish oil, and vitamin E.[5,10,11]

While it is recommended that all vitamins be discontinued 2 to 3 weeks prior to surgery, dermatologists advise against the cessation of anticoagulation medications, as management of potential embolic or cardiac events pose more difficulties than the treatment of postoperative bleeding complications.[1] Several studies have demonstrated that in patients taking aspirin or NSAIDs, there is not a significant increase in bleeding complications.[2,8] Aspirin should be continued for high-risk patients, including those with a history of cerebrovascular disease, unstable angina, coronary stent placement, or cardiac

TABLE 1.

Summary of Risk Mitigation Strategies	
Preoperative Risk Mitigation	
1. Medication list	1. Platelet blockers: clopidogrel, ticagrelor, prasugrel 2. DOACs: apixaban, rivaroxaban, dabigatran 3. Warfarin: assess most recent INR 4. Over the counter supplements: ginkgo biloba, ginseng, ginger, saw palmetto, feverfew, St. John's wort, garlic, fish oil, and vitamin E
2. Medical history	1. Diabetes - check most recent HbA1c 2. Hypertension - controlled vs uncontrolled, assess previous blood pressures 3. Kidney disease (thrombocytopenia) 4. Liver disease (deficient clotting factors) 5. Other bleeding disorders, genetic syndromes at risk of bleeding (Von Willebrand, Ehlers Danlos, etc.)
3. Social history	1. Alcohol use 2. Tobacco use
Intra-Operative Risk Mitigation	
1. Site of surgery: head, neck > trunk > extremities	
2. Use of epinephrine	
3. Size of defect	
4. Size of surgical flap	
5. Amount of undermining	
6. Electrosurgery required	
7. Ligation required	
8. Topical hemostatic agents required	
Postoperative Risk Mitigation	
1. Hold firm pressure to surgery site for 10 to 15 minutes immediately following closure	
2. Place secure layered pressure dressing consisting of petroleum jelly, non-adherent film, gauze, adhesive tape; self-adherent wrap may be employed for patients with delicate skin	
3. Every patient receives verbal and written instructions on wound care, what to do if there is bleeding (either oozing or frank bleeding), activity levels, alcohol use, signs and symptoms of infection or wound dehiscence or necrosis, and when to call the surgeon	
4. Have patient discontinue any over the counter vitamins/supplements that may increase risk of bleeding	
5. Instruct patient to withhold from any strenuous activities/exercise and be cautious of any activity that could increase systolic blood pressure, bending, lifting heavy objects, avoid placing excessive wound tension on surgical site	
6. Provide specific instructions for surgery sites in the perioral area: minimize talking/laughing, eating soft or well-cooked foods, avoiding sucking action via a straw, and care when inserting or remov-ing dentures	

surgery.[9] However, if a patient is taking aspirin prophylactically, surgeons may consider holding for a week prior to surgery.[9] Other antiplatelet medications include the class of thienopyridines, namely clopidogrel, ticlopidine, and prasugrel. Use of either clopidogrel or prasugrel places the patient at increased risk of perioperative and postoperative bleeding complications.[8] Additionally, the combination use of clopidogrel and warfarin is associated with a 40 times increased risk of bleeding complications.[8,9] There are no specific investigations about risk of postoperative bleeding following dermatologic surgery in patients taking ticagrelor; guidelines for ticagrelor and prasugrel follow recommendations for other antiplatelet therapy.[9]

Patients taking warfarin have up to 7 times increased risk of bleeding complications; therefore, surgeons should assess an international normalized ratio (INR) on patients taking warfarin, accepting those at therapeutic levels of 2.5 to 3.5.[8,12,13] Ah-Weng et al recommends completing an INR within 24 hours of the procedure, postponing surgery if INR > 3.5.[13] Risk mitigation strategies should be entertained prior to surgery to decrease the incidence of bleeding complications and prevent poor surgical outcomes.

Although literature is limited, DOACs have been shown to increase bleeding complications in cutaneous surgeries. Patients on apixaban and rivaroxaban are 7 times more likely to experience hemorrhagic complications, and up to 10 times more likely when taken in conjunction with aspirin.[14] Despite the increased risk, the overall incidence is low. A retrospective study found that out of 41 cutaneous surgeries in patients taking dabigatran or rivaroxaban, only 1 resulted in a mild bleeding

complication.[15] Given the lack of larger studies investigating DOACs in dermatologic surgery, it is recommended that these novel agents are managed similarly to traditional antiplatelet therapies in the postoperative period.

Dermatologic surgeons should also be aware of pertinent comorbidities of the patient undergoing surgery. Cook et al found that among 1,358 MMS cases, the incidence of complications was 1.64%, of which 31% were related to hematomas.[3] Notably, 71% of those who developed hematomas had a history of hypertension.[3] Inadequate control of hypertension (ie, blood pressures greater than 150/100 mmHg) may have both intraoperative and postoperative implications and require an assessment prior to surgery.[4] Jayasekera et al demonstrated that patients with an elevated preoperative systolic blood pressure were more likely to have intraoperative bleeding and thus longer operative times; however, they did not find a significant association between elevated systolic blood pressure and postoperative bleeding-related complications.[16] Ultimately, mild to moderate hypertension, which is defined as blood pressures 140/90 to 179/109, should not impede or postpone a surgical procedure.[2] It is widely accepted among dermatologic surgeons that if a patient maintains 3 separate blood pressures > 180/110 mm Hg over 1 hour, the surgical procedure should be deferred until blood pressure has stabilized.[2] Finally, specific bleeding diathesis, liver disease, and kidney disease places the patient at increased risk of bleeding due to the underlying defect in platelet aggregation or clot formation.[5] Other conditions that may reduce available platelets from contributing to clot formation include chronic lymphocytic leukemia and a history of splenectomy, both of which demonstrate defects in platelet quality or quantity.[5] If the patient presents with petechiae, gingival bleeding, or a platelet level less than 20,000, then hematology should be consulted. Otherwise, thrombocytopenia typically does not affect hemostasis in dermatologic surgery.[17] Other patient risk factors documented by different medical specialties include male sex, alcohol use, smoking, and low BMI.[2,18,19]

Intraoperative Risk Mitigation

Intraoperative risks include those that result in increased damage to surrounding vasculature. It is paramount for the dermatologic surgeon to be intimately familiar with vascular anatomy to reduce the risk of damaging critical structures. In addition, anatomical location of the surgical site in areas with high vascularity (ie, temple, mandibular rim, nose, scalp) will require a delicate and meticulous technique to minimize risk of bleeding.[3-5,7,19-21] Utilizing lidocaine with epinephrine for anesthesia can be very helpful since the epinephrine can assist in vasoconstriction and hemostasis during the surgical procedure. Size of surgical defect, size of surgical flap, and the extent of undermining performed have all been correlated with increased risk of bleeding complications.[2,5,22]

Obtaining adequate hemostasis during dermatologic surgery is critical for preventing bleeding complications. Methods to achieve hemostasis include electrosurgery, vessel ligation, topical hemostatic agents, and firm pressure.

Electrosurgery is a quick and effective method to achieve hemostasis intraoperatively. However, it can cause collateral thermal damage to the surrounding tissue leading to suboptimal healing. The smoke plume can also pose health hazards to the dermatologic surgeon and aerosolization of viral and bacterial pathogens.[23] A recent study compared the complication rates for patients undergoing MMS who had received more electrosurgery versus those who received less electrosurgery. There were no statistical differences in 3-month postoperative surgical complications including bleeding complications and abnormal scarring. However, hematomas were only noted in the nonelectrodessication group.[24] While electrosurgery is a useful method to achieve hemostasis, it does not come without risks, and judicious use is recommended.

Hemostasis can also be achieved with certain suturing techniques.[17] In instances where there is brisk bleeding from an identifiable dermal vessel >2 mm, vessel ligation is recommended. Hemostats can initially be used to secure these vessels, and care should be taken to avoid clamping and ligating excess tissue since this could cause unnecessary tissue necrosis. The vessel can then be ligated with an absorbable suture utilizing the figure of 8 suture technique. If there is nonspecific oozing from the wound edges, the epidermal horizontal mattress suturing technique can be useful to improve hemostasis.

Topical hemostatic agents can also assist in hemostasis.[25] These are divided into caustic and non-caustic hemostatic agents based on mechanism. Caustic hemostatic agents achieve hemostasis by coagulating proteins leading to necrosis, occlusion of small vessels, and eschar formation. These agents include aluminum chloride, ferric sulfate, and silver nitrate. Aluminum chloride is most frequently used since ferric sulfate and silver nitrate can lead to undesirable subsequent skin pigmentation at the site of application. Noncaustic hemostatic agents can be further subdivided into physical and physiologic categories. Physical noncaustic topical hemostatic agents achieve hemostasis by providing a mesh for platelets to aggregate. These agents are useful if there is still bleeding after electrosurgery has been utilized. Physiologic noncaustic hemostatic agents contain coagulation factors that augment hemostasis. These are rarely used since they can be costly.

Post-operative Risk Mitigation

After ensuring that there is no oozing from the closure site, a secure pressure dressing should be placed consisting of 4 layers: an emollient such as petroleum jelly, non-adherent film, sterile gauze, and adhesive tape. Immediately holding firm pressure at

the surgery site for 10 to 15 minutes after bandage placement may also contribute to lasting hemostasis. Occasionally, self-adherent elastic wrap may be utilized for patients with delicate, atrophic skin. Prior to leaving the office, every patient should receive both verbal and written instructions on daily wound care, recommendations to control simple or persistent bleeding once home, activity levels, use of alcohol, signs, and symptoms of infection, wound dehiscence or necrosis, and when it is appropriate to contact the surgeon. In addition, patients should be instructed to refrain from particularly strenuous exercises, activities that may increase systolic blood pressure, bending forwards, and lifting heavy objects, all of which may provide external tension on the surgical site. Surgeons must keep in mind that postoperative waning vasoconstrictor effects of epinephrine in local anesthetic can lead to postoperative bleeding and hematoma formation, demonstrating the importance of patient education.[2,5,22] For surgical sites in the perioral area, patients should also be advised to minimize talking or laughing, eat soft foods, avoid sucking action via a straw, etc. Similar to preoperative recommendations, patients should avoid any over-the-counter supplements that may contribute to bleeding.

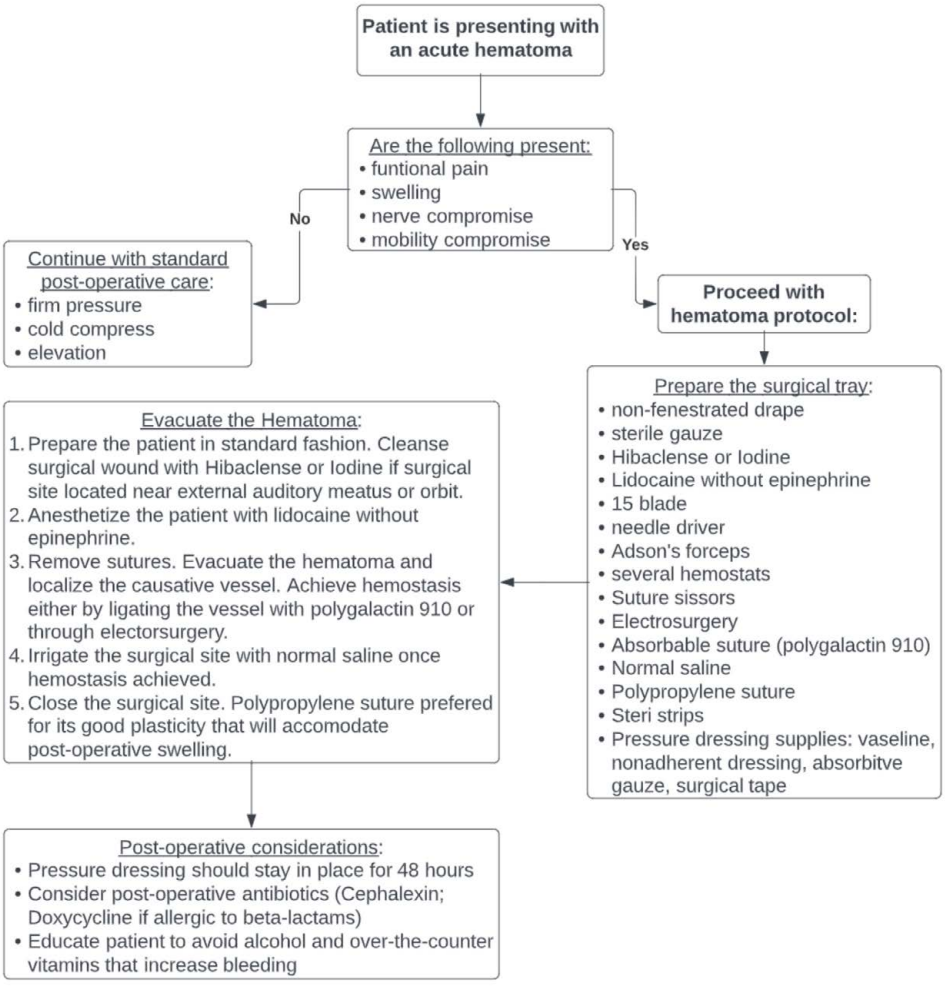
Acute Hematoma Protocol

Despite the best risk mitigation practices, an acute hematoma as a result of active bleeding may still inevitably occur. If expanding or causing functional pain to the patient, the hematoma should be urgently evacuated. Hematomas overlying vital structures are of particular concern since they can result in compression and lasting unwanted consequences.[5]

The patient should first be prepped with antiseptic, draped appropriately, and anesthetized before proceeding with hematoma evacuation. Plain lidocaine is theoretically preferred since the vasoconstrictive effect of epinephrine could mask the presence of the culprit vessel. Once the patient is anesthetized, the surgical site can be opened, and the hematoma evacuated. Electrosurgery can be used to stop the bleeding of smaller vessels. If there are larger vessels not responding to electrosurgery, vessel ligation can be helpful.

Once hemostasis has been achieved, the wound bed should be irrigated with sterile normal saline.[5] Some surgeons may opt for drain placement or utilize sterile iodophor packing gauze to

FIGURE 1. Acute hematoma protocol algorithm.



reduce the risk of recurrent hematoma. The wound can then be re-sutured. The epidermal suture of choice should have good plasticity (ie, polypropylene) to accommodate post-operative wound swelling.[26] It is standard for patients to be placed on post-operative antibiotics to prevent further surgical complications such as infection.[5] Refer to Figure 1 for a detailed algorithm and acute hematoma protocol.

CONCLUSION

Postoperative bleeding is a frequent complication of cutaneous surgery which may result in acute hematoma formation and subsequent poor healing outcomes. Employment of risk mitigation strategies throughout every step of the operative process, including pre-and post-operatively, decreases the likelihood of these complications. Cessation of anticoagulant medications prior to cutaneous surgery remains a subject of discussion. However, the following practices have been shown to lower the overall risk of postoperative bleeding: adequate blood pressure control, a delicate technique in high-risk zones, use of electrocautery and topical hemostatic agents, vessel ligation, and proper application of pressure dressing. Despite good practice, hematoma formation remains a possible outcome of cutaneous surgery. Expanding hematomas, functional pain, and compromise of surrounding nerves, vessels, and movement should prompt surgeons to evacuate the hematoma per protocol to improve wound healing and cosmetic outcomes in these patients.

DISCLOSURES

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

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Comparative Efficacy of Intralesional Steroid Injections vs Cryotherapy for the Treatment of Alopecia Areata

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ABSTRACT

Introduction: The precise etiology of alopecia areata (AA) remains unclear. Various treatments, including corticosteroids, minoxidil, immunotherapy, and phototherapy, have shown varying efficacy. Injectable corticosteroids, despite being invasive, are the first-line treatment, while topical steroids are also commonly used.

Objective: To compare the efficacy of intralesional steroid (triamcinolone acetate) versus cryotherapy for the treatment of alopecia areata over a 6-month period in the Department of Dermatology at the Pakistan Atomic Energy Commission General Hospital.

Methods: The study included 118 patients (aged 15 to 50 years, both genders) with a single patch of alopecia areata on the scalp. Exclusion criteria included active secondary infections, cold intolerance, multiple patches, iatrogenic or primary immunosuppression, pregnancy, or breastfeeding. Patients were randomly assigned to two groups: Group A received intralesional steroid injections, and Group B underwent cryotherapy with liquid nitrogen. Treatment efficacy was then evaluated.

Results: The mean age was 27.78 ± 4.68 years in Group A and 26.63 ± 4.91 years in Group B. Most patients (95, 80.51%) were aged 15 to 30 years. Males predominated with 86 (72.27%) participants, resulting in a male-to-female ratio of 2.6:1. The mean duration of alopecia areata was similar in Group A (8.51 ± 3.94 months) and Group B (8.39 ± 3.13 months). Group A (intralesional corticosteroids) had a significantly higher efficacy rate, with 49 patients (83.05%) responding positively, compared to 30 patients (50.85%) in Group B (cryotherapy) (P=0.0001), as shown in Table 1.

Conclusion: The study concluded that the efficacy of intralesional steroids may be superior to cryotherapy for the treatment of alopecia areata.

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INTRODUCTION

Alopecia areata (AA) is a distinct pathological condition characterized by non-scarring hair loss due to autoimmune processes and inflammation.[1] It can present as patchy alopecia, alopecia totalis (AT), or alopecia universalis (AU).[2] About 2% of the population experiences AA at some point, predominantly as patchy alopecia on the scalp.[3] The clinical spectrum of AA varies from isolated patches of hair loss to complete baldness on the scalp (AT) or the entire body (AU), leading to psychological distress, especially in severe or chronic cases.[4]

Although a cause was suggested in the 1970s, it has not been substantiated. A genetic study by Yang et al showed 8.4% of patients had a family history of AA, indicating a polygenic additive mode of inheritance. AA is now considered an organ-specific autoimmune disorder with a genetic predisposition triggered by environmental factors.[5] It can affect individuals of any age or gender, sometimes occurring alongside other autoimmune disorders like vitiligo or thyroid disease.[4,5] Diagnosis is primarily clinical, based on distinct circular, non-scarring areas of hair loss with "exclamation mark" hairs at the periphery.[5] Skin biopsy shows increased telogen follicles and an inflammatory lymphocytic infiltrate in the peribulbar region.[6]

Although AA is mainly a cosmetic concern, it causes significant emotional distress, particularly in children and women. Up to 80% of localized AA cases spontaneously remit within a year.[7] A Cochrane review highlighted the lack of randomized controlled studies on effective treatments for AA.[8] Treatments

aim to mitigate disease activity, as well as educate patients on treatment outcomes.

Various therapies, including corticosteroids, minoxidil, immunotherapy, and phototherapy, have been explored with variable outcomes. Injectable corticosteroids, despite being invasive, are the frontline therapy for AA, and topical steroids are also commonly used.[9] Cryotherapy has recently been explored as a treatment option. A study found intralesional steroid injections to be more effective than cryotherapy, with 83.3% efficacy for steroids compared to 56.7% for cryotherapy (P<0.05).[9]

In this context, we conducted a quasi-experimental study to compare the efficacy of intralesional steroid (triamcinolone acetate) versus cryotherapy (liquid nitrogen) in treating AA over six months in the Pakistani population. This study aims to provide insights into optimal management strategies for AA patients in this region, where such research is lacking.

MATERIALS AND METHODS

Following approval from the hospital's Ethical Review Committee, this quasi-experimental study was conducted from February 2018 to August 2018, in the Department of Dermatology at the Pakistan Atomic Energy General Hospital. Using the World Health Organization (WHO) sample size calculator, 118 patients were selected by non-probability convenience sampling. The inclusion criteria included patients aged 15 to 50 years, of both sexes, who had not received prior treatment for alopecia areata. The exclusion criteria included individuals with active secondary infections, known allergy to triamcinolone acetate, intolerance to cold, multiple patches of alopecia areata, any generalized dermatosis, primary immunosuppression, and pregnant or breastfeeding individuals. The treatment's efficacy in addressing AA was graded based on hair regrowth: a "Good Response" was 90 to 100% regrowth, an "Intermediate Response" was 50 to 89% regrowth, and a "Poor Response" was less than 50% regrowth. Efficacy was defined as achieving an intermediate to good response.

Patients were randomly assigned to 2 groups, with Group A receiving intralesional corticosteroid treatment and Group B receiving cryotherapy with liquid nitrogen. Group A patients were administered 5 mg/ml of intralesional corticosteroid (triamcinolone acetate) using an insulin syringe. Group B patients underwent cryotherapy with a cotton bud. Treatments were repeated at 4-week intervals for up to three sessions or until complete clearance of alopecia. After three months of treatment, all patients were followed up to evaluate the efficacy based on the operational definition.

All relevant data, including patient demographics and study variables, were recorded using a specially designed proforma. Data analysis was performed using SPSS version 21.0. Quantitative continuous variables, such as age, patch size, and duration, were presented as mean ± SD. Qualitative variables, such as gender and the outcome variable, efficacy, were expressed as frequencies and percentages. The comparison of efficacy between the two groups was conducted using the chi-square test, with a significance level set at P<0.05.

RESULTS

In this study, 118 patients aged 15 to 30 years were selected, with a mean age of 27.21 ± 4.58 years. Participants were divided into 2 groups: Group A, with a mean age of 27.78 ± 4.68 years, and Group B, with a mean age of 26.63 ± 4.91 years. Among the participants, 86 (72.27%) were males and 33 (27.73%) were females, resulting in a male-to-female ratio of 2.6:1. The average duration of alopecia areata among all participants was 8.41 ± 3.53 months, with Group A having a mean duration of 8.51 ± 3.94 months and Group B had a mean duration of 8.39 ± 3.13 months.

The average size of involvement of alopecia areata was 6.14 ± 2.88 cm, with Group A having an average size of 6.31 ± 2.33 cm and Group B having an average size of 6.89 ± 2.09 cm. The efficacy of the two treatment modalities was compared, showing that Group A (intralesional corticosteroid) had an efficacy of 83.05%, with 49 patients showing a positive response, while Group B (cryotherapy) had an efficacy of 50.85%, with 30 patients showing a positive response (Table 1). The study also analyzed treatment efficacy stratified based on age groups and gender, as shown in Table 1. Additionally, the comparison of efficacy based on the duration and size of alopecia areata is presented in Table 2.

TABLE 1.

Comparison of Efficacy With Respect to Age Groups and Gender

Variables		Group A (n=59)		Group B (n=59)		*P*-value
		Efficacy		Efficacy		
		yes	no	yes	no	
Age of patients (years)	15-30	38	09	23	25	0.001
	31-50	11	01	07	04	0.104
Gender	Male	36	07	20	22	0.0001
	Female	17	03	10	07	0.074

TABLE 2.

Comparison of Efficacy With Respect to Duration and Size of Patch of Disease

Variables		Group A (n=59)		Group B (n=59)		*P*-value
		Efficacy		Efficacy		
		yes	no	yes	no	
Duration of Disease	≤12 months	25	06	16	17	0.007
	>12 months	24	04	14	12	0.010
Size of the patch of disease	≤5	26	07	15	16	0.011
	>5	23	03	15	13	0.005

DISCUSSION

Alopecia areata is an autoimmune disorder characterized by hair loss on the scalp and other body parts. Despite advances in understanding its pathogenesis, evidence-based therapies are lacking, leading to chronic and unpredictable disease courses.[10-12] Recent literature suggests the scarcity of randomized controlled trials investigating effective treatments for AA.[13] Triamcinolone acetonide has been a longstanding option for AA treatment.[14] Intralesional corticosteroids, particularly triamcinolone acetonide, remain the preferred first-line therapy for adults with limited, patchy AA.[15] Cryotherapy involves targeted tissue destruction using cold substances and is advocated as a second-line treatment with recent mounting evidence supporting its efficacy.[16]

This study aimed to compare the efficacy of intralesional corticosteroid and cryotherapy in treating AA in a population aged 15 to 30 years. Among 118 patients, 86 (72.27%) were males, and 33 (27.33%) were females, with a male-to-female ratio of 2.6:1. The mean age was 27.21 ± 4.58 years, with Group A (intralesional corticosteroid) showing an efficacy of 83.05%, compared to 50.85% for Group B (cryotherapy) (*P*-value = 0.0001). These results align with prior findings.1[7-18]

Intralesional corticosteroids demonstrated better outcomes than cryotherapy, consistent with previous studies.[19] For localized conditions, intralesional corticosteroids are preferred over topical options, with more accelerated healing and longer-lasting effects.[20] Concentrations of 5 and 10 mg/mL of triamcinolone acetonide have shown superior outcomes compared to lower concentrations.[19] Notably, intralesional corticosteroid therapy resulted in fewer adverse effects when compared to cryotherapy alone.

These findings underscore the importance of personalized treatment decisions in AA, considering factors such as disease severity and patient preference. Further research, particularly large-scale randomized controlled trials, is crucial for validating these findings and establishing evidence-based treatment guidelines.

CONCLUSION

Intralesional corticosteroid therapy has emerged as a pivotal treatment modality for managing AA, offering superior efficacy and tolerability compared to cryotherapy alone. This study affirms this finding, with intralesional corticosteroids demonstrating a significantly higher efficacy compared to cryotherapy monotherapy. These findings underscore the importance of personalized treatment approaches, which account for patient-specific factors such as age, gender, and disease characteristics. Larger-scale randomized controlled trials are warranted to validate these results and provide insights into treatment outcomes and long-term safety profiles.

DISCLOSURES

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

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The Multifaceted Effects of Berberine: Potential Uses in Dermatology

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ABSTRACT

Berberine is a natural alkaloid found in several plant species and has been used in traditional medicine for its antimicrobial, anti-inflammatory, and antioxidant properties. Berberine supplements are readily available over-the-counter in the United States. It has recently gained popularity on social media and is increasingly being used as complementary and alternative medicine. Berberine possesses a broad spectrum of pharmacological properties, which may be a result of its potent antioxidant properties and its regulatory effects on the gut microbiome. Acne, atopic dermatitis, pigmentary disorders, hidradenitis suppurativa, psoriasis, and skin aging are complex disorders, often requiring multifaceted treatment strategies. Berberine's broad mechanisms of action make it a promising candidate for the management of these conditions. This review explores the mechanisms of action of berberine and its clinical relevance in the management of dermatologic diseases.

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INTRODUCTION

Berberine supplements are readily available over-the-counter in the United States. It has recently gained popularity on social media and is increasingly being used as a form of complementary and alternative medicine.[1] Healthcare providers should learn the mechanisms of action, potential clinical utility, and safety considerations of berberine in order to effectively counsel patients who choose to take this supplement.

Berberine is a quaternary ammonium alkaloid found in various plant families and genera. Plants belonging to the *Berberis* genus are the most widely distributed natural source of berberine. Commonly encountered species include *Berberis vulgaris* (barberry), *Berberis aristata* (Indian barberry), and *Berberis aquifolium* (Oregon grape). Berberine is also found in other plant species such as *Coptis chinensis* (goldthread).[2] Berberine is present in the bark, stem, rhizomes, roots, leaves, and fruits. However, the bark and roots contain the highest concentrations of the alkaloid.[3] These plants have been used for thousands of years for cooking and in the treatment of infections, gastrointestinal disorders, diabetes, and inflammatory conditions in traditional medicine systems, including Traditional Chinese Medicine, Ayurvedic Medicine, and traditional medicine in Iran.[4]

Berberine possesses a broad spectrum of pharmacological properties, which may be a result of its potent antioxidant properties,[5] and its regulatory effects on the gut microbiome.[6] Preclinical studies have demonstrated antimicrobial, anti-inflammatory, anti-tumor, cardioprotective, nephroprotective, neuroprotective, hypolipidemic, hypoglycemic, and anti-obesogenic properties.[2,6]

Berberine's modern-day applications are just beginning to be explored. Clinical efficacy has been previously demonstrated for the treatment of dyslipidemia[7] and type 2 diabetes.[8] In a recent, open-label clinical trial berberine use was associated with clinical improvement in topical steroid withdrawal.[9] Promising preclinical data suggest a potential role for berberine in the management of several dermatologic diseases including atopic dermatitis,[10] pigmentary disorders,[11] melanoma,[12] skin aging,[13,14] and psoriasis.[15] Additional ongoing clinical trials aim to study the effectiveness in the treatment of polycystic ovarian syndrome, metabolic syndrome, non-alcoholic fatty liver disease, and the chemoprevention of colorectal cancer.[16]

Mechanisms of Action

The therapeutic potential of berberine in dermatologic diseases is attributed to its multifaceted mechanisms of action.

Anti-inflammatory Activity

Berberine inhibits pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-6, and IL-1β through suppression of key inflammatory pathways such as nuclear factor-kappa B (NF-κB) and modulation of regulatory T cell/T helper 17 lymphocyte (Treg/Th17) Treg/Th17 homeostasis.[17,18] It also reduces proinflammatory oxidative stress by modulating reactive oxygen species (ROS) levels,[17] and inhibits mast cell degranulation and histamine release.[19] These properties suggest a potential role for berberine in treating TNF-α, IL-17, and IL-23 mediated dermatoses such as hidradenitis suppurativa, psoriasis, and pyoderma gangrenosum. Additionally, berberine's effects on mast cell degranulation may serve as an adjunct in the management of itch, atopic dermatitis, and urticaria.

Antioxidant Properties

Berberine possesses potent antioxidant effects by scavenging ROS and upregulating antioxidant enzymes like catalase and superoxide dismutase.[17] Oxidative stress-induced damage to the epidermis and dermis is a critical factor in intrinsic and extrinsic skin aging.[20] This ability to modulate oxidative stress suggests that berberine may delay skin aging and ameliorate other oxidative stress-induced dermatologic disorders such as melasma and other disorders of hyperpigmentation.[21,22,23] An additional mechanism of its antioxidant effects may stem from berberine's direct inhibition of mitochondrial oxidative phosphorylation.[24]

Antimicrobial Effects

Berberine exhibits broad-spectrum antimicrobial effects, including activity against *Staphylococcus aureus*, *Cutibacterium acnes*, and *Candida albicans*, by inhibiting bacterial DNA replication and protein synthesis, and increasing membrane permeability.[23,25,26] These properties suggest a role for a topical preparation of berberine in the treatment of cutaneous Staphylococcal infections and candidiasis. There seems to be an even more convincing argument for the potential use of berberine in the management of acne vulgaris. In addition to its antimicrobial effect on *C. acnes*,[26,27] preclinical studies have demonstrated that berberine also reduces androgen synthesis and decreases sebum production by suppressing lipogenesis in the sebaceous glands.[28,29]

Modulation of the Gut-Skin Axis

Berberine's low solubility at gastric pH levels contributes to its low oral bioavailability and curtails systemic absorption.[30] Yet, berberine still exerts many systemic effects. Emerging evidence suggests that berberine may be exerting at least some of its systemic effects via its interaction with the gut microbiome and its effect on intestinal permeability.[31,32] Berberine can modify the composition of the gut microbiome and restore gut microbial balance by reducing pathogenic bacteria such as *Escherichia coli* and promoting the proliferation of beneficial strains such as *Lactobacillus acidophilus* and *Akkermansia muciniphila*.[33] Additionally, the gut microbiome plays a crucial role in systemic inflammation. The interactions of the gut microbiome, the intestinal mucosal barrier, and the intestinal immune system modulate systemic inflammation. Disruption of the intestinal mucosal barrier, which can occur in the setting of gut microbiome dysbiosis, may result in intestinal permeability and subsequent leakage of luminal lipopolysaccharide (LPS) and other bacterial products into the circulation. This stimulates a robust systemic immune response via activation of Toll-like receptor 4.[32] In animal models, berberine decreases intestinal permeability and reduces circulating LPS, thereby decreasing systemic inflammation.[31,32] Although causal links have not yet been established between the gut microbiome and skin diseases, emerging data on the gut-skin axis suggest that microbial dysbiosis in the gut contributes to the pathogenesis and severity of inflammatory dermatologic diseases such as psoriasis, hidradenitis suppurativa, atopic dermatitis, acne vulgaris, and acne rosacea.[34,35]

Dosage, Safety, and Side Effects

The optimal dosage for berberine has not been established. Additionally, there is significant variability in the amount of berberine and its potency in over-the-counter supplements.[1] However, according to a meta-analysis of randomized controlled trials studying the effect of berberine supplementation on cardiovascular disease risk factors, the most effective dose was 1000 to 1800 mg per day, and the most significant clinical differences were noted after 40 to 50 days of treatment.[36]

Data suggest that there are few adverse reactions to berberine at conventional doses, with gastrointestinal discomfort being the most commonly reported.[36] Berberine is classified as pregnancy category C in the previous U.S. Food and Drug Administration (FDA) classification system,[37] and should not be used in infants, pregnant or lactating patients. It displaces bilirubin from albumin, resulting in hyperbilirubinemia and increasing the risk of kernicterus in exposed infants.[38,39] Berberine should also be avoided in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency since it induced hemolysis in G6PD-deficient rats at very high doses.[37] Berberine is metabolized in the liver. CYP2D6 is the major cytochrome P450 involved in berberine metabolism, as well as CYP1A2, 3A4, 2E1, 2C19.[30,40] Berberine can interact with prescription medications, particularly those metabolized by the liver.[41] Berberine should thus be avoided in patients taking cyclosporine,[37] macrolides,[42] and statins.[43] Co-administration of metformin with berberine could further improve insulin sensitivity; however, caution is necessary to avoid potential hypoglycemia in diabetics taking blood-sugar-lowering medications or those with concerns of irregular glucose control.[41] There also may be an increased risk of bleeding with oral berberine.[44] There are also potential

dermatologic side effects of berberine. One case of berberine-induced symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) has been reported to date.[45] Topical berberine can produce phototoxic reactions after exposure to ultraviolet A light, especially when the berberine is produced in a non-aqueous solvent. Photoprotection should therefore be recommended with topical berberine.[37] Phototoxicity with the use of oral berberine has not been reported.

CONCLUSION

Berberine is widely available over the counter and is currently being used by patients with dermatologic diseases. A thorough medication history should include specific questions about supplement use. A non-judgmental approach and open patient-provider communication will facilitate healthcare providers' ability to counsel patients about the safety and potential efficacy of berberine. Given its multifaceted pharmacological actions, berberine holds significant promise in the field of dermatology, including anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory effects. It has the potential to be an adjunctive or alternative treatment for several common dermatologic conditions, including acne, atopic dermatitis, hyperpigmentation, hidradenitis suppurativa, psoriasis, and skin aging.

Despite its long history in traditional medicine, promising preclinical evidence supporting its efficacy in multiple diseases, and multiple clinical studies on berberine's use in metabolic disorders, several challenges hinder the widespread clinical adoption of berberine in dermatology. Although berberine is widely available, its concentration and potency are inconsistent across different commercial brands. Additionally, the cost of berberine supplements may be inaccessible to some patients. Moreover, there are few clinical studies of berberine in dermatologic diseases, and a dearth of long-term data on the safety and efficacy in this patient population. Further clinical studies are required to fully establish its therapeutic potential and optimize its use in dermatologic practice.

DISCLOSURES

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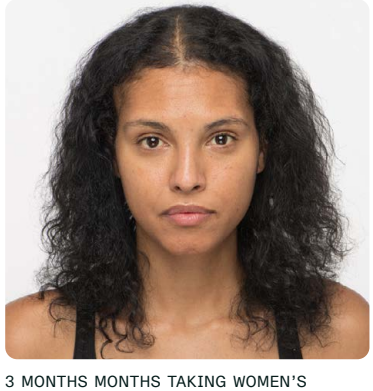
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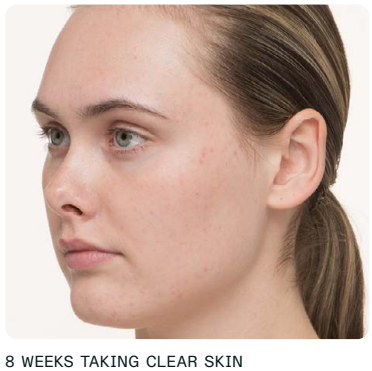


3 MONTHS MONTHS TAKING WOMEN'S VEGAN HAIR GROWTH NUTRACEUTICAL

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Effect of Recombinant Human Hyaluronidase on Conventional Hyaluronic Acid Fillers: An In Vitro Analysis

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ABSTRACT

Background: Hyaluronic acid (HA) fillers offer an advantage in being easily reversible with enzymatic hyaluronidase administration. Yet, there are no clear guidelines regarding the amount of hyaluronidase that should be administered given that commercially available fillers differ in constituent properties.

Methods: Six HA fillers were mixed with aliquots of human recombinant hyaluronidase (0 mL, 0.1 mL, 0.2 mL, and 0.3 mL). Filler dilution photography was obtained with the addition of various doses of hyaluronidase. Final filler and hyaluronidase mixture was then visualized on light microscopy at 40X magnification.

Results: None of the fillers responded to the direct addition of hyaluronidase alone. Active mixing was required to stimulate the enzymatic effect. Restylane® products which have equal concentrations at 20 mg/mL exhibited similar rates of dissolution. In contrast, Juvederm™ products, which differ in concentration, exhibited variable rates of dissolution. Juvederm™ Volbella (15 mg/mL) was the most easily dissolvable filler, in contrast, Juvederm™ Ultra (24 mg/mL) was the least easily dissolvable filler. Microscopically, Juvederm™ fillers appeared more refined whereas the Restylane® fillers appeared more globular following hyaluronidase.

Conclusion: This study demonstrates the in vitro response of different HA fillers to hyaluronidase. Each filler exhibited a variable dose effect. HA concentration (mg/mL) was the critical variable in determining the rate of hydrolysis. Therefore, HA concentration may be an important factor when calculating the dose of hyaluronidase needed to reverse HA fillers.

J Drugs Dermatol. 2025;24(3):303-306. doi:10.36849/JDD.8428

INTRODUCTION

Soft tissue augmentation is an increasingly popular aesthetic medical procedure. Hyaluronic acid (HA) fillers are commonly utilized for soft tissue augmentation.[1] An advantage of HA fillers includes easy reversibility with enzymatic hyaluronidase administration.[2] In clinical practice, HA degradation is utilized to manage adverse effects from HA filler including intra-vascular filler placement. Current guidelines for HA filler reversal recommend flooding the treatment area indiscreetly with hyaluronidase.[3] Yet, there are no clear guidelines regarding the amount of hyaluronidase that should be administered, frequency of administration, or other dose adjustments based on filler type.[4] Commercially available HA fillers differ in constituent properties such as crosslinking technology, concentration, and G' prime.[5] Given this variability, it is reasonable to conclude that the HA fillers may have discordant responses to hyaluronidase-induced hydrolysis. This in vitro study demonstrates the dynamic response of 6 different commercially available HA fillers to hyaluronidase using gross and microscopic photography.

MATERIALS AND METHODS

Restylane® (manufactured by Q-Med and marketed by Medicis, Inc.) and Juvederm™ (manufactured by Lea Derm and marketed by Allergan, Inc.) received FDA approval in 2003 and 2006, respectively.[6] HA fillers used were Restylane® Lyft (Lot# 20482, expiration date 02/28/2025), Restylane® Defyne (Lot# 19915, expiration date 10/31/2023), Restylane® Refyne (Lot# 20418, expiration date 02/28/2024), Juvederm™ Voluma XC (Lot# 1000552552, expiration date 03/30/2024 with 0.3% w/ lidocaine in physiologic buffer), Juvederm™ Ultra XC (Lot# 1000533484, expiration date 12/04/2023 with 0.3% w/ lidocaine in physiologic buffer), and Juvederm™ Volbella (Lot# V15LB10889, expiration date 10/13/2023).

For the HA fillers, 0.1 mL aliquots were placed on separate slides. Then 0.1 mL of Hylenex (human recombinant hyaluronidase, 150 USP units/mL, NDC 18657-117-02) was mixed into each filler sequentially at 3 different time points approximately 2 minutes apart. Filler dilution photography was obtained with the addition of various doses of hyaluronidase (total 0 mL, 0.1 mL, 0.2 mL,

TABLE 1.

Filler Properties			
Filler	**Crosslinking Technology**	**Percentage Cross-Linked**	**Concentration mg/mL**
Juvederm™ Voluma XC	Vycross	High (proprietary)	20
Juvederm™ Ultra XC	Hylacross	~6%	24
Juvederm™ Volbella	Vycross	High (proprietary)	15
Restylane® Lyft	NASHA	~1.2%	20
Restylane® Defyne	XpressHAn	~8%	20
Restylane® Refyne	XpressHAn	~6%	20

and 0.3 mL). Final filler and hyaluronidase mixture (total 0.1 mL HA filler and 0.3 mL hyaluronidase) was visualized on light microscopy at 40X magnification.

RESULTS

Six commercially available HA fillers with varying constituent properties were assessed (Table 1). None of the fillers responded to the direct addition of hyaluronidase alone (Figure 1). Mixing with a pipette tip was required to stimulate the enzymatic effect. Restylane® products exhibited similar rates of dissolution (Figure 2); significant responses were not appreciated until the filler to hyaluronidase mixture reached a 1:3 ratio. Juvederm™ products exhibited variable rates of

FIGURE 1. Photographs of HA fillers before and after the addition of hyaluronidase.

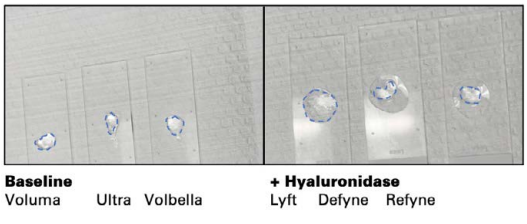


FIGURE 2. Photographs of Restylane® HA fillers following reaction to hyaluronidase.

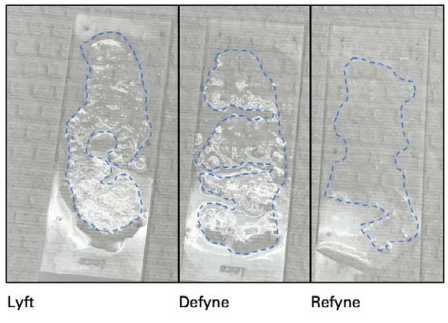


FIGURE 3. Photographs of Juvederm™ HA fillers following reaction to hyaluronidase.

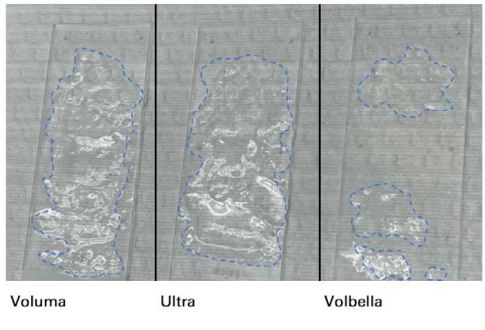
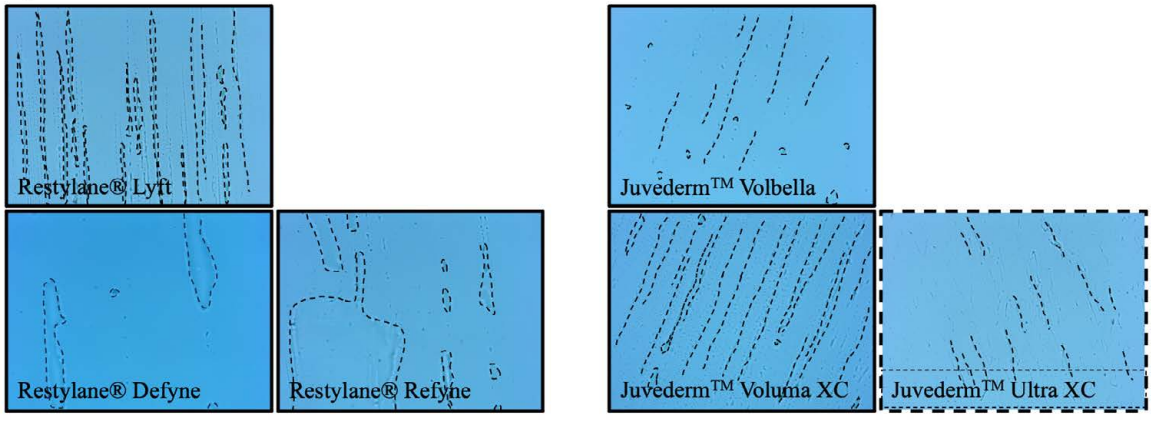


FIGURE 4. Microscopy of HA fillers following reaction to hyaluronidase.



dissolution (Figure 3). Juvederm™ Volbella was the most easily dissolvable HA filler; an early response was appreciated with filler to hyaluronidase mixture at a 1:1 ratio. Juvederm™ Ultra was the least easily dissolvable filler; a significant response was not appreciated until the filler to hyaluronidase mixture reached a 1:3 ratio. When comparing fillers used for similar indications, Restylane® Defyne liquefied more than Juvederm™ Ultra, Restylane® Refyne liquefied less than Juvederm™ Volbella, and Restylane® Lyft had a similar response to Juvederm™ Voluma. Microscopically, the Juvederm™ fillers appeared more refined whereas the Restylane® fillers appeared more globular following hyaluronidase treatment (Figure 4).

DISCUSSION

HA is a glycosaminoglycan characterized by its regular repeating non-sulfated disaccharide units comprising glucuronic acid and N-acetylglucosamine.[7] Notably hydrophilic,[8] HA can create concentrated structures that can occupy a substantial volume relative to its mass. Even at low concentrations, research has demonstrated its ability to form gels,[9] which is clinically used to restore volume, minimize the appearance of rhytids, stimulate collagen production, and promote local fibroblast activity.[10] HA is a naturally occurring biopolymer expressed ubiquitously across species and therefore exhibits low risk of inducing an immunologic reaction when used for soft tissue augmentation.[10] An additional advantage of HA fillers is easy reversibility via enzymatic degradation. There is currently no consensus on how to appropriately administer hyaluronidase for HA filler reversal. Current recommendations are largely anecdotal with a paucity of evidence to demonstrate which factors contribute to the dynamics of the enzymatic reaction.[4] Reliable evidence-based guidelines are needed given the potential emergent indication for this procedure as rarely intra-vascular occlusion of HA fillers can lead to tissue necrosis and even blindness. This study sought to evaluate filler properties affected by hyaluronidase-induced hydrolysis.

In this study, HA enzymatic degradation did not spontaneously occur following the addition of hyaluronidase alone; rather active mixing was required to stimulate the chemical reaction. Ugradar et al demonstrated similar findings after incubating various HA fillers with hyaluronidase in vitro for up to 30 min with minimal hydrolysis.[11] These findings support the current recommendation for HA filler reversal protocols to perform vigorous massage after administration of hyaluronidase to stimulate the enzymatic response.

Endogenous HA has a half-life of approximately 24 hours due to rapid enzymatic and oxidative degradation. In contrast, exogenous HA filler products exhibit biosustainability due to crosslinking technology.1[0] This allows for the advantage of remaining susceptible to degradation upon the addition of exogenous hyaluronidase, which cleaves glycosidic linkages in HA backbone. In this study, crosslinking technology did not appear to be a critical variable for HA degradation. Both Restylane® and Juvederm™ products are non-animal HAs crosslinked with BDDE.[6] XpresHAN® or OBT® is a technique that crosslinks BDDE with HA chains to allow for standard gel calibration with differing degrees of gel firmness.[12] NASHA® is a technique by which tiny amounts of BDDE are crosslinked with HA to form a matrix, which is then passed through a sieve to produce gel particles of varying sizes.[13] Hylacross® technique crosslinks many BDDE molecules to a mixture of HA with a high ration of high molecular weight to low molecular weight molecules. Vycross® technique also creates crosslinks with many BDDE molecules however the mixture of HA has a low ration of high molecular weight to low molecular weight molecules. The proprietary Vycross technology used to manufacture Juvederm™ Voluma and Juvederm™ Volbella should display the highest amount of crosslinking of the HA fillers assessed, which in theory, should translate into product longevity and similar rates of resistance to enzymatic degradation. Yet in this study, Juvederm™ Voluma and Juvederm™ Volbella exhibited different rates of dissolution, and Juvederm™ Volbella was the most easily dissolvable filler.

Prior in vivo studies in humans and rats found no statistical difference between HA filler degradation with different doses of hyaluronidase over 14 and 30 days, respectively.[2,14] This study suggests that HA filler concentration may determine the rate of hydrolysis via hyaluronidase within minutes. Juvederm™ Volbella, which had the lowest concentration at 15 mg/mL, was the most responsive filler to hyaluronidase, whereas Juvederm™ Ultra, which had the highest concentration at 24 mg/mL, was the least responsive to hyaluronidase. Restylane® Lyft, Refyne, Defyne, and Juvederm™ Voluma, which all had the same concentration at 20 mg/mL but differed in particle size and crosslinking technology,[13] exhibited similar responses to hyaluronidase. Jones et al found similar results when assessing the in vitro dose response of 3 HA fillers (24 mg/mL smooth gel, 20 mg/mL particulate gel, and 5.5 mg/mL particulate gel with 0.3% lidocaine) to ovine testicular hyaluronidase.[15]

Michel et al microscopically compared HA fillers with different crosslinking technologies and found that at baseline NASHA® filler particles were readily visible and balloon shaped, whereas Hylacross® and Vycross® fillers were more ill-defined with less continuous networks.[13] We also examined the microscopic appearance of HA fillers. Following treatment with hyaluronidase, the Juvederm™ fillers appeared more refined whereas the Restylane® fillers, particularly those with XpressHAN® crosslinking, appeared more globular.

Limitations of the study include the inability for in vitro analysis to replicate in vivo findings. Additionally, there is no quantitative data to determine if the apparent differences in the rate of hydrolysis reach statistical significance.

CONCLUSION

This study demonstrates the in vitro response of 6 different HA fillers to hyaluronidase. The findings emphasize the importance of aggressive massage after hyaluronidase in vivo as mixing was required to initiate the enzymatic effect. Each filler exhibited a variable dose effect, and HA filler concentration was the critical variable in determining the rate of hydrolysis. As such, HA filler concentration is an important factor when calculating the dose of hyaluronidase needed to reverse HA fillers.

DISCLOSURES

Drs Handfield and Wyles have no relevant disclosures. Dr Hooper is investigator, speaker, and trainer for Galderma, investigator and trainer for Abbvie, and investigator and member of the advisory board for Revance.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Social Media's Impact on Hair Loss Information Dissemination: A Systematic Review

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ABSTRACT

Objective: This systematic study examines the quality of hair loss information disseminated on social media platforms, as well as its potential effects on users' decision-making, emotional states, and societal attitudes toward hair loss.

Methods: A thorough search of MEDLINE and PubMed databases was conducted until May 13th, 2023 to identify research into the role of social media in disseminating hair loss knowledge.

Results: The systematic review encompasses 11 studies investigating platforms such as Facebook, Twitter, Instagram, TikTok, and YouTube. We discovered significant variations in the quality of hair loss-related information on social media. The DISCERN scores ranged from 1.47 to 2.66, while the percentage of videos/posts created by dermatologists ranged from 0 to 18.9%. While certain reliable content from medical professionals was present, there was an overabundance of personal anecdotes, unproven remedies, and recommendations based on personal experiences. The potential impacts of such information are wide-ranging, potentially influencing user decision-making and societal perceptions. Misinformation and subpar content could also heighten distress and anxiety among individuals seeking hair loss solutions.

Conclusion: This review highlights the need for enhanced content quality on social media platforms. It advocates for greater involvement of medical professionals, stricter adherence to evidence-based information, and the cultivation of critical thinking skills among users.

J Drugs Dermatol. 2025;24(3):307-311. doi:10.36849/JDD.7990

INTRODUCTION

The internet has become a widely used source for health information, including hair loss. Social media platforms – interactive digital applications where users generate and share content – have also become important channels for sharing health information.[1] Platforms such as Facebook, Instagram, YouTube, Twitter, and, more recently, TikTok serve as communities where people share personal experiences, seek advice, and support each other with various health concerns, including hair loss.[2]

However, social media's nature as a democratizer of information has its drawbacks. The lack of content supervision can spread misinformation and unsubstantiated or incorrect health-related content, which can contribute to misinformation, unhealthy habits, and negative health outcomes.[4] Misinformation about hair loss can arise from ineffective treatments, incorrect understandings, and unrealistic treatment expectations. This can lead to increased mental health distress and hinder effective treatment.[5] Additionally, the commercial interests of companies marketing hair loss products and treatments can further complicate and potentially distort the information available on these platforms.[6]

Despite these concerns and the growing popularity of social media as a health information source, its impact on hair loss education still needs to be studied. This research gap emphasizes the need for a comprehensive study of the quality, content, and impact of hair loss information on social media.

This systematic study aims to answer two important questions: (1) How reliable is hair loss information on social media? (2) What potential effects can be attributed to this information?

MATERIALS AND METHODS

A comprehensive search was conducted on Pubmed/MEDLINE databases for peer-reviewed articles up to May 13th, 2023, using relevant keywords such as "hair loss," "social media," and "alopecia", resulting in a total of 38 articles. The screening and review process followed the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) guidelines. Two independent reviewers (RZE and NMB) screened articles based on titles and abstracts to exclude duplicate and non-English articles, yielding 16 reports. Of these, 11 articles were included in our analysis. Subsequently identified studies were then subjected to full-text review. See Table 1 for inclusion and exclusion criteria.

TABLE 1.

Inclusion and Exclusion Criteria		
	Inclusion Criteria	Exclusion Criteria
Study Type	Randomized controlled trials, case-control studies, cohort studies (prospective or retrospective), cross-sectional studies, review articles, and case series.	Conferences abstracts, editorials, and non-research articles.
Topic	Peer-reviewed articles that assessed hair loss or scalp alopecia in social media.	Studies that did not adequately evaluate the relationship between social media and hair loss.

RESULTS

A summary of the findings from 11 selected studies is presented, shedding light on the quality of hair loss-related information on various social media platforms and its potential impacts. The studies revealed considerable heterogeneity in content reliability, accuracy, and comprehensiveness.

What is the quality of hair loss-related information on social media platforms?

"Characterizing and assessing the reliability of TikTok's most viewed alopecia-related videos" revealed a significant variance in content reliability. While videos shared by physicians were universally considered reliable, only 56% of those posted by non-physicians met the same criterion. Despite board-certified dermatologists achieving the highest mean DISCERN scores (a recognized measure of information quality) at 2.33, compared to 2.13 among non-dermatologist physicians, the overall average score across all videos remained relatively low. This suggests that TikTok's potential as a tool for patient education has yet to be fully realized. The low overall DISCERN scores on TikTok may also be due to the platform's focus on short and quick clips, making it difficult to convey accurate and comprehensive information, even for dermatologists. Notably, videos produced by non-physicians garnered even lower scores. Barbers/hair stylists, self-proclaimed hair experts, and patients exhibited the lowest mean DISCERN scores, recording 1.38, 1.40, and 1.40, respectively. Average scores falling within the range of 1.8 to 2.5 are categorized as 'poor', while scores below 1.8 are classified as 'very poor,' in contrast to the 'excellent' range of scores from 4.2 to 5.0.

Comparable results were obtained from the research conducted in "The Utilization of YouTube as a Resource for Hair Loss Treatments." The average DISCERN score across all videos was 2.66. Despite the abundance of influencers, companies, and advertisers, a mere 18.9% of the videos showcased board-certified dermatologists. Among the 90 analyzed videos, each averaged 1,202,672 views. Pharmaceuticals, including minoxidil and finasteride, were the most frequently mentioned treatments (30% of videos), followed by nutraceuticals (20%). This extensive viewership underscores social media's potential role in shaping public understanding and attitudes toward hair loss. However, misleading or inaccurate information can foster misconceptions about available treatments, perpetuate societal stigmas around hair loss, and influence public discourse.

Amplifying these concerns, the study "Fake News in Dermatology: Findings from an Observational, Cross-Sectional Study" revealed significant amounts of inaccurate or confusing material concerning hair loss on various platforms, including Facebook, Twitter, Pinterest, and Reddit. Roughly 40% of content related to alopecia was classified as precise, 20% confusing, and 40% imprecise. Alarmingly, imprecise content often attracted more followers, suggesting that misinformation can readily gain momentum.

Similarly, the analysis conducted in "Hair Loss Treatment Information on Facebook: Content Analysis and Comparison with Other Online Sources" revealed a prevalence of product advertisements and promotions for hair restoration clinics, with a scarcity of posts grounded in substantial medical evidence. Merely 3% to 13% of hair loss treatment posts had the support of medical evidence, and user engagement with such content remained low. The limited user engagement with evidence-based posts underscores the urgent need for more comprehensive health literacy promotion efforts.

"What's Being Recommended to Patients on Social Media? A Cross-Sectional Analysis of Alopecia Treatments on YouTube" offered a slightly different perspective, indicating that videos created by physicians are more inclined to adhere to evidence-based guidelines.

Regarding emotional and psychological impacts, the study "The Bald Emoji Effect: Alopecia and Twitter." Out of 808 alopecia-related tweets, 329 were categorized as personal experiences, with the majority describing alopecia as "confidence-wrecking." The 344 tweets addressing alopecia treatment options, such as wigs, hair transplants, or minoxidil, further underscore this trend. These personal narratives, coupled with potentially misleading treatment information, could exacerbate distress and anxiety in individuals seeking effective hair loss solutions.

Lastly, the study titled "An Analysis of Alopecia-Related Content on Instagram and TikTok" found that only 4% of the hair loss related posts analyzed on Instagram were created by medical professionals, while 10% of the hair posts analyzed on TikTok

TABLE 2.

Summary of Studies on Hair Loss-Related Information on Social Media

Title	Author/Year	Type of Study	Social Media Platform	Hair Loss Type	Conclusion
An Analysis of Alopecia Related Content on Instagram and Tiktok[7]	Laughter M et al, 2022	Cross-sectional analysis	Instagram, TikTok	General Alopecia	Most skincare and beauty content on Instagram and TikTok is from non-medical influencers, not board-certified dermatologists.
The Evidence Behind Topical Hair Loss Remedies[8]	Azhar AF et al, 2023	Review article	TikTok	General Alopecia	Many natural hair loss remedies on Tiktok lack clinical evidence and standardized dosage, so their benefits are questionable.
Alopecia Areata And Pattern Hair Loss On Social Media – Current Public Interest Trends And Cross-Sectional Analysis Of YouTube And Tiktok Contents[9]	Gupta AK et al, 2023	Cross-sectional analysis, quantitative and qualitative analysis.	YouTube, TikTok	Alopecia areata, Pattern hair loss (androgenic alopecia)	Alopecia areata (AA) videos on TikTok with female subjects had high engagement. Healthcare provider videos on YouTube had high DISCERN scores compared with TikTok.
Characterizing and Assessing the Reliability of Tiktok's Most Viewed Alopecia-Related Videos[10]	Nguyen B et al, 2023	Observational study, cross-sectional analysis	Tiktok	General Alopecia	Most Tiktok videos were created by patients. Out of all the videos posted, those made by physicians were deemed more reliable than 56% of those made by non-physicians. Board-certified dermatologists were found to have the highest average DISCERN scores.
Hijab and hair loss: a cross-sectional analysis of information on YouTube[11]	Shareef SJ et al, 2023	Cross-sectional analysis	YouTube	Hijab-related alopecia	Hijab-related alopecia videos lacked thorough explanations and scientific evidence for recommended solutions. Personal experiences were cited without sources.
What's Being Recommended to Patients on Social Media? A Cross-Sectional Analysis of Alopecia Treatments on Youtube[12]	Killion L et al, 2022	Cross-sectional analysis	YouTube	Alopecia areata (AA); Androgenetic alopecia (AGA); Traction alopecia (TA); Central centrifugal cicatricial alopecia (CCCA)	Most videos (51%) were made by patients or bloggers, while only 18% were made by dermatologists. Physician-made videos have more evidence-based treatment suggestions. 46% of videos disclosed sponsorships with branded products.
Hair Loss Treatment Information on Facebook: Content Analysis and Comparison[13]	Gupta AK et al, 2021	Content analysis, Comparison study	Facebook	General alopecia	Hair loss pages on Facebook mostly advertise clinics and products, or fundraise for alopecia organizations. But only a few posts (3%-13%) have medical evidence for treatment, and user engagement is usually low.
Fake News in Dermatology. Results from an Observational, Cross-Sectional Study[14]	Iglesias-Puzas A et al, 2021	Observational study, Cross-sectional analysis	Facebook, Pinterest, Twitter, Reddit	General alopecia	Out of all the content related to alopecia, 40% was classified as accurate, 20% was considered confusing, and 40% was deemed inaccurate. Unfortunately, content that was marked as inaccurate tended to attract more followers than accurate or confusing content. This suggests that false information can spread quickly.
Analysis of YouTube Hair Loss Treatment Information: What Makes for Engaging Content?[15]	Gukpta Ak et al, 2020	Observational study, Cross-sectional analysis	YouTube	General alopecia	Videos that receive a lot of viewer engagement may provide helpful information for making treatment decisions. However, some of these videos may have a bias towards promoting dermatology and hair restoration clinics. Videos made by hair restoration experts are generally trustworthy but could benefit from including links to additional sources for even more reliable information.
The Bald Emoji Effect: Alopecia and Twitter[16]	Asfour L et al, 2021	Observational study, Cross-sectional analysis	Twitter	Alopecia areata, chemotherapy-induced, androgenetic alopecia, traction alopecia, cicatricial alopecia	The tweets mainly centered on advertising hair growth products, wigs, and hair transplantation procedures. Personal experiences shared were emotionally impactful and vulnerable. However, there was some misleading treatment information that might alter patients' expectations of conventional therapies.
The Utilization of YouTube as a Resource on Hair Loss Treatments[17]	Behbabhani S et al, 2020	Cross-sectional analysis	YouTube	General Alopecia	Out of all the authors, YouTube influencers made up 37.8%, while only 18.9% were certified dermatologists. Companies or advertisers made up 15.6% of the authors.

TABLE 3.

Average DISCERN Scores Across Various Studies

Title	Author/Year	Platform	DISCERN Scores
Alopecia Areata And Pattern Hair Loss on Social Media – Current Public Interest Trends and Cross-Sectional Analysis of Youtube and Tiktok Contents	Gupta AK et al, 2023	Tiktok and YouTube	DISCERN Healthcare providers: 2.15 DISCERN Non healthcare providers: 1.47
Characterizing and Assessing the Reliability of Tiktok's Most Viewed Alopecia-Related Videos	Nguyen B et al, 2023	Tiktok	DISCERN Physicians: 2.22 DISCERN Non Physicians 1.52
The Utilization of YouTube as a Resource on Hair Loss Treatments	Behbabhani S et al, 2020	YouTube	DISCERN Overall: 2.66

TABLE 4.

Percentage of Content Created by Medical Professional Across Various Studies

Title	Author/Year	Platform	Percentage of Posts by Medical Professionals
An Analysis of Alopecia Related Content on Instagram and Tiktok	Laughter M et al, 2022	Instagram and Tiktok	4% of posts created by medical professionals on Instagram. 10% of posts created by medical professionals on TikTok
Hijab and Hair Loss: A Cross-Sectional Analysis of Information on YouTube	Shareef SJ et al, 2023	YouTube	0% of videos created by dermatologists
What's Being Recommended to Patients on Social Media? A Cross-Sectional Analysis of Alopecia Treatments on Youtube	Killion L et al, 2022	YouTube	18% of videos created by dermatologists
The Utilization of YouTube as a Resource on Hair Loss Treatments	Behbabhani S et al, 2020	YouTube	18.95% of videos created by dermatologists

were created by medical professionals. None of the top posts was created by board-certified dermatologists. The content, primarily generated by influencers and patients lacking medical expertise, raises concerns about information accuracy and reliability. This overemphasis on non-expert perspectives can potentially propagate misinformation and incomplete knowledge, impacting individuals seeking evidence-based hair loss treatments. It underscores the critical necessity for evaluating and verifying information derived from social media.

In summary, although social media does have the potential to showcase reliable and high-quality information regarding hair loss, there exists an urgent requirement for enhancements in content quality. Achieving this could involve increased engagement of medical professionals in content creation, more stringent adherence to evidence-based information and referencing standards, and a focused effort to cultivate critical thinking and evaluation skills among users.

DISCUSSION

The Role of Artificial Intelligence and Digital Health Platforms

Our findings align with the global trend of using digital health platforms for health information, thereby reshaping patient expectations. Recent research, exemplified by Young et al (2022), indicates that as patients become increasingly comfortable with online consultations, telemedicine, and artificial intelligence (AI)-driven health solutions, they may reduce the frequency of their office visits.[18] The change in online accessibility emphasizes the need for innovative approaches to providing healthcare to tech-savvy individuals.

While the advantages of ChatGPT and other AI-based virtual assistants range from using it for medical education or in patient monitoring, it is also limited in its ability to give accurate and reliable results.[19] As AI continues to expand in this field, rigorous quality control procedures are imperative to ensure the reliability of information. Implementing measures such as fact-checking, keeping up with the latest scientific advancements, and regulatory oversight can mitigate the risks of misinformation and enhance patient safety.[19]

These platforms also raise questions about the evolving roles of healthcare practitioners. As individuals increasingly embrace digital health technologies, healthcare providers may need to incorporate these tools into their practices. This could entail advising patients on the judicious use of health information from digital sources, verifying online content, and engaging with these platforms to provide accurate, authoritative content.

These findings emphasize the need for a multistakeholder strategy to enhance online health information within the context of our analysis of hair loss-related content on social media. This endeavor necessitates the involvement of medical specialists, social media platforms, AI developers, regulatory bodies, and users. Collaborative efforts among these stakeholders can amplify the potential of health information dissemination

through social media and AI, while minimizing the propagation of disinformation and substandard material.

Limitations of this Review

Our comprehensive systematic review does encompass several limitations. We restricted our scope to English-language research, potentially excluding perspectives from non-English social media platforms or communities. The research we evaluated may have omitted certain contextual elements. Factors like algorithms, user demographics, and temporal dynamics, such as trending topics and current events, influence the transmission of social media information. Although these factors could impact user engagement and information propagation, they might not have been fully accounted for in our analysis.

Lastly, the swift change in social media trends and platforms suggests that our evaluation might not precisely capture the landscape of hair loss-related material on social media. Given these constraints, future studies should encompass a broader array of platforms and languages, delve into social media algorithms and user demographics, and directly measure the effects on users.

CONCLUSION

Health information, particularly about hair loss, is widely sought after on social media platforms. This systematic analysis examines hair loss-related content across numerous platforms, uncovering significant disparities in reliability, accuracy, and comprehensibility. Moreover, this review sheds light on how such information profoundly influences patient decision-making processes, emotional well-being, and the broader societal perception of hair loss.

Given the perpetual evolution of social media platforms and their substantial potential as health information conduits, subjecting them to continuous monitoring and research is imperative. A subsequent study should adopt a broader scope, encompassing an array of platforms and languages, while delving into the assessment of social media algorithms and user demographics. Furthermore, direct measurement of the effects on users is crucial.

This systematic review emphasizes the need for collaboration among healthcare professionals, researchers, social media platforms, and users. This collaborative effort aims to optimize the health information and support capabilities of social media while minimizing the dissemination of misinformation and substandard content.

DISCLOSURES

Antonella Tosti is a consultant for DS Laboratories, Monat Global, Almirall, Thirty Madison, Leo Pharmaceuticals, Bristol Myers Squibb, and P&G; and is a compensated consultant/advisory board member for Eli Lilly and Company. The other authors have no conflicts of interest to disclose.

Data Availability: All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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CASE REPORT

Journal of Drugs in Dermatology

Alopecia Universalis: Never Give Up?

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ABSTRACT

Introduction: Oral Janus kinase inhibitors (JAKi) have demonstrated significant promise in hair regrowth for severe alopecia areata. Baricitinib and ritlecitinib are two medications within this class that have been FDA-approved in recent years, with data supporting treatment response over the course of a few months.

Case Presentation: We present the case of a 28-year-old female with alopecia universalis and a Severity of Alopecia Tool (SALT) of 100%, who failed 1 year of baricitinib therapy and was switched to ritlecitinib. She experienced regrowth of vellus hairs on the scalp and some eyebrow hair after 6 months of therapy and subsequent robust growth of terminal hair after 1 year of ritlecitinib and 2 total years of total JAKi therapy. The patient also had regrowth of the eyelashes, eyebrows, and resolution of nail pitting.

Conclusion: The authors aim to report this case to highlight the success of prolonged JAKi therapy for patients with severe refractory alopecia areata and the success of JAKi therapy after failure of a prior JAKi. Dermatologists should consider longer courses of these medications and switching within the class for patients who experience poor response with initial agents.

J Drugs Dermatol. 2025;24(3):316-318. doi:10.36849/JDD.8587

INTRODUCTION

Alopecia universalis is a type of alopecia areata (AA) characterized by total body hair loss. The mechanism of this loss is primarily due to autoimmune disruption of the hair follicle. AA has historically been treated with corticosteroids, minoxidil, and other immune therapies that possess limited efficacy with high recurrence rates and adverse effects.[1] However, in recent years the Janus kinase inhibitors (JAKis) have emerged with novel immunomodulatory effects by blocking interferon-gamma and interleukin-15, involved in immune activation at the hair follicle.[2] Currently, three oral JAKis, baricitinib, ritlecitinib, and deuruxolitinib, have been studied under phase 3, randomized, controlled trials for AA.[2-5]

CASE REPORT/CASE PRESENTATION

We present the case of a 28-year-old female with alopecia universalis who experienced rapid onset improvement in hair growth over a 6-month period after 18 total months of JAKi therapy. The patient initially presented to our institution's dermatology clinic with abrupt onset loss of scalp hair with progression of total body hair loss within a few months. At that time, her exam showed scattered terminal hairs on the scalp with few vellus hairs as well as nail pits on multiple nails. The patient's past medical history was significant for Turner's syndrome, hypothyroidism, atopic dermatitis, and an isolated episode of unspecified alopecia at age 11. Her mother reportedly also has a history of alopecia areata. The patient was initially started on an oral prednisone taper, topical corticosteroids, and minoxidil titrated up to 3.75mg with poor response. After 3 months with little to no improvement, baricitinib was added at 2mg and was promptly titrated to 4mg.

Over the next 6 months, the patient noted no regrowth of hair on any body surface area and down-titrated baricitinib to 2mg due to difficulty tolerating the higher dose and minoxidil to 2.5mg, due to weight gain. After one full year on baricitinib, the patient's Severity of Alopecia Tool (SALT) remained at 100%, but she did note improvement in her nail pitting. Her therapy was switched to ritlecitinib at 50mg adjunct with 1.25mg minoxidil, and at 6-month follow up, she began to notice some regrowth of eyelashes and eyebrows as well as the return of fine, vellus hair on the scalp, as seen in Figure 1. With the promising return of vellus hair, the same regimen was continued and after approximately one year of ritlecitinib and two total years of

FIGURE 1. Scalp and eyebrows after 18 months of JAKi therapy.

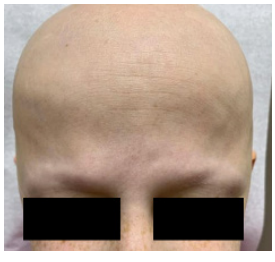


FIGURE 2. Scalp regrowth after 24 months of JAKi therapy and 1 year of ritlecitinib.



JAKi therapy, she had remarkable improvement in regrowth of terminal hairs on the vertex scalp, eyelashes, and eyebrows, as seen in Figure 2, with a SALT score of 17.2. The patient did not yet have axillary or body hair regrowth. Isolated patches of scalp hair loss were treated with intralesional triamcinolone acetonide. Overall, the patient tolerated both JAK inhibitors well throughout treatments without adverse effects.

DISCUSSION

Prior to the emergence of JAK inhibitors, alopecia areata, particularly universalis, was known to be highly refractory to therapy. For severe and recalcitrant disease, this drug class has proven its efficacy in clinical trials, and baricitinib became the first-in-disease FDA-approved treatment in 2022.[6] Trial outcomes were assessed via primary endpoints of SALT scores <20 at 36 and 24 weeks for baricitinib and ritlecitinib, respectively, in comparison to placebo.[3-4] In this trial, atopic history and the presence of alopecia universalis were reported, but no data was reported regarding the association of these factors with primary endpoints. In the ritlecitinib trial, higher baseline SALT scores of individuals with alopecia totalis and alopecia universalis were reported, but subgroup analyses demonstrated consistency of treatment effect compared to those without alopecia totalis or alopecia universalis.[4] Post-hoc analyses have also supported ritlecitinib efficacy independent of hair loss profile at baseline.[7]

Our patient had an initial SALT score of 100 and failed to improve at 1 year of treatment with baricitinib, and it was not until 6 months of ritlecitinib therapy, she began to see vellus hair regrowth. Of note, improvement to a SALT score of <20 was necessary to meet primary endpoints in both baricitinib and ritlecitinib clinical trials, which this patient would not have met until more than 1.5 years of total JAKi treatment. It is also notable that trial patients were excluded based on the use of or failure of any previous JAKi therapy.[3,4] This patient's case poses the question of whether their hair re-growth was responsive to prolonged JAKi therapy in general or if the trial of ritlecitinib was more efficacious than baricitinib. The presence of baseline nail pitting in this patient has also been considered to reflect AA disease severity.[8] Nail pitting resolution in this patient preceded hair regrowth by many months and may be a positive prognosticator in eventual hair regrowth. Additionally, AA has been suggested to be more prevalent in Turner's syndrome, along with other autoimmune conditions, such as hypothyroidism, as seen in this patient.[9] Important considerations in this case include the unique factors that may have contributed to this patient being an initial poor responder to JAKi including atopic history, Turner's syndrome, and presence of nail pitting. The novelty and significance of this case lie in the prolonged latency period between JAKi initiation and treatment response. Providers should be fervent in the treatment of recalcitrant alopecia areata by providing adequate trials of at least 1 year with each individual therapy if possible. This case lends insight into the safety of JAKis' long-term use, as evidenced by the lack of adverse effects for this patient. Further trials and reports outside of trial settings are needed for this patient population to compare the efficacies of JAKis to each other and in the long term.

CONCLUSION

The authors aim to highlight a real-world case of delayed JAKi response in a 28-year-old patient with alopecia universalis refractory to baricitinib with an eventual robust response to ritlecitinib. In this case, JAKis were well tolerated for a prolonged course. After 2 years of total treatment, this patient's outcomes demonstrate the benefit of diligence when trialing JAKis as well as attempting alternative medications within the class when treatment response is inadequate.

DISCLOSURES

Boni Elewski has served as an investigator for Abbvie, Anaptys-Bio, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Incyte, Leo, Lilly, Novartis, Pfizer, UCB and Janssen. Boni Elewski has served as a consultant for Amgen, Arcutis, Boehringer Ingelheim, BMS, Leo, Novartis, Pfizer, UCB, Ortho dermatology, and Janssen. Tiffany Mayo has served as an investigator for Acelyrin, BMS, ChemoCentryx, Galderma, Janssen, Lilly, and Pfizer. Tiffany Mayo has served as a consultant for Abbvie, Arcutis, BMS, Bodewell, Janssen, Lilly, Leo Novartis, and Pfizer. Victoria Jiminez and Anna Riess have no conflicts to disclose.

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CASE REPORT

Journal of Drugs in Dermatology

Concurrent Lichen Planopilaris and Female Androgenic Alopecia in Skin of Color: A Case Series

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ABSTRACT

Background: Trichoscopy findings can differ in the skin of color requiring a dedicated approach with adequate examination in order to ensure proper diagnosis and treatment. This case series details three cases of concurrent lichen planopilaris (LPP) and female androgenic alopecia (FAGA) in the skin of color.

Methods: Gross examination of all cases revealed mild to moderate hair density thinning of the temporal and frontal scalp. Trichoscopy was done in all three cases before biopsy. The temporal scalp of each patient showed diffuse hair follicle miniaturization with minimal terminal hairs and brown follicular halos, all findings were consistent with FAGA. However, upon inspection of the frontal scalp, each case revealed findings associated with scarring alopecia including scale, erythema, and peripilar casts in addition to the presence of follicle miniaturization.

Results: In the first two cases, two punch biopsies were taken, one from the temporal scalp and one from the frontal scalp. Temporal biopsy revealed FAGA and frontal biopsy revealed LPP arising in a background of AGA. In the third case, only the frontal scalp was biopsied, which showed LPP in a background of FAGA. All three cases received the same treatment regimen; clobetasol 0.05% solution and minoxidil 5% foam/solution topically for treatment of FAGA and monthly intralesional triamcinolone acetonide for treatment of the LPP.

Conclusion: Our report suggests the importance of total scalp dermoscopy and the need for biopsies in areas with varying dermoscopy findings as opposed to areas with the most significant hair loss.

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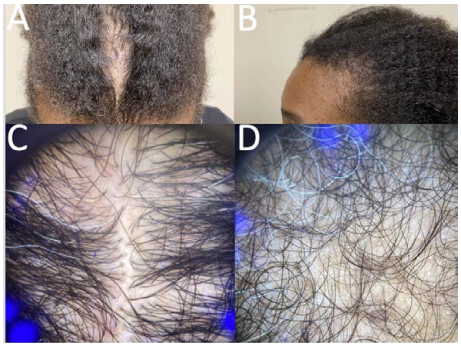
INTRODUCTION

Lichen planopilaris (LPP) is a primary scarring alopecia and a follicular version of lichen planus (LP), which can present in association with LP or more often presents alone.[1] Androgenetic alopecia is a nonscarring alopecia with a genetic predisposition that leads to pattern baldness.[2] In males, it classically begins with bitemporal thinning of the frontal scalp and can involve the vertex while women can present with vertex and frontal scalp involvement.[2] Trichoscopy, or scalp dermoscopy, findings can differ in skin of color requiring a dedicated approach to ensure adequate examination to provide proper diagnosis and treatment.[3-4] This case series details three cases of concurrent lichen planopilaris (LPP) and female androgenic alopecia (FAGA) in the skin of color.

Case 1

A 52-year-old Black female with a past medical history significant for lupus, depression, and iron deficiency anemia presented to the office with several years of hair loss and recently acquired "bald spots." Her hair loss was reported to be exacerbated by stress. She denied any scalp itching, dryness, pain, or flaking, and denied loss of hair on other parts of her body. In the past, she has had tight braids but removed them because of migraines. Examination revealed moderate thinning at the frontal scalp (Figure 1A) with trichoscopy of the region revealing perifollicular scale, mild erythema, and interruption of honeycomb pattern with the presence of vellus hairs (Figure 1C). Examination of the temporal scalp revealed mild hair density thinning with diffuse hair follicle miniaturization with the presence of pinpoint white dots and brown halos around the hair follicles (Figure 1D). Differential diagnoses included FAGA, cutaneous lupus, diffuse alopecia areata, or traction alopecia exacerbated by telogen effluvium. Due to the differences in trichoscopy findings, two 4

FIGURE 1. (A) Frontal scalp (B) Temporal scalp (C) Trichoscopy of frontal scalp (D) Trichoscopy of temporal scalp.

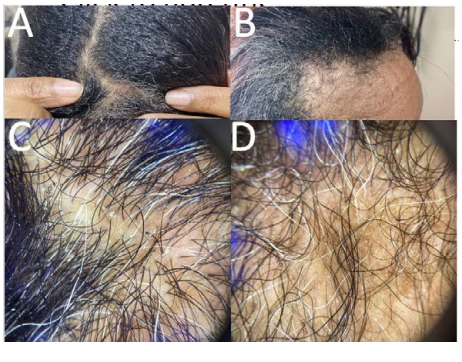


mm punch biopsies were performed; one of the left frontal scalp and one of the right temporal scalp. The left frontal scalp biopsy showed LPP. Both biopsies showed AGA. She was treated with clobetasol 0.05% solution and minoxidil 5% foam/solution for treatment of FAGA and monthly intralesional triamcinolone acetonide (TAC) for treatment of the LPP.

Case 2

A 43-year-old Black female with a past medical history of hypertension presented to the office for hair loss coinciding with cessation of oral birth control. The patient used Rogaine 2% for 2 months with improvement. She stopped relaxing her hair five years prior and has not had braids for three years. Frontal scalp revealed mild hair density thinning (Figure 2A) with trichoscopy revealing peripilar casts and scale with white blotches interrupting the honeycomb pattern with some vellus hairs present (Figure 2C). Examination of the temporal scalp revealed moderate thinning (Figure 2B), with trichoscopy revealing increased vellus hair density with pinpoint white dots and minimal scale (Figure 2D). The differential diagnosis was either FAGA, LPP, or traction alopecia exacerbated by telogen effluvium. Two 4 mm punch biopsies were taken from the left temporal scalp and the frontal mid scalp. The frontal mid-scalp biopsy suggested LPP, and both biopsies showed evidence of AGA. This patient was also treated with clobetasol 0.05% solution and minoxidil 5% foam/solution topically for FAGA and monthly intralesional TAC for the LPP.

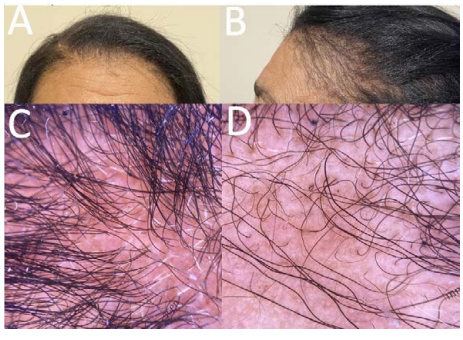
FIGURE 2. (A) Scalp Vertex (B) Temporal scalp (C) Trichoscopy of mid frontal scalp (D) Trichoscopy of temporal scalp.



Case 3

A 68-year-old Hispanic female with a history of hypertension, pre-diabetes, and GERD presented for an evaluation of her hair loss (Figures 3A-3B). Her hair loss started in 2020 after infection with COVID-19. She feels that her hair sheds easily and occasionally has pruritus on her scalp. She denies any scalp pain or dandruff. She had a negative hair pull test. On dermoscopy, she had perifollicular pallor and mild scale (Figures 3C-3D). The differential included telogen effluvium, AGA, traction alopecia, and LPP. Hair loss labs were within normal limits. A 4 mm left frontal scalp biopsy showed LPP on a background of AGA. This patient was treated with the same regimen as the first two cases.

FIGURE 3. (A) Scalp front (B) Temporal scalp (C) Trichoscopy of the frontal scalp (D) Trichoscopy of the temporal scalp.



DISCUSSION

Trichoscopy (dermoscopy) requires a methodical and dedicated approach that involves the entire scalp as different areas of the scalp can present with different findings. In LPP, the most common trichoscopy findings are perifollicular scale (hair casts) plus or minus perifollicular erythema in active disease, with areas of white dots and areas of fibrosis in end-stage disease.[1] Special considerations must be made for the recognition of these diseases in skin of color. Trichoscopy of LPP in dark scalps maintains the peripilar casts and scale with blue-grey dots in an annular pattern or target pattern.[3] AGA presents with a preserved honeycomb pattern with pinpoint white dots and sometimes with brown peripilar halos on the dark scalp.[3] As in AGA in lighter skin types, the hair density in AGA in dark scalp is associated with more than 20% vellus hair scalp involvement.[6] On trichoscopy of the temporal scalp, all of our cases show greater than 20% variability with the presence of vellus hairs. The background shows pinpoint white dots with brown halos. This should be recognized as androgenetic alopecia without much doubt. However, the frontal scalp on examination showed different trichoscopy patterns. While we still see some presence of vellus hairs and variability of hair density diameter, we also see scale and erythema as evidence of an underlying inflammatory disorder. The scale and peripilar casts should be recognized with the corresponding scarring pattern as seen with the disruption of honeycomb pattern and white patches. Without noting the other changes, the scale and casts could be mistaken for seborrheic dermatitis. This distinction is clinically important as solely treating these patients for AGA and seborrheic dermatitis could lead to irreversible progression of LPP. Of note, it is also important to remember that frontal fibrosing alopecia, which is a variant of LPP, usually involves the frontal and temporal scalp but will have peripilar casts and more prominent perifollicular erythema or violaceous color in temporal areas.

A case series of AGA with subtle LPP has been described in the context of hair transplantation. Correctly identifying LPP is an important factor in hair transplantation as it is a contraindication to the procedure.[5] While addressing the disease changes, this

case series by Baquerizo Nol et al does not address any patients of color. Our findings agree with this case series and provide examples of three cases in skin of color. While a variant of LPP mimicking AGA has been described, our case series is a different entity.[6]

Trichoscopy should be used to evaluate the total scalp. It is critical for clinicians to identify respective changes within the scalp. In Case 3, we identified similar findings on clinical and trichoscopic exams that led us to biopsy only the frontal scalp. The frontal scalp on clinical exam shows less gross hair loss on physical exam, however, trichoscopy reveals active changes within the hair follicle. The biopsy results came back with the same pathology as the first two cases. All cases were treated with the same regimen, and we saved our patient a second biopsy. Our report suggests the importance of total scalp dermoscopy and the need for biopsies in areas with varying dermoscopy findings as opposed to areas with the most significant hair loss and trichoscopic findings. We further emphasize that dermatologists must be familiar with the presentation of diseases in skin of color.

DISCLOSURES

The authors have no conflicts of interest to declare.

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JOURNAL OF DRUGS IN DERMATOLOGY
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TREAT TO (STAY ON) TARGET(TED THERAPIES)



HOST
Dr. Adam Friedman, MD, FAAD



GUEST
Dr. Jonathan Leventhal, MD

Cancer has met its match with the rise of new targeted therapies. However with the expanding cancer busting armament comes with the baggage of new and emerging cutaneous adverse events that prevent our patients from having their chemo cake and eating it, too. Never fear as the supportive oncoderms are here....well just two, podcast host Dr. Adam Friedman and guest Dr. Jonathan Leventhal, Associate Professor of Dermatology, the Dermatology Residency Program Director and Director of the Oncodermatology Clinic at the Yale Cancer Center. Curl up with your favorite blanket and learn about the most recent multidisciplinary-guided algorithm for preventing and managing cutaneous targeted therapy related adverse events in cancer patients (as one does). From erosive stomatitis to other dermatologic complications, this podcast is packed with actionable insights to ensure your patients can focus on fighting cancer without unnecessary setbacks. You are going to want to listen up!

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CASE REPORT

JOURNAL OF DRUGS IN DERMATOLOGY

Differentiating and Managing Cutaneous Lupus Erythematosus-Associated Alopecia and Patchy Alopecia Areata: Therapeutic Insights From Case Studies

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ABSTRACT

Cutaneous lupus erythematosus (CLE) is an autoimmune disease with diverse clinical manifestations, including patchy hair loss resembling alopecia areata (AA). This report describes two cases of CLE presenting as AA mimickers, emphasizing the need to consider CLE in differential diagnosis for patchy hair loss. Early and accurate diagnosis is crucial for effective management and preventing scarring alopecia.

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INTRODUCTION

Cutaneous lupus erythematosus (CLE), a group of autoimmune skin diseases characterized by skin eruptions including, but not limited to photosensitivity, malar rash, discoid lupus erythematosus (DLE), and subacute cutaneous lupus erythematosus (SCLE), as well as generalized non-scarring alopecia, which manifests in up to 85% of systemic lupus erythematosus (SLE) patients.[1]

SLE diagnostic criteria, as established by prominent health organizations like the Systemic Lupus International Collaborating Clinics (SLICC), European League Against Rheumatism (EULAR), and American College of Rheumatology (ACR), incorporate non-scarring alopecia, potentially complicating the differential diagnosis for patients with both SLE and hair loss.[2,3] Differentiating between solely alopecia areata (AA), AA concomitant in the setting of SLE, or other conditions initially resembling AA, such as DLE or syphilitic alopecia, may present a clinical challenge, necessitating comprehensive patient history and diagnostic tools.[4-6]

This article illuminates the need for a multidisciplinary approach in managing CLE-associated alopecia and patchy AA through the examination of two case studies. With an emphasis on diagnosis and treatment, this study accentuates the critical importance of a comprehensive understanding of these conditions, collaboration among healthcare professionals, and ongoing research to refine treatment strategies and ultimately improve patient outcomes.

Case 1

A 36-year-old Asian male with a 22-year history of Systemic Lupus Erythematosus (SLE) presented to a dermatology clinic in 2016, reporting rapid hair loss and intense headaches (Figures 1 and 2). His SLE history included Discoid Lupus Erythematosus

FIGURE 1 AND 2. Multiple round alopecic patches on the bilateral parieto-temporal scalp in patient with SLE (Case 1). The bilateral manifestation of hair loss is a common feature of cutaneous lupus erythematosus.



FIGURE 3. CT Scan Illustrating Subcutaneous Fat Stranding in patient with SLE (Case 1). This CT scan image reveals extensive subcutaneous fat stranding in the skull of a 36-year-old SLE patient, presenting with rapid hair loss and intense headaches. This finding suggests the impact of systemic inflammation associated with SLE.

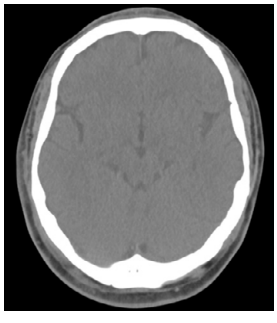
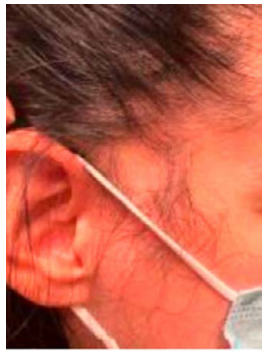


FIGURE 4. Distinct alopecic patch in right preauricular area within the temple in patient with no known prior autoimmune disease history (Case 2).



(DLE) confirmed by scalp biopsy in 2014, antiphospholipid antibodies, pyoderma gangrenosum-like lesions, and chronic kidney disease.

In December 2016, he experienced a significant increase in hair loss, with no scalp symptoms. His medical records indicated previous SLE-related alopecia. Despite using clobetasol solution, his condition did not improve. Given his history of intermittent thrombocytopenia (ITP) linked to cyclosporine, his platelet and white blood cell counts were monitored upon restarting cyclosporine therapy.

A CT scan showed extensive subcutaneous fat stranding above the skull (Figure 3). He had a prior diagnosis of patchy Alopecia Areata (AA) two decades earlier, responding well to intralesional steroid injections. Physical examination revealed multiple round alopecic patches with erythema, decreased surrounding hair density, and a negative pull test (Figures 1 and 2). A scalp punch biopsy confirmed lupus panniculitis.

Treatment adjustments included an increased dose of Thalidomide in July 2018, and later discontinuation of Thalidomide and Warfarin in February 2019, with no significant hair regrowth. In 2019, his treatment was intensified with an increase in cyclosporine to 200 mg twice daily and Vitamin D supplementation for low levels. The current regimen includes belimumab, cyclosporine, mycophenolate mofetil, and topical minoxidil. Despite this comprehensive treatment, he continued to experience Cutaneous Lupus Erythematosus on the scalp, with additional hair loss potentially due to androgenetic alopecia. Significant hair regrowth remains an unmet clinical goal.

Case 2

A 42-year-old female with no history of autoimmune diseases presented in 2022 with facial skin eruptions, scalp pruritus, and a well-defined alopecic patch on her scalp (Figure 4). Clinical evaluation revealed a round alopecic patch in the right preauricular area. Despite nine intralesional triamcinolone acetonide injections improving her alopecia, she continued to experience facial skin eruptions and scalp pruritus.

Subsequent comprehensive skin examinations showed erythema and fine scaling on her cheeks. After systemic work-up ruled out SLE, a scalp punch biopsy was performed. Histopathology showed dense superficial and deep perivascular and periadnexal lymphocytic infiltrate with vacuolar alteration. Indications of a scarring process were noted, including perifollicular fibroplasia and fibrous tracts, as revealed by an Elastin van Gieson stain showing elastic fiber thickening and clumping. Features characteristic of alopecia areata, like follicular streamers, pigment casts, and eosinophils, were also present.

Based on these findings, she was diagnosed with chronic cutaneous lupus erythematosus presenting in an alopecia areata-like pattern. Her treatment included oral hydroxychloroquine 5 mg/kg daily, topical corticosteroids, and continued intralesional triamcinolone injections. Six months later, her facial eruption and scalp pruritus had resolved, with significant hair regrowth in the alopecic patch, showing no signs of scarring.

DISCUSSION

This case series underscores the diagnostic and therapeutic intricacies in addressing alopecia, particularly in distinguishing between Cutaneous Lupus Erythematosus (CLE) and Alopecia Areata (AA). Despite their distinct nature, these conditions exhibit overlapping clinical presentations, necessitating a comprehensive diagnostic process that includes clinical, laboratory, and histopathological evaluations (Table 1).

TABLE 1.

Comparative Overview of Cutaneous Lupus Erythematosus (CLE) and Alopecia Areata (AA)

Feature	CLE	AA	Citations
Clinical Manifestations	Varied; includes oral/nasal ulcers, photosensitivity, skin infections, scarring	Predominantly hair loss without visible inflammation	8,9,12
Typical Presentation	Malar/maculopapular rash, annular/papulosquamous dermatitis, DLE, LE profundus	Well-defined, round/oval patches of complete or near-complete hair loss	4,5,8
Histopathological Features	Lymphocytic inflammation, interface dermatitis, follicular plugs, mucin deposition, basement membrane thickening	Peribulbar inflammatory infiltrate with activated T-lymphocytes, histiocytes, eosinophils	5,13
Diagnostic Testing	ANA, anti-dsDNA, skin biopsy	Clinical features, dermoscopy, scalp biopsy	9-11
First-line Therapy	Topical/intralesional corticosteroids, oral antimalarials	Intralesional/topical corticosteroids	4,10,11
Advanced Therapy	Oral corticosteroids, oral JAK inhibitors, belimumab	Topical DPCP, anthralin, systemic therapy, oral JAK inhibitors	4,11,14

AA: Alopecia Areata; CLASI: CLE Disease Area and Severity Index; CLE: Cutaneous Lupus Erythematosus; DLE: Discoid Lupus Erythematosus; JAK: Janus Kinase; SCLE: Subacute Cutaneous Lupus Erythematosus

The challenge in differentiating AA from CLE stems from their shared symptom of patch-like hair loss and the need for detailed clinical and histopathological assessment (Table 1).[5,8] These conditions also differ significantly in their clinical manifestations, diagnostic testing, and treatment approaches, as summarized in Table 1.

For CLE, the diagnostic approach integrates clinical assessment with tests like ANA and anti-dsDNA, and the treatment focuses on managing the immune response, often involving corticosteroids and antimalarials (Table 1).[4,9] Conversely, patchy AA is diagnosed primarily based on clinical presentation and dermoscopy, with treatments including corticosteroids and oral JAK inhibitors (Table 1).[10,11]

In summary, recognizing the nuances in clinical presentations, pathophysiology, and therapeutic strategies for CLE-associated alopecia and patchy AA is crucial. This case series highlights the value of a broad differential diagnosis and a multidisciplinary approach in patient management, emphasizing collaboration among various specialties to enhance patient care and outcomes (Table 1). The ongoing research in immunology and dermatology continues to enrich our understanding of these conditions and aids in the development of more targeted therapies.

DISCLOSURES

Dr Shapiro is a consultant for Pfizer, Eli Lilly, Eirion, Follica, and Replicel Life Sciences. Drs Shapiro and Lo Sicco have been investigators for Regen Lab and are investigators for Pfizer. Dr Lo Sicco is a consultant for Pfizer and Aquis. MGB, LA, EM, AA, and AC have no conflicts to disclose.

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CASE REPORT

Journal of Drugs in Dermatology

Neoadjuvant Sonidegib for the Management of Locally Advanced Basal Cell Carcinoma: A Case Report

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ABSTRACT

Neoadjuvant Hedgehog Pathway Inhibitor (HPI) therapy, utilizing sonidegib and vismodegib, has shown great potential in managing locally advanced Basal Cell Carcinoma (laBCC). While effective, the tolerability of HPI therapy may be limited due to adverse effects (muscle spasms, alopecia). However, studies have shown a lower incidence of side effects with sonidegib, compared to vismodegib. In this report, we present the case of an 86-year-old male with laBCC on the left inner canthus treated successfully with neoadjuvant sonidegib for 25 weeks prior to Mohs micrographic surgery. This case highlights the utility of sonidegib as a potential neoadjuvant treatment modality for patients who are good candidates for surgery but would benefit from tumor reduction to achieve a more favorable outcome, especially in cosmetically sensitive areas. In addition, our patient experienced minimal side effects (muscle cramps at week 18) from sonidegib treatment.

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INTRODUCTION

Neoadjuvant Hedgehog Pathway Inhibitor (HPI) therapy, encompassing sonidegib, and vismodegib has emerged as a promising strategy in the management of locally advanced Basal Cell Carcinoma (laBCC).[1]This approach is currently indicated for adults with recurrent laBCC, patients who are not surgical or radiation candidates, and those with metastatic BCC.[1]

While HPI therapy has demonstrated its efficacy in patients with advanced BCC, its tolerability varies due to adverse effects (AE). Among the most common AEs of any grade are muscle spasms (49%), alopecia (43%), dysgeusia (38%), nausea (33%), elevated creatine kinase (CK; 29%), fatigue (29%), weight loss (27%), and diarrhea (24%).[2,3] The most serious AEs reported were elevated CK and rhabdomyolysis (1%).[4]

The BOLT study significantly solidified sonidegib's role in advanced BCC treatment, with a higher objective response rate, fewer adverse events, prolonged treatment duration, a lower discontinuation rate, and a more favorable benefit-to-risk profile at the 200 mg daily dose compared to the 800 mg dose.[5] An earlier case report also demonstrated the successful use of sonidegib in conjunction with radiation therapy for recurrent basal cell carcinoma, delivering a complete clinical response with no significant toxicities.[5]

The choice between the two available HPI therapies, vismodegib, and sonidegib, predominantly relies on expert opinion and indirect comparisons, as there are no direct head-to-head trials. Vismodegib, the first approved HPI, has a longer track record of use and more extensive supporting medical literature. Sonidegib offers a higher objective response rate, longer median progression-free survival, an extended median duration of response for laBCC, and is slightly less expensive than vismodegib.[6,7] Sonidegib is associated with the same AEs as vismodegib but exhibits a lower incidence by approximately 10%, with less severity and a slightly longer median time to onset.[8] Specifically, the median time to onset of the most frequent AEs, such as muscle spasms, alopecia, and dysgeusia, was 1 to 2 months for patients on vismodegib 150 mg daily, compared to 2 to 6 months for patients taking sonidegib 200 mg daily.[8] Nevertheless, pinpointing the subset of patients who could benefit more from one HPI over the other remains a challenge, necessitating further research to confirm the effectiveness of sonidegib in treating BCC.[8]

Case reports and clinical trials have underscored the potential of sonidegib in inducing tumor remission and its effectiveness as a neoadjuvant treatment for laBCC before Mohs surgery. In this report, we describe a case of a locally advanced basal cell carcinoma on the left inner canthus treated with neoadjuvant sonidegib prior to Mohs micrographic surgery.

CASE

An 86-year-old male with a significant cardiovascular history (congestive heart failure, atrial fibrillation, hyperlipidemia), stage 3 chronic kidney disease, and psoriasis vulgaris managed with risankizumab presented with a 2 to 3 cm pearly erythematous nodule with telangiectasias on the left inner canthus. Histopathology revealed aggregates of basaloid cells with peripheral palisading and tumor retraction, consistent with basal cell carcinoma. Given that the BCC was in a cosmetically sensitive area and near the nasolacrimal duct, several options were discussed prior to surgery, and per his preference was started on sonidegib (200 mg daily) and L-carnitine to prevent muscle cramps. After 4 weeks of treatment, the tumor flattened and decreased in size significantly to 1 to 2 cm, and with continued treatment, there was an observed 80% reduction in size by week 8.

The patient experienced no side effects from the sonidegib (muscle cramps) or worsening of his other medical conditions until week eighteen, during which he experienced tolerable mild cramps in his hands. At week 25, the size of the tumor was 1.0 x 0.8 cm, almost a 90% decrease from baseline. The basal cell carcinoma was then successfully removed with 1 stage of Mohs micrographic surgery, and the defect was reconstructed with an inferiorly-based rotation flap with preserved eyelid position and excellent cosmesis.

FIGURE 1. Locally advanced basal cell carcinoma prior to initiation of sonidegib.



FIGURE 2. Basal cell carcinoma with 4 weeks of treatment with sonidegib.



FIGURE 3. Basal cell carcinoma with 8 weeks of treatment with sonidegib



FIGURE 4. Basal cell carcinoma with 25 weeks of treatment with Sonidegib.

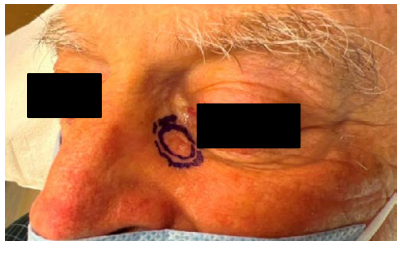


FIGURE 5. Treated basal cell carcinoma status post-four weeks after Mohs micrographic surgery and 25 weeks of sonidegib.



DISCUSSION

In this case report, we have documented the successful management of a locally advanced periorbital basal cell carcinoma using neoadjuvant sonidegib, followed by Mohs micrographic surgery. Basal cell carcinoma (BCC) may present unique challenges when they occur on functionally and cosmetically sensitive areas. Mohs micrographic surgery remains the gold standard for managing BCCs on the face.[9] However, for cases where surgical intervention may be challenging or associated with morbidity, neoadjuvant therapy may offer a benefit. Vismodegib, another Hedgehog Pathway Inhibitor (HPI), has shown efficacy in treating locally advanced BCC, but it is not without side effects.[9,10] Our patient's experience exemplifies the potential of sonidegib to reduce the size of a tumor, making surgical extirpation easier. Moreover, the treatment course was relatively uncomplicated, with only mild hand cramping after week 18.

In addition to HPI therapy, alternative neoadjuvant strategies are available for BCC, including topical imiquimod, pembrolizumab, and cemiplimab. Topical imiquimod is indicated for patients with low-risk, superficial BCC below the neck; however, its cure rates are inferior to surgery and radiation.[11] Notably, imiquimod has been employed as a neoadjuvant therapy before Mohs micrographic surgery.[11] The high tumor mutational burden of BCCs suggests that programmed cell death-ligand 1 (PD-L1) inhibitors, like pembrolizumab, may be active against advanced BCCs.[12] For patients who are refractory to or experiencing recurrence after HPI therapy, pembrolizumab, a PD-L1 inhibitor, may be used as a monotherapy or in conjunction with HPIs.[12] Furthermore, cemiplimab, a humanized monoclonal antibody against PD-1, demonstrates potential in the treatment of BCC, with an overall response rate of 78% and a disease control rate of 100%.[13] It represents a therapeutic alternative for locally advanced or metastatic BCCs that fail to respond to or recur after HPI treatment.[13]

CONCLUSION

This case underscores the importance of individualized treatment approaches, considering both the patient's health, treatment goals and the characteristics of the tumor. While more research is needed to further validate sonidegib's efficacy as a neoadjuvant therapy for locally advanced BCCs, this case offers evidence of the potential benefits of this approach. As the field of cutaneous oncology continues to evolve, it is essential to explore and optimize diverse treatment strategies to provide the best possible outcomes for patients.

DISCLOSURES

Authors Hollield and Amara do not have any conflicts of interest to disclose. Author Lewin is an employee of Mount Sinai and does not have any conflicts of interest to disclose. Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB, Inc., and is a consultant for Almirall, AltruBio Inc., AnaptysBio, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Brickell Biotech, Boehringer-Ingelheim, Bristol-Myers Squibb Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, EPI, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica.

Ethical statement: Our unidentifiable patient gave consent for publication.

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CASE REPORT

Journal of Drugs in Dermatology

The Potential Risk of Povidone-Iodine in Sperm Quality: A Case Report

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ABSTRACT

To report a rare case of severe oligoasthenoteratozoospermia which seems to be associated with long-term topical povidone-iodine (PVP-I) therapy. A 45-year-old man with secondary infertility was diagnosed with mild asthenospermia before undergoing in vitro fertilization (IVF). A repeat sperm analysis (SA) on June 30, 2022, after 3 months of using compound PVP-I liniment to treat fungal infection under a fingernail and toenail, revealed severe oligoasthenoteratozoospermia. After 77 days of drug withdrawal, sperm concentration, and normal morphology gradually returned to normal, but motility was only partially restored. It seems that the usage of PVP-I has a side effect of causing a decline in sperm quality. Although the exact mechanism of this adverse effect of PVP-I is unclear, men who are in fertility treatment should be informed of the potential risks.

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INTRODUCTION

Compound PVP-I liniment is a widely used over-the-counter dermatology drug indicated in the treatment of fungal or bacterial infections of the skin or nails, in which each milliliter contained 30 mg of PVP-I and 120 mg of aspirin. The auxiliary materials used are glycerin, polyethylene glycol, phenol, ethanol, and povidone K30. PVP-I is a complex of polyvinylpyrrolidone and iodine and its bactericidal component is the free iodine.[1] It has the ability to penetrate microorganisms quickly and oxidize proteins, nucleotides, and fatty acids, eventually causing cell death.[2] Several adverse effects have been reported for PVP-I, including allergic reactions,[3] kidney failure, and hypothyroidism.[4,5] No studies, however, have reported an adverse effect of PVP-I on sperm quality. There is evidence in this case report that PVP-I negatively impacts male reproductive function.

CASE

A 45-year-old man and his 37-year-old female partner experienced secondary infertility for 5 years following a spontaneous

TABLE 1.

Changes in Sperm Parameters

Date (Drug withdrawal period)	Days of abstinence	"Semen volume (ml)"	"Sperm concentration (×106/ml)"	"Total spermatozoa in ejaculate (×106)"	"Total motility (%)"	"Progressive motility (%)"	"Total progressive motile sperm in ejaculate (×106)"	"Sperm morphology (%)"
09/09/2019	3	2.6	31.6	82.2	30	22	18.1	4
03/15/2021	5	2.0	165.2	330.4	42	26	83.6	7
06/30/2022(0)	5	1.2	0.8	1.0	0	0	0	1
07/04/2022(4)	2	1.3	2.9	3.8	0	0	0	1
07/18/2022(18)	5	1.8	25.6	46.1	3	2	0.9	None
08/12/2022(43)	5	2.3	17.6	40.5	5	3	1.2	None
09/04/2022(66)	6	2.0	11.7	23.4	31	16	3.8	None
09/15/2022(77)	5	2.1	23.4	49.1	22	11	5.5	10
Reference values*	--	≥1.5	≥15	≥39	≥40	≥32	--	≥4

*Reference values accordingly to World Health Organization, 2010.

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abortion in June 2017. According to the sperm classification established by the WHO (WHO, 2010), his sperm concentration and morphology in 2019 and 2021 were normal, except for a slight reduction in motility (Table 1). It was diagnosed in 2021 that his female partner had a low ovarian reserve. They have undergone 3 cycles of in vitro fertilization (IVF) procedure at another IVF center since May 2021. Due to only one matured follicle, the first cycle was eventually canceled. After retrieving one mature oocyte from the second cycle, fertilization occurred normally and an 8-cell embryo of good quality grade 1 was obtained on day 3. His wife was not pregnant after frozen embryo transfer (FET). One mature oocyte was retrieved in the last cycle, resulting in normal fertilization and a good quality day 3 embryo (7 cells, grade 1). Finally, his wife did not become pregnant after undergoing FET.

He came to our center in June 2022 seeking treatment for Assisted Reproductive Technology. He reports no drinking or smoking habits, no family history of infertility, and no difficulties with sexual function. No previous medical or surgical history has been reported. In physical examination of the scrotum, there was no sign of varicocele. Using Prader orchidometry, the left testis volume was measured to be 15 mL and the right to be 14 mL. At our center, the patient's first sperm analysis (SA) was carried out on June 30, 2022, and showed a 0.8×10^6 sperm/mL concentration, a 1% normal sperm morphology rate, and 100% type D spermatozoa. As of this time, the patient reported having used compound PVP-I liniment on his left index fingernail and right fourth toenail for 3 months because of fungal infection (Figure 1). He used this drug twice a day. Each time he applied the liniment, he rubbed the infected nails with a metal nail file, and frequently bleeding. The liniment did not cause any complications during the treatment. PVP-I liniment was the only medication he was using during that time.The patient voluntarily suspended the antifungal treatment to see if it contributed to the severe oligoasthenoteratozoospermia.The SA was repeated after 4 days and showed a 2.9×10^6 sperm/ml concentration, a 1% normal sperm morphology rate, and still no sperm motility. Eighteen days after the medication was interrupted, a new SA showed a sperm concentration of 25.6×10^6 sperm/ml, and 3% sperm motility. On days 43, 66, and 77 after discontinuation of the liniment, the SA was repeated, respectively (Table 1). Sperm concentration and morphology gradually returned to normal, but sperm motility did not return to baseline levels.

FIGURE 1. Fungal infection of left index fingernail (A) and right fourth toenail (B).



One week before discontinuation, the patient underwent thyroid hormone measurements during his annual health check-up, which showed normal thyroid-stimulating hormone (TSH), serum thyroxine(T4), triiodothyronine(T3), free thyroxine (FT4), and free triiodothyronine (FT3). Results: TSH 1.438 μIU/mL 3.3-4.5 uIU/mL, T4 7.63μg/dL (4.9-13.8 μg/dL), T3 1.27 ng/mL (0.75-1.96 ng/mL), FT4 0.93 ng/dL (0.75-1.6 ng/dL), and FT3 2.37 pg/mL(1.8-4.3 pg/mL). On the 77th day of drug termination, the patient's sex hormone test showed a mild decrease in serum testosterone levels, the results are as follows: luteinizing hormone (LH) 4.94 IU/L, follicle-stimulating hormone (FSH) 3.55IU/L, total testosterone (TT) 8.43 nmol/L, total estradiol (E2) 158.90 pmol/L, prolactin (PRL) 248.70 mIU/L.

DISCUSSION

We experienced a rare case of a patient suffering from severe decreased sperm quality due to topical treatment with PVP-I. Despite its safety in skin and mucosa, excessive iodine absorption from PVP-I can cause toxicity.[6] It is estimated that one-third of the iodine entered into the body is absorbed by thyroid tissues and thyroid hormones, and the rest is distributed in various tissues such as breast tissue, eyes, gastric mucosa, cervix, prostate, testes, ovaries, and salivary glands, increasing the risk of organ toxicity.[7,8] As a result of rubbing infected nails with a metal nail file, the mucosa was exposed, even bleeding, which facilitated the absorption of iodine. It is possible for excess iodine to damage reproductive organs.[9] As a result of excess iodine, semen quality declines,[10] sperm counts decline,[11] and dead spermatozoa and abnormal sperm morphology occur.[9] Despite this, there are still no reports of sperm quality declining after topical application of PVP-I. In this case report, based on the changes in SA before and after drug withdrawal, we speculate that long-term use of PVP-I liniment may have serious consequences for sperm quality. Germ cells need nearly 76 days to complete their maturation, it would take approximately this time to recover normal sperm production after impaired spermatogenesis. In this case, the patient`s sperm quality was partly restored after 77 days of PVP-I interruption. Therefore, whether this adverse effect is completely reversible needs further observation.

Reactive Oxygen Species (ROS) may contribute to the correlation between iodine excess and semen quality. Iodine accumulation causes an imbalance in antioxidant and pro-oxidant levels in the testis, resulting in excessive ROS production, which promotes apoptosis through the mitochondrial pathway.[7,12] A high amount of iodine can disrupt the blood-testis barrier and cytoskeleton, as well as disrupt the communication between Sertoli cells and Sertoli cells and germ cells, leading to the loss of structural and functional support required for germ cell development.[7]

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CONCLUSION

To our knowledge, this is the first case of adverse effects on sperm quality associated with PVP-I use. Caution should be advised against the use of PVP-I in male partners of couples who are attempting to become pregnant. Considering that this study is a case report, further experimental studies are required to investigate the effect of PVP-I on sperm quality.

DISCLOSURES

The authors certify that they are not involved in any organization with any financial or nonfinancial interest, in the subject matter discussed in the manuscript.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

TikTok as a Source of Information for Seborrheic Dermatitis: A Cross-Sectional Analysis

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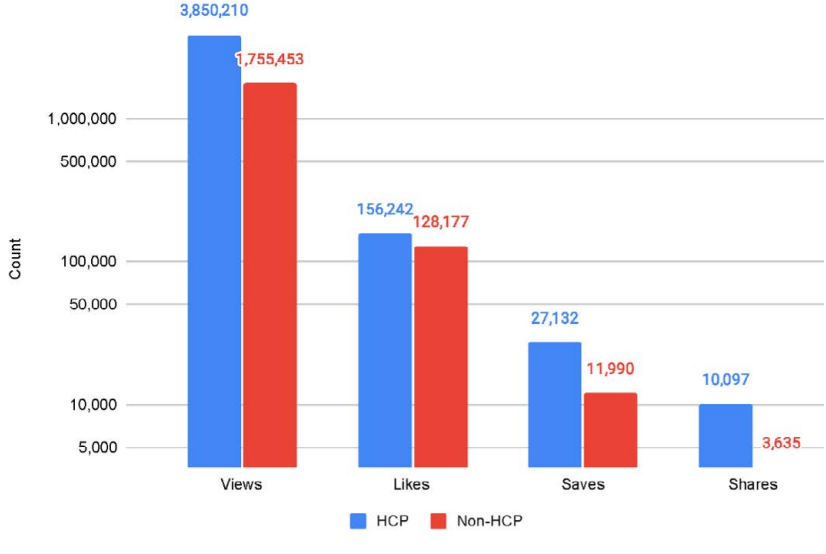
Dear Editor,

Seborrheic dermatitis (SD) is a persistent inflammatory skin condition, marked by red scaly patches primarily on the scalp, nasal area, and chest, often with itching and flaking.[1] Despite its prevalence, the exact causes and effective targeted treatments are still under investigation, presenting complex management challenges.[1] There is a growing reliance on online resources for health information, a trend also noted among patients with chronic skin conditions.[2,3] TikTok, a rapidly expanding video-sharing platform, has become a significant medium for disseminating various health-related topics. Specifically, TikTok has been found to be a reliable source for dermatological information when videos are made by healthcare professionals (HCPs).[5] This cross-sectional analysis examines the quality of SD information on TikTok with a focus on the information presented by HCPs and non-HCPs. While a similar study on YouTube's SD content indicated a predominance of misleading information,[5] we hypothesize that TikTok's SD content will be primarily scientifically accurate, with videos made by HCPs being the most popular among users.

A TikTok search was performed on December 19, 2023, using the following keywords: "seborrheic dermatitis," "dandruff," and "cradle cap." The inclusion criteria were English-language videos primarily addressing SD education or treatment, created by either healthcare professionals (HCPs) or non-HCPs. Repeated videos, non-English content, videos classified as autonomous sensory meridian response (ASMR), advertisements, or those not related to SD were excluded. For each keyword, results were filtered by like count, and videos were screened in descending order until 50 videos meeting the criteria were identified.

The videos were sorted based on whether they were created by HCPs or non-HCPs. Key metrics such as views, likes, saves, and shares, as well as product recommendations, were recorded. Video content was independently reviewed by two authors (DJ and RA), with a third author (NI) resolving any discrepancies. Content was categorized as "useful" for accurate, scientifically proven information, or "misleading" for incorrect or unproven information. Videos sharing personal

FIGURE 1. Percentage of useful and misleading video content by hcps and non-HCPs.



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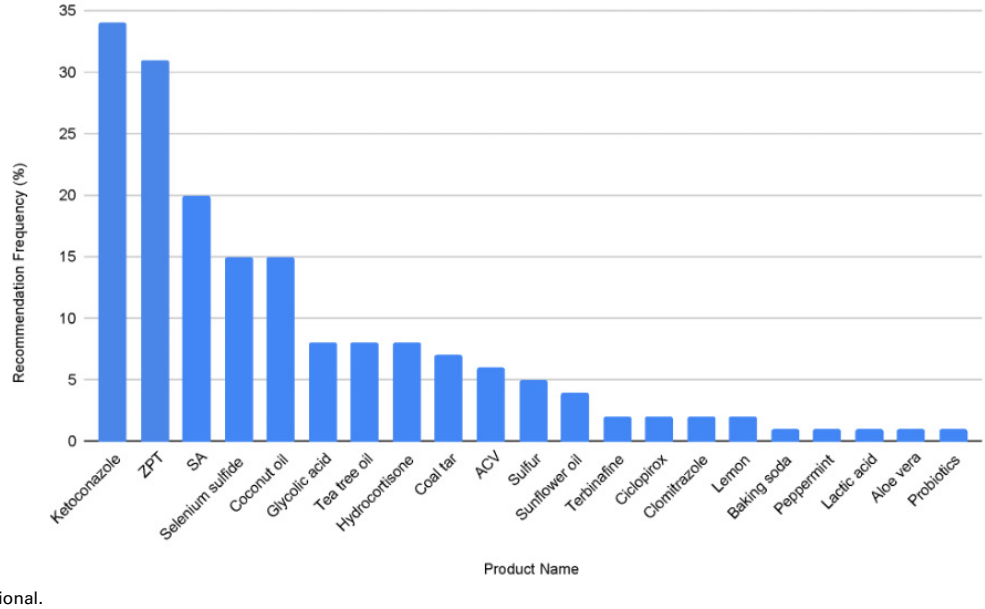
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TABLE 1.

Examples of Useful Versus Misleading Statements	
Useful	**Misleading**
HCP: "The cause is multifactorial and includes excessive sebum production, overgrowth of *Malassezia* yeast, and an individual's response to the yeast."	HCP: "I tell patients their dandruff is caused by them sleeping with wet hair."
HCP: "The oil glands are not necessarily dysfunctional, but the yeast does need oil to grow so the condition may flare when the glands are more active, like during puberty."	Non-HCP: "Yeast and carbohydrates from grains are going to keep your scalp dry, itchy, flaky, scaly."
Non-HCP: "It comes from this normal yeast that we all have and it feeds off of oils and when it builds up, it flakes."	Non-HCP: "The anti-dandruff shampoo that you are using is probably the main reason why you have dandruff."
Non-HCP: "Scalp oiling will make your dandruff worse."	Non-HCP: "I decided to treat the root cause of my dandruff which happens to start in my gut."
Non-HCP: "Cradle cap is extremely common in babies. It appears as little white or yellow flakes in their hair."	Non-HCP: "Most of the time with cradle cap, the baby has a zinc deficiency."

FIGURE 2. Percentage of useful and misleading video content by HCPs and non-HCPs.



HCP = healthcare professional.

experiences with SD were further classified as either "useful" or "misleading" based on the content's accuracy.

Of the 336 screened videos, 150 were included and 186 were excluded. Among the included videos, 67% were from non-HCPs and 33% from HCPs (78% dermatologists). Useful content was found in 87% of the videos, whereas 13% were misleading (Figure 1). Of the 19 misleading videos, 84% were by non-HCPs and 16% by HCPs. Additionally, all 69 videos discussing personal experiences were by non-HCPs, with 87% useful and 13% misleading. Examples of misleading and useful statements are shown in Table 1.

The included videos averaged 2,453,705 views, 137,532 likes, 17,037 saves, and 5,789 shares, with a mean duration of 91 s (HCPs: 95 s; non-HCPs: 90 s). HCP-created videos were more popular, with higher counts across all key metrics (Figure 2). Approximately 57% of the videos suggested products for SD treatment (Figure 3).

Our analysis revealed a disparity in the source of SD content, with approximately two-thirds of the videos made by non-HCPs. This disparity was particularly apparent in videos concerning cradle cap, where only five out of 50 videos were from HCPs, and only one was from a dermatologist. This highlights the necessity for more HCPs to contribute content, given their increased popularity compared to non-HCPs.

A notable portion of the misinformation stemmed from confusion between dandruff and dry scalp, conditions often

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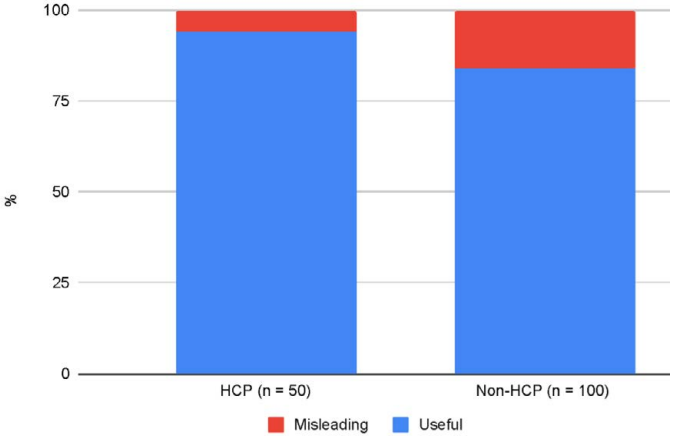
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FIGURE 3. Frequency of individual product recommendations. Y-axis represents the frequency of product.



mistaken for one another due to similar symptoms, such as flaking. However, the treatments differ significantly, emphasizing the need for clear and accurate information. Enhanced HCP participation on social media can improve public understanding of SD and other conditions, improve patient outcomes, and minimize the spread of misinformation.

DISCLOSURES

The authors declare that they have no conflict of interest. The authors have no funding sources to disclose.

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Disparities in Alopecia Areata and Vitiligo FDA-Approved Therapies in Medicaid Formularies

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INTRODUCTION

Vitiligo and alopecia areata (AA) are two common, autoimmune dermatologic diseases that significantly impact quality of life.[1,2] Oral and topical JAK inhibitors are innovative, emerging treatments. The FDA has approved ritlecitinib (Litfulo), baricitinib (Olumiant), and in the last month, deuruxolitinib (Leqselvi) for AA and ruxolitinib (Opzelura), monobenzyl ether of hydroquinone (Benoquin), tacrolimus (Protopic), and pimecrolimus (Elidel) for vitiligo.[3] The Centers for Medicare & Medicaid Services (CMS) has a mandate to determine if FDA-approved drugs are reasonable and necessary for the 73,793,274 Medicaid beneficiaries.[4] Patients without the financial means to pay out-of-pocket are unable to access treatments that are not covered by CMS. This study aimed to identify whether formulary coverage acts as a barrier to treatment for patients with vitiligo and alopecia areata.

MATERIALS AND METHODS

Current Medicaid formularies for all fifty states and Washington, D.C. were accessed via state websites. The search terms included both brand and generic names. Medication coverage was categorized as specified, unspecified general (disease state not mentioned), requiring prior authorization (PA), not covered, or absence of published information. Preferred drugs were considered to be covered. The data from each state was reviewed by two study personnel.

RESULTS

All states except Hawaii had publicly available Medicaid formularies. There was no direct coverage for any AA treatment in any state, with the exception of baricitinib in California. For AA, Ritlecitinib was not listed on the formulary in the majority of states (31, 60.78%), while 5 (9.80%) denied coverage and 14 (27.45%) required PA (Table 1). Baricitinib required PA for approval in 30 states (58.82%), the majority of which specified coverage for other conditions and specifically did not include AA (Table 1). Similarly, there was no direct coverage for vitiligo, with monobenzyl ether of hydroquinone often not listed on the formulary and the vast majority of states without coverage for other treatments: ruxolitinib (33, 64.71%), tacrolimus (30, 58.82%), and pimecrolimus (30, 58.82%; Table 1).

TABLE 1.

Vitiligo and Alopecia Areata Medication Coverage on Medicaid in the US

Medication	# of States w/ Specified Coverage	# of States w/ Unspecified General Coverage	# of States w/ PA Required	# of States w/o Coverage (4)	# of States w/ Drug Not on Formulary	# of States w/o Public Formulary
Ritlectinib (Litfulo)	0 (0.00%)	0 (0.00%)	14 (27.45%)	5 (9.80%)	31 (60.78%)	1 (1.96%)
Baricitinib (Olumiant)	1 (1.96%)	0 (0.00%)	30 (58.82%)	14 (27.45%)	5 (9.80%)	1 (1.96%)
Ruxolitinib (Opzelura)	0 (0.00%)	1 (1.96%)	9 (17.65%)	33 (64.71%)	7 (13.73%)	1 (1.96%)
Benoquin (Hydroquinone)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (5.88%)	47 (92.16%)	1 (1.96%)
Protopic (Tacrolimus)	0 (0.00%)	11 (21.57%)	8 (15.69%)	30 (58.82%)	1 (1.96%)	1 (1.96%)
Elidel (Pimecrolimus)	0 (0.00%)	10 (19.61%)	8 (15.69%)	30 (58.82%)	2 (3.92%)	1 (1.96%)

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DISCUSSION

Alopecia areata and vitiligo are not cosmetic diseases, but rather, they profoundly impact quality of life, mental health, and impose economic burdens on patients.[1,2] The FDA has approved safe and effective JAK inhibitors for treatment, but CMS has failed to determine these treatments as reasonable and necessary. Resulting prior authorizations and complex formularies inherently limit a dermatologist's ability to utilize guideline-directed medical therapy. Failing to provide coverage for these effective therapies disproportionately and inhumanely impacts low socioeconomic populations that constitute the majority of Medicaid beneficiaries that exhibit substantial price sensitivity.[5] These individuals do not have the means to pay for medications not covered in these formularies and federal regulations prevent them from using standard pharmaceutical-sponsored patient assistance programs that are readily available to commercially insured patients. Ritlecitinib, baricitinib, ruxolitinib, monobenzyl ether of hydroquinone, tacrolimus, and pimecrolimus are medications that must be covered in every state in the nation to rectify this healthcare inequity. This letter serves as a call to action to CMS and our respective state healthcare departments to recognize their oversight of these important treatments and to provide coverage for these essential medications.

DISCLOSURES

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FEATURED CONTENT

Journal of Drugs in Dermatology

NEWS, VIEWS, AND REVIEWS

Keeping Cool: An Updated Review on Cold-Induced Dermatoses and Cold-Associated Injury

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INTRODUCTION

The skin's protective role as the first defense against environmental exposures makes it susceptible to climatic stressors. Low temperatures, in particular, compromise the skin's barrier through the activity of transient receptor potential ion channels in keratinocytes, immune cells, and nerves. Cold exposure induces the production of proinflammatory cytokines, causing a deficiency of epidermal barrier proteins and an increase in transepidermal water loss.[1]

While cool temperatures have been shown to exacerbate chronic skin conditions, like atopic dermatitis, there is a subset of cutaneous dermatoses and injuries that are induced entirely by cold exposure.[1] Cold-induced dermatoses are a diverse group of conditions, ranging from benign perniosis to cold anaphylaxis. As accurate diagnosis, guided by clinical features and targeted testing, is essential for effective management and prevention of complications, this review highlights the key presentations, diagnostic considerations, and treatment strategies for these conditions.

Cold Perniosis (Chilblains)

Perniosis, also known as chilblains, results from exposure to cold, damp environments. Commonly occurring in young and middle-aged women, perniosis may be idiopathic or present secondarily to other conditions such as systemic lupus erythematosus, in which patients may develop chilblains lupus erythematosus (CLE) in response to cold.[2] The erythematous, painful, pruritic, purpuric nodules and plaques of perniosis affect acral surfaces, with an affinity for the dorsal digits.[3]

Perniosis may be diagnosed clinically, with skin biopsies reserved for cases of diagnostic uncertainty. In one investigation of 23 cases of perniosis, chilblains, and CLE, the authors determined that evaluation of cryoglobulin levels in the initial workup of perniosis is not indicated.[3] Perniosis occurs within hours of cold exposure and often self-resolves within weeks.[4]

An array of treatments are available as second-line therapies for severe or persistent manifestations of perniosis, including calcium channel blockers, pentoxifylline (400 mg three times daily for 2-3 weeks), and topical steroids (betamethasone valerate 0.1% twice daily for 6 weeks).[5,6] Available evidence best supports the use of nifedipine at varying dosing regimens (10-20 mg daily to three times daily), with studies often employing therapy for 1 to 6 weeks before down titrating or discontinuing treatment.[6]

Cold-induced Panniculitis

Cold panniculitis occurs due to trauma to the subcutis secondary to cold exposure. Prolonged exposure to popsicles, tight clothing, and ice packs can induce cold panniculitis. Interestingly, the use of aesthetic cryolipolysis harnesses cold-induced adipocyte destruction, and in one patient report, cryolipolysis caused cold panniculitis.[7]

Cold panniculitis more often occurs in infants and children due to the higher saturated fatty acid concentration in their subcutaneous tissues, allowing for less severe cold temperatures to induce adipocyte solidification. The presenting location may vary; it is commonly seen in the cheeks of children with "popsicle panniculitis" or the upper thighs of equestrians wearing tight, non-insulated pants. After cold exposure, erythema appears within 15 to 20 minutes, and "pruritic, erythematous to violaceous, hard papules, nodules and/or plaques" develop within 48 to 72 hours.[7-10]

Cold panniculitis is a clinical diagnosis that should be elucidated through a careful history, avoiding unnecessary testing. The condition has a benign, self-limiting course, with management focused on minimizing exposures. While healing typically occurs within 2 to 3 weeks, postinflammatory hyperpigmentation may develop.[8-11]

Raynaud's Phenomenon

Raynaud's phenomenon (RP) describes reversible digital vasospasm-induced skin blanching. RP induced by cold is considered primary RP, while secondary RP is observed in an array of connective tissue disorders, occupational and drug exposures, endocrinopathies, malignancies, or other trauma. RP may manifest in other acral locations, including the tongue, ear lobes, nasal tip, and nipples. While perniosis has a similar predilection for acral sites, it is regarded as less painful and more pruritic than RP with a differing morphology. Interestingly, RP may occur in areas of previously healthy ischemic tissue damage after cold exposure.[12]

As with other cold-induced dermatoses, a thorough patient history is key in diagnosing RP. However, unlike previously discussed conditions, testing is indicated, including a CBC, ESR or CRP, and ANA. Treatment is dictated by a patient's level of pain and quality of life. Level C evidence supports lifestyle changes, including donning warm clothing and avoiding cold exposures, while level A evidence recommends calcium channel blockers, specifically nifedipine 10 to 20 mg taken twice daily or three times daily, as the first-line treatment if lifestyle management is not sufficient. Limited evidence supports

the use of other vasodilatory medications like losartan, fluoxetine, and phosphodiesterase inhibitors, while oral prostaglandins and endothelin receptor antagonists are not evidence-backed options. While surgical management of RP is not supported by strong evidence, it may be indicated in cases of severe digital ulceration.[12]

Cold Urticaria and Cold Anaphylaxis

Cold is among the many causative agents of chronic inducible urticaria. Exposure to cold air, liquids or solids, and consumption of cold food or drinks are all culprits. In typical presentations of cold-induced urticaria (CindU), wheals form at the site of cold stimulation, while in atypical CindU wheals form adjacent to exposure sites.[13] CindU can be diagnosed using the ice cube test, and a CBC and CRP are recommended upon diagnosis to rule out alternative etiologies. Treatment is with doses of second-generation antihistamines titrated to up to four times the standard dose. Any patient with a history of severe CindU should be prescribed an autoinjectable adrenaline kit.[14]

Cold anaphylaxis is a severe, life-threatening presentation occurring in 4 to 47% of patients with typical CindU. In one cross-sectional multinational study of 551 patients with CindU, researchers identified those with angioedema, oropharyngeal/laryngeal symptoms, and pruritic earlobes as meeting criteria to be prescribed an autoinjectable adrenaline kit.[13]

CONCLUSION

Cold-induced dermatoses encompass a spectrum of conditions, each with distinct pathophysiologies, clinical presentations, and management strategies. Perniosis, cold panniculitis, Raynaud's phenomenon, cold urticaria, and cold anaphylaxis highlight the diverse effects of cold exposure on skin and tissue. Multiple case reports of adult patients using ice packs for chronic low back pain have described a cold-induced dermatosis with features of both cold panniculitis and perniosis, highlighting the existence of these conditions along a spectrum.[15,16]

Accurate diagnosis of cold-induced dermatoses relies on a thorough history and clinical evaluation, with testing reserved for specific conditions or cases of uncertainty. Many cold-induced dermatoses, such as perniosis and cold panniculitis, are self-limited, while others, like Raynaud's phenomenon and cold urticaria, may require targeted pharmacological interventions to mitigate symptoms and improve patients' quality of life. For severe conditions like cold anaphylaxis, rapid identification, and management are critical to prevent long-term complications or life-threatening outcomes. Advancing our understanding of these conditions and optimizing treatment approaches can significantly improve the care of patients with cold-induced dermatoses.

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