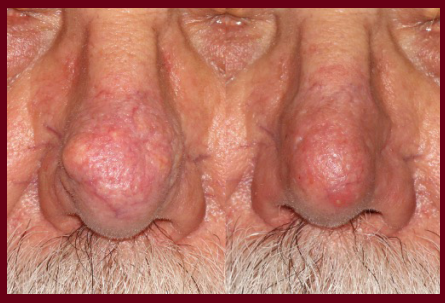
ISSN: 1545 9616

November 2024 • Volume 23 • Issue 11

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS



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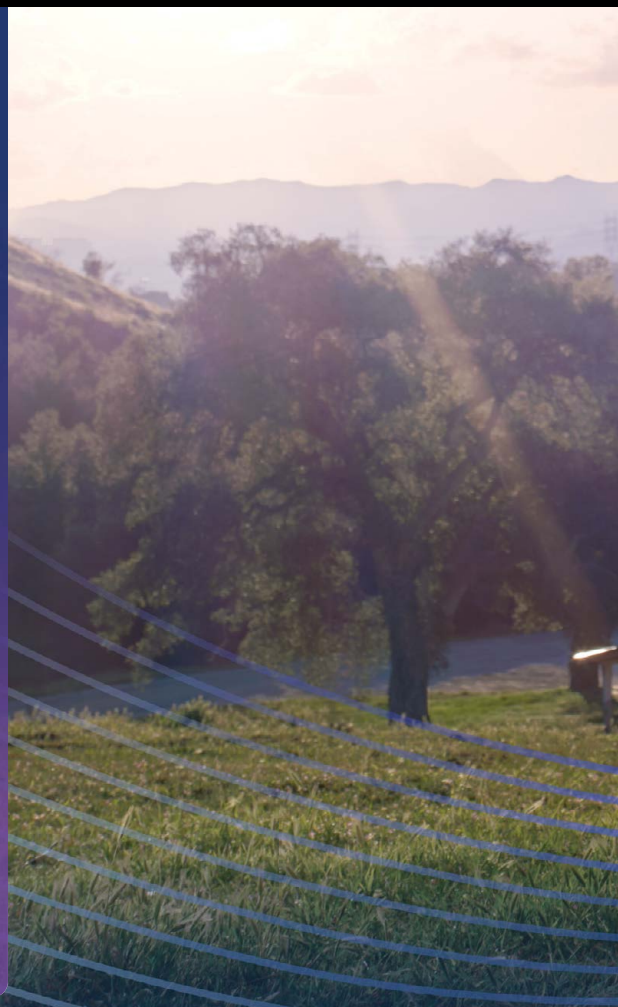
250mg/2mL injection



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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.

PP-LK-US-0148 09/2024

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).*

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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.

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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.

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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.

LK HCP BS AD APP

PP-LK-US-0272

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ORIGINAL ARTICLES

CASE REPORT

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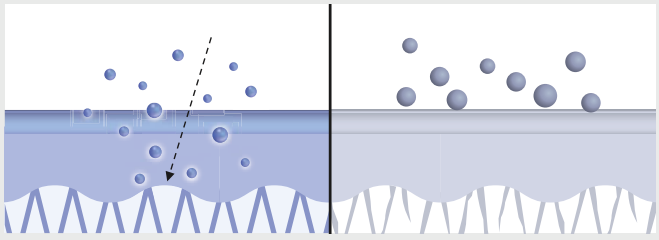

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 Journal of Drugs in Dermatology

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Journal of Drugs in Dermatology (JDD) (ISSN 1545-9616) is published monthly for $300 per year US Individual subscriptions/$600 per year International Individual subscriptions/(Corporate and Institutional rates contact Sales for a quote) by the *SanovaWorks*, c/o WebMD, 283 - 299 Market St, 2 Gateway Center, 4th Floor, Newark, NJ 07102. Periodicals postage paid at New York, NY and additional mailing offices.

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POSTMASTER: Send address changes to the Journal of Drugs in Dermatology,
PO Box 2008, Cedar Rapids IA 52406-2008

Journal of Drugs in Dermatology (JDD)
is indexed in MEDLINE®/PubMed® and is published monthly by the
***SanovaWorks*, c/o WebMD**
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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Efficacy of Intense Pulsed Light and Laser Hair Removal in Hidradenitis Suppurativa Treatment

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a multifactorial disease that presents with chronic cycles of inflammation, healing, and scarring and that elicits a profoundly negative impact on patient quality of life regarding self-image, fear of stigmatization, and social isolation. Patients commonly develop painful, odorous abscesses that evolve into draining sinus tracts and disfiguring scarring.

Objective: While systemic medications and surgical therapies are often effective in reducing active lesion activity and inflammation, these therapies sometimes only provide modest success in the prevention of future recurrences and disease progression, warranting adjunctive therapies such as laser and light-based therapies.[1] Herein, this systematic review has been conducted to assess the current level of evidence supporting intense pulsed light (IPL) and laser treatment for HS, with a focus on a decrease in the number of lesions with associated HS flares.

Methods: GRADE assessments were performed using PubMed and Scopus. Of 428 studies identified, 10 studies (n=235) evaluated IPL or laser hair removal treatment and their effectiveness in reducing HS flares.

Results: Significant reductions in the overall count of inflammatory lesions were observed in all studies, with percentages ranging from 50% to 75%, and in some cases achieving complete resolution. However, durations of disease remission varied.

Conclusion: These results provide a moderate level of evidence supporting the effectiveness of IPL and laser hair removal as adjunctive therapy in the treatment of HS; however, further long-term studies are required to provide future guidance on the most effective treatment duration and intervals for sustaining disease clearance.

J Drugs Dermatol. 2024;23(11):926-930. doi:10.36849/JDD.8627

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic condition that presents with inflammatory lesions which commonly present at sites bearing apocrine glands. HS is a multifactorial disease, and factors such as genetics, existing inflammatory conditions, hormonal imbalances, and smoking all contribute to its pathogenesis.[2,3] HS lesions are often deep seated and develop as nodules, abscesses, or draining sinus tracts. Severe progression of the disease may also lead to the formation of open comedones, disfiguring scarring, and fistulas.[4] These lesions often reappear in areas where skin surfaces come in contact, such as the groin, axilla, perianal, and sub-mammary regions.[5] The pathogenesis of HS is complex and nonlinear, involving follicular occlusion and an inappropriate and robust inflammatory response when the occlusion ruptures, leading to cycles of tissue destruction and scarring.[2] The quality of life of patients with HS is greatly affected, demonstrated by patients with HS scoring low on a self-reported level of health status scales and taking a higher frequency of sick leave from work.[6]

Management strategies for HS have many limitations because there lacks a universally accepted treatment protocol, and it is often treated with a combination of modalities, including topical and systemic medications and surgical interventions.[2,3] Laser hair removal has been used as a means for hair depilation. It works by selectively targeting melanin within hair follicles photothermally while sparing the surrounding tissue.[7] Melanin within hair follicles absorbs wavelengths admitted by lasers, converts it to heat, and diffuses it to cause damage to the stem cells within the follicle.[7] A variety of laser types are used in hair depilation and vary in range in the wavelengths they emit, with longer wavelengths causing fewer adverse effects and penetrating deeper melanin.[7] The wavelength of the alexandrite laser is 755 nm, while the wavelength for the long-pulsed neodymium-doped yttrium aluminium garnet (Nd:YAG) laser is 1,1064 nm; and intense pulsed light (IPL) 590 nm to 1200 nm.[7]

While laser hair removal has long been used for cosmetic hair removal, its use in the treatment of dermatologic conditions

has gained recent acceptance. Recently, laser hair removal has demonstrated some success in the treatment of HS as well as in conditions such as hirsutism, hypertrichosis, and hair-bearing skin grafts.[8] As HS is a multifactorial disease with a large variation in approach to treatment, a multifaceted treatment regime, including the efficacy of laser hair removal, must be evaluated. In this systematic review, we assess the current level of evidence supporting IPL and laser treatment for refractory HS, with a focus on a decrease in the number of total lesions in each flare-up.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the PRISMA guidelines.[9] PubMed and Scopus were searched on September 28, 2023, with search terms including "hidradenitis suppurativa" OR "acne inversa" AND "laser" OR "hair removal" OR "epilation" OR "depilation." A total of 386 papers were screened based on their abstract, with a resulting inclusion of 39 papers progressing to full-text review.

After independent screens by 2 researchers and evaluation by a third researcher when discrepancy occurred, 10 total studies were included for systematic review. Study selections were exclusive to randomized clinical trials (RCTs), retrospective studies, and case reports evaluating IPL or laser treatment in a diagnosed condition of HS. The reference lists in the 10 studies were then manually checked for possible inclusion of further studies.

Of 386 studies identified after screening, 10 studies (n= 235) evaluated IPL or laser hair removal treatment and their effectiveness for reducing HS flares and associated pain, and data were extracted from these studies (Table 1). Data extraction was documented in an Excel spreadsheet and included author, publication year, study design, laser type, number of patients, Hurley stage, Sartorius score, treatment area, level of evidence, lesion reduction, and pain reduction. Grade of evidence was assigned to studies using Grading Recommendations and Evidence Quality published in the *Journal of American Medical Association* (JAMA) in 2008.[10]

RESULTS

Study Heterogeneity

Out of the 10 studies included, 6 used the Nd:YAG laser,[11-16] 3 used IPL,[17-19] and 1 used the alexandrite laser.[20] The total number of patients included in all 10 studies was 235, of which 102 received treatment with Nd:YAG, 93 received treatment with IPL, and 40 received treatment with alexandrite laser. Of the patients, 48.1% were female, 15.7% were male, and 36.2% of patients' sex was not specified. Out of studies that reported age, the age range of patients was from 10 to 71 years old and patients ranged from Hurley stage I to III to less severe disease presentations, making the sample a heterogeneous population. The studies included were too heterogenous to perform a meta-analysis.

Nd:YAG Laser

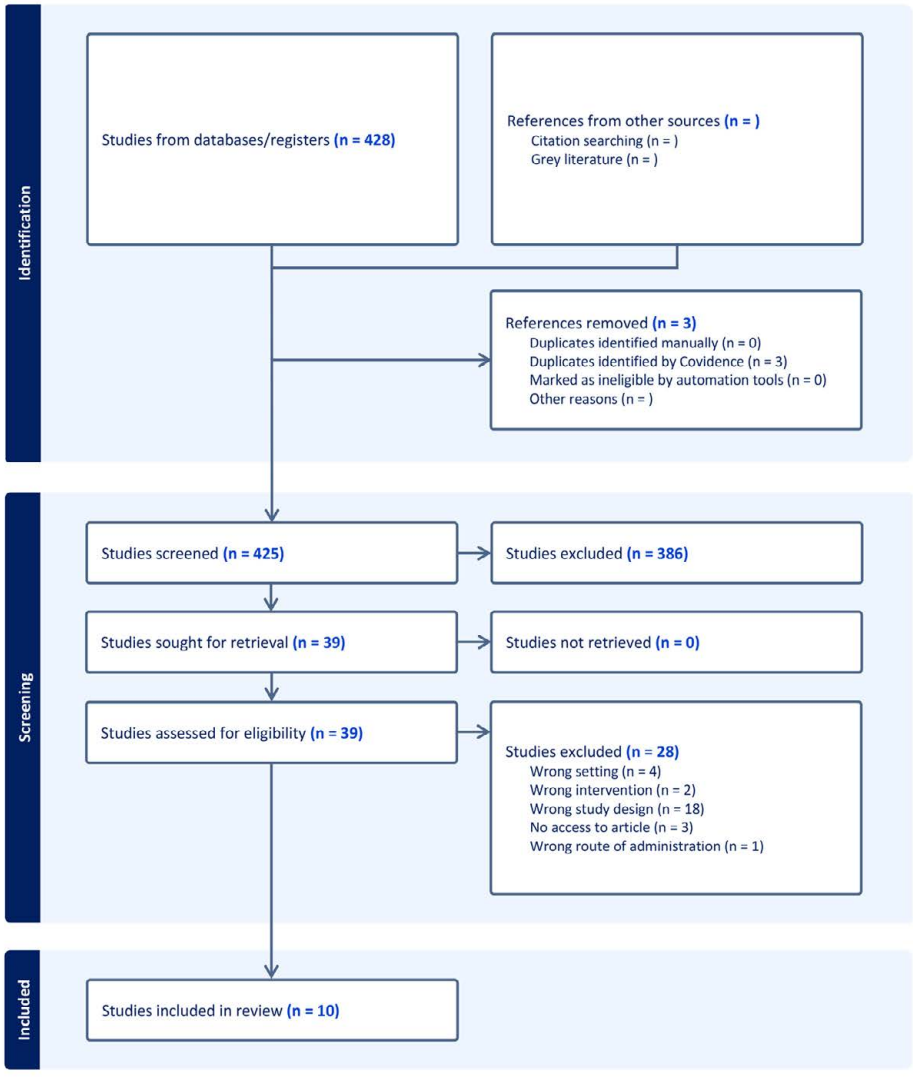
Of patients treated with Nd:YAG laser, over 33 different anatomical sites were treated, with a majority of patients receiving treatment at the axilla, inguinal, gluteal, or inframammary regions. An average of 4.5 total treatment sessions were given across all studies, with the average number of treatments ranging from 2 to 9.8 per patient. The interval

TABLE 1.

Total Studies Included

Author	Year	Title
Andersen PL, Riis PT, Thorlacius L, et al.	2020	Intense pulsed light treatment for hidradenitis suppurativa: a within-person randomized controlled trial.
Vossen ARJV, van der Zee HH, Terian M, et al.	2018	Laser hair removal alters the disease course in mild hidradenitis suppurativa.
Naouri M, Maruani A, Lagrange S, et al.	2020	Treatment of hidradenitis suppurativa using a long-pulsed hair removal neodymium: yttrium-aluminium-garnet laser: a multicenter, prospective, randomized, intraindividual, comparative trial.
Koch D, Pratsou P, Szczecinska W, et al.	2013	The diverse application of laser hair removal therapy: a tertiary laser unit's experience with less common indications and a literature overview.
Tierney, E. Bassel MH, Hexsel C, et al.	2009	Randomized control trial for the treatment of hidradenitis suppurativa with a neodymium-doped yttrium-aluminium-garnet laser.
Piccolo D, Di Marcantonio D, Crisman G, et al.	2014	Unconventional use of intense pulsed light.
Highton L, Chan WY, Khwaja N, et al	2011	Treatment of hidradenitis suppurativa with intense pulsed light: a prospective study.
Molinelli E, Sapigni C, Simonetti O, et al.	2022	Alexandrite laser as an adjuvant therapy in the management of mild to moderate hidradenitis suppurativa: a controlled prospective clinical study.
Mahmoud BH, Tierney E, Hexsel CL, et al.	2010	Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminium-garnet laser.
Xu LY, Wright DR, Mahmoud BH, et al.	2011	Histopathologic study of hidradenitis suppurativa following long-pulsed 1064-nm Nd: YAG laser treatment.

FIGURE 1. Flowchart of methods provided by Covidence.



between sessions varied between 4 and 6 weeks, with the average interval being 4.6 weeks. Follow-up periods showed a larger distribution ranging from 1 month post treatment to over 1 year post treatment. Across studies, a significant reduction in the number of lesions was seen at the end of treatment and at least 1 month post treatment.[11-16] Of studies that divided results by region, all showed statistically significant reductions in each of the axilla, inguinal, and inframammary regions.[14-16] Naouri et al revealed that the reduction in lesions remained significant but decreased at the 3-month post treatment follow up;[12] however, Vossen et al found that lesion reduction remained significant 1 year post treatment.[11]

Two randomized control studies used similar protocols and applied a combination of Nd:YAG treatment with topical antibiotics to only a single side of the patient, making the opposite side the control group with only applied 10% benzoyl peroxide wash.[14,15] Both studies used the HS Lesion, Area, and Severity Index (HS-LASI) to report their findings. Tierney et al reported a 65.3% reduction averaged over all anatomic sites (P<0.01);[14] while Mahmoud et al found a reduction in HS-LASI by 72.7% (P<0.05).[15] Tierney et al further divided results by region and reported a 73.4% reduction for the inguinal region, 62.0% reduction for the axillary region, and 53.1% reduction for the inframammary region on the HS-LASI.[14]

Vossen et al identified patients with HS who had undergone Nd:YAG depilation treatment from their records and reported a significant decrease in monthly flares (P=0.019) and HS disease severity (P=0.01) using a numerical rating scale.[11] The researchers took into consideration other medications that may have been used at the time of treatment and declared that none of these treatments statistically affected the study outcomes.[11] Vossen et al also assessed patient satisfaction with Nd:YAG treatment and

the likelihood of patients recommending laser hair removal to other HS patients. Patient satisfaction scored 6.4 ± 2.8 on the numerical rating scale ranging from 0 to 10; and 67% of patients reported that they would recommend treatment to other HS patients.[11]

Intense Pulsed Light

Three studies looked at the use of IPL for photothermolysis of hair follicles.[17-19] Highton et al performed a prospective study in 2011 in 18 patients with Hurley stage II or III HS. Patients received IPL therapy on a single side of the axilla, groin, or inframammary region, using the contralateral side as control.[17] Patients were required to cease topical and systemic therapy 2 weeks prior to the start of treatments and received IPL sessions twice per week for a total of 4 weeks. Patients were assessed based on Sartorius scale characteristics prior to treatment, immediately post treatment, and at 3, 6, and 12 month follow ups by a blinded, non-treating plastic surgeon.[17] Results showed a reduction in examination score at all sites, with an average reduction of 55% immediately post treatment, 56% 3 months post treatment, 44% 6 months post treatment, and 33% percent 12 months post treatment.[17] Statistical analysis showed a significant reduction in examination score on the treated side that was maintained 12 months post treatment (P=0.001).[17] Highton et al also studied the patient satisfaction with treatment outcome on a Likert scale, and concluded a high level of patient satisfaction.[17]

Anderson et al conducted a similar single-blinded randomized control trial in 2020 in 17 patients with symmetric Hurley stage I and II HS who received IPL therapy on a single side, using the contralateral side as control.[19] Efficacy analysis in this study was trifold, including Hidradenitis Suppurativa Clinical Response (HiSCR), modified Sartorius score (MSS) and patient-reported outcomes.[19] HiSCR was only used in the assessment of patients with inflammatory nodules or abscesses prior to treatment, and showed an insignificant difference from pre therapy to post therapy (P=0.467); however, a significant reduction of MSS was seen in the treatment side (P=0.006).[19]

Intense pulsed light has been used in an unconventional manner in several dermatologic conditions. One study performed by Piccolo et al in 2014 evaluated the use of IPL in patients with cutaneous conditions, including: rosacea, port-wine stain, disseminated porokeratosis, pilonidal cyst, seborrheic keratosis, hypertrophic scar, and keloid scar, Becker's nevus, sarcoidosis, and hidradenitis suppurativa. Out of 58 total cases, 2 were case reports on patients with HS.[18] One male patient with Hurley stage II and previous surgical intervention and one female patient with Hurley stage I underwent 4 IPL sessions at 15- to 20-day intervals. Following these 4 sessions, 2 additional sessions were performed with spaced pulses to target inflammation specifically.[18] After treatment, both pain and inflammatory components of HS were completely removed in both patients.[18]

Alexandrite Laser

The alexandrite laser was used in the treatment of 40 females with Hurley stage I and II HS in a controlled clinical study performed in 2022.[20] Twenty of the 40 women received 5 alexandrite laser treatments with 6-week intervals – 10 of these females were treated in the inguinal region alone, while the other 10 were treated in both the axilla and inguinal region. The remaining 20 females served as the control group receiving no laser treatment. All 40 patients were treated with antiseptic chlorhexidine washes and oral gluconate zinc 90 mg daily for 30 weeks and were evaluated at baseline, week 15, and week 30.[20] At week 15, HiSCR was achieved in 50% of patients in the laser-treated group and 10% of patients in the control group. The data increased at the 30-week evaluation to 70% of patients in the laser-treated group and 20% in the control (P<0.001), suggesting that the use of the alexandrite laser may be a beneficial adjuvant therapy to oral zinc in achieving therapeutic benefit in patients with mild-to-moderate cases of HS. Moreover, Molinelli et al reported a significant reduction of acute flares and pain reported by patients (P<0.005).[20]

DISCUSSION

Given the complex multi-faceted pathogenesis of HS, treatment regimens must also be multi-pronged, as no single therapy producing overwhelmingly positive outcomes has been identified.[21] Laser hair removal techniques and IPL have been used as treatment modalities in HS and have been shown to be effective in reducing flares. As all modalities target hair follicles, the inflammatory role of the hair follicle in HS flares can be presumed to be profound. The use of all 3 therapies – Nd:YAG laser, alexandrite laser, and IPL – saw significant clinical improvement in HS lesions when compared with controls.

While studies using the Nd:YAG laser reported varying durations of symptom reduction, all studies concluded a reduction in HS flares greater than 50%.[11-16] These studies suggest the inclusion of the Nd:YAG laser in the treatment regime of patients with HS may offer favorable outcomes when given in combination with other HS treatment modalities, such as topical antibiotics, as tested in 2 different control trials.[14,15] Alternatively, the use of IPL in HS patients was tested with the cessation of topical antibiotics and offered a significant decrease in both Sartorius and modified Sartorius scores, suggesting that it may be a potential monotherapy for HS.[17-19] Although only examined in one study, the alexandrite laser may be a promising longer-term treatment option in combination with oral zinc therapy in HS patients, as the achievement in HiSCR increased from 50% of patients to 70% of patients from week 15 to week 30 of treatment.[20]

These combined data from the different treatment modalities offer promising outcomes when using laser hair removal or IPL as an adjunctive therapy in the treatment of HS. However,

the studies varied in definitions of reporting scale, decreasing congruence between them. The protocols of the studies were heterogenous regarding the number of patients, Hurley stage, laser settings, treatment sessions and intervals, treated regions, evaluation criteria, and follow up duration. As such, studies were too heterogeneous to perform a meta-analysis. Two such differences across studies include the setting of lasers during sessions and the number of sessions undertaken. These factors will limit treatment guidelines and evidence-based conclusions and, as such, further research should be conducted investigating the dose-response relationship to determine the optimal number of sessions and laser settings to achieve substantial improvement in disease outcomes.

Understanding the dose-response relationship will not only help in standardizing treatment protocols but will also aid in developing individualized treatment plans, enhancing patient outcomes. Additionally, investigating the long-term effects and potential side effects of these laser therapies will be crucial in establishing comprehensive treatment guidelines for HS. The integration of patient-specific factors such as skin type, severity of the disease, and response to previous treatments will be essential in tailoring effective treatment plans. Moreover, combining laser therapy with other treatment modalities, such as systemic medications or lifestyle modifications, could potentially enhance overall efficacy and improve the quality of life for patients with HS. While some studies determined confounding variables and controlled the use of additional treatment while patients were undergoing laser treatments, some studies did not, influencing the efficacy of laser treatment. One major obstacle in advocating for the inclusion of laser hair removal or IPL therapies in the treatment of HS lies in their cost. Laser and light-based therapies are costly procedures, often requiring multiple sessions to yield results, and may not be covered by a patient's insurance. Thus, future studies should be performed with higher grades of evidence supporting the use of IPL and laser hair removal therapies in HS treatment protocols.

CONCLUSION

IPL and laser hair removal using the Nd:YAG and alexandrite lasers may all have adjunctive effects in the treatment of HS and should be considered in standard-of-care practices for patients with HS. As our understanding of HS and its pathogenesis evolves, a more personalized approach to treatment that incorporates advancements in laser technology and other therapeutic options will be key to managing this challenging condition effectively. Although substantial heterogeneity was seen among studies, findings across studies indicate the therapeutic benefits of IPL and laser therapy in refractory HS patients. Further studies should examine these effects with a higher grade of evidence.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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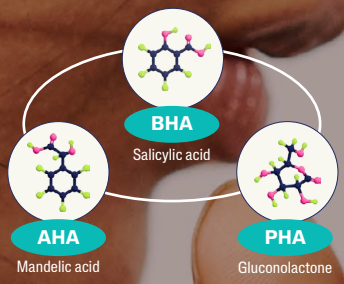

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doi:10.36849/JDD.8199

November 2024 932 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

From CO_2 to Er:YAG: A Comprehensive Review of Laser Treatments for Rhinophyma

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ABSTRACT

Background: Rhinophyma, a benign condition resulting in nasal sebaceous tissue hypertrophy, predominantly affects Caucasian males. There are numerous surgical and medical treatments for rhinophyma with varying degrees of success. This review aims to provide a comprehensive overview of ablative therapies, highlighting our preferred treatment approach.

Methods: This review analyzes the evidence behind ablative lasers in treating rhinophyma, with a focus on the 10600 nm carbon dioxide (CO_2) and 2940 nm erbium: yttrium-aluminum-garnet (Er:YAG).

Results: Both CO_2 and Er:YAG have demonstrated efficacy in treating rhinophyma. CO_2 laser ablation results in a higher incidence of scarring and hypopigmentation. Er: YAG has high water absorption, which results in less thermal damage, allowing for quicker healing and fewer complications.

Conclusion: Management of rhinophyma can remain challenging; however, ablative lasers are an effective treatment. Both laser types have promising outcomes, each with different advantages and complications. In particular, Er:YAG presents fewer complications compared to CO_2 lasers.

J Drugs Dermatol. 2024;23(11):932-936. doi:10.36849/JDD.8199

INTRODUCTION

Rhinophyma is a common, benign, and disfiguring condition characterized by hypertrophy of the nasal sebaceous tissue. The name is derived from the Greek words "*rhis*" for nose and "*phyma*" for growth. This condition predominately affects Caucasian males between the fifth and seventh decade of life, with a 20:1 estimated incidence ratio of male to female.[1,2] It is rare in the Asian and African populations.[2] While less frequent in women, it may present earlier, in the late thirties to early sixties years of age.[3]

The pathogenesis of rhinophyma is unknown but is suspected to correlate with long-standing rosacea, even classified by some as rosacea's fourth stage.[4] Historically, it was thought to be secondary to heavy alcohol consumption; however, studies have found no significant difference between alcohol intake in rhinophyma patients and control groups.

The clinical progression of rhinophyma starts with dilated pores at the nose's distal tip and may advance to severe hypertrophy of sebaceous glands, creating large bulbous nodules. The affected regions typically are the lower distal parts of the nose, such as the nasal tip, ala, and dorsum.[5] Severe cases may be at risk of nasal obstruction, sleep apnea, and obliteration of the nasal cosmetic subunits.[4,5]

Rhinophyma has been classified into 4 different subtypes based on the clinical appearance: glandular type with increased sebum secretion, fibrous type with connective tissue overgrowth, fibroangiomatous type with edema and telangiectasia, and lastly actinic type with nodular masses of elastic tissue.[3] Additionally, these phymatous features may extend beyond the nose, rarely affecting the chin (gnathophyma), forehead (metophyma), ears (otophyma), and eyes (blepharophyma).[5]

The history of surgical treatments for rhinophyma dates back to 1845, when Johann Friedrich Dieffenbach removed rhinophymatous tissue through vertical and horizontal incisions.[2,6] In 1912, Wood removed rhinophymatous skin, followed by skin grafts, which resulted in poor results. Radiation therapy has also been used to decrease the number of sebaceous glands and atrophy of the pilosebaceous units. A study by Skala et al reported significant improvement in rhinophyma following 20 treatments of 40 Gy within one month.[7] However, given the increased risk of malignancy with repeated radiation, this treatment modality has fallen out of favor.

Before treatment, a thorough examination is critical to confirm that nasal disfigurement is due to rhinophyma. There have been several reports of neoplasms mimicking rhinophyma, or a

malignancy may be masked by existing rhinophyma. The reported incidence of basal cell carcinoma within rhinophyma is 3% to 10%; however, rhinophyma is not a risk factor for skin cancer.[5,8-10]There have also been reports of eosinophilic granuloma,[11] chilblain lupus,[11] cutaneous squamous cell carcinoma,[12,13] B-cell neoplasms,[14,15] schwannoma,[16] cutaneous angiosarcoma,[12,17,18] and sebaceous carcinoma appearing clinically similar to a rhinophyma.[19,20]

In this review, we focus on ablative lasers for treating rhinophyma. We will explore the current evidence in managing this common disfiguring condition and share our clinical experience and treatment preferences.

Lasers

Physical destruction of the rhinophyma provides the best chance for positive aesthetic outcomes and care.[2] Several different procedural and surgical approaches can be done, including scalpel excision, electrosurgery, electrocautery, dermabrasion, laser ablation, cryosurgery, as well as a combination of these treatments. Fully ablative lasers, including 10600 nm carbon dioxide (CO_2) and 2940 nm erbium: yttrium-aluminum-garnet (Er:YAG), have been used for rhinophyma and will be reviewed in detail. Both lasers target water as their chromophore. Small case series comparing ablative lasers to electrosurgery or excision have yielded similar patient outcomes.[21,22] The goal of these physical modalities is the removal of the phymatous tissue while reestablishing and preserving the nasal cosmetic subunits. The pilosebaceous units can then promote reepithelization.[5]

CO_2

Carbon dioxide (CO_2) lasers generate a coherent, collimated beam that emits light with a wavelength of 10600nm with a focused mode for tissue cutting and a defocused mode to promote the absorption of water and subsequent tissue loss.[5] A recent systematic review done by Chauhan et al evaluated 12 studies, containing a total of 247 patients treated with carbon dioxide laser. Since this review, there have been several additional case series and trials further demonstrating the efficacy of CO_2 laser for rhinophyma (summarized in Table 1).[23-29] The largest study to date was a retrospective review of 124 patients (111 men, 13 female) treated with CO_2 laser for rhinophyma over 12 years.[24] Treatment involved a single CO_2 treatment, initially using continuous mode to debulk (10-20 W defocused 1 mm spot size), followed by resurfacing mode (20-40 W at 4-7 mm spot size) to contour the nose.

All 124 patients had a 3-month follow-up. Reepithelization was complete within one month, though erythema persisted for up to 12 weeks. Unfortunately, 4 out of 124 patients developed hypopigmentation. Other complications included alar notching in two patients and hypertrophic scarring in one patient. Fifty-two patients did follow up in the long-term questionnaire which demonstrated long-lasting results.[24] A second study on 3 patients, 2 of whom were female, underwent ablative fractional resurfacing with a CO_2 laser at 15 mm spot size and 40-70 J, with 4 passes. After 3 months, physicians reported roughly a 70% improvement with no adverse events.[30]

A separate clinical trial of 12 patients (10 male and 2 female) demonstrated improvement in the patient's self-esteem post-treatment.[29] One study reported using the CO_2 laser to delineate the area of the correction (5 W focused to 1 mm) and then penetrated the skin by 0.5 mm (15 W focused to 3 mm) to sculpt the nose and eliminate hypertrophic tissue. One case report has discussed CO_2 laser for rhinophyma in an African American male. This patient did not experience any complications following treatment, but it is important to highlight the potential risk of hypopigmentation when using the CO_2 laser, especially in this population.[28] Across all of the CO_2 laser-treated studies, complications include leukoderma, hypertrophic scarring, hypopigmentation, and worsening dilated sebaceous follicles (Table 1).[5]

Erbium:YAG

This is a solid-state laser that emits a wavelength of 2940 nm, which corresponds to the peak absorption of water. Its shorter wavelength allows for more specific absorption and decreases the depth of penetration when compared to the CO_2 laser. The laser's absorption in water is 16 times higher than that of the CO_2 laser, resulting in minimal heat conduction to the surrounding tissue. This results in less thermal damage to surrounding tissues, resulting in shorter healing times and decreased incidence of complications.[31] The benefit of Er:YAG is a reduction in the thermal energy. However, this thermal energy in CO_2 laser may be beneficial in the coagulation of blood vessels and resulting in a bloodless field.[21] A combination of both CO_2 and Er:YAG treatments has been published. Good et al and Fincher et al treated both with Er:YAG for ablation and CO_2 laser with low settings for its coagulative effects.[32,33]

For Er:YAG, a systematic review found a total of 4 studies and 18 patients treated for rhinophyma. The first series was described by Orenstein et al where 6 patients were treated with Er:YAG laser, resulting in all patients showing cosmetic improvement with no complications.[34] These patients showed a significantly shorter healing time when compared to other modalities such as CO_2 laser (Table 2).[31-34] Another study used 4 passes of dual-mode Er: YAG (3 mm spot, 100 mm ablation) with excellent cosmetic outcomes.[33] Badawi and colleagues treated 16 patients with fractional ablative 2940 nm Er:YAG laser for mild to moderate rhinophyma with 12 (75%) patients either being "very satisfied" or "satisfied" at their 3-month follow-up following 4 treatments over 4 weeks. No patients developed scarring or pigmentary changes. However, this study did have a short follow-up time frame. One patient did develop recurrence

TABLE 1.

CO_2 Laser Studies in the Last 15 Years[23-29]

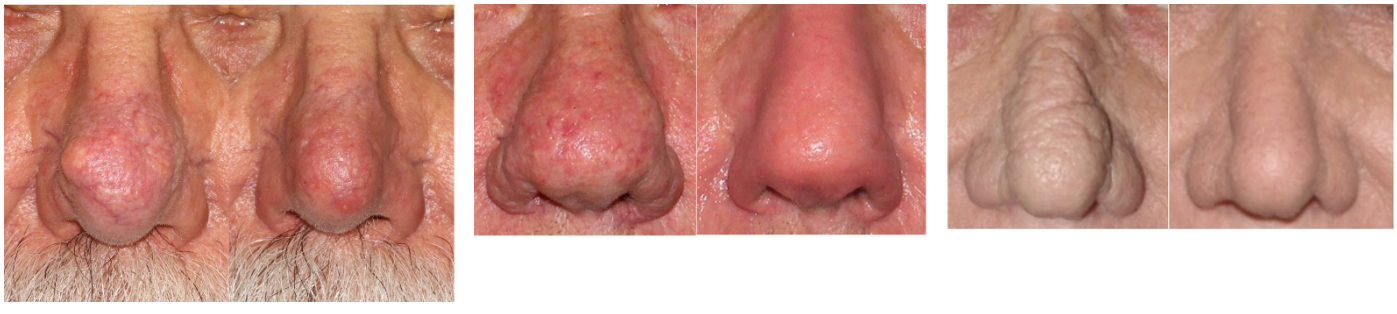
Study	Number of patients (male/ female)	Type of study	Number of sessions	Settings used	Re-epithelialization / post operative erythema (weeks)	Complications (No)	Results
Kilty 2008	4 (4/0)	Retrospective Case Series	1	Energy of 225 mJ; Frequency of 175 Hz	NR / NR	1	5/7 patients had an excellent or very good result
Madan 2009	124 (111/13)	Retrospective Review	2-4 sessions	Cutting mode (10-20W with 1mm spot size focal length of 125 mm) to debulk Resurfacing (20-40W; 4-7 mm spot size)	3-4 / 8-12	Hypopigmentation (4) Hypertrophic scar (1) Infection (1) Alar notching (2)	Good to excellent (118) Poor (6) High satisfaction in 52/111
Cravo 2009	4 (4/0)	Case Series	NR	Fluence ranging from 6-8 J/cm2; 2 mm spot size	3-4 / NR	0	2/4 with excellent results 2/4 with good results
Lazzeri 2013	22 (22/0)	Retrospective review	NR	7.5-10 W with focused spot of 0.1 mm	4 / NR	2	High patient satisfaction following post-treatment questionnaires
Serowka 2014	5 (5/0)	Case Series	1	70 mJ energy; 70% density; 16-18 passes	1/ NR	None however too short follow up time	Patient and physician noted improving and reduction in rhinophyma
Kraeva 2016	1 (1/0) in Fitzpatrick 6	Case Report	2	Treatment 1: 1 pass; 500 microsec pulse duration; 18 W; 600 Micron spacing Treatment 2: 3 passes; 500 microsec pulse duration; 18 W; 700 Micron spacing	NR / NR	None	Patient satisfaction after two treatments
Amaral 2019	12 (10/2)	Clinical Trial	4	Based on severity: Ranging from 20-25 J; 3-5 passes; 20-25 J/cm2	1-2 / NR	1 (prolonged erythema)	Decrease in Rosenberg Self-Esteem Scale, indicating improvement in self-esteem

TABLE 2.

Erbiuym:YAG Laser Studies[31-34]

Study	Number of patients (male/ female)	Number of sessions	Settings used	Re-epithelialization / post operative erythema (weeks)	Complications (No)	Results
Orensteinn 2001	6 (5/1)	1	5mm spot size, 1.2J pulse and a frequency of 10 Hz, 3-10 passes	1-2/ 4	0	All patients were satisfied with the treatment with minimal scar formation and normal nasal contour
Goon 2004	6 (6/0)	1 (Er:YAG followed by CO2)	10W (CO2) and 1.2 J (Er:YAG) with focusing spot of 5 mm	1-2 / NR	Revision (1)	Improved Nasal counter, symmetry with mild scarring in all patients
Fincher 2004	6 (5/1)	1	3 mm spot size with 100-um ablation + 50 um of coagulation, 4 passes	4 / NR	0	All patients were satisfied with treatment
Badawi 2020	16 (10/6)	4	7mm spot size; energy 250 to 300 mJ, with 5 um ablation depth, frequency 6 to 8 Hz	<1 week / NR	Recurrence (1) at 6 mos	Patient questionnaire at 3 mos follow up: 8 patients were "very satisfied", 4 patients were satisfied, and 4 patients were somewhat satisfied

FIGURE 1. Before and after treatments or moderate to severe rhinophyma following a single treatment with Er: YAG laser where the settings of 50 um coag/100 um ablative were used in multiple passes without wiping to debulk the lesion followed by 1-2 passes at 0 coag/50 um ablative to vaporize any non-specific thermal damage. (*Photos provided by Dr. Mitchel Goldman*)



at a 6-month follow-up.[31] None of these studies demonstrated complications such as scarring, hypopigmentation, leukoderma, or hyperpigmentation, as previously reported in the CO_2 studies.

Reports of rhinophyma treatment with Nd:YAG[35] and argon[36] lasers have been reported, but these lasers caused delayed healing and prolonged redness.[34] Finally, a case series of 5 patients treated with the 1450 nm Diode laser showed improvement following 4 treatments for mild rhinophyma.[37]

Adjunctive Treatments

Numerous medical treatments are helpful for other forms of rosacea but not for rhinophyma. Low-dose isotretinoin is helpful in early pre-fibrotic rhinophyma to slow the progression.[2,4,5] However, recurrence of the disease occurs after discontinuation. Inflamed rhinophyma may be treated with oral doxycycline, reducing inflammation and decreasing sebaceous gland size; however, to restore the original contour of the nose, a physical modality is needed.[5] Topical treatments are not as helpful. Kempiak et al published a case report of the addition of spironolactone to surgical procedures, resulting in improvement in the rhinophyma and no recurrence.[38] There is a growing body of evidence suggesting that botulinum toxin can be used in controlling sebum production on the nose by hindering acetylcholine release in sebocytes and paralyzing the arrector pili muscles, which otherwise contribute to sebum secretion if contracted.[39] By inhibiting the sympathetic innervation of these glands, oil production can be reduced. Fully ablative lasers can also be an adjunct with surgical excision for providing hemostasis.[40]

How We Do It

Unfortunately, there have been no head-to-head studies comparing the efficacy of CO_2 and Er:YAG as the treatment for rhinophyma. However, in our experience, Er: YAG (Sciton, Inc, Palo Alto, CA) results in less nonspecific tissue damage compared to CO_2 laser (Ultrapulse, Lumenis, Santa Clara, CA).[40] Since the Er: YAG has a high absorption of water, this results in minimal thermal damage, resulting in less damage to surrounding tissue. Thus, there is a decreased risk of hypopigmentation with the Er:YAG laser compared to the CO_2 laser. However, blood vessels in the superficial dermis are not occluded via heat coagulation, so bleeding may occur when pulsed less than 10 ms.[34]

It is important to fully anesthetize the treated area, as ablative laser resurfacing of rhinophyma can be painful. Pain control for the nasal area can be challenging due to the large number of sensory nerves. In our practice, we use 5-8 cc of 1% lidocaine with epinephrine to anesthetize the entire nasal area and use a diluted 1% lidocaine mixed with normal saline in a 1:3 ratio to achieve further pain control. The epinephrine also helps to decrease the risk of bleeding.

In our experience, Er:YAG alone can be used to treat rhinophyma. First, multiple passes with 50 um of coagulation are used to sculpt the area, followed by 0 um of coagulation to further decrease any non-specific thermal damage. We do not debulk the lesions but rather use 100um of ablative Er:YAG to vaporize and sculpt the nose. These typically require only one treatment with excellent cosmetic results (Figure 1A-1D). If additional Er:YAG laser treatments are requested to sculpt the nose, we advise waiting 2-3 months until the next treatment to allow appropriate wound healing.

CONCLUSION

Rhinophyma, although benign, can affect the aesthetic appearance of many. Over the years, numerous different treatment modalities have been explored, with ablative lasers, especially the Er:YAG laser offering promising results. By minimizing thermal damage to surrounding tissues, Er:YAG can result in fewer complications from our author's experience and based on the evidence presented in this review.

DISCLOSURES

The authors have no conflicts to disclose.

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doi:10.36849/JDD.7938

November 2024 937 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Safety and Effectiveness of Synchronized Monopolar Radiofrequency and High-Intensity Facial Electrical Stimulation in Patients Injected With Botulinum Toxin

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ABSTRACT

Background: Botulinum toxin (BT) has become one of the most frequently sought after aesthetic procedures for wrinkle reduction.
Objective: This study investigated the effectiveness and safety of a novel device using radiofrequency (RF) and high-intensity facial muscle stimulation high-intensity facial electrical stimulation (HIFES) in patients injected with BT.
Methods: Twelve patients were divided into an Active (N=10) and a Control group (N=2), where the Active received 4 treatments and the Control none. The facial expressions documented by digital photographs (neutral) and videos (frown, smile, surprise expressions) were taken at all visits (baseline, after last Tx, 1 and 3-month follow-ups) and were evaluated using the Global Aesthetic Improvement Scale (GAIS) and 3D automated analysis. The subject's therapy comfort and satisfaction were assessed.
Results: The Active group reported high satisfaction with treatment comfort (6.3±0.2 points on the 7-point Likert scale). 3D analysis showed reduced wrinkle severity (37.4%) and volume increase (+1.5 mL) on the cheeks at 3 months. GAIS evaluation demonstrated the most prominent improvement in smiling facial expression by 2.2±0.1 points. No adverse events were observed.
Conclusion: The study results suggest that the combination of HIFES and synchronized RF is a safe and effective treatment for improving facial appearance and muscle tone in patients injected with BT.

J Drugs Dermatol. 2024;23(11):937-942. doi:10.36849/JDD.7938

INTRODUCTION

To mitigate the signs of aging, including wrinkles and fine lines resulting from loss of collagen, elastin, and hyaluronic acid, individuals often resort to cosmetic interventions.[1–5] Botulinum toxin (BT) has emerged as a popular option for those seeking a rapid and non-invasive approach to achieving a more rejuvenated and refreshed look. It is currently among the most frequently sought after aesthetic procedures.[6] BT-based wrinkle treatment involves injecting small amounts of the toxin into specific muscles of the face, causing temporary weakening or paralysis of the targeted muscles by blocking the pre-synaptic release of acetylcholine, a neurotransmitter that regulates muscle contractions in the injected region.[7–11] In order to sustain these effects, patients need to undergo multiple treatments since the effects of BT typically last from three to four months.[8] Despite the effectiveness of BT treatment, the risk of developing resistance can arise, and the facial muscles can become weaker due to continuous treatment, eventually leading to facial muscle atrophy[12–17] Facial muscle atrophy, especially in elevator muscles, is not desired and may negatively contribute to the loss of natural support and a sunken appearance, which can be especially problematic in areas such as the cheeks and temples. To enhance the rejuvenating effects of BT treatment and mitigate its potential disadvantages, we investigated the use of a novel non-invasive device that delivers monopolar radiofrequency (RF) and high-intensity facial electrical stimulation technology simultaneously. HIFES technology stimulates and tones specific facial elevator muscles (frontalis muscle, zygomaticus major and minor muscles, and risorius muscle) and overlying fascial tissue. Synchronized RF heating induces structural changes in collagen and elastin fibers without exceeding the 43°C threshold needed for fat apoptosis initiation.[18]

The combination of RF and HIFES treatment with BT-based injections may become the ideal method to preserve and support the facial elevators' proper and healthy function while still having the high rejuvenating effect of BT treatment. The safety of RF, when used in conjunction with BT injections, is well-established, as it does not result in any migration or deactivation of the BT.[19,20] However, further investigation is required for the RF and HIFES technology combination. The aim of the study was to investigate the safety and effectiveness of the novel technology in patients injected with BT and its effects

on overall facial appearance.

MATERIALS AND METHODS

Demography of the Study Population

Thirteen (13) subjects were recruited for this study. The inclusion and exclusion criteria and the medical history were reviewed for each subject. To be eligible for participation, subjects had to be healthy males or females over 21 years of age, have a clear understanding of the investigational nature of the treatment, its potential benefits and side effects, and be willing and able to abstain from any facial treatments other than the study procedure during the course of the study. Additionally, subjects had to commit to complying with study instructions, attending all required clinic visits, and allowing photographs of their face to be taken. All the enrolled participants underwent injection with BT type A for facial wrinkles improvement within the past month, with a minimum of one week and a maximum of one month prior to the studied procedure. Subjects who met any of the exclusion criteria were excluded from participation in the study. Patients' demography and characteristics are shown in Table 1.

TABLE 1.

Baseline Patient Characteristics (N=12)	
	N
Patients	12
Sex	
Male	2
Female	10
Age (years)	
Mean	59.7±1.9
Range	52-69
Median	60.0
Skin types	
I	2
II	5
III	4
IV	1
Time from BT injection to the first treatment	
One week	2
Up to 14 days	4
More than 14 day	4
Units of BT	
Mean	101.0±7.4
Range	36-192
Median	84
Location of BT injections	
Forehead	10
Glabella	8
Crows feet	8
Neck	5
DAO	5
Chin	4

Ethics

This is a single-site, single-arm, open-label, and randomized interventional study, which received approval from the Advarra Institutional Review Board (ClinicalTrials.gov Identifier: NCT05524766), and its conduct adhered to the ethical principles outlined in the 1975 Declaration of Helsinki. Prior to undergoing any study-related procedure, all patients provided their voluntary informed consent, and a unique subject identification number was assigned to each patient to ensure their anonymity.

Treatments

The subjects were randomly allocated using a computer-generated list in a ratio of 5:1 (Active: Control). The active group was subjected to treatment with the novel EMFACE (BTL Industries Inc., Boston, MA) device using adhesive single-use applicators on the forehead and bilateral cheeks at the same time, simultaneously delivering RF and HIFES technology. Before each therapy, the treatment area was cleared of any cosmetics, sunscreen lotions, jewelry, and prominent hairs. The treatment administration phase consisted of four 20-minute treatment visits, delivered 5 to 10 days apart. At each therapy, the intensities of RF and HIFES stimulation (on a scale of 0 to 100%) were adjusted according to the patient's feedback, mitigating any possible discomfort. The control group did not receive any treatment. All patients were required to complete three follow-up visits: after the last treatment, at 1-month and 3-month follow-up. Patients were monitored and examined for the occurrence of any adverse events throughout the study duration.

Data Collection and Evaluation

After the final treatment and at all follow-up visits, patients were given the 7-point Likert scale Subject Satisfaction Questionnaire (SSQ) to evaluate their satisfaction with the therapy results. Similarly, the Therapy Comfort Questionnaire (TCQ) was administered after the final treatment to assess patient comfort during treatments. The TCQ included the 10-point Visual Analog Scale (VAS, 0 - no pain, 10 - maximum bearable pain) and a 7-point Likert scale.

At baseline and all 3 follow-up visits, 2-dimensional (2D) photographs of the face (neutral expressions) and facial expression videos (frown, smile, surprise) were taken and evaluated according to the Global Aesthetic Improvement Scale (GAIS). Three blinded independent evaluators assigned the GAIS score (-1 = worse, 0 = no change, 1 = improved, 2 = much improved, 3 = very much improved) to the subjects' pre- and post-treatment photographs and videos to assess overall facial

appearance improvement.

The 3-dimensional (3D) automated analysis was performed using a standardized system to evaluate the severity of wrinkles and changes in volume. A 3D photographic imaging system, LifeViz® Mini (QuantifiCare S.A., France), was used to capture facial photographs of twelve (12) patients who were to be evaluated. At baseline, after the treatment and both 1- and 3-month follow-up visits, the 2D photographs were taken from the left, right, and front views of the face at multiple angles and compiled into a 3D model by using Quantificare software suite. 3D models were evaluated for the wrinkle severity and volume shifts by analyzing the combination of depth, length, and width of the wrinkles in the treated areas according to the subject's age, gender, and skin type. Every analysis was assigned a score ranging from -10 to +10, where a negative score means the wrinkle severity is worse than in the average individual, and positive scores above 0 (ie, average) indicate how much better the patient's result is than in the case of an average individual of similar age, gender, and skin type as a concerned subject.

Statistical Methods

The descriptive statistic was calculated (mean, standard error mean, and median value). All data were analyzed for statistical significance. One-sample t-tests were used to determine whether a mean of GAIS point difference showed a significant improvement compared to the "no change" set on the baseline. Paired variables measured at multiple time points were tested by Repeated Measures ANOVA followed by a post-hoc Tukey HSD test used to analyze the significance of observed changes. The significance level was set to α=0.05 (5%).

RESULTS

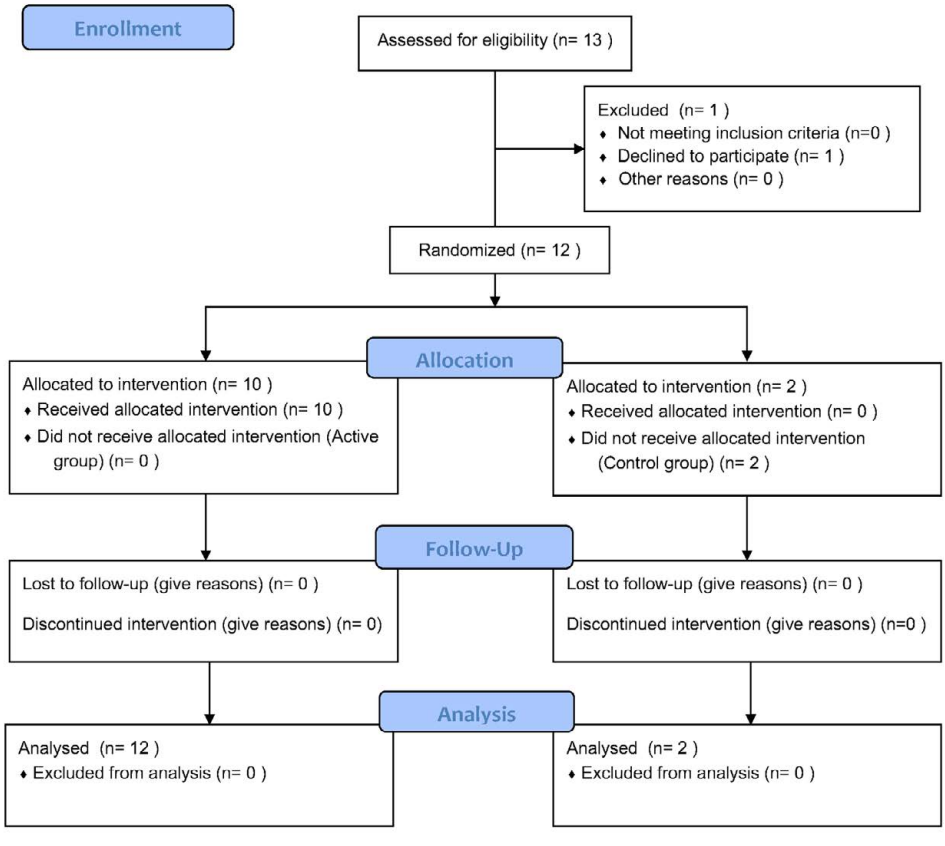
Out of thirteen (13) recruited subjects, 12 (2 males, 10 females; 59.7±1.9 years, skin types I-IV) were enrolled in this study and divided into the Active group (N=10) and Control group (N=2) as shown in Table 2.

Subjects' Satisfaction and Therapy Comfort

Based on the TCQ evaluation, the Active group was highly satisfied with the therapy comfort (6.3±0.2 points on the 7-point Likert scale) and felt none to minimum discomfort during the treatments (1.2±0.4 points on the 10-point analog scale). At 1 and 3 months, patients reported their satisfaction with the treatment results, including skin-tightening and lifting effects (5.4±0.4 points) and a better definition of their facial contours (5.1±0.3 points). The patients also agreed that they felt and looked better

TABLE 2.

CONSORT Flow Diagram



after the treatments (5.3±0.4 points). In conclusion, the majority of patients were satisfied with the treatment results (5.4±0.4 points).

GAIS Evaluation

According to the digital photo evaluation using the GAIS scale, 90% of subjects showed improved facial appearance at 1 and 3 months when displaying a neutral expression (P<0.05; Figure 1). At 1 month, the average score of +1.5 ± 0.2 points was achieved, and it was maintained for up to 3 months (1.3 ± 0.3 points). Compared to the Active group, both subjects from the Control group did not show any positive changes in the GAIS photo evaluation with neutral expression at both follow-ups (no change a

FIGURE 1. A 53-year-old subject at baseline (left) and at 3 months (right) after the final treatment. Visible improvement in wrinkles related to the depressor anguli oris (DAO) muscle. Botulinum toxin injection included the forehead, glabella, and crow's feet.

The overall facial appearance improvement in the Active group was also supported by video evaluation of frown, smiling, and surprised facial expressions. At 3 months, the frown and surprised facial expressions achieved 2.1 ± 0.2 points and 1.8 ± 0.2 points of improvement as the highest. The greatest improvement (P<0.05) was shown in smiling facial expression (Figure 2) by an average value of 2.2 ± 0.2 points and 2.2 ± 0.1 points at 1 a

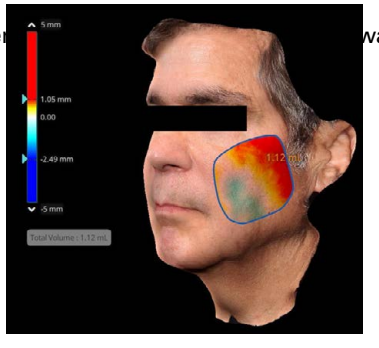
FIGURE 2. Smiling facial expression in a 52-year-old female subject at baseline and 1-month follow-up visit. Botulinum toxin injection included the forehead, glabella, crow's feet, DAO area, and neck.

3D Analysis

The 3D models were compiled from photographs (neutral facial expressions) and evaluated for wrinkle severity and volume changes by QuantifiCare software. The wrinkle severity average baseline score (-1.2±0.8 points) of the Active group gradually increased (P<0.05) by +3.4 points at 1 month (21.0%) and +4.8 points at 3 months (37.4%). The 3D analysis of the Control group did not show any significant improvement. Moreover, a decline by -2.5 points at the 3 months (-14.5%) was observed in the overall facial appearance.

Cheek volume measurement from the 3D photos showed a significant (P<0.05) volume improvement against baseline by +1.0 mL and +1.5 mL at 1 and 3 months (Figure 3). Interestingly, the Control group showed a volume increase by 0.7 mL at 1 month, however was observed.

FIGURE 3. Volume increase on the cheek in 68-year-old male subject at 3-month follow-up visit. Botulinum toxin injection included the forehead, glabella, crow's feet, and chin.



DISCUSSION

The effectiveness and safety of treatment utilizing the novel RF and HIFES device were significantly (P<0.05) documented through the overall facial appearance. Improvement was observed in all Active patients regardless of the time from BT injection to RF and HIFES treatment (7 days, 14 days, and more than 14 days). GAIS outcomes of digital photographs showed the most prominent improvement at 1 month and were supported by the GAIS evaluation of video facial expressions (frown, smile, and surprise), showing even greater improvement due to dynamic display and maintaining up to 3 months after the treatment. Based on the 3D analysis, wrinkle severity was reduced by 37.4% at 3 months, respectively. At 3 months, the volume measurement revealed the most significant increase, with fuller cheeks showing a gain of +1.5 mL. The majority of treated patients (92%) reported high satisfaction with the treatment results and comfort. In addition to the assessment tools employed, 90% of patients reported noticing a more natural appearance. There was no significant improvement observed in the control group across all types of evaluations.

Clinical studies have already shown the effectiveness and safety of the novel RF and HIFES device in overall facial improvement. The findings of this study are in line with those

of other studies.[21,22] Additionally, our study showed the greatest improvement at 3 months, which corresponds with Kent et al[23] findings, confirming the fact that collagen and elastin structural remodeling occurs within 3 months after the RF treatment, resulting in clinically evidenced skin rejuvenation. Due to the novel RF and HIFES technology targeting specific facial muscles, visible wrinkle reduction, and volume improvement were documented. This noninvasive approach offers an effective alternative option for facial rejuvenation.

We suggested RF and HIFES treatment with BT injections, which appears to be safe, as it does not result in any migration or deactivation of the BT or any adverse events. The effect of BT was not aggravated by the treatment, as was shown in videos of facial expressions in Active subjects. Moreover, facial appearance improved regardless of the BT injections compared to the Control group. In addition, there was no negative effect on the longevity or duration of the botulinum toxin effect.

When BT (Botulinum Toxin) is used repeatedly, there is a possibility that the paralyzed muscles may atrophy due to a lack of sufficient time to regain tone and fiber density. In an animal histology study, Fortuna et al[16] suggested that repeated use of BT application causes a reduction of muscle mass, strength, and loss of contractile material, and these findings were supported by Schroeder et al[24] human histology study showing denervation atrophy of a considerable number of muscle fibers. The muscle paralysis and atrophy is beneficial in some of the facial depressors (eg, platysma, the largest depressor muscle), resulting in a more relaxed and less frowning appearance, but the related risk of muscle atrophy is not desired in the elevators responsible for natural support of the facial tissue.[25] In this study, only specific facial elevators were stimulated by RF and HIFES technology in patients with BT injections. There are studies proposing possible ways of external stimulation of BT-paralyzed muscles.[17,26] In our study, a visible contraction was observed in all patients during RF and HIFES treatment. We suggest that muscle atrophy and its related consequences can be prevented or avoided by the use of the novel device, combining the effect of synchronized RF on the skin tissue and the selective stimulation of underlying fibromuscular tissue and fascia by the HIFES technology. This is supported by histology study outcomes demonstrated by Kinney et al[27] showing positive muscle changes, especially densification and overall function improvement after the RF and HIFES treatment shown at 3 months. Moreover, the use of these two techniques consecutively can positively affect the final result by combining desired muscle paralysis while avoiding degeneration and atrophy of facial elevators responsible for facial volume and natural support. Therapy with BT dose reduction or even replacement with supportive RF and HIFES treatment may be considered an option to meet patients' aesthetic requirements, especially in the younger population.

To document changes in overall facial appearance, digital photographs supplemented with videos of facial expressions were taken, with videos showing even greater appropriate dynamic improvement. Although subjects had varying BT injection locations and units injected, consistent improvement was observed in all treated patients. Future research on more specific patient groups would be valuable to better understand the treatment's effectiveness with simultaneous RF and HIFES technology.

The use of a novel device simultaneously delivering RF and HIFES technology as a supportive treatment for BT application may help minimize the risk of facial muscle atrophy and maximize the cosmetic benefits of BT, resulting in less facial heaviness and a more youthful and natural-looking appearance. The combined treatment is fully non-invasive and highly comfortable with minimal discomfort. In conclusion, no negative effects or adverse events on BT effectiveness were observed after the treatments, suggesting the safety of using HIFES combined with synchronized RF in patients injected with BT.

CONCLUSION

After the course of 4 therapies, the data indicate high satisfaction with treatment outcomes, revealing noticeable changes in the subject's facial appearance, which persisted up to 3 months after finishing the last therapy session. No negative effects on BT effectiveness or duration were observed. The results suggest that the application of monopolar RF and HIFES is safe and effective in subjects who undergo BT injections and can positively affect the result of BT treatment.

DISCLOSURES

This IRB-approved study (ClinicalTrials.gov Identifier: NCT05524766) was sponsored by BTL Industries. The investigators may be contracted to speak or present this work on behalf of BTL Industries.

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doi:10.36849/JDD.8196

November 2024 943 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Single-Center, Open-Label, Prospective Study of a 589/1319 nm Dual Wavelength Laser for the Treatment of Facial Hyperpigmentation

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ABSTRACT

Background: Facial hyperpigmentation, characterized by the excessive production of melanin in the skin, is a prevalent dermatological concern affecting individuals of various ethnic backgrounds.

Aims: To evaluate the safety and efficacy of a multi-wavelength 589/1319 nm dual-pulse duration laser device for the treatment of hyperpigmentation

Patients/Methods: A total of 17 healthy women (mean [SD] age of 43.4 [11.6] with skin phototype II-IV) were enrolled in this prospective, single-center study. Eligible participants received up to 3 treatments spaced 3 to 5 weeks apart with 2 follow-up visits at 4 and 12 weeks after the final treatment. Assessments included investigator ratings of skin quality, global aesthetic improvement, and hyperpigmentation. Safety and tolerability were monitored throughout the study.

Results: Significant improvements in hyperpigmentation and skin quality were observed at the 2 follow-up visits from baseline in most patients per investigator assessments. Patient satisfaction was high, and treatments were safe with transient self-resolving side effects such as erythema.

Conclusions: Laser treatments using a dual-wavelength 589/1319 nm device significantly improve facial hyperpigmentation in patients of various skin types.

J Drugs Dermatol. 2024;23(11):943-947. doi:10.36849/JDD.8196

INTRODUCTION

Facial hyperpigmentation, characterized by the excessive production of melanin in the skin, is a prevalent dermatological concern affecting individuals of various ethnic backgrounds. Among the various forms of facial hyperpigmentation, melasma stands out as a distinct and challenging condition. This multifactorial disorder is characterized by symmetrically distributed, brownish facial hyperpigmentation, often affecting sun-exposed areas, particularly the forehead, cheeks, and upper lip.

The epidemiology of facial hyperpigmentation, including melasma, exhibits a notable predilection for women, with estimates suggesting a prevalence of up to 10% to 50% among females and a considerably lower prevalence among males. Furthermore, there is a higher incidence in individuals with darker skin phototypes, emphasizing the role of ethnicity in melasma development.[1]

The pathogenesis of facial hyperpigmentation, particularly melasma, is intricate and involves the interplay of genetic, hormonal, and environmental factors.[2,3] Genetic predisposition is evident in familial cases, emphasizing the hereditary component of melasma. Hormonal factors, including pregnancy, oral contraceptive use, and hormonal replacement therapy, contribute to the dysregulation of melanogenesis and are mediated by the upregulation of melanocyte-stimulating hormone (MSH) and estrogen receptors, which contributes to the gender disparity observed in melasma. Chronic exposure to UV radiation exacerbates melanin production by stimulating melanocyte activity and promoting the release of proinflammatory mediators. Additionally, inflammatory pathways, such as increased expression of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), further contribute to melanin hyperproduction, linking inflammation to the pathogenesis of melasma.

Effective management of facial hyperpigmentation, especially melasma, involves a comprehensive approach targeting various aspects of its pathogenesis. Sun protection, including the regular use of broad-spectrum sunscreen with a high sun protection factor (SPF), is fundamental in preventing UV-induced exacerbation. Topical agents, such as hydroquinone, retinoids, and corticosteroids, are commonly employed to inhibit melanin synthesis and promote skin turnover. Procedural interventions, including chemical peels, laser therapy, and intense pulsed light (IPL), offer additional modalities for pigment reduction by

targeting melanin-containing cells.[4-7] Combination therapies, incorporating various topical agents and procedures, are often recommended to optimize treatment outcomes.[3]

In ongoing efforts in therapeutic development to enhance treatment efficacy and address the diverse needs of affected individuals with facial hyperpigmentation, this single-center prospective study evaluated the safety and efficacy of treatments with a dual-wavelength 589/1319nm device for facial hyperpigmentation.

MATERIALS AND METHODS

Patients

A total of 17 participants were enrolled in this trial. All participants provided written informed consent prior to receiving any study-related procedures. Eligible participants were healthy individuals (>18 years of age, Fitzpatrick photo skin types I-V) with moderate-to-severe hyperpigmentation on their faces who agreed not to use any skin-lightening treatments for the duration of the study. Negative urine pregnancy test results were required for women with childbearing potential before enrollment. Participants with dermatologic conditions, including acne, rosacea, eczema, psoriasis, actinic keratosis, severe sun damage, scars, or a history of keloids, were also excluded from the study.

Study Design

This was a prospective, single-center study conducted in accordance with the principles of the Declaration of Helsinki, current good clinical practice guidelines, and International Review Board approval. The treatment phase consisted of a baseline visit, up to 3 visits at 3- to 5-week intervals, and 2 follow-up visits at 4 and 12 weeks after the last laser treatment. All participants were treated first with a 589 nm solid-state laser (ADVATx; Advalight) at 25-35 J/cm2, with the use of a scanning handpiece followed by the 1319 nm wavelength (20 J/cm2). Pulse duration was 45 ms for both wavelengths. No cooling was used. The scanning handpiece consisted of a 1 mm spot size scanned in a circle, line, or square pattern of up to 10 × 10 spots, adjusted based on the treatment region. Standardized photographs were taken at 0°, 45°, and 315° angles using the Visia® CR system (Canfield Imaging Systems), with the right and left sides of the face independently evaluated. Baseline photographs were obtained at the screening visit, and photographs were then obtained prior to and directly after each treatment. Final photographs were obtained at the follow-up visit. Evaluations were performed by both the investigator and the participant. Safety was assessed based on participant-reported and/or investigator-reported side effects.

Assessments

The assessment of skin quality was performed by patients and a trained investigator blinded to the visit number at baseline, before each treatment, and at the 4- and 12-week follow-up using a customized 10-point scale (Table 3). Each patient's satisfaction with their facial appearance, hyperpigmentation, and treatment was assessed at every visit using the participant satisfaction assessment scales.

Statistical Analysis

Ordinal variables were analyzed using the Wilcoxon test for paired samples. For ratio scaled variables, normal distribution was verified by the Kolmogorov-Smirnoff test and then analyzed using the Student-T test for paired variables or the Wilcoxon test. All statistical tests were 2-sided and tested in conjunction with a 0.05 nominal significance level. Analyses were carried out using SAS version 9.4 statistical software (Cary, NC).

RESULTS

Out of the 17 patients initially enrolled in the study, 3 were lost to follow-up and thus excluded from data analysis. Of the remaining 14 patients, all completed the study. Patients were female, mean (SD) age of 43.4 (11.6) with skin phototype II through IV (Table 1).

Investigator assessments demonstrated an improvement in GAIS score in all patients at both follow-up visits from baseline (P<0.05) (Figure 1A). Scores of hyperpigmentation (scale of 1 to 6, higher values indicate increased hyperpigmentation) also significantly improved from baseline both at the first and second follow-up visits (Figure 1B). Representative pictures of patients before and after 3 laser treatments are presented in Figures 2 and 3. Assessment of skin quality demonstrated that all parameters (radiance, smoothness, pore size, erythema, pigmentation) improved from baseline to both follow-up 1 and 2 by one point (Table 2).

The majority of patients shared their satisfaction with the treatment (60% very satisfied, 20% satisfied, 20% somewhat satisfied), noting visible changes in their skin, such as improvement in pigmentation, a noticeable reduction in

TABLE 1.

Patient Demographics	
Parameter	**Value (N=14)**
Age, mean (SD)	43.4 (11.6)
Skin Type, (n/N)	
I	0 (0/14)
II	1 (1/14)
III	8 (8/14)
IV	5 (5/14)
Ethnicity, (n/N)	
Hispanic	9 (9/14)
Nonhispanic	5 (5/14)

FIGURE 1. (A) Investigator assessments of GAIS at the 4- and 12-week follow up. (B) Hyperpigmentation score change at the 4- and 12- week follow-up from baseline. Asterisk denotes statistical significance.

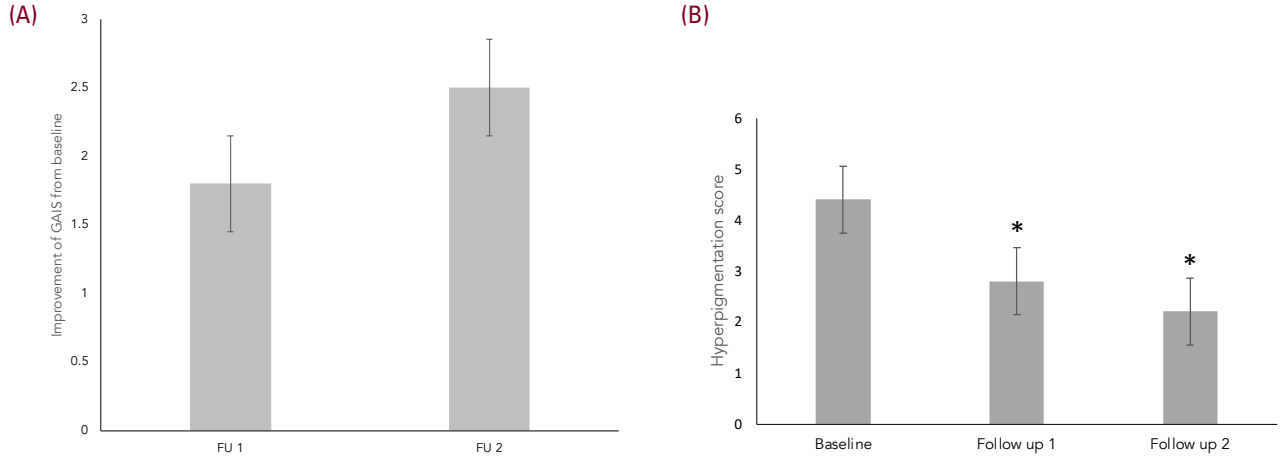

TABLE 2.

Investigator Rated Skin Quality Score					
	Radiance	Smoothness)	Pigmentation	Erythema	Pore Size
Baseline	6.3 (1.6)	7.1 (1.4)	5.5 (1.2)	7.4 (1.5)	6.9 (1.3)
Follow up 1	7.6 (0.9)	7.9 (0.7)	6.9 (1.2)	7.6 (1.2)	7.61 (1.0)
Follow up 2	7.8 (1.2)	8.1 (0.9)	6.8 (1.5)	8.1 (1.0)	7.57 (1.0)

Values are mean (SD).

FIGURE 2. Representative clinical photographs of a 59-year-old participant before (A) and after (B) 12 weeks after the third laser treatment. Reduction of pigmentation, pore size, increased radiance, and smoother, more even tone is noted.

(A) (B)

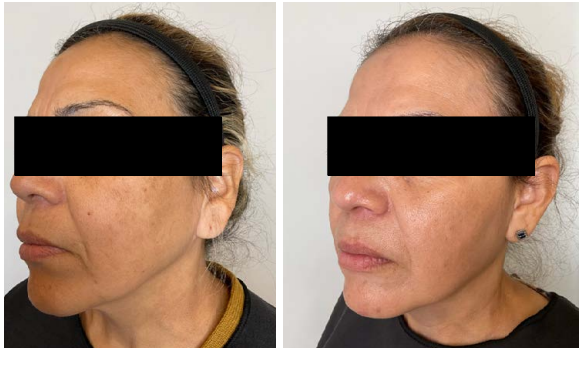

FIGURE 3. Representative clinical photographs of a 29-year-old participant before (A) and after (B) 12 weeks after third laser treatment. Reduction of pigmentation, pore size, increased radiance, and smoother, more even tone is noted.

(A) (B)

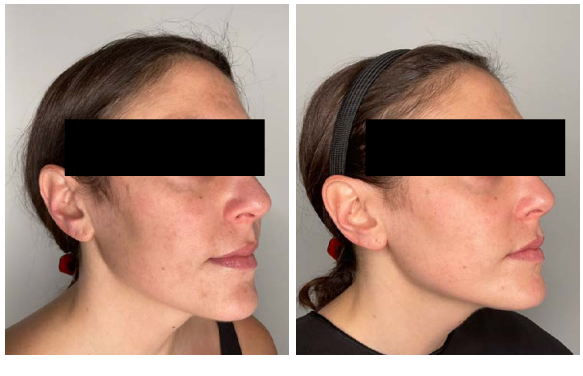

TABLE 3.

Customized 10-Point Scale for Rating of Skin Quality
Radiance 1 2 3 4 5 6 7 8 9 10 I----------I----------I----------I----------I----------I----------I----------I----------I----------I No radiance Maximum radiance
Smoothness 1 2 3 4 5 6 7 8 9 10 I----------I----------I----------I----------I----------I----------I----------I----------I----------I Very rough Very smooth
Pigmentation 1 2 3 4 5 6 7 8 9 10 I----------I----------I----------I----------I----------I----------I----------I----------I----------I Very irregular pigmentation Very uniform pigmentation
Erythema 1 2 3 4 5 6 7 8 9 10 I----------I----------I----------I----------I----------I----------I----------I----------I----------I Intense redness No redness
Pore size 1 2 3 4 5 6 7 8 9 10 I----------I----------I----------I----------I----------I----------I----------I----------I----------I Very large pores Minimal pores

freckles, and an overall clearer complexion. Positive reviews also highlighted the effectiveness of the treatment for individuals with sensitive skin, emphasizing their contentment with the non-aggressive approach that still resulted in "significant improvement." One patient also noted treatments did not feel like "too big of an intrusion on life," highlighting the lack of downtime from the treatment.

Safety and Tolerability

Patients perceived the treatments tolerable, with no pain or mild pain reported.

No serious adverse events or unexpected side effects were observed or reported for any of the participants. All side effects are self-resolved (erythema) within 48 hours of treatment.

DISCUSSION

This single-center prospective study demonstrated that a 589/1319 nm laser device can safely and effectively treat hyperpigmentation and improve skin quality within a short treatment period in patients with skin types II through IV. Investigator assessments showed improvement in skin quality, global aesthetic improvement, and importantly, reduction in hyperpigmentation in all patients, with a high patient satisfaction. Side effects were quite mild and limited to immediate post-treatment erythema in all patients ranging from none to mild.

While histological examination of the skin of patients with melasma shows increased epidermal melanin content, enlarged melanocytes, and prominent dendrites, accumulating evidence has shown that photoaging, inflammation, and angiogenesis are also involved in the pathogenesis of melasma. Given that melasma is typically chronic and long lasting, with exacerbations and remissions and resistance to treatment, treatment regimens for melasma must utilize a multifactorial approach. The use of the dual-wavelength 589/1319 nm laser treatment protocol is designed as such to facilitate a 2-prong approach to treating melasma. First, the 589 nm targets both the melanosomes and the dermal microvascular component of melasma that participates in the maintenance of hyperpigmentation. By treating the vessels, the laser decreases the stimulus to melanocytes and subsequently the recurrence of the spots. Treatment of the same area with the 1319 nm laser that targets both the melanocytes in the dermal-epidermal junction and the fibroblasts that reside in the dermal layer stimulating neocollagenesis leads to a reduction in pigment and improvement in skin quality. Thus, aside from targeting the pigment, the improvement in photoaging reduces the paracrine stimulus to the melanocytes, and the reduction in dermal vasculature from which inflammatory cells are derived is what leads to the improvement of both dermal and epidermal melasma.

Limitations of the study include the small number of participants, the fact that only female participants were enrolled, and the relatively short period of follow up. The duration of the treatment effect, the appropriate regimen for long-lived results, and the combination with other treatments such as topicals are an important topic of future research.

For long-lasting and optimal improvement of a condition like melasma that is notoriously difficult to treat, a strategy that includes extreme sun protection consisting of broad-spectrum sunscreens as well as regular treatment with dual-wavelength lasers, such as the one presented herein, can ensure remission of the condition and improvement in the overall appearance and quality of life of patients.

DISCLOSURES

SA, AS, ZE, and NS have nothing to disclose.

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Opzelura®
(ruxolitinib) cream 1.5%

For mild to moderate atopic dermatitis in non-immunocompromised patients 12 and older[1]

#1 PRESCRIBED JAK INHIBITOR IN DERMATOLOGY[2]

RELIEF REIMAGINED

JAK INHIBITION IN A TOPICAL.[1] IMAGINE THAT.

Images are for illustration only.
Results were measured at 8 weeks.[1]
Results may vary.

~3 YEARS OF REAL-WORLD UTILIZATION[3]*

>400 000 PATIENTS TREATED[4]†

>25 000 UNIQUE PRESCRIBERS[5]†

...and counting

*Postmarketing use since initial approval in September 2021.[3]
†Across all FDA-approved indications.[4,5]
JAK, Janus kinase.

INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitations of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Please see the Brief Summary of the Full Prescribing Information, including Boxed Warning, and Medication Guide on the last page.

MORE THAN 1 IN 2 PATIENTS ACHIEVED CLEAR OR ALMOST CLEAR SKIN (IGA 0/1)
with ≥2-point improvement from baseline* at Week 8 (primary endpoint; 53.8% vs. 15.1% and 51.3% vs. 7.6% with vehicle†; *P* < 0.0001).[1,6,7]

PATIENTS WITH ATOPIC DERMATITIS ARE LOOKING FOR RELIEF FAST.[8]

HOW FAST IS FAST?

FIND OUT

Opzelura OnTrac™ Resources to help patients get access, start treatment, and stay on track with OPZELURA.

STUDY DESIGN: OPZELURA was studied in two identical, double-blind, vehicle-controlled trials with 1249 patients ≥12 years old, with 3% to 20% affected BSA and an IGA score of 2 or 3. Patients were randomized to monotherapy with OPZELURA, ruxolitinib cream 0.75%, or vehicle twice daily for 8 weeks.[1]

*Measured by IGA-TS, defined as the achievement of clear (IGA 0) or almost clear (IGA 1) skin with at least a 2-point improvement from baseline; IGA is assessed on a severity scale of 0 to 4.[1]
†In TRuE-AD1 and TRuE-AD2, respectively.[1,6]
BSA, body surface area; IGA, Investigator's Global Assessment; IGA-TS, Investigator's Global Assessment treatment success.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib.

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

See Important Safety Information continued on the next page.

IMPORTANT SAFETY INFORMATION FOR OPZELURA® (RUXOLITINIB) CREAM 1.5% (CONTINUED)

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

MALIGNANCIES

Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OPZELURA in patients who have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS

Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately.

Thrombocytopenia, Anemia, and Neutropenia

Thrombocytopenia, anemia, and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions

In atopic dermatitis, the most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy

There is a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Lactation

Advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5-6 elimination half-lives).

Please see the Brief Summary of the Full Prescribing Information, including Boxed Warning, and Medication Guide on the next page.

REFERENCES: **1.** OPZELURA Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Data on File. This information is an estimate derived from the use of information under license from the following IQVIA information service: NPA Market Dynamics for the period from July 2022 through June 2024. IQVIA expressly reserves all rights, including rights of copying, distribution and republication. **3.** Business Wire. Incyte announces U.S. FDA approval of Opzelura™ (ruxolitinib) cream, a topical JAK inhibitor, for the treatment of atopic dermatitis (AD). Updated September 21, 2021. www.businesswire.com/news/home/20210921006072/en/Incyte-Announces-U.S.-FDA-Approval-of-Opzelura%E2%84%A2-ruxolitinib-Cream-a-Topical-JAK-Inhibitor-for-the-Treatment-of-Atopic-Dermatitis-AD. Accessed June 18, 2024. **4.** Data on File. This information is an estimate derived from the use of information under license from the following IQVIA information service: NPA Market Dynamics for the period from October 2021 through June 2024. IQVIA expressly reserves all rights, including rights of copying, distribution and republication. **5.** Data on File. This information is an estimate derived from the use of information under license from the following IQVIA information service: Xponent Subnational Rx data for the period from October 2021 through August 2024. IQVIA expressly reserves all rights, including rights of copying, distribution and republication. **6.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* 2021;85(4):863-872. doi:10.1016/j.jaad.2021.04.085 **7.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* 2021;85(suppl):863-872. doi:10.1016/j.jaad.2021.04.085 **8.** Feldman SR, Thyssen JP, Boeri M, et al. Adult, adolescent, and caregiver preferences for attributes of topical treatments for mild-to-moderate atopic dermatitis: a discrete-choice experiment. *J Dermatolog Treat.* 2024;35(1):2304020. doi:10.1080/09546634.2024.2304020

Incyte Dermatology

Opzelura®
(ruxolitinib) cream 1.5%

OPZELURA® (ruxolitinib) cream, for topical use

Brief Summary of FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitations of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including cryptococcosis, and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.

MALIGNANCIES

Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OPZELURA in patients who have experienced a myocardial infarction or stroke *[see Warnings and Precautions]*.

THROMBOSIS

Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral Janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: In a large, randomized, postmarketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

Major Adverse Cardiovascular Events (MACE): In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

Thrombosis: Thromboembolic events were observed in clinical trials with OPZELURA. Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers. Avoid OPZELURA in patients who may be at increased risk of thrombosis. If symptoms of thrombosis occur, discontinue OPZELURA and evaluate and treat patients appropriately.

Thrombocytopenia, Anemia, and Neutropenia: Thrombocytopenia, anemia, and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (TRuE-AD1 and TRuE-AD2), 499 adult and pediatric subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in TRuE-AD1 and TRuE-AD2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary: Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30, or 60 mg/kg/day in rats and 10, 30, or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD; the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% atopic dermatitis-affected body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in 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. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5-6 elimination half-lives).

Data: Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

Pediatric Use: Atopic Dermatitis: The safety and effectiveness of OPZELURA for the topical treatment of mild-to-moderate atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuE-AD1 and TRuE-AD2, which included 92 pediatric subjects aged 12 to 17 years with mild-to-moderate atopic dermatitis. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age with atopic dermatitis have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 (9%) were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between subjects less than 65 years and subjects 65 years and older.

PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections: Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious *[see Warnings and Precautions]*.

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA. Advise patients that exposure to sunlight, and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions]*.

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions]*.

Thrombosis: Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions]*.

Thrombocytopenia, Anemia, and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia, or neutropenia *[see Warnings and Precautions]*.

Administration Instructions: Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration]*.

Advise patients to limit treatment to one 60 gram tube per week or one 100 gram tube per 2 weeks *[see Dosage and Administration]*.

Pregnancy: Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations]*.

Lactation: Advise a patient not to breastfeed during treatment with OPZELURA and for about four weeks after the last dose *[see Use in Specific Populations]*.

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Issued: July 2022 PLR-OPZ-00020-JUN23

doi:10.36849/JDD.8420

November 2024 953 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

New Formulations of Acyclothymidine Dinucleosides Reduce Damaging Effects of Ultraviolet Radiation in an Ex Vivo Skin Model

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ABSTRACT

The greatest risk factor for skin cancer is exposure to ultraviolet (UV) rays of the sun. Among the 3 types of solar radiation (UVA, UVB, UVC), UVB rays are most commonly associated with skin cancer. UVB exposure promotes the formation of cyclobutane pyrimidine dimers (CPDs) in the DNA of cells in the epidermal skin layers, which can lead to mutations as DNA repair machinery attempts to repair the damage. These mutations can lead directly to skin carcinogenesis. Previous studies in animal and in human ex vivo skin models have shown that topical application of acyclothymidine dinucleosides protects DNA from UV-induced damage by preventing the formation of CPDs and helps initiate repair through the activation of DNA repair enzymes. Here we review the biological evidence leading to the development and formulation of ProteXidine™ (Topix Pharmaceuticals, Inc., Amityville, NY), as a UV protective agent for topical human application. We also provide clinical data pertaining to four ProteXidine™ formulations (test materials 1-4) tested for their abilities to reduce CPDs in an ex vivo human skin tissue model.

J Drugs Dermatol. 2024;23(11):953-956. doi:10.36849/JDD.8420

INTRODUCTION

Despite numerous public warnings about protecting the skin against sun's UV exposure and extensive research into topical protective formulations, the incidence of melanoma and non-melanoma skin cancers continues to rise.[1] However, UV exposure to skin can also lead to signs of aging, such as wrinkling and pigmentary disorders, including hyperpigmentation and photocarcinogenesis.[2,3] For decades, researchers have been working on topical skincare products that contain DNA repair enzymes, and collagen or collagen-protecting components to protect skin against UV-induced damage and reduce signs of skin aging and carcinogenesis.[4-6] As DNA repair machinery works to remove UV-induced DNA damage, mutations can be introduced into DNA. If these mutations occur in tumor-suppressive genes such as p53 or others, skin carcinogenesis can occur.[7] Active DNA repair enzymes themselves have been formulated to initiate the DNA repair process more quickly and effectively than the natural repair proteins.[8] There remains a need to explore alternative methods that can potentially mitigate the effects of sun exposure. This involves considering innovative solutions that offer protection against the harmful effects of sunlight, thereby broadening the approach to sun-related issues more comprehensively.

UV-exposed cells generate mutagenic photoproducts, primarily from absorbing radiation in the UVB range (280–320 nm). These include cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) photoproducts within the DNA of cells in the epidermal skin layers. CPDs, being slower to repair compared to (6–4) photoproducts, emerge as the key contributors to mutations in mammals.[9] Current photoprotective agents work by absorbing, reflecting, or scattering UV radiation. However, their effectiveness is constrained by the production of potentially harmful photodegradation products for the skin.[10-13]

Previous research has shown that the dinucleotide pTpT, isolated from DNA, offers protection against UV-induced skin tumors in mice, including melanoma and non-melanoma skin cancer.[14-16] However, these molecules have notable drawbacks, including instability, high production cost, and the complexity involved in their preparation and purification. We created a biomimetic

molecule, acyclothymidine dinucleoside, by arranging 2 thymine units on a simplified, non-glycosyl phosphate linkage to mimic a natural DNA segment.[17] This decoy molecule is designed to absorb the desired UV spectrum, protecting natural DNA. Furthermore, the resulting acyclothymidine dinucleoside dimer has the potential to recruit DNA repair enzymes activated by the excised pTpT dimer. These new compounds had the advantage of eliminating the complex and unstable phosphate-linked diribofuranosyl moieties in oligonucleotides. We have demonstrated the protective efficacy of these molecules against UV exposure, preserving both plasmid and cellular DNA. The topical application to hairless mice exposed to UV resulted in reduced CPDs and reduced UV-induced carcinogenesis. After 20 weeks of regular UV exposure, only 40% of the mice treated with acyclothymidine dinucleosides had measurable tumors compared to 80% of the vehicle treated mice.[18]

Acyclothymidine dinucleosides have now been formulated for topical application to human skin (ProteXidine™, Topix Pharmaceuticals Inc., Amityville, NY). Here, we detail trials in human ex vivo skin cultures derived from one individual showing that ProteXidine™ can reduce the formation of CPDs and increase the number of pyknotic epidermal cells, indicating damaged cells exiting the skin after UV damage.

MATERIALS AND METHODS

Skin Tissue Model

The ex vivo human skin tissue (11 mm, NativeSkin®, lot# 202208301, Genoskin Inc., Boston, MA) was obtained from one 34-year-old Caucasian of Fitzpatrick skin type II[19,20] following abdominoplasty. The sample was collected with IRB approval, and informed consent was provided by the individual. Genoskin states in the product manual and has shown in publications that samples have normal skin barrier function (assessed by Lucifer Yellow dye penetration assay and electric impedance spectroscopy), mature stratum corneum, functional basal layer, and all cell types and skin appendages in vivo human skin.[21] After receipt, tissue was placed into culture wells with an equilibration medium provided by Genoskin and equilibrated overnight at 37°C with 5% CO_2 and ~95% relative humidity for 24 hours. The equilibration medium was then removed from each well and replaced with 1 mL fresh maintenance medium (GenoSkin NSA11 Media) prior to performing the experiments.

Test Materials and Application Protocol

Test materials (TMs, Topix Pharmaceuticals, Inc., Amityville, NY) were provided ready to use, stored at room temperature, and protected from light until use. The ProteXidine™ and PRD-Tech™ trademarks are owned by and used under license from the Regents of the University of Minnesota and the UMN Center for Drug Design, US Patent 9,364,406. TMs were TM1 (ProteXidine™ Universal Treatment Complex w/ SPF [Sheer]), TM2 (ProteXidine™ Universal Treatment Complex w/ SPF [Tinted]), TM3 (ProteXidine™ Night Treatment Cream), and TM4 (ProteXidine™ Skin Discoloration Defense). Ex vivo human skin samples were either left untreated, or a total of 15 mL of each TM was pipetted into the center of each ex-vivo culture. A sterile glass spreader was used to distribute the topical material across the surface of each culture. Cultures were visually inspected to ensure even distribution as observed by a lack of pooled liquid or dry spots on the skin. The treated cultures were returned to the incubator at 37°C with 5% CO_2 and ~95% relative humidity for 20 minutes. Cultures were removed, placed in Dulbecco's Phosphate Buffered Saline (DPBS, Sigma-Aldrich, St. Louis, MO), and either positioned on a platform 30 cm from a SOL 500 solar simulator lamp with an H2 filter (Honle UV America Inc., Marlboro, MA) or incubated in DPBS for an equivalent duration at room temperature, outside of the tissue culture incubator not exposed to solar simulated UV light. UV-exposed samples received a UVB dosage of 100 mJ/cm^2 measured with a PMA2106 UVB detector (Solar Light Company, LLC, Glenside, PA, USA) and UVA of 3200-3300 mJ/cm^2. TMs remained on the skin during UV exposure. UV irradiated tissues were returned to the incubator at 37°C with 5% CO_2 and ~95% humidity for 4 or 12 hours. TMs were then washed from the surface of each culture with sterile DPBS. Each washed culture was split in half. One half was fixed in 10% formalin and held in 70% ethanol prior to tissue processing. The other half was snap-frozen and stored at -80°C for future studies. Formalin-fixed tissues were embedded in paraffin and sectioned to 3mm to 5mm size for hematoxylin and eosin (H and E) staining, immunochemistry (IHC) of CPDs and immunofluorescence (IF) of collagen.

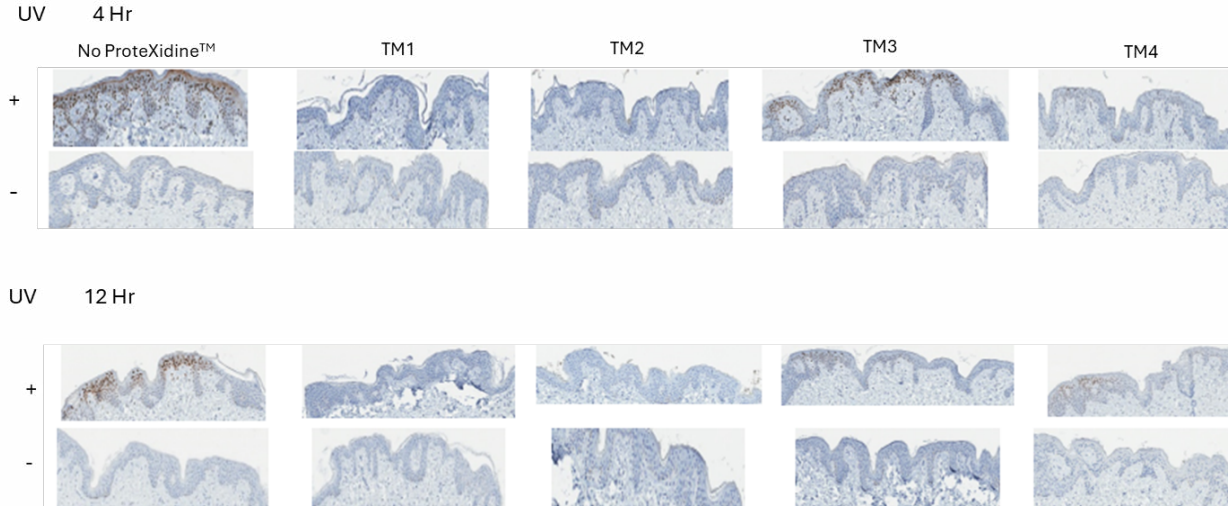
Immunohistochemistry (IHC)

CPD retrieval was performed using a standard protocol (PT Module, Epredia, Seattle, WA) at 98°C for 20 minutes with retrieval solution Dewax and HIER L Buffer (Epredia, TA-999-DHBL). Specimens were incubated with the primary antibody (mouse anti-thymine dimer antibody, H3, Abcam plc, Cat# ab10347, Cambridge, UK, diluted 1:100) and then secondary antibody (Goat Anti-Mouse IgG H&L, Alexa Fluor® 594, Abcam plc, Cat# ab150120, diluted 1:200) for one hour each at room temperature and then mounted in VECTASHIELD® HardSet™ Antifade Mounting Medium with DAPI (Vector Labs, Cat# H-1500-10, Detroit, MI) and protected by a cover slip. Digital images of the stained slides were captured at 40x magnification using a Leica Scanscope CS2 (Leica Biosystems, Deer Park, IL, USA). One tissue section was analyzed per block.

Hematoxylin and eosin staining (H&E)

Tissues were also processed for H and E staining to view the histology of the samples. One tissue section was analyzed per block.

FIGURE 1. CPD Immunohistochemistry 4 hours and 12 hours after UV exposure. Blue indicates cell nuclei and brown indicates CPDs. Fewer CPDs are observed with ProteXidine™ treatment compared to those without ProteXidine™ treatment after UV exposure. TM1-TM4 indicates four formulations of ProteXidine™.



RESULTS AND DISCUSSION

Following successful testing of the acyclothymidine dinucleosides in vitro and in vivo in animal models[17,18] we formulated ProteXidine™ for topical delivery to human skin. For proof of principle, we tested the formulations on an ex vivo skin model derived from one individual to determine whether we observed reduced signs of damaging effects of UV exposure upon application of ProteXidine™. Figure 1 shows CPDs in ex vivo skin 4 and 12 hours after UV exposure with and without each ProteXidine™ formulation (TM1-TM4). Reduced detection of CPDs was observed in the ProteXidine™ treated samples at both time points, although CPDs remained with the TM3 formulation.

We next examined single histological sections from each sample and observed increased pyknotic nuclei in the UV-exposed ex vivo skin models treated with ProteXidine™, indicating damaged cells being removed from the skin structure (Figure 2).

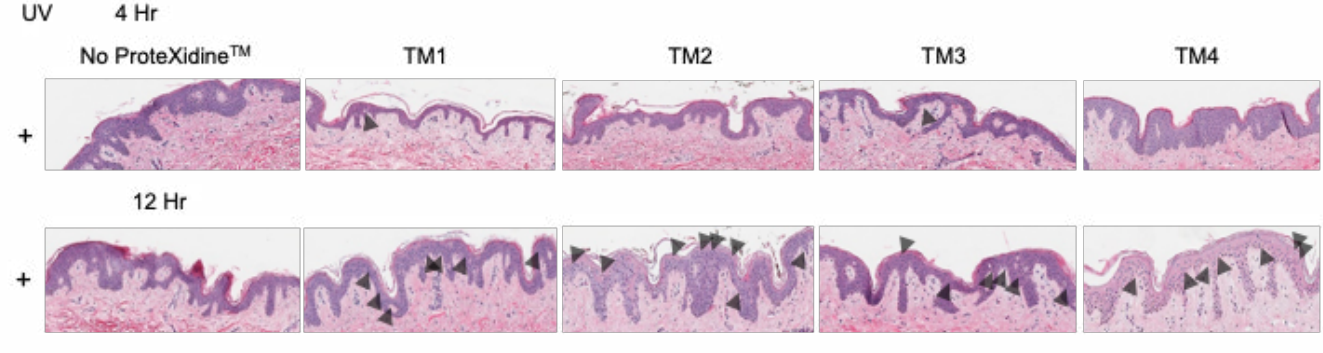
The effect was more pronounced at the 12-hour time point than the 4-hour time point, with all four formulations implicating that ProteXidine™ induced selective apoptosis of the UV-damaged cells.

The proof of principle study indicates that ProteXidine™ treatment of an ex vivo skin model reduced the effects of UV damage compared to samples without ProteXidine™.

CONCLUSION

ProteXidine™ formulated for topical application to human skin and tested on an ex vivo skin model resulted in less detectable CPDs following UV exposure compared to the UV-exposed sample without ProteXidine™. All four formulations of ProteXidine™reduced the detection of CPDs to various extents. Examination of histological sections revealed higher numbers of pyknotic nuclei in UV-exposed ProteXidine™ treated samples compared to the UV-exposed sample without ProteXidine™.

FIGURE 2. Hematoxylin and Eosin stain 4 hours and 12 hours after UV exposure. Pyknotic nuclei are marked by black arrows indicating damaged cells exiting the skin structure. TM1-TM4 indicates four formulations of ProteXidine™.



Finally, one formulation of ProteXidine™ appeared to reduce collagen damage after UV exposure. Together, the data support that topical ProteXidine™ delivery to the skin may be useful to reduce several damaging effects of UV exposure.

DISCLOSURES

AR, CD, and RV are inventors of Protexidine. NTI has received honorarium as consultant and speaker for Topix Pharmaceuticals. LK has received honorarium as consultant and speaker for Topix Pharmaceuticals.

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doi:10.36849/JDD.8171

November 2024 957 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Treatment of Mild to Severe Acne Vulgaris With a 650-Microsecond 1064-nm Nd:YAG Laser

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ABSTRACT

Background: Effective treatment of acne remains a challenge to dermatologists.

Objective: To evaluate the efficacy and tolerability of a 650-microsecond, pulsed 1064-nm Nd:YAG laser therapy for mild to severe facial acne vulgaris.

Methods: Human subjects of Fitzpatrick skin types I to VI with mild, moderate, or severe acne enrolled in the prospective, single-center study. Subjects received 5 treatments at 2-week intervals with the 650-microsecond, 1064-nm, pulsed Nd:YAG laser. Follow-up visits were 30 days and 90 days after the final treatment. At each visit, subject global assessments, lesion counts, investigator's global assessments (IGAs), and tolerability appraisals were performed.

Results: The median percent reduction in lesion count was 48.15% after 1 treatment and 83.72% at treatment 3 and remained at 86.67% at 90 days. Sixty percent of subjects noted improvement after treatment 1, and most subjects noticed improvement on or before treatment 3. Median IGA values decreased rapidly to reach a plateau of 1.0 (almost clear) at week 6 and remained there at the 30- and 90-day follow-up. Ninety percent of subjects were slightly to highly satisfied after 3 treatments, and 90% slightly to strongly agreed that their acne treatments improved their self-esteem after 4 treatments. Anesthesia or skin cooling were not used, and adverse events were not observed.

Conclusions: The 650-microsecond, pulsed 1064-nm Nd:YAG laser has been proven to deliver long-lasting clearance of mild to severe facial acne vulgaris with high subject satisfaction and without adverse effects on skin types I to VI.

J Drugs Dermatol. 2024;23(11):957-964. doi:10.36849/JDD.8171

INTRODUCTION

Acne affects approximately 50 million people in the United States.[1] Therapies include retinoids, antibiotics, hormones, lights, lasers, and various combinations of these modalities.[2] Topical and/or oral medications are associated with adverse effects, partial response, contraindications, and reoccurrences.[3]

The advantages and disadvantages of various lasers used alone or in combination with other modalities to treat acne have been described.[2] Reluctance to use laser devices historically for acne therapy has included concerns about pigmentary side effects (particularly on Fitzpatrick skin types IV-VI), treatment pain, and low treatment efficacy.

A recent review[4] reported that high-level studies support the effectiveness of Nd:YAG laser devices compared with other laser devices. The present study evaluates the efficacy and tolerability of a 650-microsecond, pulsed 1064-nm Nd:YAG laser for the treatment of mild to severe facial acne vulgaris.

MATERIALS AND METHODS

Study Design

Subjects (n=23, aged 29.4 ± 6.7 years [mean ± SD], 20 females and 3 males, Fitzpatrick skin types I-II [35%], III [9%], IV [30%], V[17%], VI [9%]) with mild (4%), moderate (57%), or severe (39%) acne enrolled in the prospective, single-center study.

Subjects received 5 treatments at 2-week intervals with the 650-microsecond, 1064-nm, pulsed Nd:YAG laser (Neo Elite, Aerolase Corp., Tarrytown, NY) without topical anesthetic. At visit 1, qualified subjects (n = 20) received a physical exam, dermatological history, and review of concomitant medications. Women of childbearing potential were required to have a negative urine pregnancy test at each treatment visit. Follow-up visits were 30 days and 90 days after the final treatment. At each visit, photographs, adverse event inquiries, subject global assessments (treatment pain, satisfaction with treatment, posttreatment improvement, self-esteem), lesion counts, investigator's global assessments (IGA), and safety appraisals were performed. Subjects did not use anti-acne prescription or

topical OTC medications for 2 weeks prior to or during the study. All subjects provided signed informed consent.

Subjects

Qualified subjects were males or non-pregnant females aged 19 to 40 years with mild to severe facial acne with inflammatory lesions and no more than a single nodule or 2 acne cysts. Exclusions were pregnancy, unwillingness to use an effective method of birth control for women on child-bearing potential, male with facial hair that would interfere with the study, use of topical retinoid within the previous month, use of topical antibiotic within the previous 2 weeks, use of oral antibiotic or isotretinoin within the previous month, participation in another clinical trial in the past 30 days, or presence of a serious medical condition that could put the subject at risk or interfere with interpretation of trial results.

Laser Treatment

Prior to laser treatment, the skin was thoroughly cleaned with alcohol swabs and dried thoroughly. Eye shields were placed over the eyes.

Laser treatments were performed in 2 steps. In the first step, the clinician applied 4 passes with the laser over the entire face. Laser settings for each subject were based on the Fitzpatrick skin type, as shown in Table 1.

In step 2, as in step 1, settings varied with the subject's skin type. For skin types I through III, the clinician changed the lens to a 2-mm spot size. Additional pulses were applied only to active acne lesions. Three to 5 pulses were applied to smaller lesions and 5 to 15 pulses to larger nodular/cystic acne lesions; the larger the lesion, the more pulses were applied. Typically, active acne lesions became lighter in color and smaller in size and may have purged sebum. For skin types IV through VI, settings are shown in Table 2. Three pulses were applied to each smaller lesion and 5 pulses to the larger nodular/cystic acne lesions.

Photography

Three digital photographs were taken of each subject at each visit: one at 0° in the front face with the camera within the sagittal plane and two at +45° and -45° in front of the face, respectively, with the camera between the sagittal and coronal planes.

Adverse Events/Safety

Adverse events and safety were monitored at each visit before treatment. Edema, erythema, acne flare-ups, dryness, and itchiness were graded as none, mild, moderate, or severe.

Acne Lesion Count

Acne lesion counts were performed "live" by the investigator (not from a photograph) prior to treatment and included only the active lesions. Inflammatory lesions on the forehead, left cheek, right cheek, nose, and chin were counted, excluding red, brown, or hyperpigmented spots caused by acne.

Investigator's Global Assessment

The IGA assesses acne severity from 0 to 5, where 0 = clear skin, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe, and 5 = very severe.

Subject Global Assessment

After each treatment, subjects provided feedback on the level of treatment pain on a scale of 1=no pain to 10=intolerable pain. Subject satisfaction with the treatment was assessed on a scale of 1=highly dissatisfied, 2=slightly dissatisfied, 3=neutral, 4=slightly satisfied, and 5=highly satisfied. Subjects were asked to specify the treatment (0 [baseline] to treatment 5), after which he or she first noticed an improvement in acne. Subjects were asked to (1) judge the percentage of clearance (0-100%) from when the treatment began and (2) if the treatment improved the subject's self-esteem, using the scale 1=strongly disagree, 2=slightly disagree, 3=neutral, 4=slightly agree and 5=strongly agree.

TABLE 1.

Step 1 Laser Settings				
Fitzpatrick Skin Type	Lens Type (mm)	Pulse Width (ms)	Energy Mode	Fluence (J/cm²)
I-III	6	0.65	6	21
IV	6	0.65	5	18
V-VI	6	0.65	4	14

TABLE 2.

Step 2 Laser Settings				
Fitzpatrick Skin Type	Lens Type (mm)	Pulse Width (ms)	Energy Mode	Fluence (J/cm²)
I-III	2	0.65	2	64
IV	6	0.65	6	21
V	6	0.65	5	18
VI	6	0.65	4	14

TABLE 3.

Demographics and Clinical Results

Subject	Age	Gender	Skin type	Acne Severity	Lesion count (initial, final)	IGA[1] (initial, final)	Adverse events
1	35	Male	V	Mild	6/0	2/0	None
2	30	Female	II	Moderate	13/2	3/1	None
3	31	Female	II	Moderate	11/9	3/3	None
4	28	Female	II	Severe	43/1	4/1	None
5	24	Female	II	Severe	19/0	4/1	None
6	39	Female	III	Moderate	15/2	3/1	None
7	20	Male	VI	Severe	13/1	4/1	None
8	23	Female	IV	Moderate	13/3	3/1	None
9	19	Female	II	Severe	37/16	4/4	None
10	26	Female	V	Moderate	11/0	3/0	None
11	23	Female	II	Severe	21/7	4/2	None
13	40	Female	IV	Moderate	10/0	3/0	None
15	22	Female	IV	Severe	22/6	4/2	None
16	33	Female	II	Moderate	13/0	3/0	None
18	28	Female	V	Moderate	14/6	3/2	None
19	40	Female	IV	Moderate	22/2	3/1	None
20	34	Female	II	Severe	18/1	4/1	None
21	38	Female	IV	Moderate	12/3	3/1	None
22	39	Female	IV	Moderate	10/0	3/1	None
23	25	Female	V	Severe	12/1	4/1	None

[1]Investigator's global assessment.

Data Analysis

Data consisted of small whole numbers not normally distributed, as shown by the Shapiro-Wilk test. Nonparametric statistics were therefore used to analyze data. The Friedman test was used to compare multiple populations, and the Wilcoxon test was used to compare two populations. The Bonferroni correction was applied for multiple comparisons. In these cases, the cutoff *P* value for significance (P=0.05) was divided by the number of comparisons to arrive at an adjusted P-value.

RESULTS

Twenty subjects completed the study. The data are shown in Table 3.

Acne Lesion Counts

As shown in Figure 1, inflammatory acne lesions decreased rapidly by week 2 and continued to decrease throughout the study. The median inflammatory acne lesions decreased from 13.5 to 7.0 by week 2 and to 1.5 at 90 days. The Wilcoxon test was used to compare week 6 data and 90-day data with baseline. *P*-values were 0.0010 in both cases, which, when the Bonferroni correction was applied (P=0.025 as the cutoff value), was significant.

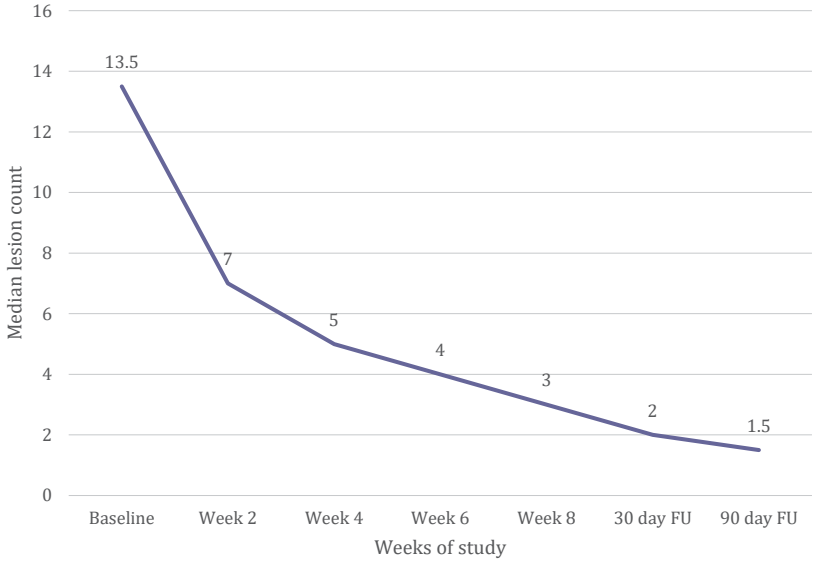
The median percent reduction in inflammatory lesion counts from baseline was calculated for week 6 and 90 days by the following formula:

% reduction = 100 x (count at week 6 or 90 days – counts at baseline)/count at baseline

The median percent reduction in lesion count was 83.72% (range 36.36 to 100.00) at 6 weeks (after treatment 3) and 86.67% (range 18.18 to 100.00) at 90 days.

Six non-independent comparisons were made with baseline, and the Bonferroni-adjusted significance level was 0.05/6 = 0.0084. Decreases in counts compared to baseline were significant as early as week 2 (P<0.0001), a pattern that continued for the remainder of the study. Friedman's test for week 6, week 8, 30 days, and 90 days showed that the difference among the median lesion counts for these four populations was insignificant (P=0.1328), suggesting that lesion counts reach a minimum at week 6, after only 3 treatments, and that the reduced counts persisted for the remainder of the study.

FIGURE 1. Median acne lesion counts of subjects during the study period.



Discomfort During Treatment

The median discomfort was 2.0 for the first, second, and final treatments and 3.0 for the third and fourth treatments. Differences in median scores among treatments were not significant.

Percentage of Subjects Showing Improvement After a Specific Treatment Session

Subjects were asked to specify after which treatment, ie, 0 (baseline) to treatment 5, he or she first noticed an improvement in their acne. At week 6 (after treatment 2), 60% of subjects noted improvement after treatment 1, while an additional 35%, ie, a total of 95%, reported improvement after treatment 2.

Percent Clearance of Acne

The percentage clearance of acne was estimated by subjects after each treatment and at the 30-day follow-up visit. Clearance increased steadily throughout the study period and reached a median of 90% (30%-100%) at 30 days. All but 6 subjects achieved at least 80% clearance at 30 days.

Investigator's Global Assessment

Figure 2 shows the median IGA values throughout the study period. Median values decreased rapidly and reached a plateau at week 6. These results were confirmed when subject scores at week 6, week 8, 30 days, and 90 days were compared by Friedman's test. The *P* value of 0.1870 indicates that the median values of the 4 populations did not differ significantly. These results suggest that most subjects achieved noticeable clearance by week 6, after 3 treatments, and that clearance persisted for up to 90 days.

FIGURE 2. Median Investigator's Global Assessment (IGA) scores of subjects during the study period.

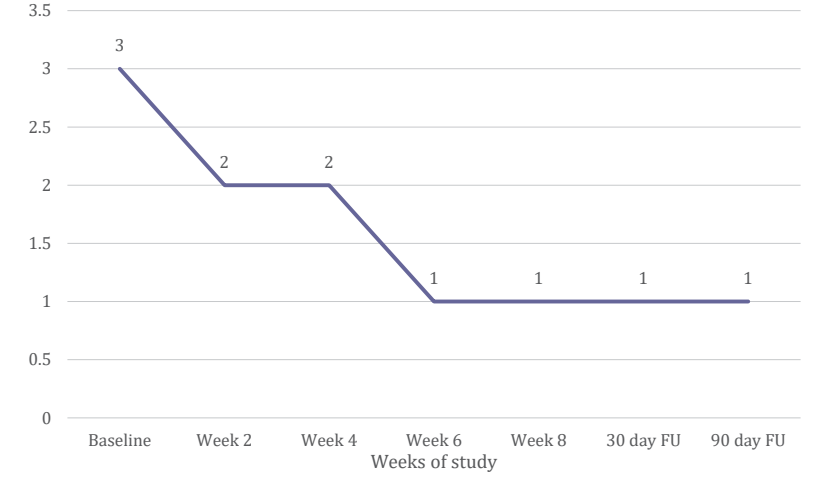
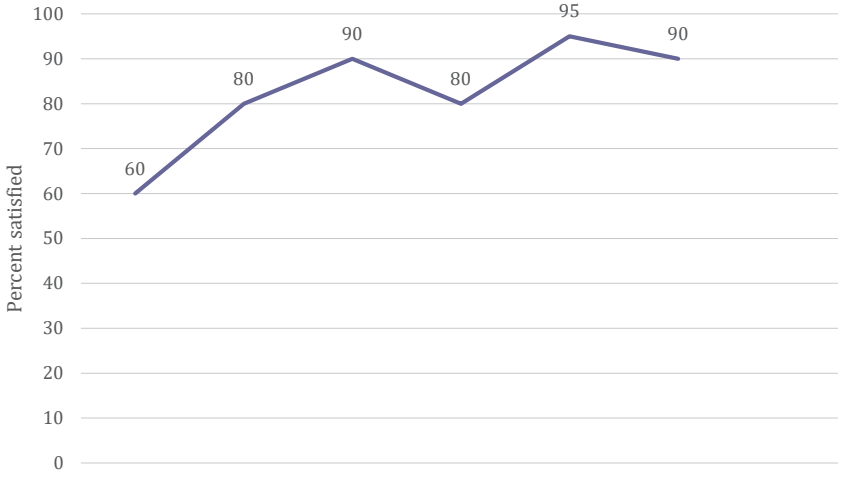


FIGURE 3. Percentage of subjects slightly to highly satisfied (4 to 5) with treatment during the study period.



The Wilcoxon test was used to compare week 6 data and 90-day data with baseline. *P*-values were <0.0001 in both cases, which, when the Bonferroni correction was applied (*P*=0.025 as the cutoff value), was significant.

The median percent reduction in IGA score was 66.67% (range 0.00 to 100.00) at both 6 weeks and 90 days.

Satisfaction With Treatment

Figure 3 shows steadily increasing satisfaction with treatment; 90% of subjects were slightly to highly satisfied by the 90-day follow-up. Comparison of satisfaction at week 6 (after 3 treatments) through 90 days by Friedman's test revealed a *P* value of 0.7182, confirming that the median values of the 4 populations (5.0 at week 6, 4.5 at week 8, 4.5 at 30 days, and 5.0 at 90 days) did not differ significantly. This suggests that most subjects achieved satisfaction by week 6 (after 3 treatments), and that satisfaction persisted for the remainder of the study.

Self-Esteem

Figure 4 shows the percentage of subjects that agree that their acne treatments have improved their self-esteem at each time point. Self-esteem increased during the study with peaks at week 8 and 30 days. Friedman's test for week 6, week 8, 30 days, and 90 days yielded a p value of 0.6861, indicating that the medians of the 4 populations (4.0, 5.0, 4.0, 5.0, respectively) did not differ significantly. The minimum and maximum values were 3 and 5, respectively, for each population. These results suggest that most subjects achieve improved self-esteem by week 6, after 3 treatments, and that self-esteem persisted through the rest of the study.

FIGURE 4. Percentage of subjects slightly to strongly agree (4 to 5) that their acne treatments have improved their self-esteem during the study period.

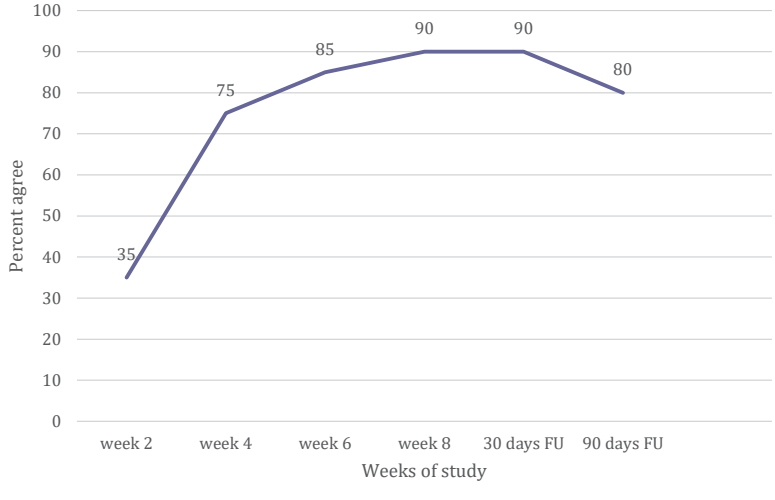


FIGURE 5. A 28-year-old female before (A) and at 90 days (B) after the fifth treatment with the 650-microsecond, 1064-nm pulsed Nd:YAG laser.

(A) (B)

FIGURE 6. A 24-year-old female before (A) and at 90 days (B) after the fifth treatment with the 650-microsecond, 1064-nm pulsed Nd:YAG laser.

(A) (B)

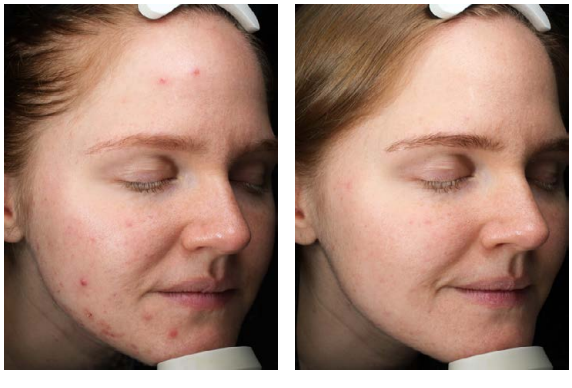


FIGURE 7. A 20-year-old male before (A) and at 90 days (B) after the fifth treatment with the 650-microsecond, 1064-nm pulsed Nd:YAG laser.

(A) (B)

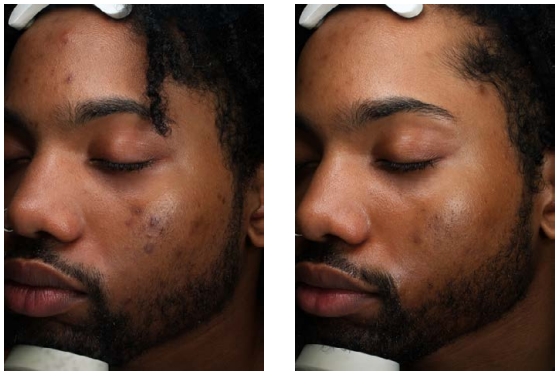
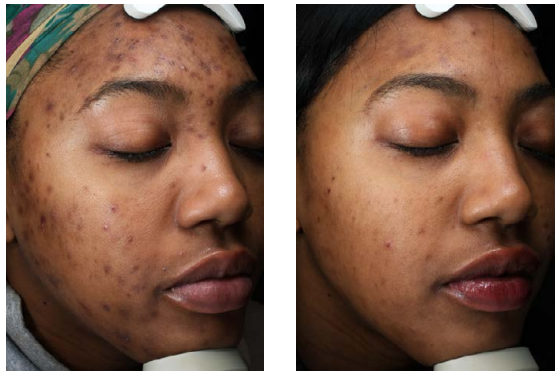


FIGURE 8. A 25-year-old female before (A) and at 90 days (B) after the fifth treatment with the 650-microsecond, 1064-nm pulsed Nd:YAG laser.

(A) (B)



Adverse Events

Edema, erythema, acne flare-ups, dryness, and itchiness on a scale of none, mild, moderate, or severe were not observed during the study.

Clinical examples are shown in Figures 5 through 8.

DISCUSSION

The results show that clinically meaningful results in acne lesion counts, subjective improvement, IGA values, satisfaction with treatment, and self-esteem are obtained for subjects with a wide range of skin types (ie, Fitzpatrick I-VI) in 3 to 5 treatments with the 650-microsecond, 1064-nm, pulsed Nd:YAG laser. Edema, erythema, acne flare-ups, dryness, and itchiness were not observed. Subjects reported minimum discomfort with no anesthetic or skin cooling.

The 650-microsecond 1064-nm Nd: YAG laser is a recent development for the treatment of acne. In a study by Khatri and colleagues,[5] 100 patients (aged less than 25 years, skin types II to III) with moderate to severe acne received three treatments at 1-week intervals with the 650-microsecond laser. For inflammatory lesions, treatment settings were similar to those of the present study. Anesthetic or pre-cooling were not used, and pain was minimal during and after treatment. Patient satisfaction was high and hyperpigmentation, burns, scars, and other adverse effects were not observed.

In a clinical evaluation of acne treatment using the 650-microsecond pulsed Nd:YAG 1064-nm laser,[6] all patients noted improvement of their acne as early as 2 weeks after their first treatment. Several patients also experienced lightening of post-inflammatory hyperpigmentation and all patients noticed an overall reduction in larger cystic and inflammatory lesions. They reported a well-tolerated procedure without complications or downtime.

Kesty and Goldberg,[7] in a randomized, sham- controlled study, reported the efficacy of the 650-microsecond laser in the treatment of 20 subjects (aged 12 to 40 years, skin types I to VI) with moderate to severe facial acne. As in the present study, treatment settings varied with Fitzpatrick skin type. All subjects received 3 treatments at 2-week intervals and an additional treatment 4 weeks later, all with either the laser or sham control. For the laser-treated group, IGA improvement was 26% compared with 7% for the sham group and the number of inflammatory lesions decreased by 42% vs 26% for the sham group. The laser-treated subjects achieved a reduced total number of comedones, a lower total porphyrin score, and an 18% reduction in sebum production. With this study by Kesty and colleagues the reduction in lesion count and IGA score was not as dramatic as with the present study, which indicates that the method of the current study of 5 laser treatments every two weeks delivers higher rates of reduction in lesion count.

In the present study, the median percent reduction in IGA score was 66.67% at both 6 weeks (after 3 treatments) and 90 days (after 5 treatments) and the median percent reduction in lesion count was 83.72% at 6 weeks and 86.67% at 90 days. The differences from the results of Kesty and colleagues may be attributed to different treatment methods used, both in number of treatments and interval between treatments. The present study used 5 treatments at bi-weekly intervals, versus 3 treatments at bi-weekly intervals followed by a fourth treatment after a 4-week pause in Kesty and colleagues. Another difference was the expression of Kesty and colleagues' IGA and lesion count results as mean values rather than median values. The 5 biweekly treatment protocol was proven to be optimal to maximize the acne clearance effectiveness and long-term results.

When used to treat acne, the 650-microsecond 1064-nm laser energy is clinically proven to reduce sebum output,[7] thus reducing a key component of the pathogenesis of acne. One hypothesis is that this laser's effect of coagulating small capillaries in the skin tissue[8] may be a contributing factor to the reduction of output of sebaceous glands. Regardless of the exact mechanism of action, suppressing sebum output without actually destroying sebaceous glands can be advantageous since sebum production is critical for maintaining skin homeostasis, lubrication, and physiological defense against environmental and infectious insults.[9,10]

Isotretinoin is a common systemic therapy for active acne, and the question often arises regarding whether laser therapy can be performed on a patient who is being treated with this medication. In a study by Gold and colleagues,[11] 46 patients (aged 18 to 30 years, skin types I to III) with moderate to severe acne received a combination therapy of systemic isotretinoin at a low dosage (0.2-0.3 mg/kg/day) and 12 facial laser treatments at 2-week intervals with the 650-microsecond laser at 21 J/cm2. All patients completed the study. IGA reduction was 72.2% and Dermatology Life Quality Index reduction was 72.3%. Inflammatory elements resolved without scarring and without adverse effects.

Traditional 1064-nm lasers often use pulse durations of 5 to 30 milliseconds, which are well in excess of the thermal relaxation time (TRT) of skin tissue, which is approximately 0.8 milliseconds. With these ultra-long pulse durations, the skin must be cooled continuously during treatment with gels, sprays and/or contact cooling plates. Additionally, in spite of the cooling, treatment with these traditional lasers can still be very painful. This new 1064-nm laser technology with a 650-microsecond pulse duration treats the skin beneath its TRT, negating the need for numbing and skin cooling and enabling uniquely gentle, sanitary and effective laser treatment experiences for patients of color.[12] In addition to the skin type versatility of this laser it has also shown to be safe and efficacious for other indications such as permanent hair reduction, hyperpigmentation, melasma and onychomycosis.[5,13,14-17]

Limitations of the study include the relatively short 90-days posttreatment follow-up time and the absence of a control group.

CONCLUSION

The 650-microsecond, pulsed 1064-nm Nd:YAG laser has been shown to improve mild to severe acne vulgaris with high subject satisfaction and without adverse effects.

DISCLOSURES

Dr Saedi is a consultant for Aerolase. Dr Griffin and Sara Kelly have no conflicts of interest to disclose.

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doi:10.36849/JDD.8159

November 2024 965 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Attitudes on, Practices, and Recommendations for Visible Light Protection Amongst Dermatology Practitioners

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ABSTRACT

Background: Iron oxides, antioxidants, and pigmentary titanium dioxide are sunscreen additive ingredients that enhance visible light protection, reduce associated hyperpigmentation, and protect against certain photosensitive dermatoses There are currently no standardized recommendations for visible light protection with these additive ingredients, leading to varied clinical recommendations.
Objectives: This study aimed to evaluate dermatology practitioners' counseling practices for visible light protection.
Methods: An electronic survey was distributed to dermatology practitioners. Survey responses were compiled for analysis, and statistical significance was calculated using a standard 95% confidence interval.
Results: 91.68% of 974 respondents actively counsel patients about visible light protection, primarily emphasizing its role in exacerbating pigmentation in patients with melanin-rich skin (70.92%). Of these, 10.34% recommended sunscreens with visible light protective additive ingredients specifically for patients with melanin-rich skin, and 48.89% recommended them for managing melasma or post-inflammatory hyperpigmentation. Iron oxide additive ingredients were most frequently recommended (90.92%), followed by antioxidants (69.08%) and pigmentary TiO2, (58.85%). 8.32% of respondents reported not counseling patients about visible light protection, with major reasons encompassing the lack of standardized guidelines (50.62%), challenges in recommending suitably tinted sunscreens (27.16%), limited availability of sunscreen options (23.46%), and insufficient supportive data (18.52%).
Conclusion: There is a need for increased education and awareness regarding visible light protection strategies and the identification of patients who may benefit the most from a targeted photoprotective strategy. Establishing standardized guidelines and broadening the availability of sunscreen options conferring visible light protection may help address these gaps.

J Drugs Dermatol. 2024;23(11):965-971. doi:10.36849/JDD.8159

INTRODUCTION

Exposure to solar radiation (SR) is associated with a range of adverse effects on the skin, including photocarcinogenesis, sunburn, photoaging, and pigmentation. While the primary focus of SR-induced pathologies has historically centered on the consequences of ultraviolet (UV) radiation, humans are exposed to visible light (VL, 400-700 nm), 12 to 14 orders of magnitude greater than UV.[1]

Wavelengths within the VL spectrum penetrate the full thickness of the epidermis and dermis, extending into the subcutaneous adipose layer;[2] whereas UVA penetration does not extend beyond the dermis, and UVB only penetrates the epidermis.[3] In addition to exposure from SR, VL is transmitted from flash lamps, computers, televisions, and cell phones.[2] Given its pervasive presence and profound penetrative properties, the impact of VL on the skin cannot be disregarded.

Over the past decade, a growing body of literature has strengthened our understanding of the harmful effects of VL on the skin. VL exposure is associated with erythema, post-inflammatory hyperpigmentation (PIH), melasma, and exacerbation of photodermatoses. VL has been shown to induce immediate erythema in skin phototype (SPT) I to III and immediate and prolonged erythema in SPT IV to VI.[2] Exposure to VL triggers inflammation and stimulates melanocytes through the generation of reactive oxygen species (ROS), exacerbating hyperpigmentation. In SPT IV to VI, VL has been shown to induce more severe and prolonged pigmentation as compared with UVA1-induced pigmentation,[4] underscoring its role in pigmentary disorders in individuals with melanin-rich (MR) skin. VL also plays a role in exacerbating solar urticaria, chronic actinic dermatitis, polymorphous light eruption, and cutaneous porphyrias.[2]

Accordingly, the importance of sunscreen with VL protection is gaining recognition, especially in the prevention and treatment of pigmentary disorders in individuals with MR skin, who constitute nearly 40% of the United States (U.S.) population.[5] Recent studies have demonstrated that additive sunscreen ingredients, including iron oxides, antioxidants, and

pigmentary titanium dioxide (TiO2) enhance VL protection and improve outcomes in patients with hyperpigmentation.[2,6-11] Iron oxides and pigmentary TiO2 scatter and reflect VL photons, imparting VL photoprotection. Antioxidants, including vitamin E (atocopherol), vitamin C, licochalcone A, and diethylhexyl syringylidene malonatecombate, combat oxidative stress mediated by UV and VL.[2]

In the US, the sunscreen active ingredients approved by the Food and Drug Administration (FDA) largely protect against UVA and UVB, offering no protection from VL. Guidelines for clinicians outline recommendations for UV protection; however, there are currently no standardized guidelines for VL protection, leading to varied clinical recommendations, if any at all. Whether sunscreens containing VL-protective compounds are routinely recommended to patients in practice remains unknown. This study aims to better understand how dermatologists are currently advising patients regarding VL protection, understand where gaps in counseling may exist, and make recommendations to improve protection against VL.

MATERIALS AND METHODS

A 15-question, Institutional Review Board (IRB)-approved (No. NCR235167) survey was created using SurveyMonkey, a third-party cloud-based survey tool. The survey was electronically distributed to dermatology practitioners registered to the Orlando Dermatology Aesthetic and Clinical Conference (ODAC) e-mail list, and responses were collected anonymously. The ODAC listserv encompasses a heterogeneous population of dermatology practitioners from a variety of demographic backgrounds, subspecialties, and practice settings and locations, exemplifying a representative study population of dermatology practitioners.

Dermatology practitioners included board-certified dermatologists (BCDs), residents, fellows, physician assistants, and nurses practicing clinical dermatology. Eligibility criteria included dermatology practitioners over the age of 18 practicing in the US. Surveys completed by dermatology practitioners practicing outside of the U.S. were excluded.

Survey questions evaluated 1) counseling practices for VL protection; 2) the circumstances under which recommendations for VL protection were made; and 3) sunscreen additive ingredient preferences. The survey included questions with multiple choice, checkbox, and free response answer choices. Survey responses were compiled for analysis, and statistical significance was calculated using a standard 95% confidence interval.

RESULTS

Demographics

There were 1,311 respondents who were examined for eligibility. 974 respondents met the eligibility criteria and were included in the study. The response rate was 20.19% (974/4823). Demographic information is summarized in Table 1.

Counseling Practices

91.68% (893/974) of respondents reported that they counsel patients about protecting their skin from VL. Those who counseled primarily discussed the role of VL in inducing more prominent and long-lasting pigmentation in patients with MR skin (70.92%, 617/870, Figure 1). Other topics discussed included the exposure to VL from light bulbs, computers, and cell phones (59.31%, 516/870), the synergistic effects of VL with UV radiation (48.39%, 421/870), and the role of VL in inducing immediate erythema in all patients (23.22%, 202/870).

Among the respondents, 8.32% (81/974) reported that they did not offer counseling to patients concerning VL protection. The primary reasons for this included the absence of standardized guidelines (50.62%), difficulties in recommending appropriately tinted sunscreens (27.16%), limited availability of VL-protective sunscreens (23.46%), insufficient data supporting the efficacy of VL protection (18.52%), and a relatively small patient population susceptible to pathologies mitigated by VL (19.75%, Figure 2).

FIGURE 1. Topics addressed when counseling about visible light protection.

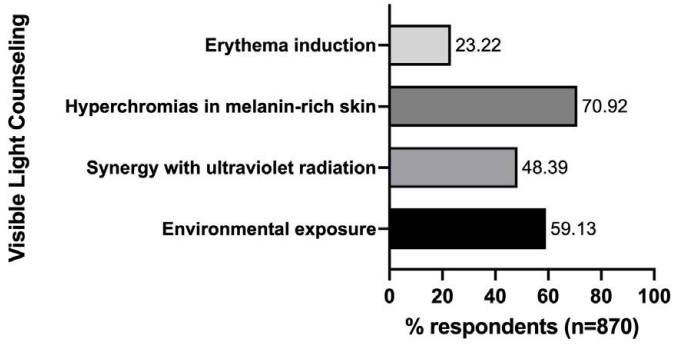


FIGURE 2. Factors influencing the decision to not counsel on visible light protection.

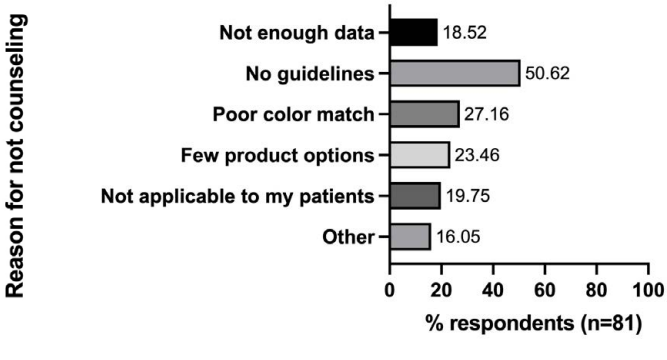
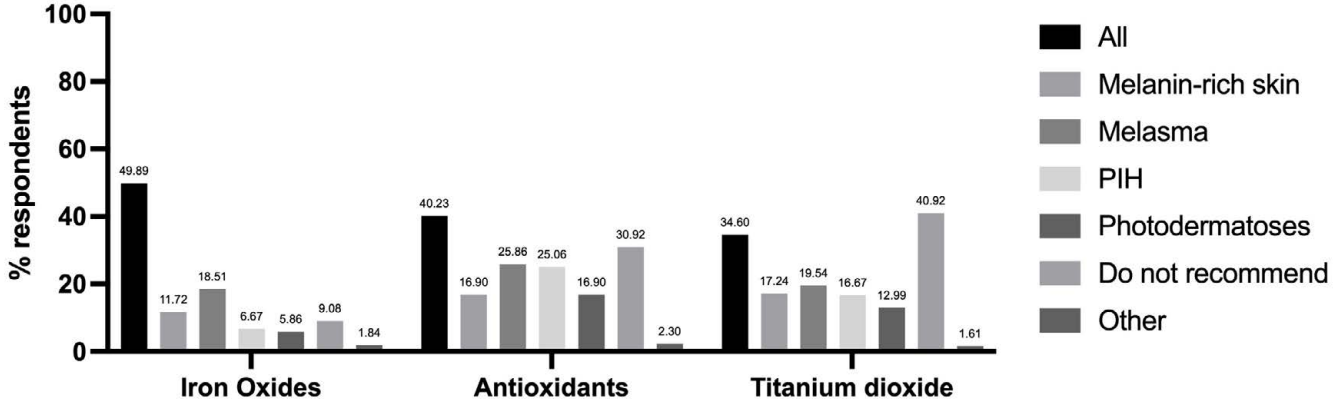


TABLE 1.

Study Respondent Self-Reported Demographic Data		
		No. (%)[a]
Gender (N=968)	Male	263 (27.17)
	Female	691 (71.49)
	Non-binary	3 (0.31)
	Prefer not to answer	10 (1.03)
Age (N=970)	25-34	511 (52.68)
	35-44	230 (23.71)
	45-54	129 (13.40)
	55-64	61 (6.29)
	65+	38 (3.92)
Race[b] (N=973)	American Indian or Alaskan Native	9 (0.92)
	Asian	224 (23.02)
	Black	51 (5.24)
	African American	33 (3.39)
	African Caribbean	9 (0.92)
	Latinx	56 (5.86)
	Middle Eastern or North African	34 (3.49)
	Native Hawaiian or other Pacific Islander	8 (0.82)
	White/Caucasian	563 (57.86)
	Prefer to self-describe	4 (0.41)
	Prefer not to answer	44 (4.52)
Level of Training (N=974)	Board certified dermatologist	312 (32.03)
	Resident	334 (34.29)
	Fellowship year	38 (3.90)
	Nurse practitioner	98 (10.06)
	Physician assistant	192 (19.71)
Practice Setting (N=974)	Academic or university	361 (37.06)
	Private solo practice	156 (16.02)
	Private group practice	315 (32.24)
	Combined academic and private practice	48 (4.93)
	Community hospital	57 (5.85)
	Military	15 (1.54)
	Other	22 (2.36)
Practice Location (N=974)	Northeast US	294 (30.18)
	Southeast US	221 (22.69)
	Midwest US	169 (17.35)
	North Central US	24 (2.46)
	South Central US	76 (7.91)
	Northwest US	66 (6.78)
	Southwest US	123 (12.63)

[a]Percentages may not sum to 100 due to rounding.
[b]Self-identified racial categories, respondents allowed to choose all that apply; 62 (N=973, 6.37%) respondents chose more than one answer.

FIGURE 3. Sunscreen additive ingredient recommendations for treatment of visible light-mediated cutaneous pathologies.



Other reasons indicated in the free response text included a lack of knowledge of VL protective strategies, limited clinic time, and the high costs associated with tinted sunscreens.

Those self-identifying as African American or Black treated a patient population consisting of over 75% of patients with MR skin more frequently than all other groups. They were also significantly more likely to counsel on VL protection than their White counterparts (P<0.05). General counseling about VL protection did not significantly vary based on the proportion of MR patients in one's practice, though practitioners treating patients comprising 25% to 50% and 50% to 75% of MR skin patients were significantly more likely to counsel on VL's role in inducing more prominent and long-lasting pigmentation than practitioners with less than 25% (P<0.05).

Respondents from the South-Central region of the US counseled about VL protection significantly more than those from the Northeast, Midwest, and Southwest regions (P<0.05); however, topics discussed during counseling did not vary significantly with location. Additionally, those between the ages of 45 and 54 counseled significantly more than those over the age of 55 (P<0.05). BCDs counseled patients about VL exposure from the environment, synergy with UV radiation, hyperpigmentation in patients with MR skin, and induction of erythema significantly more than dermatology residents (P<0.05).

Preferred Additive Ingredients

Of the surveyed respondents who counsel on VL protection, sunscreens containing iron oxide additive ingredients were most frequently recommended (90.92%, 791/870), followed by antioxidants (69.08%, 601/870) and pigmentary TiO2, (58.85%, 512/870); though the circumstances under which they were recommended differed (summarized in Figure 3). Overall, 49.88% (434/870) of respondents recommended tinted sunscreens containing an additive ingredient conferring VL protection to treat all patients, 10.34% (90/870) recommended them as a treatment specifically for MR patients, 46.89% (408/870) recommended them for patients with melasma or PIH, and 5.05% (44/870) recommended them for photodermatoses induced by VL. 9.08% (79/870) of the respondents who counsel patients on VL protection did not recommend a tinted sunscreen containing any of the surveyed additive ingredients. Free text response answers indicated that some practitioners were unaware of pigmentaryTiO2 as an additive sunscreen ingredient, and others recommended the application of antioxidants via a non-sunscreen product.

Prevention

Survey respondents most frequently recommended a sunscreen conferring VL protection to prevent melasma (84.48%) and PIH in patients with MR skin (83.45%). Sunscreen conferring VL protection was also recommended to patients for the prevention of photoaging (73.22%), photodermatoses exacerbations (58.51%), and erythema (47.59%). Additionally, some respondents indicated recommending these sunscreens to prevent skin cancer, PIH secondary to acne, and rosacea exacerbations. Recommendations to use VL-protective sunscreen to prevent certain skin conditions did not significantly vary between the proportion of patients with MR-skin treated or practice location in the US, although respondents between the ages of 25 and 34 recommended VL-protective sunscreens to prevent melasma and PIH in patients with MR skin significantly more than those aged 45 to 54 (P<0.05).

Patient Preferences

Survey respondents predominantly recommended sunscreens with VL protection to patients seeking the highest level of photoprotection (77.24%) and those aiming for improved skin tone uniformity (65.63%). Additionally, they suggested such sunscreens to patients interested in color-based coverage (48.62%), those concerned about photoaging (61.15%), and those comfortable with or indifferent to a potential white cast (28.28%).

DISCUSSION

To the best of the authors' knowledge, this is the first study to characterize the state of VL counseling and recommendations practiced by US dermatology practitioners. Emerging research continues to strengthen our understanding of the role that VL plays in dermatologic disease and conditions, so these results present a timely cross-sectional account of counseling and recommendation patterns while standardized guidelines remain absent on this topic.

The topics discussed during counseling on VL-protection as well as recommendations for VL-protective sunscreens for preventing specific skin conditions varied among respondents based on certain demographic factors. These results are likely due to several variables, including differences in education regarding the photobiology of VL, expertise in treating and managing certain VL-related skin conditions, patient population composition and concerns, and the provider's personal experience and familiarity with VL-protective sunscreens. Practitioners residing in South-Central US, the region of the US with the largest self-identified Black population,[12] provided VL counseling more frequently than practitioners in other regions. Similarly, practitioners treating a self-reported patient population with a relatively higher percentage of patients with MR skin showed trends towards providing more comprehensive VL counseling, highlighting VL's perceived and understood relevance to those with MR skin, and making more targeted recommendations to patients with MR skin, melasma, and PIH. Such practitioners also tended to make more appropriate recommendations regarding the use of iron oxides or antioxidants to said patients, and for melasma and/or PIH. Altogether, this suggests that practitioners with more experience treating patients with MR skin may be more comfortable and informed in providing comprehensive photoprotective strategies to patients most susceptible to or actively with VL-mitigated conditions.

Of notable concern is that only 10.34% of all respondents recommended sunscreens with additive ingredients, with evidence supporting VL protection specifically to patients with MR skin. Approximately half of the respondents suggested such sunscreens for the management of melasma or PIH, while most respondents recommended them more generally to all patients, highlighting a gap in the provision of tailored and targeted photoprotective strategies amongst dermatology practitioners. The apparent mismatch between the proportion of practitioners counseling on VL-induced hyperpigmentation and the proportion of practitioners making clinical treatment recommendations with sunscreens for hyperpigmentation suggests the need for increased recognition of sunscreens as an effective treatment option for hyperchromias. Guidelines regarding VL-protective sunscreens as a treatment strategy and increased education surrounding the appropriate sunscreen options may increase the degree of their implementation into photoprotective routines, particularly in patients most susceptible and affected. Additionally, data characterizing the threshold for sufficient VL protection in sunscreen products are lacking, and this likely further hinders clinical guidance. Further studies are necessary to establish efficacy criteria for the formulation of sunscreens that adequately protect against VL.

The increased counseling about VL protection observed amongst middle-aged practitioners, as opposed to their older counterparts, may be attributed to the first evidence of skin damage associated with VL being published 17 years ago;[13,14] this age cohort was possibly still in or recently graduated from medical education programs when this research was becoming integrated into their curriculum and counseling practices. Similarly, practitioners in younger age groups are benefitting from more recent knowledge regarding the role VL plays in hyperpigmentation, particularly in darker skin tones. This likely contributes to our study findings, which show that younger cohorts are more likely to recommend VL-protective sunscreens for preventing melasma and PIH in patients with MR skin. Our finding that BCDs counseled on a variety of VL-related topics more than dermatology residents is most likely explained by greater expertise and experience on the photobiology of VL and clinical relevance.

Tinted sunscreens are relatively novel products that use iron oxides (available in yellow, red, and black pigments) and pigmentary TiO2 (ie, non-nanoscaled) to provide VL protection, reducing transmission by over 90% (Table 2).[6] A variety of tints are created by combining different proportions of iron oxides and pigmentary TiO2, so these products can be formulated to blend

TABLE 2.

Additive Sunscreen Ingredients Protective Against Visible Light			
Additive Ingredient	**Compounds**	**Mechanism of Action**	**Limitations**
Iron Oxides	Black, yellow, and red Fe_2O_3	Scatter and reflect VL[c] photons	Limited shade ranges, high cost of formulated products
Antioxidants	Vitamin E, vitamin C, licochalcone A, diethylhexyl syringylidene malonate	Scavenge free radicals	Difficult to maintain stability in sunscreen formulations
Physical UVR[a] filters	Pigmentary TiO_2[b] (non-nanosized TiO_2)	Scatter and reflect VL photons	May leave white cast after application

[a]UVR, ultraviolet radiation
[b]TiO2, titanium dioxide
[c]VL, visible light

into a range of natural skin tones.[9] Tinted sunscreens reduce the appearance of cutaneous hyperchromias after 60 days of application,[15] and provide better protection against VL-induced pigmentation than non-tinted sunscreens.[16] They may be the product of choice for patients who are diagnosed with melasma as studies have found that they are superior in managing and preventing relapses of melasma compared with sunscreens with only UV-protective properties.[7,8] Herein approximately 20% of respondents recommended sunscreens containing either iron oxides or pigmentary TiO2 specifically for patients with melasma, highlighting a potential knowledge gap regarding the use of these ingredients for VL protection. Furthermore, a higher percentage of respondents did not recommend pigmentary TiO2 compared with other ingredients, which may be due to its noticeable, opaque white cast.[9] Some respondents recommended a mineral sunscreen for VL protection; however, it is important to note that only non-nanoscaled TiO2 contains particles conferring VL protection. Many mineral sunscreens are formulated with nanoscaled physical filters, and this discrepancy is also indicative of a knowledge gap regarding appropriate VL-protective additive ingredients.

Systemic and topical antioxidants neutralize ROS and other free radicals generated by VL exposure, thereby protecting against melanogenesis, inflammation, and DNA damage.[2,17] Sunscreens with added antioxidants and free radical scavengers show promise in mitigating the effects of VL + UV-A1 exposure in patients with SPT IV to VI.[18] The production of antioxidant-enriched sunscreens is a meaningful advancement of our photoprotection armamentarium as these non-tinted options may be more cosmetically suitable for a diverse array of skin tones. This in turn may increase the use of sunscreen with VL protection in those with darker skin tones who are additionally more prone to hyperchromias. Our study found that respondents were divided in their recommendation of sunscreens with added antioxidants, such that approximately 40% recommended them for all patients while approximately 30% did not specifically recommend them. It seems likely that this may be due to the variability in access and stability of sunscreen products with antioxidant additives, although more research is needed to explore these results further.

While broad-spectrum SPF 30+ sunscreen is generally recommended for all patients, individuals with MR skin are more susceptible to hyperchromias induced and exacerbated by VL. For these patients, a particular emphasis on shielding against VL using tinted sunscreens and antioxidants is an important part of a comprehensive photoprotective strategy.[19] Mounting evidence underscores the necessity for tailored sunscreen recommendations that factor in SPTs and photosensitive dermatoses, enabled by advancements in sunscreen additive ingredients and formulations.[20] The practice of personalized photoprotection aims to provide precise guidance concerning sunlight exposure and its impact on skin health, tailored to individuals across a spectrum of skin types.[19]

Limitations

Limitations of our study include possible selection bias such that dermatology practitioners who are interested in and well-practiced in counseling on VL protection were more likely to complete the survey. Additionally, we did not ask about respondents' counseling on VL protection through wearing photoprotective clothing and accessories and seeking shade; further studies should examine these recommendation patterns. Finally, although our study was completed by a large and diverse group of respondents, its cross-sectional nature limits the generalizability of our findings.

CONCLUSION

Overall, while some significant patterns were revealed in our results, the variety in recommendation practices highlights the need for uniform education and guidelines for dermatology practitioners to follow. There is a need for increased education and awareness regarding VL protection strategies and the identification of patients who may benefit the most from a tailored photoprotective strategy. Establishing standardized guidelines to provide unified recommendations and broadening the availability of sunscreens conferring VL protection can collectively address these gaps, ensuring comprehensive, consistent, and effective photoprotection.

DISCLOSURES

SAA's work is funded through independent fellowship grants from Lilly and Pfizer; CW's work is funded through an independent fellowship grant from Galderma.

Funding: This work was supported by an independent research grant from CeraVe.

Ethics Approval: The questionnaire and methodology for this study were approved by the George Washington University Committee on Human Research, Institutional Review Board (FWA00005945).

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doi:10.36849/JDD.8239

November 2024 972 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Physician Opinions on Artificial Intelligence Chatbots in Dermatology: A National Online Cross-Sectional Survey of Dermatologists

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ABSTRACT

Background: Artificial intelligence chatbots (AIC) have sharply risen in popularity. Dermatology, heavily involving visual, clinical, and pathological pattern-recognition techniques, will be impacted by AIC. Thus, this study aims to categorize the attitudes and beliefs of American dermatologists towards AIC and their potential uses, benefits, and risks.

Methods: An online cross-sectional survey was distributed to dermatologists across the United States. Questions explored opinions on AIC along with perceived benefits, risks, and important considerations for the incorporation of AIC into the practice of dermatology. Demographic data and self-reported understanding of AIC were also collected.

Results: 192 complete responses were received. 53.6% of respondents were female. 44.3% were between ages 30 to 39. 41.1% had 0 to 10 years of experience as attending physicians. 76.5% of participants believed it is somewhat or very likely that AIC will be formally incorporated into dermatology. Higher self-reported understanding of AIC was associated with an increased perceived likelihood of AIC implementation as well as decreased perceived risk associated with AIC. Notably, 86% of respondents believed AIC would impact "patient education," while concerns regarding "misinformation" and "incorrect diagnoses" were prevalent (89% and 78.5%, respectively). Participants anticipated AIC's role primarily in administrative tasks, with 75.7% citing "reduced work burden on physicians" as a potential benefit.

Conclusion: Dermatologists in the United States foresee the integration of AIC into their practice, emphasizing its potential in administrative roles. Concerns revolve around the complexity of medical understanding and effective patient communication. As AIC continues to evolve, ongoing studies are crucial to evaluate their safety and efficacy in dermatological practice.

J Drugs Dermatol. 2024;23(11):972-978. doi:10.36849/JDD.8239

INTRODUCTION

New artificial intelligence (AI) tools are being incorporated into the practice of medicine. Research has focused on AI's potential usage in disease diagnosis and patient care, treatment efficacy, and processing of large data.[1] One AI tool recently experiencing a sharp rise in use is the AI chatbot (AIC). The release of ChatGPT (Generative Pre-trained Transformer) by OpenAI in November 2022 was received with the fastest growing consumer base for an internet application, reaching 100 million users in two months.[2] Incorporating advanced language-learning technology, ChatGPT offers anyone with an internet connection the opportunity to receive a targeted response to virtually any prompt, including those related to medicine.

Dermatology, heavily involving visual, clinical, and pathological pattern-recognition techniques, will likely be impacted by AI. Currently, some AI tools have been developed to facilitate certain aspects of dermatological practice such as tracking nevus morphology and evolution, identifying concerning skin lesions, and even producing a differential diagnosis for a provided image.[3] Given the broad accessibility of AIC and their potential to process images, these tools may become highly relevant in the future of dermatology. However, with this possibility comes new concerns: how will AIC impact physicians, patients, or medical care delivery? To better understand the current role and future of AIC in dermatology, our study aimed to identify current opinions held by dermatologists. We deployed a survey designed to categorize the attitudes and beliefs of dermatologists towards AIC along with its potential uses, benefits, and risks for providers and patients.

MATERIALS AND METHODS

Study Population

This study employed an online cross-sectional survey distributed to dermatologists across the United States. Contacted groups included the Association of Professors of Dermatology, the American College of Mohs Surgery, the San Diego

Dermatological Society, the Board-Certified Dermatologists Facebook group, and individual dermatologists. An exact response rate could not be calculated due to unknown total engagement across each contacted group. Participants were asked to confirm their status as board-certified dermatologists or dermatology residents and given informed consent prior to their participation. Given the deidentified nature of responses and the low risk associated with the subject matter, this study was given exemption approval by the University of California San Diego Institutional Review Board.

Survey

An anonymous, online survey of 19 questions was created through Qualtrics to assess medical providers' opinions on AI. Demographic data collected included age, sex, degree, stage of career, United States region, practice setting, and practice type. Questions assessed participants' opinions on AIC use, accuracy, and the likelihood of AIC future incorporation into the formal practice of dermatology, which was defined to include use by physicians or patients, integration into electronic medical records or clinic workflow, healthcare management by third parties, or other potential implementations. A further subset of questions asked participants to select all potential benefits, risks, and important considerations they believed to be associated with the implementation of AIC. Self-reported understanding of AIC was also assessed on a 5-point scale with a higher score indicating higher understanding.

Statistical Analysis

Frequencies and percentages were reported for categorical variables while means and standard errors were reported for continuous variables. Analysis of variance (ANOVA) and Chi-squared analysis were performed to assess differences between groups for continuous and categorical outcomes, respectively. Linear regression was performed to assess the impact of demographic variables on perceived risk associated with AIC incorporation into dermatology. Analyses were performed using SPSS 28.0 (IBM, Chicago, IL) and all tests were two-sided with an alpha level set at 0.05.

RESULTS

Demographics

A total of 214 responses were received with 192 complete responses selected for analysis. Demographic data are outlined in Table 1. 53.6% of respondents were female. The majority of respondents were between 30 and 39 years of age (44.3%) and had between 0-10 years of experience as attending physicians (41.1%). Most practiced either in academic centers or private practice institutions (43.8% and 37.5%, respectively) and resided in the Western US (43.2%).

Opinions on AICs

An aggregate of 64% of participants reported that they understand AIC 'not well at all,' 'slightly well,' or 'moderately well.' Most participants (71.9%) reported that they never utilize AIC in their medical practice, but an aggregate of 76.5% of participants believe that it is 'very likely' or 'somewhat likely' that AIC will be incorporated into the formal clinical practice of dermatology. Most participants (84.3%) believed that 0 to 20% of their patients use AIC to answer dermatology questions and that patient AIC usage was limited to 'monthly,' 'yearly,' or 'never.' A minority of 18.6% of participants believed that the information provided by AI chatbots was 'somewhat inaccurate' or 'worse,' (Table 2).

TABLE 1.

Demographics	
Demographic	**N (%) 192 total**
Sex	
Female	103 (53.6)
Male	86 (44.8)
Prefer not to say	3 (1.6)
Age	
18-29	7 (3.6)
30-39	85 (44.3)
40-49	47 (24.5)
50-59	30 (15.6)
60-69	17 (8.9)
70-79	6 (3.1)
Degree	
MD	158 (82.3)
MD/PhD	21 (10.9)
DO	13 (6.9)
Career Stage	
Residency	22 (11.5)
Fellowship	12 (6.3)
Junior attending (0-10 years' experience)	79 (41.1)
Mid-career attending (11-20 years' experience)	44 (22.9)
Advanced-career attending (21+ years' experience)	35 (18.2)
US Region	
West	83 (43.2)
Midwest	29 (15.1)
South	47 (24.5)
Northeast	33 (17.2)
Practice Setting	
Urban	188 (97.9)
Rural	4 (2.1)
Practice Type	
Academic center	84 (43.8)
Multispecialty medical groups	14 (7.3)
Private equity	21 (10.9)
Private practice	72 (37.5)
Retired	1 (0.5)

TABLE 2.

Opinions on AI Chatbots	
Question	**Percent Response**
How well do you understand AI chatbots?	
Not well at all	28.1%
Slightly well	35.9%
Moderately well	25%
Very well	6.3%
Extremely well	4.7%
How often do you utilize AI chatbots in your medical practice?	
Daily	1.6%
Weekly	9.9%
Monthly	13.0%
Yearly	3.7%
Never	71.9%
What percentage of patients use AI chatbots to answer their dermatology questions?	
0-20%	84.3%
21-40%	13.6%
41-60%	1.6%
61-80%	0.5%
81-100%	0%
How often do you believe patients use AI chatbots to answer their dermatology questions?	
Daily	2.1%
Weekly	9.0%
Monthly	28.4%
Yearly	26.3%
Never	34.2%
How accurate is the information provided by AI chatbots?	
Completely inaccurate	0.5%
Mostly inaccurate	3.2%
Somewhat inaccurate	14.9%
Neutral	35.1%
Somewhat accurate	34.0%
Mostly accurate	12.2%
Completely accurate	0%
What is the likelihood that AI chatbots will be incorporated into the formal clinical practice of dermatology?	
Very unlikely	4.2%
Somewhat unlikely	7.8%
Neutral	11.5%
Somewhat likely	38.0%
Very likely	38.5%

ANOVA comparing groups within demographic categories discovered that higher self-reported understanding of AIC was significantly associated with an increased perceived likelihood of AIC implementation on a 5-point scale ($P<0.001$, Table 3a). Career stage, sex, and age were not associated with increased perceived likelihood of AIC implementation.

Risks, Benefits, and Important Considerations for AIC

Figure 1 summarizes participant opinions on which elements of dermatological practice would be impacted by the implementation of AIC. "Patient education" was the most selected at 86% while "administrative work," and "prior authorizations" were close behind (76.8% and 75.8% respectively). 54.7% of respondents believed "billing" would be impacted while only 36.8% believed "clinical decision-making" would be impacted. Through free text response, 3 responses identified "appointment triage" as an additional important factor.

When asked to select which factors should be considered for the future implementation of AIC in dermatology, 86.4% of respondents identified the "complexity of medicine", 83.2% identified the "availability of high-quality answers," and 80.1% identified "data privacy" as important elements (Figure 2). 69.1% of respondents thought the "level of autonomy for AIC" was also important while only 47.1% thought the "costs associated with AIC" should be considered. Four additional free-text responses identified "bias" as an important consideration and two additional responses highlighted the importance of the availability of "non-English responses."

Regarding potential pitfalls of AIC, most respondents selected "misinformation" or "incorrect diagnoses" (89% and 78.5%, respectively, Figure 3). 56.5% identified "dehumanization of healthcare" as a potential issue. Less than half of participants believed AIC would lead to "increased harm to patients" (40.3%), "reduction in physician's compensation" or "reduction in physician's skills" (34.6% and 28.3%, respectively), or "obsoletion of the role of healthcare providers in the workforce" (26.7%).

When asked about the potential benefits of AIC, 75.7% of respondents identified "reduced work burden on physicians" (Figure 4). 50.8% believed AIC would lead to "improved patient literacy" and "improved access to healthcare." Few respondents believed AIC would lead to "improved patient outcomes" or "improved physician-patient relationships" (23.8% and 11%, respectively). Six free text responses stated that no benefit would come from AIC use in dermatology.

Perceived risk associated with AIC implementation into dermatology was assessed on a 5-point scale with '5' indicating the highest risk. Participants on average believed AIC implementation would be associated with intermediate risk (3.32).

FIGURE 1. Which of the following elements of dermatologic practice will be impacted by AI chatbots?

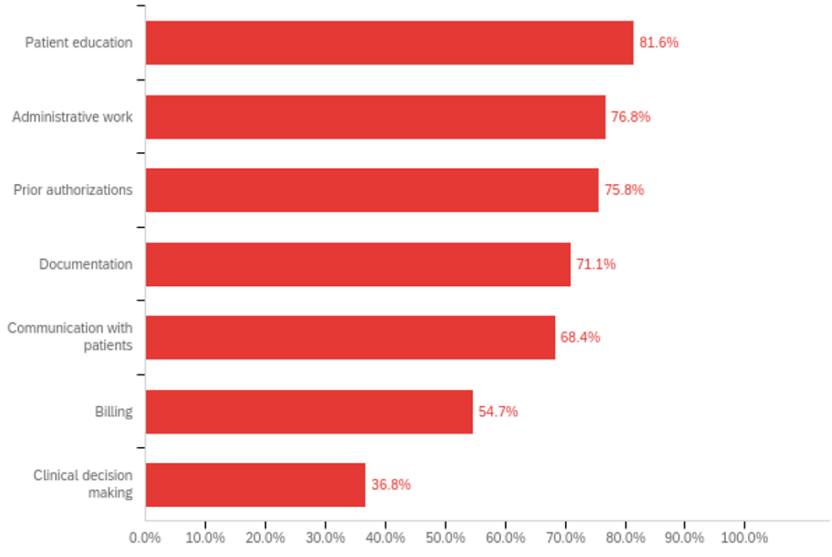


FIGURE 2. Which of the following should be considered while implementing AI chatbots into dermatologic practice?

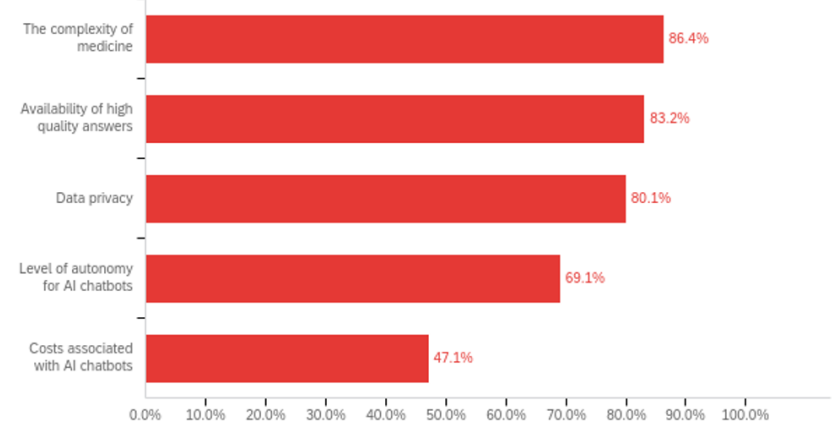


FIGURE 3. Which of the following issues will arise with the implementation of AI chatbots into dermatologic practice?

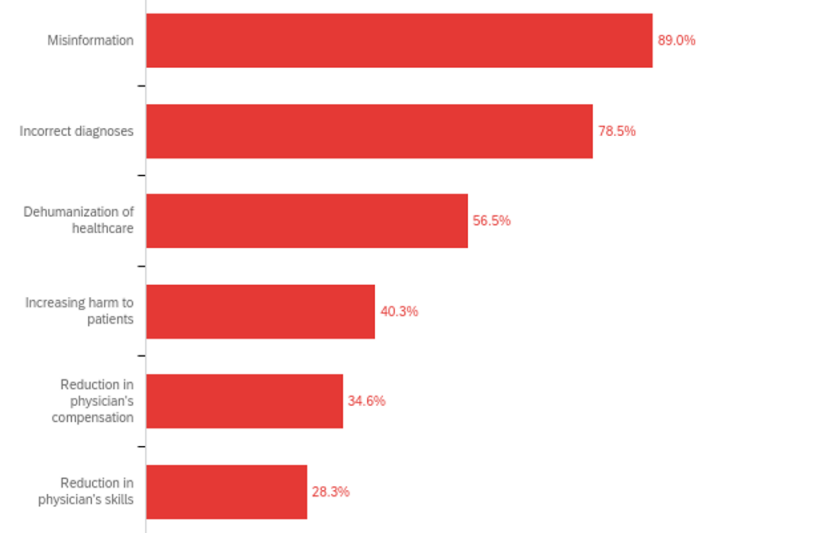
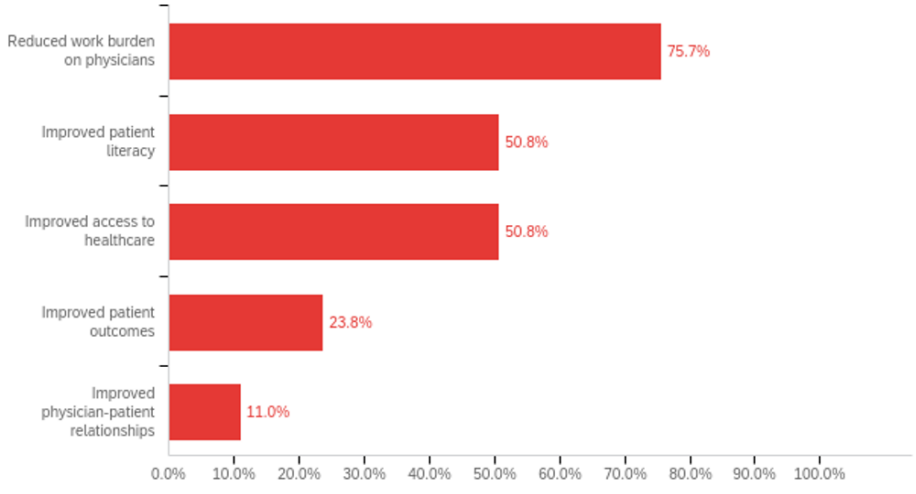


FIGURE 4. Which of the following benefits will arise with the implementation of AI chatbots into dermatologic practice?



ANOVA comparing groups within demographic categories discovered that older age, later career stage, and lower self-reported understanding of AIC were significantly associated with increased perceived risk (*P*=0.01, *P*=0.05, and *P*=0.05, respectively, Table 3b). Linear regression analysis using the same demographic variables found that older age (*P*=0.04) and lower self-reported understanding of AIC (*P*=0.05) remained significant predictors of increased perceived risk., while career stage was no longer statistically significant (*P*=0.95, Table 3c). Female sex was also significantly associated with higher perceived risk after linear regression analysis (*P*=0.03).

TABLE 3A.

ANOVA Comparing Belief in Future AI Chatbot Incorporation

Variable	AI likelihood, mean (SE)	*P*-value
Age		
18-39	3.88 (0.13)	0.19
40-79	4.09 (0.10)	
Sex		
Female	3.93 (0.11)	0.78
Male	4.05 (0.12)	
Career stage		
Residency to junior attending	3.93 (0.11)	0.40
Mid-career to advanced-career attending	4.06 (0.11)	
Understanding of AI chatbots		
Not well to slightly well	3.78 (0.10)	<0.001***
Moderately to extremely well	4.35 (0.10)	

TABLE 3B.

Belief of Risk Associated with AI Chatbot Incorporation for Age, Sex, Career Stage, and Self-Reported AI Chatbot Understanding

Variable	Risk, mean (SE)	*P*-value
Age		
18-39	3.14 (0.08)	0.01**
40-79	3.49 (0.09)	
Sex		
Female	3.45 (0.09)	0.08
Male	3.16 (0.09)	
Career stage		
Residency to junior attending	3.22 (0.07)	0.05*
Mid-career to advanced-career attending	3.47 (0.11)	
Understanding of AI chatbots		
Not well to slightly well	3.42 (0.07)	0.05*
Moderately to extremely well	3.16 (0.11)	

TABLE 3C.

Linear Regression Predicting Belief of Risk Associated with AI Chatbot Incorporation for Age, Sex, Career Stage, and Self-Reported AI Chatbot Understanding

Variable	β	*P*-value
Age	0.24	0.04*
Sex	-0.16	0.03*
Career stage	-0.01	0.95
Understanding of AI chatbots	-0.14	0.05*

DISCUSSION

To the best of our knowledge, this is the first study categorizing dermatologists' attitudes towards the use of AIC in dermatology and offers key insight into what dermatologists believe is important and concerning. Opinions will change over time as exposure to AIC increases, but understanding contemporary attitudes provides insight into the future role and implementation of AIC. Furthermore, current opinions highlight the value of continued education and research into this rapidly evolving field.

Most participants affirmed to not understand AIC well or use them at all in their practice, a result consistent with previous surveys assessing physician familiarity with AI.[4-8] Despite this, most participants believed that AIC would be integrated into the future practice of dermatology. This belief was shared by participants who had a higher self-reported understanding of AIC. Similarly, perceived risk associated with AIC was positively associated with older age and lower self-reported understanding of AIC, even after controlling for other demographic variables. A study by Polsie et al surveying 1271 dermatologists internationally revealed that physicians who had a strong familiarity with AI were more likely to express a positive attitude toward its use.[8] Although our study surveyed a smaller portion of physicians, our results indicate that there is a similar association between knowledge and approval of AIC for American dermatologists. As AIC continues to be developed, these results suggest that appropriate training in AIC and its use in the field will be critical for both current and future dermatologists to ensure their successful implementation and emphasize the appropriate risks and benefits that may be associated with their use.

In evaluating the potential downsides associated with AIC implementation, participants were most concerned about the ability of AIC to accurately process complex medical information and respond with relevant and vetted medical advice, especially if acting as an autonomous provider. AlZaabi et al found in a survey of 293 physicians and medical students in Gulf Cooperation Council countries that participants shared similar concerns about AI's ability to handle the complexity of medicine.[4] Nevertheless, most participants in our study were not concerned that AIC would cause increased harm to patients or a reduction in physician compensation and skills. Only a quarter of respondents believed AIC may lead to the obsoletion of healthcare providers. These results concur with previous studies finding that few physicians believe AI may one day replace them. Although AI and AIC may serve as useful tools within medicine, many physicians believe their capabilities will fall short of the proficiency of human physicians.[5,7-9] Indeed, the reliability of AIC acting in a physician-like capacity is unclear. One study by Lewandowski et al found that ChatGPT exceeded the 60% pass rate of 3 dermatology specialty certificate multiple-choice tests with a minimum of 80% correct.[10] However, another study by Stoneham et al found that ChatGPT was only able to offer a correct diagnosis on 56% of assessed questions, and only when given relevant clinical information by a dermatologist.[11] Future studies should aim to further assess the diagnostic capacity of AIC and its potential utilization by dermatologists. Finally, the most important consideration of AIC use in dermatology is safety when used in patient care. Although our survey addresses some concerns physicians may have with AIC, it does not provide direct data regarding safety. Thus, clinical studies that evaluate the effects of AIC on patient safety outcomes are required to ensure appropriate applications of AIC in patient care.

A limited number of dermatologists identified potential benefits with AIC implementation. The most identified benefit was a reduction in physician work burden. However, only half of respondents believed that AIC would improve patient literacy or access to healthcare. Even fewer believed AIC would lead to improved patient outcomes or physician-patient relationships despite 86% identifying "patient education" as an element of medicine likely to be impacted by AIC. A survey of 632 ophthalmologists, radiologists, and dermatologists in Australia and New Zealand by Scheetz et al found a similar result – physicians answered that AI will have a positive impact on workflow and professional duties but not much else.[12] Various additional perspective papers on AIC use have also identified the potential for AIC to streamline physician administrative burden.[13-15] These results may indicate that dermatologists view AIC as potentially useful administrative assistants but not as potential mediators between physicians and patients. Recent research may indicate this belief is somewhat well-founded – a study by Young et al found that various AIC produced responses lacked appropriate readability when asked questions about melanoma pathology.[16] A similar study by Mu et al produced similar results.[17] Although AIC can mediate communication between the medical community and the general population, future studies should aim to further analyze how physicians may appropriately use AIC in this capacity.

This study has limitations that should be considered when interpreting its results. Artificial intelligence is difficult to define, and it is possible that our participants had varying notions regarding the science of AI and AIC. Moreover, the utilization of an online cross-sectional survey and the potential factors influencing participants to respond may have led to selection bias in our cohort. Finally, our specific method of distribution did not allow for the calculation of an exact response rate, potentially limiting the generalizability of our findings.

CONCLUSION

This study has produced key insights into the beliefs dermatologists across the United States hold towards artificial intelligence chatbots. Most participants believed that AIC would eventually be incorporated into dermatology practice. Common

concerns were related to the ability of AIC to understand the complexity of medicine well enough to produce high-quality medical advice in addition to its ability to communicate effectively with patients. Ultimately, participants viewed the future role of AIC as administrative assistants with the potential to impact patient education and access to care. Should AIC become incorporated into dermatologic practice, the results from this study highlight the importance of adequate training to ensure an appropriate understanding of the benefits and risks associated with AIC use.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.7983

November 2024 979 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Critical Insights on Preparation of Platelet-Rich Plasma in Tubes With a Thixotropic Gel Separator

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ABSTRACT

Thixotropic gels are the preferred choice in the collection of platelet-rich plasma as an easy solution to operator variability. One often unnoticed shortcoming is the entrapment of platelets in the gel layer's uppermost surface. We provide instructions to optimize platelet yield, ie, agitation to re-suspend platelets, setting the optimal G-force and time of centrifugation, and the essential use of a horizontal swing bucket centrifuge. We conclude that this technique represents a new clinical and research direction, particularly to optimize platelet counts. We therefore encourage others to utilize this technique in future endeavors.

J Drugs Dermatol. 2024;23(11):979-985. doi:10.36849/JDD.7983

INTRODUCTION

Platelet-rich plasma (PRP) is a blood-derived product containing a higher concentration of platelets in plasma relative to whole blood, which supports its rejuvenating effects. The use of PRP from a patient's own blood (autologous) to promote tissue regeneration began in the 1980s as a technique to hasten recovery from surgery, but in the last 20 years its use has expanded into numerous applications including wound care, aesthetics, and androgenetic alopecia.[1-3] With the increased utility of platelet isolates, the quality of PRP and platelet-poor plasma (PPP) is being evaluated with more rigor as it relates to platelet concentration, growth factor release, and clinical outcome.

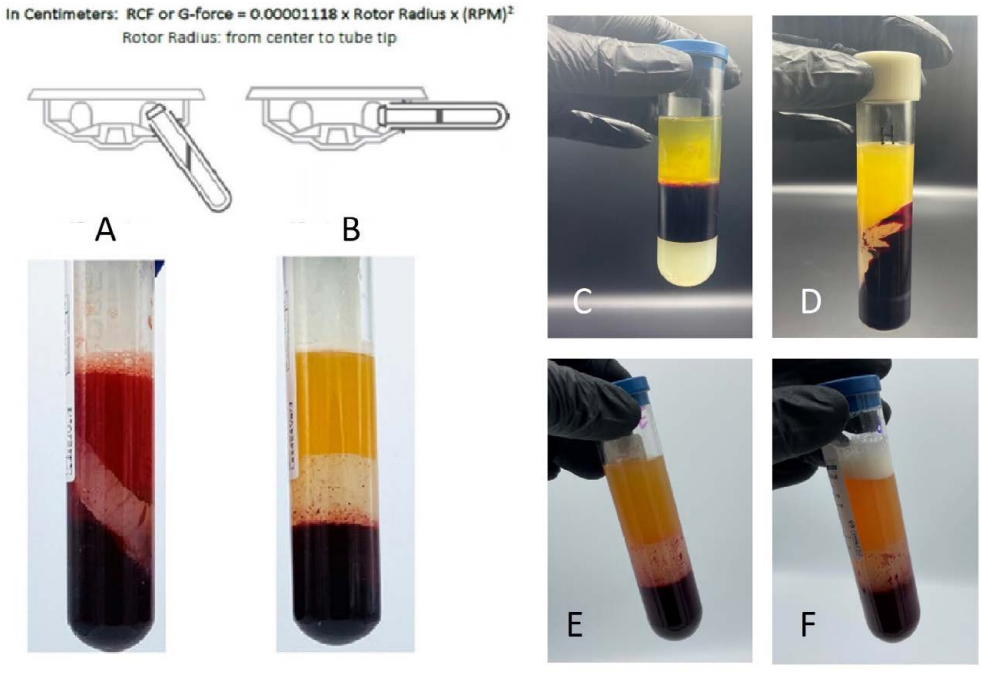
The rejuvenating effect of PRP owes to the many growth factors, hormones, nutrients, and protein stabilizers (such as albumin), that naturally elicit cellular and tissue regeneration.[4] The required concentration and relative proportion of each differs according to the intended procedure.[5] The various PRP systems currently produce biologic matrices with a range of platelet counts and differing degrees of leukocytes and erythrocytes. It is necessary to standardize preparations to ensure reproducibility and create targeted biologic matrices that are specific to the therapeutic niche.

PRP innovations have a longstanding history of continued safe use. Commercially available kits for the production of PRP are now more specific to their intended application. Thus, great caution should be taken by any PRP or PPP therapist when it comes to using tubes or devices that are not cleared by the US Food and Drug Administration (FDA) for the preparation of platelet plasma at the patient's point of care. The FDA has provided guidelines on its collection and the appropriate types of medical devices.[6]

To suit the needs of the procedure, it is important to differentiate between PRP and PPP. The technician may also include or exclude an anti-coagulant, to differentiate between platelet plasma and platelet fibrin.[7] Furthermore, calcium chloride might be added to convert fibrinogen to fibrin in a procedure known as platelet-rich fibrin or "platelet gel."[8] Considering the wide range of procedures that benefit from platelets in plasma, the production technique needs to remain versatile while maintaining high reproducibility. The precision of the technique needs to be qualified with repetitions from the same patient, because of variability of platelet count across patients, ranging from 150 k to 450 k platelets/μL.[9] When normalized for inter-patient variability, there are many methodological factors that account for a lack of precision. In this regard, steps to optimize PRP collection, to capture platelets in the final isolate, are not widely known or practiced.

For example, a recent letter to the editor in the *Journal of the American Academy of Dermatology* highlights a significant lack of consistency with various technologies for PRP production, demonstrating lower platelet counts than promised by the manufacturers, including platelet concentrations lower than whole blood in many instances.[10] Some solutions to these challenges were proposed in response,[11] to which the original

FIGURE 1. (A) and (B) Fixed angle compared to horizontal swing buckets for PRP. (A) Red cell contamination in fixed-angle centrifugation, caused by a thinner gel barrier. (B) Horizontal swing bucket centrifugation provides better separation and creates a higher vertical width of gel, creating a better barrier between PRP and erythrocytes. (C) and (D) Influence of timing and gravitational force. (C) Insufficient gravitational force to lift gel. (D) Insufficient gravitational force and/or time (partial gel reconstitution). (E) and (F) The agitation technique before and after respectively. (E) Before agitation protocol (fewer platelets, lighter color, no foam). (F) After agitation protocol (higher platelet count, darker color, and foam).



authors were able to address, and it was reiterated that devices cleared by the FDA were allegedly insufficient.[12] However, the current viewpoint explains how FDA-approved devices are sufficient, provided that the guidelines presented herein are incorporated into standard practice.

Having directly tested most thixotropic gel separator tubes in our laboratory, and following numerous iterations developed through troubleshooting over the last 6 years, we have the following critical insights as they relate to optimizing platelet yield in any PRP system that uses a thixotropic gel separator. In the current viewpoint, tips for the preparation of standardized quality plasma are provided in the context of optimal G-force and time, the agitation technique is explained step by step, and the rationale for a horizontal swing bucket is provided.

From the current viewpoint, the intersection of G-force and time is emphasized. The product of gravitational force and time is not commonly considered in standard laboratories. Nevertheless, the objective is to spin the tube with sufficient gravitational force and time to allow the gel to move from the bottom of the tube and reset at the appropriate level based on density, thus isolating platelets and plasma from red blood cells (RBCs) and possibly white blood cells (WBCs) (Figure 1).

The Importance of Quality PRP

In trials and the published literature, the focus has traditionally been on maximal platelet concentration over baseline,[13] and while important, it is becoming apparent that the ideal PRP for dermatologic application is context specific, wherein some applications require platelet concentrations in the supraphysiologic range, ie, 1.5 to 3 times baseline.[5,14] Further, previous studies that determined optimal platelet concentrations need to be revisited with consideration to other parameters not explored in those studies (ie, leukocytes, erythrocytes, plasma proteins, prostaglandins). Higher platelet concentration is generally of benefit in other applications (eg, orthopedics). Still, these systems typically produce a biologic matrix with RBCs and WBCs,[5] differentiating them from product used in dermatological applications.

In dermatologic procedures, PRP and PRP-related products should be without contaminating RBCs to the greatest extent possible. This is very important because when RBCs are lysed, hemoglobin becomes oxidized and may lead to a permanent bruise known as a hemosiderin stain. In addition, while circulating WBCs play a role in initiating the early phases of wound repair, there is some debate as to their role in a final PRP product. WBCs may inhibit healing in certain situations and

induce more local pain than with pure PRP alone.[14] For instance, it is known that granulocytes are inflammatory and may result in the opposite effect than is desired, particularly in the field of aesthetic medicine. In this regard, lymphocytes and monocytes may be thought to be good, but not granulocytes.

Lastly, case studies are starting to demonstrate that variability across blood proteins in individuals may add inconsistencies to the separation of plasma using thixotropic gels. One case study saw a correlation between monoclonal gammopathy and improper serum separation,[15] and two other studies observed the gel above the plasma in association with hyperproteinemia,[16,17] rather than between plasma and the layer with RBCs. If improper serum separation is observed or incorrect positioning of the gel occurs, the patient should be advised to consult with their general practitioner about a possible protein abnormality.

Thixotropic Separators in Blood and PRP Collection

The preferred technique to produce platelet plasma utilizes a thixotropic gel that becomes a barrier between RBCs and plasma-containing platelets. For this reason, it is sometimes also called a cell selector gel. The gel is less dense (lower specific gravity) than RBCs and WBCs, but denser than the platelets and plasma. When it arrives from the manufacturer, the gel is at the bottom of the tube, phase separated from the anticoagulant mixture.

The thixotropic gel is a hydrophobic gel with high viscosity in the absence of gravitational force. It becomes less viscous with agitation, centrifugation, or while under pressure.[7] To achieve proper separation of PRP and other blood components (and thixotropic gel separation), the intercept of gravitational force vs time must be elucidated and optimized (Figure 1). Thereafter, when the gel becomes less viscous with centrifugal force it is displaced in the direction against the gravitational pull, as RBCs migrate to the bottom of the tube through the gel in aggregates ranging in size from micelles to larger clumps.[18] The thixotropic gel settles between the two phases (RBCs and plasma) and reversibly stiffens when the centrifugal force is reduced.

The earlier versions of thixotropic gels were constructed of polybutadiene units,[19,20] but to improve clinical safety for use in pharmaceutical applications, the non-toxic polyester gels were developed. These safer thixotropic gels were defined by Kessler.[21] Kessler developed several types of polyester gels via condensation (esterification) of polycarboxylic acids with polyhydric alcohols, creating products that are inert in blood and blood components. Examples of carboxylic acids are succinic, adipic, or azelaic acid, just to name a few, and polyhydric alcohols can include polyethylene glycol, ethylene glycol, or butanediol, among others.

Although the thixotropic gel is not mixed with the plasma prior to clinical use, the risk of contamination is real in patients with hyperproteinemia, due to improper positioning of the gel in blood plasma.[16,17] The use of polyesters is an assurance of safety because they are easily degraded in human plasma by cleavage of the ester linkage.[22] Degradation products are dependent upon the chemical composition of the polymer. Modern polyesters are designed to release benign degradation products.

Thus, in the production of platelet plasma, a polyester gel with thixotropic properties is chosen. It is usually combined with the anti-coagulants, sodium citrate and/or acid-citrate dextrose, which mix with whole blood during agitation.

Centrifugation Parameters

Horizontal Swing Bucket vs Fixed Angle Rotor

The quality of platelet plasma is dependent upon the parameters used in the centrifugation step. For gel separator techniques (thixotropic gels) it is recommended that a horizontal "swing bucket" rotor centrifuge is chosen over a "fixed angle" design (Figure 1A and B). All the major manufacturers of thixotropic gel tubes recommend the use of a horizontal swing bucket, such as Becton, Dickinson, and Company (BD), Greiner Bio-One, and others. However, it is surprising how little this recommendation is put into practice. Numerous manufacturers of PRP kits sell centrifuges with a fixed-angle rotor, and the lower cost seems to be the primary motivation.

The horizontal swing bucket substantially reduces the risk of contamination of plasma with sub-cellular components, importantly hemoglobin. This is because fixed-angle designs tend to lead to RBC contamination or hemolysis (Figure 1A) more often than in horizontal swing bucket designs.

Miron et al[23] explain that by using fixed-angle centrifuges, the denser cells travel in a direction that causes them to meet the vertical wall of the tube, rather than the tube's bottom or to the surface of the RBC layer that is forming. Compaction of RBCs against the vertical wall of the tube causes entrapment of less dense blood components, importantly the platelets. In ideal circumstances the RBCs displace the less dense components, causing platelets to move up as RBCs move down. However, with prematurely compacted RBCs, the entrapped platelets also move downward, which reduces the efficiency of separation.

Miron et al[23] explain further that the movement of moderately compacted RBCs along the tube's vertical wall on passage to the tube's bottom creates a shear stress that can cause rupturing (hemolysis), or interference with the displacement of cells in the direction of gravitational pull. The resultant plasma will acquire a reddish tinge, which indicates that hemoglobin is contaminating the plasma, which is considered not ideal.

Aside from the quality of the product, fixed-angle centrifuges add a logistical disadvantage to the processing of samples in a

high-demand laboratory. Fixed-angle centrifuges require longer spin times at the same RPM. This is due to a smaller spin radius, causing a lower gravitational force (Figure 1).

Other advantages of using horizontal swing buckets include the greater final thickness of the gel layer allowing for better and more stable separation. To the former point, fixed-angle spinning produces layers that have a greater 2-dimensional surface area. This reduces the volume of gel available for depth. In a horizontal swing bucket, the thicker layer of gel serves as a better plug against the RBC layer (Figure 1A and B). To the latter, the technician prefers aspirating against a horizontal gel barrier to reduce the chances of drawing gel material into the syringe during clinical procedures. This point is a worthy point to consider in laboratories where long hours of repetitious activities increase the chances of error.

Timing and Gravitational Force to Move Gel and Create Barrier
The relative centrifugal force, or gravitational force, determines the acute viscosity of the thixotropic gel layer. The two have an inverse relationship, ie, as gravitational force increases, the viscosity of the thixotropic gel decreases. It is, therefore, significant to achieve a suitable gravitational force and centrifugation time of spinning, to maximize the separation of blood layers without causing hemolysis or contamination of the platelet plasma layer with RBCs.

Furthermore, the necessary gravitational force and time of spinning will differ according to the volume of blood that is spun, as the gel and blood volume are different. Several trials have been conducted in the laboratory at VIAS Partners by following a patent-pending agitation technique,[24] and it was determined that slight differences in operation parameters were necessary to optimize platelet recovery and purity. More significant differences were evident in the time of spinning, with longer times necessary for greater blood volumes, ie, 6 minutes for lower volumes vs 10 minutes for high volumes.

It was also realized that there are differences in the quality of thixotropic gel between manufacturers. While it is common for platelets to be embedded in the gel, some gels embed more than others. Some PRP separators on the market produce platelet counts lower than baseline levels, a consequence of the entrapment of platelets across the entire width of the thixotropic gel. For this reason, it is necessary to vet manufacturers before committing to bulk purchases.

Re-Suspending Platelets: The Agitation Method
When using a thixotropic gel to produce platelet plasma, it is normal for platelets to adhere to the upper surface of the gel barrier during the centrifugation step, independent of the quality of the gel media. This is an outcome of the higher density of platelets compared to plasma. Platelets pool in the lower layers of the plasma. During centrifugation, the thixotropic layer is less viscous, which causes some of the platelets to be partially submerged into the barrier. This underscores the importance of gravitational force, as higher gravitational forces will make the gel too soft and will trap more platelets in the upper surface, but lower gravitational force will not create adequate phase separation of components.

To remove the platelets that are embedded in the upper layer of gel, the manufacturer's instructions for use (IFU) prescribes gentle inversion. However, in our laboratory, we have empirically determined that agitation rather than inversion is necessary. We conducted a small trial in our laboratory to demonstrate the difference that the agitation technique can make in platelet collection (Table 1). A standard gravitational force (1,100) and time (10 minutes) were developed empirically and used to generate the data in Table 1. A fixed-angle centrifuge was compared to a horizontal swing bucket design, while testing different agitation angles and times to define optimal parameters for PRP enrichment.

It is evident from the data in Table 1 that the inversion technique prescribed by the manufacturer (IFU platelet count) derives a lower platelet count compared to any of the agitation parameters used. Adhered platelets are not adequately removed by mere inversion, as it only redistributes the platelets that are already in suspension so that they are uniformly concentrated along the vertical axis of plasma in the tube.

The comparison in Table 1 can be made using averages. The average IFU platelet count was 128.6% against the baseline for the fixed-angle centrifuge, and 158.0% for the horizontal swing bucket design. The contrasting results from agitation are as follows: If the optimal parameters for the fixed-angle design were a 0- to 15-degree angle and 15 to 30 seconds of agitation, then the platelet count was 224.0% against baseline. For a horizontal swing bucket design, if the optimal parameters were a 0- to 45-degree angle and 15 to 30 seconds of agitation, the average platelet count was 337.0% against baseline. Thus, by focusing on the swing bucket design centrifuge, the agitation technique is approximately 2.1-fold more efficient at generating PRP by comparison with the IFU.

When using the agitation technique, the agitation angle will determine the momentum of plasma cascading against the gel's upper surface. As evident in Table 1, the wrong choice of angle and time of agitation could breach the gel barrier. This was more common in samples spun in fixed-angle centrifuges, due to the outcome of a thinner gel barrier. It was also more common at angles of 90 degrees (tube upright) due to the greater inertial force of the plasma as it moved downwards in the direction of gravity. In contrast, angles of -15 degrees (tube slanting downward) tend to breach the gel barrier, likely

TABLE 1.

Brief Trial to Demonstrate Optimal Use of the Agitation Technique, the Type of Centrifuge, and Outcome.

Donor 1: PPP removed.[1] Whole blood platelet count = 202, IFU[2] platelet count = 241										
			Agitation Time (Sec)							
Centrifuge	Setting (G-force & Mins)	Angle (Degrees)[3]	5	10	15	20	30	40	50	60
Fixed	1100 x 10	-15	270	391	432	**478**	469	breach	--	--
Fixed	1100 x 10	0	281	402	460	**572**	564	596	577	--
Fixed	1100 x 10	15	300	376	442	520	563	**626**	607	--
Fixed	1100 x 10	45	266	**358**	302	371	breach	--	--	--
Fixed	1100 x 10	90	305	**398**	breach	--	--	--	--	--
Donor 2: PPP removed.[1] Whole blood platelet count = 335, IFU[2] platelet count = 437										
			Agitation Time (Sec)							
Centrifuge	Setting (G-force & Mins)	Angle (Degrees)[3]	5	10	15	20	30	40	50	60
Fixed	1100 x 10	-15	442	**461**	438	425	breach	--	--	--
Fixed	1100 x 10	0	498	529	571	602	**639**	breach	--	--
Fixed	1100 x 10	15	501	535	581	**672**	602	628	638	649
Fixed	1100 x 10	45	471	495	**502**	462	breach	--	--	--
Fixed	1100 x 10	90	521	breach	--	--	--	--	--	--
Donor 3: PPP removed.[1] Whole blood platelet count = 263, IFU [2] platelet count = 358										
			Agitation Time (Sec)							
Centrifuge	Setting (G-force & Mins)	Angle (Degrees)[3]	5	10	15	20	30	40	50	60
Fixed	1100 x 10	-15	379	**401**	breach	--	--	--	--	--
Fixed	1100 x 10	0	421	482	508	**637**	605	breach	--	--
Fixed	1100 x 10	15	439	521	595	639	**678**	654	638	--
Fixed	1100 x 10	45	444	507	**582**	604	breach	--	--	--
Fixed	1100 x 10	90	**402**	breach	--	--	--	--	--	--
Donor 4: PPP removed.[1] Whole blood platelet count = 321, IFU[2] platelet count = 447										
			Agitation Time (Sec)							
Centrifuge	Setting (G-force & Mins)	Angle (Degrees)[3]	5	10	15	20	30	40	50	60
Swing	1100 x 10	-15	487	521	591	**667**	582	--	--	--
Swing	1100 x 10	0	598	671	778	**864**	701	728	--	--
Swing	1100 x 10	15	608	788	**901**	853	846	--	--	--
Swing	1100 x 10	45	570	605	**739**	704	698	--	--	--
Swing	1100 x 10	90	683	**721**	629	--	--	--	--	--
Donor 5: PPP removed.[1] Whole blood platelet count = 172, IFU[2] platelet count = 304										
			Agitation Time (Sec)							
Centrifuge	Setting (G-force & Mins)	Angle (Degrees)[3]	5	10	15	20	30	40	50	60
Swing	1100 x 10	-15	387	419	601	**662**	583	539	--	--
Swing	1100 x 10	0	408	488	573	701	**745**	705	728	--
Swing	1100 x 10	15	584	707	**853**	690	707	--	--	--
Swing	1100 x 10	45	551	674	779	**871**	720	--	--	--
Swing	1100 x 10	90	**402**	336	--	--	--	--	--	--

[1]PPP removed, the platelet poor plasma was removed in all cases except for whole blood measurement, the volume aspirated was equal between all samples.
[2]IFU = Instructions for use (from the manufacturer).
[3]Angle in degrees is relative to the horizontal.

due to combined gravitational and inertial pull away from the supportive RBC barrier.

The proper measures to release adhered platelets were elucidated in the patent by Batra et al,[24] wherein the following steps were listed:

- After centrifugation using optimal settings, the technician may choose to remove PPP before agitation, or they may choose to use the whole plasma
- The tube is positioned in an agitator (or in a hand) at an angle against the horizontal between 0 to 45 degrees, using the bottom of the tube as the pivoting side (the same outcome may be achieved by positioning the tube at negative degrees to the horizontal axis)
- The axis length of oscillation should be 5 to 10 cm
- The oscillation frequency should be approximately 2 full oscillations (up/right + down/left = 1 oscillation) per second
- The agitation power creates a sufficient velocity in the plasma so that it assumes a crashing wave motion against the thixotropic gel barrier
- The agitation power should be high enough to achieve the intended outcome, but low enough to avoid breaching the gel (so that the RBC and WBC layers are not disturbed)
- Agitation should be done in 5-second intervals (5 seconds on, 5 seconds off)
- The visual endpoint for higher platelet concentration is (1) Color change (darker pinkish hue, not to be confused with hemolysis) and (2) formation of foam over the upper liquid surface of the plasma
- The endpoint is expected after 2 to 5 agitation increments equivalent to 15 to 40 cumulative seconds of agitation on/off cycles

This technique resuspends the platelet layer that adhered to the surface of the thixotropic gel, in effect releasing the platelets from the gel. Compared to the recommended practice of gentle inversion, this technique is many folds more efficient. Theoretically, the agitation force causes a mild change to the viscosity at the adjacent surface of the thixotropic gel barrier, which releases the platelets.

Tailoring of Platelet Concentration

The technician may tailor their procedure to produce any one of the following types of plasma: PPP, PRP, high concentrated PRP, or ultra-high concentrated PRP.

The procedure for producing or tailoring platelet concentration is dependent upon the tube volume. Generally, 15-mL tubes are used to produce PRP only, whereas tailored platelet concentrates are produced using a 30-mL separator tube.

PPP is produced by aspirating from the upper layers of plasma after centrifugation but before agitation or inversion.

- A 30-mL tube is likely to produce 15 to 16 mL of plasma
- Aspiration of the upper 11 to 12 mL will give PPP, which is approximately 50% compared to baseline
- Aspiration of the final 3.5 to 4 mL will give high concentrated PRP, which is approximately 4.9 to >5 times baseline

PRP is produced by aspirating the entire volume after centrifugation and with gentle inversion or agitation.

- A 15-mL tube is likely to produce 5.5 to 6.5 mL of plasma
- A 30-mL tube is likely to produce 15 to 16 mL of plasma
- By using the recommended spin parameters of 1,500 G for 6 minutes using 15-mL tubes and 1,600 G for 10 minutes using 30-mL tubes, PRP of approximately 1.5 to 1.6 times baseline is produced

High concentrated PRP is produced by selective removal of PPP.

- The volume of PPP removed will determine the final PRP concentration
- In a 30-mL tube, removal of 11 to 12 mL of PPP will give PRP at 4.9 to >5 times baseline
- In a 30-mL tube, removal of 5.5 to 6.5 mL of PPP will give PRP at 2.7 to 3 times baseline

Ultra-high concentrated PRP is produced by selective removal of PPP and then by using the agitation technique described by Batra et al.[24]

- Ultra-high concentrated PRP is >5 times baseline.

CONCLUSION

To optimize platelet yield and quality, it is essential to empirically determine the best gravitational force and time of spinning, use a horizontal swing bucket centrifuge, and release trapped platelets from the gel's upper surface using the agitation technique. The agitation technique should not be too intense, nor too light, to avoid breaking the gel while ensuring the maximum release of platelets from the gel layer. By following these critical insights, the platelet yield is significantly higher. While it is perceived that the clinical outcomes will be better as well, we encourage further studies and assessment of clinical outcomes when following the methods described here.

DISCLOSURES

The authors declare no conflict of interest.

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doi:10.36849/JDD.7985

November 2024 986 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Isobutylamido Thiazolyl Resorcinol (Thiamidol) for Combatting Hyperpigmentation: A Systematic Review of Clinical Studies

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ABSTRACT

Background: Tyrosinase is the rate-limiting enzyme of melanogenesis and thus an ideal inhibitory target for treating hyperpigmentation. There are many commercially available tyrosinase inhibitors with limited clinical efficacy. A recent screen of 50,000 compounds found isobutylamido thiazolyl resorcinol (ITR) to be the most potent inhibitor of human tyrosinase.

Objective: To summarize the current evidence on the efficacy and adverse effects of ITR in treating hyperpigmentation.

Methods: A literature search was conducted using PubMed and Google Scholar databases in June 2022. Fourteen clinical studies investigating the use of topical ITR in hyperpigmentation treatment or prevention were identified.

Results: Most studies (n=13) investigated topical ITR as a treatment, while only one investigated ITR as a preventative measure against hyperpigmentation. All studies (n=14) found ITR to provide statistically significant improvements to hyperpigmentation conditions, including facial hyperpigmentation (n=3), melasma (n=5), post-inflammatory hyperpigmentation (PIH) (n=3), and UV-induced hyperpigmentation (n=3). Evidence suggests that the effective dosage and duration of topical ITR appears to be 0.1% to 0.2% ITR 2 to 4 times daily for 12 to 24 weeks. Successful prevention of UVB-induced hyperpigmentation has been seen following twice-daily topical ITR application for 3 weeks ($P<0.001$).

Conclusion: Topical ITR can significantly reduce hyperpigmentation; however, the evidence for its use is limited. Further investigation is warranted to identify the optimal dosage and application schedule of ITR, as well as compare the efficacy of ITR vs hydroquinone to determine if ITR is superior to the current standard of care.

J Drugs Dermatol. 2024;23(11):986-991. doi:10.36849/JDD.7985

INTRODUCTION

Hyperpigmentation, the overproduction of melanin within the skin, is estimated to be the 11th most prevalent disorder seen in dermatology practices and the most frequent skin complaint among patients aged 40 to 45 years.[1,2] This condition predominantly affects women with Fitzpatrick skin types (FST) III to V and can be cosmetically disfiguring, alter psychosocial well-being, and adversely impact the quality of life in affected individuals.[3,4]

Current treatment options – including topicals (eg, hydroquinone, arbutin, and kojic acid), oral agents (eg, cysteamine hydrochloride, melatonin, and tranexamic acid), chemical peels, and laser therapy – have varying efficacies, side effects, and may require lengthy treatment duration to achieve desired effects.[5] Hydroquinone is currently the criterion standard for hyperpigmentation treatment. However, its use is limited by several potential adverse effects including contact dermatitis, skin irritation, hypopigmentation, and, paradoxically, exogenous ochronosis (bluish-gray or black hyperpigmentation).[6,7] In fact, the European Union banned hydroquinone from cosmetic use due to its adverse effect profile.[6] There is therefore a need for clinically efficacious and safer alternative therapies for treating hyperpigmentation.

Tyrosinase, the rate-limiting enzyme of melanogenesis, is an attractive inhibitory target for treating hyperpigmentation (Figure 1).[6] While several tyrosinase inhibitors are already

FIGURE 1. ITR inhibits the rate-limiting step of melanogenesis.

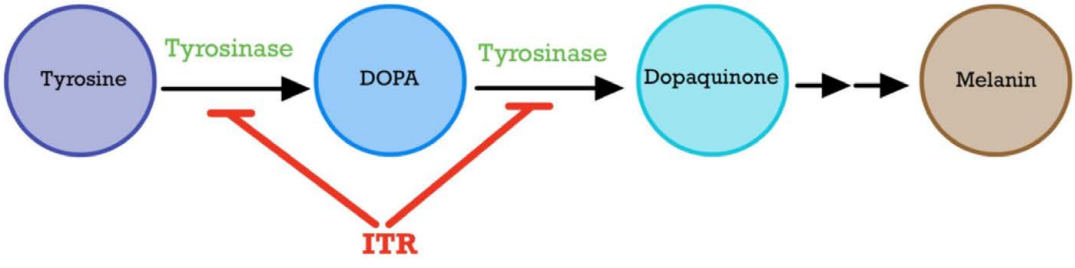
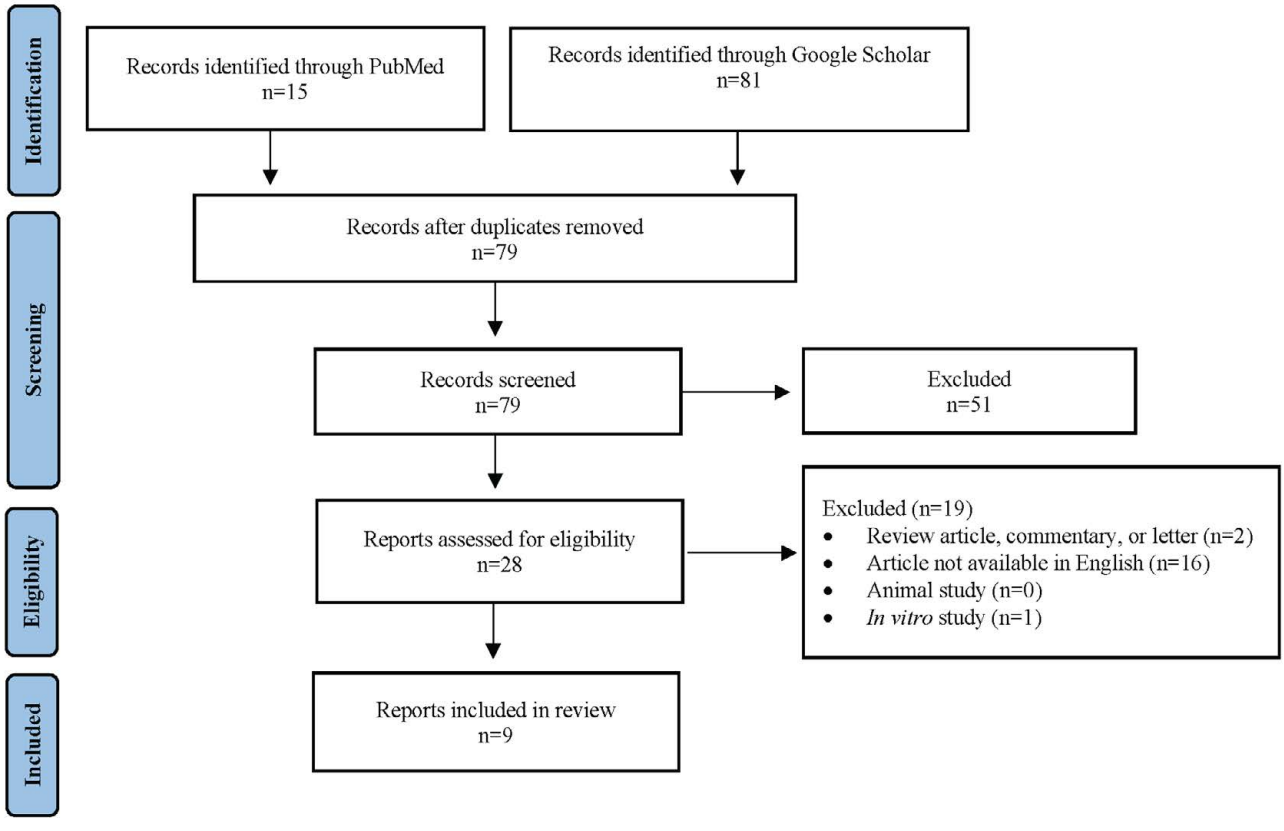


FIGURE 2. PRISMA diagram. Process of inclusion of studies



commercially available,[6] a recent screen of 50,000 compounds found isobutylamido thiazolyl resorcinol (ITR), a thiazolyl-resorcinol derivative, to be the most potent and clinically efficacious inhibitor of human tyrosinase.[6] To date, ITR has been shown to reduce facial hyperpigmentation, melasma, postinflammatory hyperpigmentation (PIH), and UV-induced hyperpigmentation. Herein, we summarize the current evidence on the efficacy of ITR and its adverse effects in treating hyperpigmentation disorders.

MATERIALS AND METHODS

A literature search was conducted in June 2022 on PubMed and Google Scholar databases for all clinical studies investigating ITR as an agent against hyperpigmentation. The following search term was used: "thiamidol" OR "isobutylamido thiazolyl resorcinol" OR "Isobutylene thiazolyl resorcinol" OR "thiazolyl resorcinol." This yielded 81 articles on Google Scholar and 15 on PubMed. The title and abstract of each article were screened (Figure 2). Exclusion criteria included (1) nonevidence-based studies (ie, review articles, commentaries, letters); (2) articles not available in English; (3) animal studies; and (4) in vitro studies.

RESULTS

Nine articles, accounting for a total of 14 clinical studies, investigating topical ITR as an agent against hyperpigmentation were identified (564 patients; age range 18-71 years). Most studies included participants with FST II to V (n=8), while 2 studies included either FST I or FST VI. Most studies (n=13) investigated ITR as a treatment, while 1 investigated ITR as a preventative measure against hyperpigmentation. All studies (n=14) found ITR to provide statistically significant improvements to hyperpigmentation conditions, including facial hyperpigmentation (n=3), melasma (n=5), PIH (n=3), and UV-induced hyperpigmentation (n=3) (Table 1).

Common Outcome Metrics

The Melasma Area and Severity Index (MASI), Facial Hyperpigmentation Severity Score on the malar area (FHSSm),[4] modified MASI (mMASI), and hemi-modified MASI (hMASI) are outcome measures for melasma or hyperpigmentation that are scored based on pigment darkness and area of involvement; note that the former two also are scored based on homogeneity. Relative lightness index (RL*I) is calculated by subtracting L*I of hyperpigmented skin from L*I of normal skin.[4] For all the

TABLE 1.

Clinical Studies Investigating Topical ITR as an Agent Against Hyperpigmentation Conditions

Hyperpigmentation Condition	Citation	Study Design	Participants, n=	Participant Sex	Participant Age Range (Mean Age)	Participant FST	Topical ITR Dosage & Application Schedule	Study Findings	Serious Adverse Effects
Facial Hyperpigmentation (n=3)	[8]	RCT, Split-face, Double-blind	34	F	25-64 (49.5)	II-IV (19), not provided (15)	ITR, BID or QID x 12 weeks	QID ITR significantly improved hyperpigmentation more than BID (P<0.001).	N/A
	[8]	Open-label, single-arm, observational	83	82F, 1M	27-71 (44.29)	I-IV (67), not provided (16)	ITR, 1 layer in AM & 2 layers in PM x 12 weeks	12-week use of an ITR-containing 3 product regimen significantly improved hyperpigmentation (P≤0.001).	N/A
	[4]	RCT, split-face, evaluator-blind	24	22F, 2M	>18 (48.04)	III-IV	0.15% ITR, BID x 12 weeks	Compared to laser monotherapy at 4 weeks, the 0.15% ITR-laser combined therapy significantly improved hyperpigmentation (P<0.05).	N/A
Melasma (n=5)	[9]	RCT, double-blind	48	F	38-64 (53)	III-V	ITR, 2 layers in AM & 1 layer in PM x 24 weeks	ITR-containing regimen significantly reduced hyperpigmentation more than ITR-free regimen at all points in time (P<0.001-0.043).	N/A
	[3]	RCT, split-face, evaluator-blind	31	F	29-63 (52)	N/A	0.2% ITR, BID x 12 weeks	ITR significantly reduced hyperpigmentation compared to baseline (P≤0.001). Control had no change from baseline.	ITR did not worsen melasma, control induced worsening melasma in 12.9% of participants.
	[3]	RCT, split-face, double-blind	28	F	31-65 (50.6)	N/A	0.2% ITR, BID x 12 weeks	ITR significantly reduced hyperpigmentation more than hydroquinone (P≤0.001).	ITR did not worsen melasma, hydroquinone led to worsening melasma in 10% of participants.
	[10]	RCT, evaluator-blind	50	F	18-50 (43)	II-V	0.2% ITR, BID for 90 days	ITR and hydroquinone both reduced hyperpigmentation (P<0.01). There was no difference between their reductions (P≥0.09).	Hydroquinone: mild erythema (8%), desquamation (8%), or a burning sensation (8%) (P= 0.235) ITR: 2 participants (8%) developed allergic contact dermatitis at days 60 and 75 of follow-up, and thus discontinued treatment.
	[11]	RCT, evaluator-blind	90	F	>18 (45.62)	IV-V	0.15% ITR, BID x 12 weeks	ITR monotherapy (P=0.027) and ITR-HA combined therapy (P=0.001) both significantly reduced hyperpigmentation compared to HA monotherapy in week 12. There was no convincing evidence that ITR-HA combined therapy was superior to ITR monotherapy.	Erythema (ITR-HA= 0%, ITR= 10%, HA= 3.3%), burning/stinging (ITR-HA= 6.7%, ITR= 16.7%, HA= 0%) and itching (ITR-HA= 6.6%, ITR= 0%, HA= 3.3%).[11]
PIH (n=3)	[12]	RCT	14	7F, 7M	28-58 (N/A)	II-III	ITR, BID x 12 weeks	At all points in time, ITR significantly improved suction blister-induced PIH compared to vehicle (P=0.009-0.034).	N/A
	[12]	RCT, single-blind	64	F	18-40 (N/A)	V	ITR, BID x 12 weeks	After 12 weeks, ITR significantly reduced (P=0.047) acne-induced PIH visibility compared to vehicle.	N/A
	[12]	Observational	29	28F & 4M were enrolled	18-50 (N/A)	V-VI	ITR, 2 layers in AM & 1 layer in PM x 12 weeks	ITR significantly improved acne-induced PIH at all points in time (P< 0.001) compared with baseline.	N/A
UV-induced hyperpigmentation (n=3)	[6]	RCT	17	F	56-71 (N/A)	N/A	0.2% ITR, BID x 12 weeks	ITR significantly lightened age spot pigmentation at all points in time compared to control (P<0.05 at weeks 4 and 8; P<0.01 at week 12).	N/A
	[6]	RCT	19	18F, 1M	58-70 (N/A)	N/A	0.1% ITR, BID for 12 weeks	ITR significantly reduced age spot pigmentation at weeks 8 and 12 vs baseline (P<0.05).	N/A
	[7]	RCT, split-arm, single-blind, pilot study	30	29F, 1M	>18 (34.77)	II-IV	0.15% ITR, 3 weeks	The ***preventive*** use of ITR 3 weeks before UVB-induced hyperpigmentation reduced the degree and duration of hyperpigmentation compared to no preventive treatment (ITR-treated arm mean lightness index [L*], 38.24 [±4.69] at baseline, 35.06 [±5.07] at 1 week after UVB irradiation; control arm L*, 38.41 [±4.23] at baseline, 32 [±4.86] at 1 week after UVB irradiation [P< 0.001]).	N/A

aforementioned metrics, a lower value indicates improvement/lightening of hyperpigmentation. In contrast, a higher mean lightness index (*L) value indicates improvement/lightening of hyperpigmentation.

Facial Hyperpigmentation

Three studies investigated ITR for facial hyperpigmentation treatment. First, a multicenter observational study (n=83) found that 12-week use of a ITR-containing 3-product regimen (SPF30 daycare, serum, and night cream) significantly improved mild-to-moderate facial hyperpigmentation (mMASI at baseline, 8.5 ± 3.9; mMASI at week 12, 3.6 ± 2.6; $P \leq 0.001$).[8] A split-face, double-blind, randomized controlled trial (RCT) (n=34) investigated the optimal frequency of ITR applications for mild-to-moderate facial hyperpigmentation treatment. Areas treated 4 times daily had statistically significant reductions ($P<0.001$) in hMASI at all points in time vs baseline (–0.72 ± 1.05 at week 4, –1.76 ± 1.69 at week 8, –2.43 ± 1.96 at week 12) and vs areas treated with ITR twice daily (–0.29 ± 0.69 at week 4, –0.84 ± 1.45 at week 8, –1.26 ± 1.52 at week 12).[8] A split-face, evaluator-blinded, prospective RCT (n=24) found that compared to Low-fluence Q-switched Nd:YAG 1064-nm laser (LFQS) alone, 0.15% topical ITR-LFQS combined therapy yielded a significantly greater reduction in both RL*I (62.5% vs 47.3% reduction, $P<0.05$) and FHSSm (54.4% vs 40.2% reduction; $P<0.05$).[4] However, ITR-LFQS combined therapy showed no significant effect on post-treatment maintenance.[4]

Melasma

Five studies investigated ITR for melasma treatment. A double-blind RCT of 48 participants with darker complexions (FST III-V) and moderate-to-severe melasma found 24-week use of an ITR-containing regimen (Dual Serum, SPF30 daycare, and night care) to yield a statistically significant reduction of MASI compared with an ITR-free regimen (–0.6 ± 0.6 at week 4, –2.4 ± 1.4 at week 8, –3.2 ± 2.1 at week 12, –3.6 ± 2.0 at week 16, –3.8 ± 2.3 at week 20, –4.2 ± 2.4 at week 24; $P<0.001$-0.043).[9] After the 24-week treatment phase, a 13- to 20-week regression phase with cessation of all treatment ensued. The MASI scores of participants in both the ITR and placebo group increased significantly during the regression phase yet remained below their respective baseline values. There was no significant difference between the groups after the regression phase.[9]

A split-face, evaluator-blinded study of 31 participants with mild-to-moderate melasma found that at week 12, twice-daily 0.2% ITR significantly reduced mMASI scores compared to baseline (baseline, 9.73 ± 4.45; week 12, 6.44 ± 4.42; $P \leq 0.001$), while twice-daily broad-spectrum sunscreen control (≥SPF30) induced no significant change in mMASI scores (baseline, 8.71 ± 4.59; week 12, 8.44 ± 4.95; $P \leq 0.001$).[3] ITR did not worsen melasma, while control led to worsening melasma in 12.9% of participants.[3]

A double-blind, split-face RCT of 28 participants compared twice-daily 0.2% ITR vs 2.0% hydroquinone in women with mild-to-moderate melasma.[3] Although ITR and hydroquinone both yielded statistically significant reductions in mMASI scores at 12 weeks compared to their respective baseline values, the improvement in the ITR side was significantly greater than that in the hydroquinone side ($P \leq 0.001$). Additionally, after 12 weeks, mMASI improvements were observed on the ITR-treated side in 78.6% of participants and on the hydroquinone side in 60.7% of participants. ITR did not worsen melasma, while hydroquinone led to worsening melasma in 10% of participants.

An evaluator-blinded RCT with 50 female participants compared twice-daily 0.2% ITR vs once-daily 4.0% hydroquinone for 90 days. Although the ITR and hydroquinone groups both yielded reductions in mMASI, Melasma Quality of Life scale, and color contrast scores ($P<0.01$), there was no difference between the groups in these reductions ($P \geq 0.09$).[10] Although neither intervention induced moderate or severe adverse events, mild adverse events did occur. Hydroquinone-treated participants experienced mild erythema (8%, $P=0.235$), mild desquamation (8%, $P=0.235$), or a mild burning sensation (8%, $P=0.235$), while no ITR-treated patients experienced these adverse events. However, 2 ITR-treated patients (8%) discontinued treatment as they developed allergic contact dermatitis at days 60 and 75 of follow-up.[10]

A prospective, evaluator-blind, RCT with 90 participants compared 0.15% ITR and hyaluronic acid (HA) combined therapy compared to both 0.15% ITR alone and HA alone in treating moderate-to-severe melasma.[11] The mMASI of all 3 groups significantly decreased at week 12 ($P<0.001$) compared to baseline. ITR-HA combined therapy ($P=0.001$) and ITR monotherapy ($P=0.027$) both yielded statistically significant reductions in mMASI in week 12 compared to the HA monotherapy group. Although the ITR-HA group had significantly lower melanin variation than the ITR group in week 4 ($P=0.027$), week 8 ($P=0.019$), and week 12 ($P=0.023$), there was no significant difference in the mMASI or average melanin level between the 2 groups.[11] Reported adverse effects include erythema (ITR-HA= 0%, ITR= 10%, HA= 3.3%) burning/stinging (ITR-HA= 6.7%, ITR= 16.7%, HA= 0%), and itching (ITR-HA= 6.6%, ITR= 0%, HA= 3.3%).[11]

PIH

Three studies investigated ITR as a treatment for either suction blister-induced PIH or acne-induced PIH.[12] A RCT induced 2 suction blisters on the upper arms of 14 participants. At 2 weeks, participants applied either an ITR-containing or vehicle formula bidaily for 12 weeks. Compared to vehicle-treated suction blisters, blisters treated with ITR yielded statistically significant improvements at all points in time ($P=0.034$, 0.023, 0.011, 0.009

for weeks 2, 5, 8, and 12, respectively). In fact, suction blisters treated with ITR for 2 weeks were, on average, lighter than blisters treated with the vehicle for 12 weeks.[12] In another RCT, 64 females with FST V and acne-induced PIH applied either an ITR-containing or vehicle formula bidaily on the entire face for 12 weeks. At 12 weeks, treatment with ITR resulted in a significant improvement in hyperpigmentation visibility when compared to vehicle (P=0.047).[12] Lastly, an observational study of 29 darker complected (FST V-VI) participants with acne-induced PIH found that an ITR-containing 3-product regimen (dual serum, SPF30 day cream, and night cream) yielded a statistically significant reduction in melanin index scores at all time points compared to baseline (melanin index score: 733.4 ± 138.8 at baseline, 654.1 ± 120.6 at week 4, 656.7 ± 116.1 at week 8, 632.7 ± 97.9 at week 12; P<0.001).[12]

UV-induced Hyperpigmentation

Three studies investigated ITR as an agent against UV-induced hyperpigmentation. A RCT (n=17) found that bidaily 0.2% ITR significantly lightened age spot pigmentation at all points in time compared to control (P<0.05 at weeks 4 and 8; P<0.01 at week 12). In fact, after 12 weeks of treatment, some ITR-treated age spots were indistinguishable from the surrounding normal skin.[6] Another RCT (n=19) found that bidaily 0.1% ITR yielded a statistically significant reduction in age spot pigmentation at weeks 8 and 12 compared to baseline (P<0.05).[6]

Beyond treatment, a randomized pilot study (n=30) investigated 0.15% ITR in preventing UVB-induced hyperpigmentation.[7] Following 3 weeks of ITR application on just one arm, UVB irradiation was used to induce 3 hyperpigmented spots on both arms of all participants. Pigmentary changes were then tracked for 4 weeks. Mean lightness index of the ITR-treated side remained significantly higher when compared to the control side at all points in time starting one week after UVB irradiation (weeks 4-7) (week 4: 32 ± 4.86 control side, 35.06 ± 5.07 ITR side (P<0.001); week 5: 33.2 ± 4.33 control side, 35.53 ± 5 ITR side (P=0.004); week 6: 34.98 ± 4.17 control side, 38.63 ± 10.21 ITR side (P<0.001); week 7: 36.25 ± 4.38 control side, 38.17 ± 5.01 ITR side (P=0.018)). Additionally, ITR treatment yielded earlier improvement, with the skin achieving baseline pigmentation 3 weeks post-UVB; while the control side remained significantly darker than its baseline value until the end of the study at 4 weeks post-UVB.[7]

DISCUSSION

Mechanism of Action

Tyrosinase is a copper-dependent enzyme that catalyzes 2 steps in melanogenesis: the conversion of tyrosine into dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to dopaquinone.[13] Tyrosinase is the rate-limiting enzyme of melanogenesis, making it an ideal inhibitory target for hyperpigmentation treatment.[6] The clinical efficacy of many commercially available tyrosinase inhibitors (hydroquinone, kojic acid, and arbutin) remains limited partly because they were tested against mushroom tyrosinase, rather than human tyrosinase, as the target.[6] ITR, however, reduces melanin production by reversibly and competitively inhibiting human tyrosinase. The reversible inhibition of human tyrosinase by ITR is superior to the irreversible inhibition induced by hydroquinone.[6] In fact, a recent screen of 50,000 compounds found ITR to be the most potent and clinically efficacious inhibitor of human tyrosinase.[6]

Efficacy and Adverse Effects

The results of the studies included in this review suggest that ITR is an effective treatment for several hyperpigmentation conditions including melasma, PIH, and UV-induced hyperpigmentation. Given that hydroquinone is considered a gold standard treatment of hyperpigmentation disorders, 2 studies sought to directly compare its efficacy with that of ITR.[3,10] Arrowtiz et al found the 12-week use of bidaily 0.2% ITR to yield a larger mMASI score reduction compared to 2.0% hydroquinone (P≤0.001).[3] In contrast, Lima et al found similar mMASI score reductions after 90-day use of bidaily 2.0% ITR and once-daily 4.0% hydroquinone.[10] A potential explanation for the contrasting findings of these 2 studies is that they used vastly different concentrations of hydroquinone (4.0% vs 2.0%). Additional head-to-head studies are warranted to compare the relative efficacies of these 2 compounds. Nevertheless, studies to date suggest that ITR is at least as efficacious as hydroquinone in treating melasma and can therefore be thought of as a viable alternative, especially in those who have failed or cannot tolerate hydroquinone.

Arguably, the best way to reduce hyperpigmentation is by preventing its development in the first place. This is why sunscreen is a staple in any anti-hyperpigmentation regimen. Interestingly, Vachiramon et al reported that the application of 0.15% ITR bidaily for 3 weeks significantly prevented subsequent UVB-induced hyperpigmentation.[7] These findings are promising and suggest that ITR may have the ability to prevent the development or progression of other forms of hyperpigmentation. Further studies investigating ITR's effect on the prevention of melasma and PIH are warranted.

Two studies investigated the effect of ITR against hyperpigmentation recurrence.[4,9] After a 24-week treatment phase with either ITR or a placebo, Roggenkamp et al conducted a 13- to 20-week regression phase and found that although the MASI scores of both groups increased, they remained below their respective baseline values, suggesting some lasting effect.[9] However, there was no significant difference between the MASI scores of the 2 groups after the regression phase. These findings suggest that ITR does not provide lasting post-treatment results, but also does not induce a rebound effect after discontinuation

of treatment.[9] Similarly, a split-face study found no statistically significant difference in the melasma recurrence rate between sides treated with 0.15% ITR vs placebo at the end of follow-up.[4] ITR's lack of reported lasting results may be explained by its reversible inhibition of tyrosinase.[9] Nevertheless, maintenance use of ITR may be sufficient to reduce recurrence.

Most studies (n=12) reported no significant adverse effects or did not address any adverse effects induced by ITR. Two studies, however, did. Lima et al reported that 2 ITR-treated patients (8%) discontinued treatment as they developed allergic contact dermatitis at days 60 and 75 of follow-up.[10] Disphanurat et al reported erythema (10% of ITR-monotherapy participants), burning/stinging (6.7% and 16.7% of ITR-HA and ITR-monotherapy participants, respectively), and itching (6.6% of ITR-HA participants) as common adverse effects.[11] Although ITR, like most medications, may induce adverse effects, they appear to be less severe and less frequent than those induced by hydroquinone. However, more studies are needed to investigate the adverse effect profile of ITR.

Effective Dosage and Application Schedule

The effective dosage and duration of topical ITR appears to be 0.1% to 0.2% ITR 2 to 4 times daily for 12 to 24 weeks. Evidence suggests that applying topical ITR 4 times daily yields greater benefits than twice-daily application.[8] ITR is commercially available over the counter in Eucerin Anti-Pigment hyperpigmentation products.

Limitations

This review is limited by studies conducted primarily in female participants with FST II to V. More studies are needed investigating ITR as an agent against hyperpigmentation for men and people with FST I and VI. Additionally, 10 of the 14 studies included in this review were sponsored by and/or have authors who are employed by Beiersdorf AG, the company that has patented Thiamidol. Further investigation of ITR as a preventative measure against hyperpigmentation conditions is needed. Further investigation is warranted to identify the optimal dosage and application schedule of topical ITR, as well as compare the efficacy of ITR vs hydroquinone to determine if ITR is superior to the current standard of care.

CONCLUSION

There is a need for more clinically efficacious and safe hyperpigmentation therapy options. Based on current evidence, ITR may serve as a safe and efficacious adjunct or alternative therapeutic option for various hyperpigmentation disorders. However, larger rigorous studies are needed to validate these early results and to compare the safety and efficacy in head-to-head trials with more established compounds.

DISCLOSURES

The authors have no competing interests to declare.

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doi:10.36849/JDD.8058R1

November 2024 992 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Clinical Efficacy and Tolerability of a Novel Retinaldehyde Serum With Firming Peptides to Improve Skin Texture and Signs of Photoaging

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ABSTRACT

Retinoids are derivatives of vitamin A prominently used in cosmeceuticals to reverse signs of photoaging. Retinaldehyde (retinal) is 10x more bioavailable than retinol and is gaining traction in the skincare industry for being the strongest over-the-counter retinoid. This study evaluated the efficacy and tolerability of a novel retinal formulation including peptides, ceramides, and lipids, designed to sustain the potency of the retinal and enhance delivery to reverse clinical signs of photoaging. This study was a trial of the test product (Retinal Night Advanced 0.1% Retinal Firming Treatment, Dr. Whitney Bowe Beauty, Greenwich, CT) in which 32 female subjects were enrolled. 47% of subjects had skin of color (Fitzpatrick Skin Type III-VI) and 57% had sensitive skin. Subjects applied the test product 3 nights weekly to the face, neck, and chest for 8 weeks. Fine lines of the face had 12% visible change by week 8 (P<0.0001). Fine lines on the chest showed progressive visible improvement of 11% at week 2 (P=0.0005) and 19% at week 8 (P<0.0001). There was a 19% improvement in visible hyperpigmentation of the face by the 8-week mark (P<0.0001). Visible texture of the face improved by 5% (P=0.0078) and pores improved by 20% at week 8 (P<0.0001). Patch testing revealed no signs of sensitization or irritation. This clinical study demonstrates that this retinal formulation is safe, well-tolerated, and effective in improving the appearance of fine lines, hyperpigmentation, texture, and pores.

J Drugs Dermatol. 2024;23(11):992-997. doi:10.36849/JDD.8058R1

INTRODUCTION

Retinoids are derivatives of Vitamin A used to treat myriad dermatological conditions including acne, psoriasis, and skin cancer. They are also prominently used in skincare as an "anti-aging" treatment in various concentrations and forms. All-trans retinoic acid, commonly known as tretinoin, is available by prescription and is the most widely investigated retinoid for photoaging. All-trans retinoic acid regulates over 3000 genes in keratinocytes and fibroblasts, and when these receptors are activated, it can increase cell turnover and motility, increase synthesis of procollagen and glycosaminoglycans, and inhibit matrix metalloproteinases.[1,2]

Retinoic acid precursors including retinyl esters, retinol, and retinaldehyde (aka retinal) are available over the counter. These precursors require enzymatic conversion in the skin prior to becoming retinoic acid, the bioactive form, and thus are considered less potent but also less irritating than retinoic acid. The potency of the retinoid inversely correlates with the number of in vivo chemical conversions necessary to create all-trans retinoic acid. Retinal specifically has been gaining traction in the skincare industry for being the most potent retinoid available without a prescription.[2]

As we age, the skin loses its proliferative capacity and becomes thinner, drier, and less elastic. The use of retinoids has been shown to increase epidermal proliferation and increase the deposition of glycosaminoglycans, essentially reversing these signs of aging. All-trans retinoic acid has been studied extensively for its ability to drive measurable clinical improvements in photoaging and overall appearance of the skin after several months of consistent use. Though tretinoin is the strongest retinoid, it can cause significant erythema, irritation, burning, or dermatitis, often causing patients to discontinue use.[2] The most dramatic benefits in terms of photoaging are often appreciated after 6 months of consistent use, and consequently, there is great demand for retinoids that are effective but better tolerated.[2] Retinol requires 2 conversion steps to become retinoic acid and is considered 20 times less potent than tretinoin.

Nonetheless, retinol has been shown to improve signs of photoaging with less transepidermal water loss, erythema, and scaling of the skin than tretinoin.[2] Retinal, on the other hand, only requires 1 conversion step to become retinoic acid, making it the strongest over-the-counter retinoid.[3] Retinal has

been shown to be 10 times more bioavailable than retinol.[4] This conversion step can only occur in keratinocytes at a specific stage of differentiation, which causes a tightly-controlled delivery of retinoic acid into the skin.[4] Therefore, there are very few adverse effects seen with the use of retinal.

Despite these advantages, retinol and retinal are both polyunsaturated compounds that are inherently unstable, easily oxidized, and lose potency over time. This calls for a vehicle that can control the stability of the compound and deliver it deep into the skin.[2] The test product uses a proprietary dermal delivery system combined with 2 firming peptides that creates an exceptionally stable formula with a hydrating lipid blend that supports the skin barrier and prevents irritation. The peptides work synergistically with the retinal to firm the skin by triggering damage-repair mechanisms.[6-8] This novel retinal utilizes Palmitoyl Tripeptide-1 and Palmitoyl Tetrapeptide-7 matrikine peptides. The former is a type 1 collagen fragment and the latter is a fragment of IgG that work together to reduce inflammation after UVB exposure, prevent collagen breakdown with UVA exposure, and stimulate collagen synthesis.[6-8] These matrikines are perfectly paired with the retinal because they work in a complementary way to strengthen the deeper layers of the skin, thereby firming and smoothing the appearance of fine lines and wrinkles over time.[7] Hydrophilic and hydrophobic ceramides (non-hydroxy fatty acid, alpha hydroxy fatty acid, and ester-linked omega hydroxy fatty acid with phytosphingosine bases) were also included to lock in moisture and support the skin barrier.[8] Ceramides, phytosphingosine, and sterols are naturally found in the skin and are important for healthy, functional skin that protects us from external factors. As we age, our ceramides become depleted.[9] Topical application of ceramides works to both bolster the skin barrier as well as trigger the skin to build more ceramides.[10-12] The pentalipid matrix in this retinal is composed of both hydrophilic and hydrophobic ceramides, phytosphingosine, and sterols that retain moisture and occlude the skin to prevent transepidermal water loss (Table 1).

The purpose of this study was to evaluate the clinical efficacy and tolerability of a novel retinal formulation (DWB-RN) designed to sustain the potency of the retinal and deliver it deeply into the skin to reverse clinical signs of photoaging without causing irritation.

MATERIALS AND METHODS

Study Ethics

These studies were sponsored by Bowe Glow, Inc. and conducted by contract research organization, Princeton Consumer Research (PCR) Corp., US, and UK. These studies conformed to the requirements of the 1964 Declaration of Helsinki and its subsequent amendments and were conducted in accordance with applicable International Council for Harmonization. 2016. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) in as much as they apply to human subjects' research consumer product testing. The protocols were approved by PCR Corp., Tampa, Florida and PCR Corp., Chelmsford, United Kingdom. All subjects provided written informed consent and consent for photo release before participating in the study.

Clinical Grading and Self-Perception of Skin

This study was a monadic, single-center trial of the test product (Retinal Night Advanced 0.1% Retinal Firming Treatment, Dr. Whitney Bowe Beauty, Greenwich, CT) in which 32 female subjects were enrolled. It was a home-use design over an 8-week

TABLE 1.

Breakdown of Major Ingredients		
Ingredient	**Clinical Benefit**	**Biologic Mechanism**
0.1% Retinaldehyde	Reverse signs of photoaging including fine lines, wrinkles, and hyperpigmentation.	Increase epidermal keratinocyte proliferation and thickness, increased deposition of glycosaminoglycans, and increased synthesis of procollagen.[1,2]
Palmitoyl Tripeptide-1	Firm the skin, reduce the appearance of fine lines and wrinkles.	Type 1 collagen fragment, triggers damage repair mechanisms to enhance collagen synthesis.[6-8]
Palmitoyl Tetrapeptide-7	Firm the skin, reduce the appearance of fine lines and wrinkles.	IgG fragment, reduces inflammation after UVB exposure and stimulates collagen synthesis.[6-8]
Hydrophilic and Hydrophobic Ceramides	Support skin barrier, maintain skin hydration.	Holds water in the skin by supporting barrier function to prevent transepidermal water loss.[8-12]
Phytosphingosine	Moisturize and soothe skin.	Ceramide precursor, triggers ceramide synthesis.[9]
Punica Granatum Sterols	Moisturize and soothe skin.	Mimics and replenishes cholesterol naturally found in skin to prevent transepidermal water loss.[19]
Vitamin E	Prevents signs of photoaging.	Prevents skin damage from reactive oxygen species.[20]
Squalane	Moisturize and soothe skin, thought to reduce acne.	Replenishes squalene in the skin to prevent transepidermal water loss, prevents lipid peroxidation.[21]
Shea Butter	Moisturize and soothe skin.	Acts as an occlusive barrier to reduce transepidermal water loss.[22]

period, meaning that subjects were dispensed the test product for home use and compliance was measured via subject journal entry. Healthy females aged 35 to 60 with mild to moderate fine lines, rhytids, and hyperpigmentation (between 2.0-6.0 by a clinical grader at baseline) were enrolled. Fitzpatrick skin types I to VI were included to ensure that a variety of skin tones were represented. All skin types (normal, dry, combination, oily) were included with at least 50% of the subjects having self-perceived sensitive skin. All enrolled subjects had to be able to provide informed consent and be willing to follow the study protocol. Subjects were excluded from this study if they had an allergy of hypersensitivity to retinol products; were pregnant or breastfeeding, or had plans to become pregnant; any skin disease or active inflammation of the face, neck or chest that would interfere with clinical grading; recent participation in a skincare study; use of topical acne treatments within 1 month or steroids, isotretinoin, prescription strength retinoids (tazarotene, tretinoin), retinol, vitamin-c or skincare with active ingredients within 4 months prior to enrollment; cosmetic treatments within the last 6 months or cosmetic medical procedures within 12 months; or a medical condition/ drug regimen that could confound the study results or possibly cause harm to the participant.

Enrolled subjects completed a 1-week washout period with a provided gentle cleanser. Subjects were instructed to apply the test product 3 nights weekly (Tuesday, Thursday, Sunday) to the face, neck, and chest. Since all subjects had to be free of topical retinoids for 4 months prior to the study, use of the test product 3 times weekly was chosen to reduce retinoid dermatitis from introducing a retinoid too quickly. In addition to the test product, subjects were instructed to continue using only their own moisturizer and sunscreen. Maintaining consistency in the subject's existing skincare routine is recommended to avoid excessive alterations, which is crucial for individuals with sensitive skin. For subjects accustomed to using physical exfoliators, they were permitted to incorporate this into their routine once every 2 weeks. Clinical grading assessments were performed for all subjects during weeks 0, 2, and 8, and the self-perception questionnaires were completed during weeks 2 and 8. Clinical grading was performed by a single, unbiased, independent expert using a validated rating scale from 0=none to 9=severe in categories such as overall skin appearance, fine lines, wrinkles, radiance, hyperpigmentation, and texture (including appearance of pores). Certain outcome measures such as global wrinkles and hyperpigmentation were only assessed at baseline and week 8 since these parameters generally require more time to show visible change. Visible and tactile skin texture, and skin radiance were only graded at baseline and week 2 since we anticipated seeing an earlier change in these parameters. Tactile skin texture was assessed by an independent clinical grader moving fingertips with even pressure across the surface of the skin to determine skin roughness. Prior to the in-person clinical assessment, all subjects were acclimated to the study room for 15 minutes. Room conditions such as humidity, temperature, and lighting were consistent throughout the study. Subjects also completed a self-perception questionnaire consisting of 26 questions (utilizing a 4-point Likert scale) pertaining to the appearance of their skin and the overall treatment experience. Adverse events were monitored and recorded throughout the study period.

Human Repeat Insult Patch Test

This was a separate single-center, single-blind study that enrolled 57 male and female participants to investigate the potential irritation and sensitization of the test product using repeated cutaneous semi-occlusive/occlusive patches. The test product was patched under semi-occlusive patches (9 inductive and 1 challenge patch) based on the modified Draize method.[15] Induction patches were worn for either 47 or 71 hours over 3 weeks. Participants had a rest period of 14 days. Challenge patches were then applied for 48 hours and read both 1 hour and 48 hours post-removal for visible signs of irritation or sensitization.

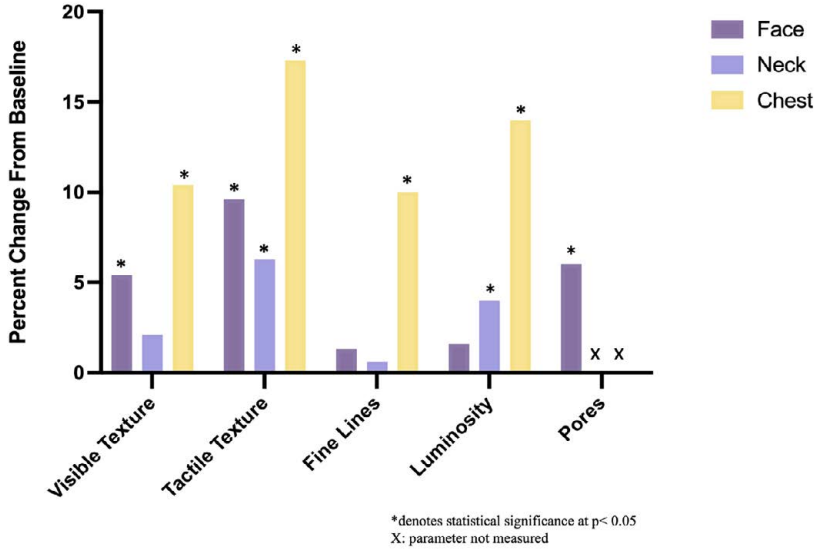
RESULTS

Clinical Grading and Self-Perception of Skin

Thirty-five subjects were screened for this study, with only 32 being enrolled and issued the test product. Of those 32, 31 subjects completed all aspects of the study. The subject was lost due to personal reasons. The subjects ranged in age from 34-59 (mean 48.5 +/- 7.4). Half of the participants self-identified as Caucasian, while the other half identified as Black or bi-racial. Forty-seven percent were Fitzpatrick Skin Types III-VI. Most participants (94.3%) were non-Hispanic. Combination skin was predominant (68.6%), followed by normal (22.9%), dry (5.7%) and oily (2.9%). 57.1% of subjects endorsed having sensitive skin.

Global fine lines, global wrinkles, hyperpigmentation, skin radiance, visible skin texture, skin softness, and appearance of pores were graded on a 10-point validated scale [0=none, 1-3=mild, 4-6=moderate, 7-9=severe]) at baseline, week 2, and week 8 by a single independent expert clinical grader. Eighty percent of subjects demonstrated improvement in fine lines of the face, neck, and chest by the end of the study period. Improvement of fine lines of the face were slow to respond to treatment: at week 2 there was a 1% reduction in fine lines of the face, but by week 8 a 12% change was appreciated (P<0.0001) (Figure 1). Fine lines of the neck showed an improvement of 4% at week 8, however, this trend did not reach statistical significance. Fine lines on the chest showed the most rapid and dramatic improvement, with 11% improvement by week 2 (P=0.0005) and 19% improvement measured at week 8 (P<0.0001). Global wrinkles were only measured at week 8, and face and neck improvement did not reach statistical significance. However, global wrinkles did improve significantly on the chest, with an average of 7% improvement by week 8 (P=0.0313)(Figure 2).

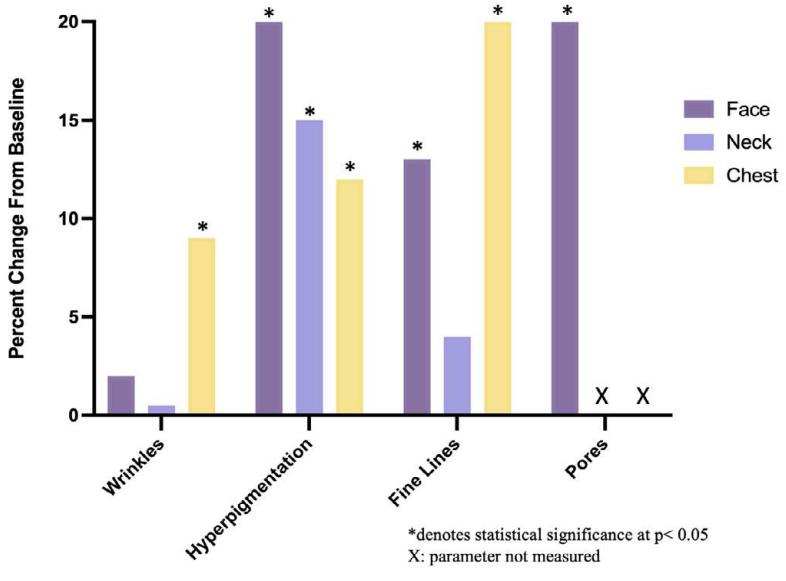
FIGURE 1. Average percent improvement from baseline for parameters as measured by independent expert clinical grader at 2 weeks. Participants used the test product 3x weekly for 2 weeks.



One hundred percent of subjects demonstrated improvement in the appearance of hyperpigmentation on the face, neck, and chest relative to baseline measurements, with a 19% improvement in hyperpigmentation of the face by the 8-week mark (P<0.0001). Hyperpigmentation of facial skin improved by 19% (P<0.0001) and hyperpigmentation of the skin of the neck and chest improved by 16% and 12% respectively (P<0.0001). The visible texture of the face improved by 5% (P=0.0078) and the tactile texture improved by 9.6% during the same period (P=0.0001). Visible skin texture on the chest showed significant improvement of 10% (P=0.0005) and a tactile assessment of skin roughness improved by 18% after 2 weeks (P<0.0001). Appearance of facial pores also showed significant progressive improvement of 6% at week 2 (P=0.0078) and 20% at week 8 (P<0.0001) relative to baseline severity.

Subjective data from subjects showed that 90% of subjects thought their skin looked and felt softer and smoother after 2 weeks of use of the test product (P<0.0001). Eighty percent of subjects felt that their skin appeared more youthful than baseline at week 2 (P<0.0001). By the end of week 8, 96% of subjects felt their skin looked firmer (P<0.0001), 87% saw fewer fine

FIGURE 2. Average percent improvement from baseline for parameters as measured by independent expert clinical grader at 8 weeks. Participants used the test product 3x weekly for 8 weeks.



lines and wrinkles (P<0.0001), and 87% said their skin was more radiant (P<0.0001). Ninety-three percent endorsed that their skin tolerated the product well (P<0.0001), with 87% stating that the product was not irritating to their skin (P<0.0001). Overall, no serious events were reported throughout the duration of the study. There were no instances of retinoid dermatitis noted. There was one adverse event during the study that was deemed unrelated to the test product.

Human Repeat Insult Patch Test

Of the 57 enrolled participants, 55 completed the study, with 2 participants withdrawing from the study for personal reasons. There were no adverse events or reactions reported throughout the course of the study. There were no questionable reactions observed during the challenge phase of the study in any of the test subjects.

DISCUSSION

This study evaluated a novel retinal formulation designed to deliver a potent retinoid deep into the skin to reverse clinical signs of photoaging without skin irritation. DWB-RN is unique in formulation and is one of the few retinals on the market to be backed by a clinical study proving efficacy and tolerability. Our study focused on a cohort of subjects representing a diverse, younger demographic than is typical of other studies evaluating retinoids for the use of photoaging. Further, our study deliberately enrolled over 50% of participants who had self-proclaimed sensitive skin to ensure DWB-RN was tolerable for all skin types. In this study, subjects used DWB-RN on their face, neck, and chest in order to treat those areas as one cosmetic unit. We clinically assessed improvement in these areas both as a complete unit and independently, as there is a need for topical treatments that can effectively reduce signs of photoaging on the skin of the neck and chest. The neck is especially important, as this thin, delicate skin is difficult to treat and very sensitive to tretinoin. DWB-RN was shown to be effective on this delicate skin without signs of erythema or irritation. Subjective data at both week 2 and week 8 demonstrated that subjects appreciated a noticeable difference in the appearance of their skin, noting that it seemed clearer, brighter, softer, and more radiant. Photoaging of the neck and chest are common cosmetic concerns that are known to be difficult to treat retroactively, often requiring expensive procedures such as laser therapy to see visible improvements in texture and tone.

Many retinol and retinaldehyde-containing products sold over the counter either do not disclose the concentration used or do not conduct testing to ensure that the percentage listed on the label is accurate. Given that the stability of retinoids is highly dependent on formulation, packaging, and storage, it becomes challenging for clinicians to advise patients on which retinoid might be the best formulated to ensure reliable and consistent delivery of a certain concentration. Retinal formulations are highly unstable and can be especially challenging to formulate. The bright yellow color of DWB-RN signifies the purity and potency of the product. The stabilized form of retinaldehyde used in the current test treatment has been tested previously in other base formulations to show a shelf-life stability of 24 months (data on file). Further testing was done using HPLC assays to verify the percentage of retinaldehyde in the current DWB-RN final formulation. The 24-month stability testing, combined with the HPLC assays, can give clinicians confidence that the 0.1% concentration of retinaldehyde listed on the label is indeed accurate. This data can help providers more predictably counsel patients regarding how many nights per week to utilize this product, and when to consider switching to a weaker or stronger retinoid based on the desired clinical outcome.

While there are topical ingredients that do not involve the retinyl to all-trans retinoic acid pathway, such as tazarotene, adapalene, and hydroxypinacolone retinoate, they are beyond the scope of this discussion.[3] Additionally, bakuchiol, a retinoid-like botanical, has recently been shown in a randomized controlled trial to have comparable results to retinol 0.5% after 12 weeks of twice daily use.[14] Another study compared 8 weeks of daily 0.1% retinal application to 3 sequential glycolic acid peels in 55 women. They found that the retinal was as effective as the peels in reducing signs of photoaging and was even superior to the peel in improving the texture of the skin. The retinal cream was better tolerated and had milder adverse effects than the peels.[15] A double-blind randomized controlled trial compared different concentrations of retinal (0.05% vs 0.1%) in 40 women who applied the retinal twice daily for 3 months. They found that both concentrations significantly improved the texture of the skin, reduced transepidermal water loss, and increased skin hydration. Only the 0.1% retinal significantly improved the melanin index by 6.5%, demonstrating that this concentration of retinal could improve hyperpigmentation.[16] A study by Creidi et al. compared nightly application of either retinaldehyde 0.05%, all-trans retinoic acid 0.05%, or retinaldehyde vehicle for 44 weeks. They found that both retinaldehyde and all-trans retinoic acid significantly improved skin roughness and wrinkles at 18 weeks, with continued improvement to week 44. Notably, the retinaldehyde group did not show signs of irritation throughout the study, whereas the all-trans retinoic acid group saw skin irritation that affected the subjects' compliance with treatment (P=0.0001).[17]

The limitations of this study include a relatively small sample size, the use of only one expert clinical grader, and the lack of a control group. We also could not include pregnant or breastfeeding women due to the potential teratogenicity of all-trans retinoic acid.[3] A longer study duration would be desirable as improvements in skin parameters appeared to be progressively improving, and studies show that retinoids can take 6-12 months to reach their full effect.[19] Some skin parameters, such as hyperpigmentation, take longer to respond to topical interventions and thus require more consistent

application over time.[18] We believe that consistent use of DWB-RN would result in progressive improvement beyond 8 weeks. Future studies looking at head-to-head comparisons of DWB-RN to varying concentrations of retinol and tretinoin would also be valuable contributions to the literature as they would help guide clinicians when counseling patients about how OTC retinoids compare in efficacy to one another and to tretinoin.

Interestingly, while irritation from retinoids appears to correlate with efficacy in terms of treating acne, there are no studies showing that increased irritation from retinoids correlates to increased efficacy in reversing photoaging. That being said, irritation does impact compliance in both populations.[17] After 8 weeks of 3x weekly use, 93% of subjects claimed that their skin tolerated the test product well despite over 50% of our cohort having sensitive skin. Additionally, our patch testing did not reveal any hypersensitivity to the test product. A future study with 5-6x weekly use is warranted to see if this impacts the overall rate and degree of improvement to the skin without increasing the incidence of irritation.

CONCLUSION

Retinoids are one of the most popular topical treatments in both cosmeceuticals and in clinical practice for their proven efficacy in addressing several skin conditions, both medical and cosmetic. Retinal is a newer retinoid that is thought to be stronger than retinol, but little clinical research has been conducted on this class of retinoids in terms of both tolerability and efficacy for the treatment of photoaging. Unlike retinol, which requires two conversion steps to be converted to the clinically active all-trans retinoic acid, retinal only requires a single conversion step. While this increased bioavailability likely translates to increased potency as compared to retinol, the overall formulation in which the retinal is delivered to the skin likely has significant implications in terms of tolerability, risk for irritation, and even efficacy. The stability of this inherently unstable molecule needs to be addressed to ensure consistent delivery of a specific retinal concentration over the lifetime of a product. The DWB-RN formula has been clinically proven to reduce fine lines and hyperpigmentation after just 8 weeks of use without causing irritation. Although fine lines of the face did ultimately show statistically significant improvement over the 8-week study, this improvement was not appreciated at the 2-week mark. This makes sense mechanistically, in that retinoids work via stimulating collagen synthesis and strengthening the extracellular matrix, which takes longer than the temporary improvement one might expect from using a humectant-based product such as a hyaluronic acid based moisturizing cream. The neck and chest are notably difficult to treat retroactively once age-related changes are underway, and therefore regular use of this topical product may reduce the need for future cosmetic interventions that tend to be cost-prohibitive and often require significant downtime. In addition, there was not a single case of irritation reported throughout the duration of the clinical study, even with deliberate inclusion of 50% of subjects with self-reported sensitive skin. The combination of efficacy of the product early on and the tolerability both add to the likelihood that people will use this retinal consistently. Overall, this study demonstrates that DWB-RN is safe, well-tolerated, and effective in improving the appearance of fine lines, hyperpigmentation, texture, and pores.

DISCLOSURES

Dr. Whitney Bowe is the founder and CEO of Bowe Glow, Inc. No other authors have anything to disclose.

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doi:10.36849/JDD.8210R1

November 2024 998 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Review of Energy-Based Device Interventions to Treat Keloid Scars

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ABSTRACT

Keloids are thickened raised scars that develop due to injury and grow beyond the boundaries of their original wound, mostly affecting individuals with skin of color. This review explores the use of energy-based devices to treat keloids, both using laser monotherapy and in combination with other drugs. Laser therapy alone has shown efficacy in treating keloids. Combination laser therapy has better keloid reduction when administered with steroids, 5-fluorouracil (5-FU), and verapamil. However, monotherapy has had less adverse reactions including dermal atrophy and local pain. Therefore, physician discretion is essential when considering treatment. This review highlights the efficacy of energy-based devices (EBDs), alone and in combination. It also reveals the need to have tailored approaches with patients. Further research is needed to develop more comprehensive treatment standards for keloids using EBDs alone or in combination.

J Drugs Dermatol. 2024;23(11):998-1002. doi:10.36849/JDD.8210R1

INTRODUCTION

Keloids are benign dermal fibroproliferative tumors, manifesting as thickened, raised scars that arise due to injury.[1] Keloids grow beyond the wound boundaries and appear firm, smooth, shiny, and may be dyschromic. They can cause psychosocial, physical, and cosmetic distress. Keloids often arise in patients with skin of color and can be caused by trauma to the skin, including physical injury, surgery, piercings, burns, and acne lesions.[2-5] The pathophysiology of keloid formation is complex and poorly understood. Researchers believe that keloids form due to overproduction of collagen and fibroblasts with increased levels of transforming growth factor and platelet-derived growth factor.[6]

Common treatment therapies include intralesional corticosteroid injections, silicone gel sheets, pressure therapy, cryotherapy, and surgical excision.[7,8] There is no universal treatment protocol for keloids due to their heterogeneity. Keloids remain a challenging dermatologic condition to treat due to their high recurrence rate, complex pathogenesis, size and location, and limited standardization. Energy-based device therapies (EBDs) such as laser therapy, radiofrequency therapy, and intense pulsed light (IPL) have emerged as potential non-invasive, and effective methods of reducing the appearance of keloids.[9] These EBDs target blood vessels within the keloid tissue to decrease inflammation, help remodel collagen to flatten and soften the keloid, and reduce pigmentation by breaking down the melanin within the scar tissue. Laser therapy can also be used in combination with other treatments, such as corticosteroid injections, to further decrease keloid appearance and prevent reoccurrence.[10]

This review explores different EBD therapies, such as lasers in combination with other modalities and laser monotherapy, as well as the efficacy of radiofrequency and intense pulsed light in treating keloids.

MATERIALS AND METHODS

A literature review was performed using SCOPUS and PubMed databases to explore contemporary applications of lasers in keloid treatment. The search covered studies published between January 2011 and September 2023. The primary search terms "keloid," "lasers," "combination therapy," "Nd:YAG," "fractional CO2," "pulsed dye," "radiofrequency," and "intense pulse light" were used as isolated and combined search terms. Inclusion criteria encompassed English-language articles of various study types, such as randomized controlled trials, systematic reviews, clinical trials, retrospective single-center studies, case series, and case reports. Exclusion criteria included non-English studies. The review aimed to analyze efficacy compared to

existing therapies as the primary outcome and adverse effects as the secondary outcome.

DISCUSSION

Isolated Laser Therapy

Laser monotherapies for treating keloids include fractional CO2 laser, Nd:YAG laser, diode laser, and pulsed dye laser. Many of the results show different levels of efficacy, but all tend to improve the appearance of keloids.The probability of recurrence, treatment-associated pain, and end-result satisfaction are factors limiting their efficacy.

10600-nm Fractional CO2 Laser

Fractional CO2 laser is an ablative laser that targets water in the skin, causing local tissue destruction and scar remodeling. A study by Tawfic et al used fractional CO2 laser monotherapy compared to Nd:YAG laser for keloid treatment. A 10600-nm CO2 laser was used with 20-watt power, 1000 µs dwell time, 800 µm spacing, and stack of 5. In this study, 30 patients with skin types II, III, and IV, according to the Fitzpatrick skin type classifications, and keloids, were treated with 10600 nm CO2 laser.[11] Treatment was assessed using the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS), as well as histopathological, morphometric, and biochemical assessments. With results comparable to the Nd:YAG laser for keloid treatment, fractional CO2 laser was shown to have effective keloid treatment with a percentage change of 47.34 ± 19.95 and POSAS of 46.50 ± 9.21.[11] However, VSS was not provided for fractional CO2 lasers alone. Unlike Nd:YAG laser, the fractional CO2 laser had a significant elastic fiber density improvement (P=0.002).[11] Other results included a reduction in transforming growth factor-βI (TGF-β1), an inflammatory marker (P=0.001), as well as collagen improvement (P=0.002).[11] However, fractional CO2 laser monotherapy has shown increased keloid recurrence rates.[10] Tawfic et al also report higher incidence of pain, greater erythema, discharge, and edema, with few reports of pigmentation changes from CO2 laser therapy.[11]

Long-Pulsed 1064-nm Nd:YAG Laser

Nd:YAG lasers have been shown to reduce keloids significantly and have few adverse reactions.[12] These lasers penetrate the deeper dermal layers and reduce vascularity, which decreases cytokines and growth factor production.[13] Multiple studies explored long-pulsed 1064 nm Nd:YAG lasers,[11-15] with varying pulse durations (0.3 ms, 20 ms, 25 ms, 60 ms).[11-15] El-Shakour et al compared the effectiveness of Nd:YAG lasers to pulsed dye lasers (PDLs) in patients with Fitzpatrick skin types II-IV. After 6 sessions, they found a significant VSS of 65.4% for Nd:YAG lasers compared to 55.1% for PDLs (P<0.001).[14] Nd:YAG lasers had greater pain scores than PDLs.[14] Further, Nd:YAG laser reached a deeper dermal region than PDL, allowing for enhanced efficacy in keloid treatment.[13] Ogawa et al also found that Nd:YAG lasers had the best results in less stretched and inflamed locations.[13] Rossi et al studied Fitzpatrick skin types I-VI and found that the Nd:YAG laser showed a clinical reduction in thickness and erythema with significant visual improvements (P<0.0001) and low incidence of pigmentation change.[12] Tawfic et al further discovered that the Nd:YAG laser presented a significant decrease in TGF-β1 (P=0.001), improvements in vascularity, and reduced collagen fibers (P=0.003). When comparing the fractional CO2 laser to the Nd:YAG laser, there was no significant difference in keloid measures, but patients reported less pain with Nd:YAG lasers.[11] Patel et al assessed the efficacy of Nd:YAG lasers on pain-associated keloids with patients representing Fitzpatrick skin types I-VI. After treatments, patients had mild erythema and edema, which self-resolved. All patients reported significant improvement in pain before and after multiple treatments (P=0.01), with zero patients experiencing adverse pigmentation or scarring. Patel et al concluded that utilizing a larger spot size of 10 mm could alleviate pain due to deeper penetration that reaches nerves and reticular vessels.[15]

1470 nm Diode Fiber Laser

Diode fiber lasers as a keloid treatment has limited research. In one study, Li et al used a 1470 nm semiconductor gallium arsenide laser with an intralesional optical fiber device, with power levels ranging from 3 to 6 watts. After 1-3 treatments, the diode fiber laser showed a significant reduction of 29.2% in keloid thickness (P<0.05).[16] Keloid pigmentation also had a 21.3% improvement (P<0.01), and blood perfusion significantly reduced by 22.7% (P<0.05).[16] VSS scores had a 37.9% improvement. Pigment changes, infections, and recurrence rates were not reported, but moderate postoperative pain was reported.[16] Although there were benefits, more research would be needed using diode fiber laser monotherapy to establish their true efficacy in treating keloids.

585-595 nm Flash-Lamp Pulsed Dye Laser

Unlike the other lasers, PDLs do not penetrate deep to the dermal layers and are mainly used for the epidermal and papillary layers of the skin.[13] PDLs work by causing hypoxia to blood vessels causing collagen realignment, fibroblast reduction, decrease in inflammatory markers, and increase in matrix metalloproteinase.[17] Cannarazzo et al focused on the efficacy of PDL keloid treatment (6-7 J/cm2) on 59 patients with skin types I-IV. Approximately 49.1% of patients reported excellent clearance, 25.4% had good-moderate clearance, 20.4% showed slight clearance, and only 5.08% had minimal or no clearance.[17] The scale included scar color, pliability, height, and texture categories. Adverse reactions included purpura, hyperpigmentation, and hypopigmentation.[17] Work by Zhu et al focused on the effect of PDLs (6-10 J/cm2) on connective tissue growth factor (CTGF), a key component in keloid growth, in cultured keloid fibroblasts. PDLs significantly inhibited keloid fibroblast proliferation and caused down-regulation of CTGF dose-dependently, using 1.5, 3, and 10 ms pulse durations

(P<0.05).[18] There was an insignificant difference when comparing pulse durations using 6, 8, and 10 J/cm2 fluences.[18]

Laser Combination Treatments

Combination laser therapy, which can include 2 lasers or laser and drug therapy, has shown the most optimized outcomes compared to laser monotherapy. Drug therapies include steroids, verapamil, and 5-fluorouracil (5-FU).These combination therapies decrease recurrence rates that are sometimes seen with laser monotherapy.[19]

Several studies exist that describe the efficacy of sequential laser and medical combination therapy. Alexander et al analyzed hypertrophy, dyschromia, and texture while comparing fractional CO2 laser therapy with intralesional steroid (triamcinolone acetonide) vs isolated intralesional steroid therapy and found significant improvement in hypertrophy and dyschromia with reduced but still significant improvement in texture.[20] Super pulse and continuous wave CO2 laser systems with 5-30 mJ of energy and 50-80 mJ energy were used for deep scars followed by superficial scars, respectively, for one pass. Fuenmayor et al analyzed keloid recurrence rates, complications, and self-perceived aesthetic results among patients who underwent 980nm continuous laser excision at 5 watts with subsequent triamcinolone at 0.1-0.2cc, 5 mg/cc. A majority of the patients in this study reported their results as "very good" (64.3%), and there was one case of recurrence of keloid (7.14%).[21] This method was well-tolerated in these categories and suggests its potential as first-line therapy.[21] Shin et al studied the effects of combination therapy with 1550-nm erbium-glass fractional laser and triamcinolone at 40mg/mL, compared to steroids alone. This resulted in significant improvement in the lesion, and categories of fewer sessions, patient satisfaction, and remission times (P<0.42).[22] Cavalie et al identified a significant improvement in keloid appearance with 2940-nm Er:YAG laser and betamethasone twice daily; however, a 22% recurrence rate for these lesions suggests there is room for further development.[23] Khattab et al analyzed 23 cases of keloids treated with PDL and subsequent verapamil and found efficacy in reducing size, hypertrophy, dyschromia, and texture of keloids.[24] Texture was the least modified factor following combination treatment. In combination with a laser's thermal effects, verapamil is known to depolymerize actin and inhibit interleukin- 6 (IL-6) as well as vascular endothelial growth factors (VEGF), which are known to contribute to keloid formation.[25] Combination therapy with 5- FU has also been effective at reducing keloid burden. Alhamzawi et al analyzed CO2 laser therapy at 20 mJ with subsequent 5-FU use at 50 mg/mL to discover a significant improvement in the lesion pliability and height. This combination had adverse effects of ulceration and hyperpigmentation with low recurrence rates after successful treatment, and it was concluded the treatment was a promising option.[26] Sabry et al analyzed 10600-nm CO2 laser with a dwell time of 700-1000 µs in sequential combination with verapamil (5 mg/2 mL) or 5-FU at 250 mg/5 mL.[27] Although 5-FU had an overall higher range of improvement, it was non-significant compared to verapamil combination therapy. Both combinations were significantly improved in comparison to CO2 laser monotherapy.[27] The adverse effects of dermal atrophy and telangiectasias are more commonly seen in steroid treatments, and each treatment option should be considered on a per-case basis.[28]

Several studies show the effects of dual laser combination therapy, suggesting a synergistic mechanism of action. Soliman et al identified combination CO2 and Nd-YAG laser as the most efficacious, utilizing molecular assessment of procollagen to analyze results.[29] In this study, a long-pulsed 1064 nm Nd:YAG laser and the fractional ablative handpiece to the CO2 laser with 40 mJ to 50 mJ of energy were used. Significant differences were identified for decreased procollagen levels for the CO2 laser and combination therapy (P<0.001).[29] Patient satisfaction using POSAS was highest for the combination group at 93.3%, compared to 86.7% and 40% for CO2 laser and Nd:YAG, respectively.[29] Similar results were obtained in a case series analyzing the combination of CO2 and PDL, where a synergistic mechanism was also observed.[30] In this series, keloids were subsequently treated with a jet volumetric remodeling tool used to inject triamcinolone, polyribonucleotides, and sodium chloride. This tool had the most improved outcomes, but nevertheless, combined laser therapy resulted in positive outcomes.[30] Tawfic et al studied the combination of 40 J/cm long-pulsed Nd:YAG (0.3 ms time) and 10,600 nm fractional CO2 laser (dwell time of 1000 µs) and concluded that the combination did not improve outcomes compared to single laser use, leading to a larger side effect profile.[11]

Moreover, much of the existing literature suggests a benefit to using combination laser-drug therapy. The literature has mixed results on the efficacy of dual laser therapy.

Intense Pulsed Light

Intense pulsed light (IPL) uses a high-output flash lamp to produce a broad wavelength light from 500 nm to 1200 nm to target specific skin regions with brief flashes that induce coagulation of the superficial blood vessels. Since IPL is non-ablative, it causes photothermolysis that is limited to hemoglobin and melanin in the skin.[31] Meymandi et al revealed that combined therapy with intralesional corticosteroids and IPL is effective in treating hypertrophic and keloid scars.[32] There was a notable clinical and color improvement (89.1%, 88.8%), respectively, with a scar height of 89.1%.[32] Minimal incidence of adverse events including telangiectasias, hyperpigmentation, and atrophy, were reported (11.6%).[32] Patient satisfaction was 88.8%.[32] Kim et al assessed the efficacy of IPL and intralesional corticosteroid combination therapy.[33] A total of 52 Korean patients were treated at 4- to 8-week intervals, and their scar

appearance was analyzed with modified Vancouver Scar Scale (mVSS), Physician's Global Assessment (PGA), and patient's satisfaction score.[33] Improved appearance of keloids and hypertrophic scars along with increased skin hydration status and skin barrier function were noted.[33] Wat et al examined the use of IPL in uncontrolled, open-label trials and retrospective studies. IPL demonstrated a high evidence (level 1) of treatment of melasma, acne vulgaris, and telangiectasia, a lower evidence (level 3) was found in the case of treating keloidal, hypertrophic, proliferative, hyperpigmented, or erythematous scars.[34] These studies, however, lack rigorous design and controls.[34] Erol et al prospectively assessed the safety and efficacy of IPL on hypertrophic scars from keloids, burns, trauma, surgery, and acne in 109 patients.[35] IPL treatment was administered at 2- to 4-week intervals with patients receiving an average of 8 treatments, and changes in scar appearance were assessed by 2 blinded physicians.[35] The results suggested that IPL is effective in improving the appearance of hypertrophic scars and keloids, regardless of their origin.[35]

Radiofrequency

Radiofrequency tissue volume reduction (RFTVR) uses low levels of radiofrequency to induce protein denaturation or necrosis in soft tissue structures.[36] This leads to tissue retraction and volume reduction in the scar.[36] Teplyi et al reported the efficacy of radiofrequency ablation (RFA) in treating 17 patients with keloids (10) and hypertrophic scars (7).[36] A faster scar volume reduction was seen after 5 sessions of RFA compared to local 5-FU injections.[36] The combination of RFA with verapamil and 5-FU strengthened the efficacy by reducing scar volume by 78.3 %.[36] Reduction in hyperemia was faster with RFA than with cytostatic drug administration.[36] The average scars volume decreased from (3260.5 ± 2057.36) mm3 at the moment after the fifth session to (2110.6 ± 1296.16) mm3, P=0.0033.[36] Aggarwal et al examined the role of intralesional triamcinolone acetonide, triamcinolone acetonide with hyaluronidase, intralesional verapamil hydrochloride, intralesional radiofrequency, and intralesional radiofrequency with triamcinolone acetonide in 100 patients.[37] Intralesional triamcinolone acetonide, intralesional triamcinolone acetonide with hyaluronidase, and intralesional radiofrequency with triamcinolone acetonide were all effective modalities, but not isolated intralesional radiofrequency.[37] Fruth et al reported RFTVR as a minimally invasive and superior option for keloids of the auricle.[38] RFTVR was used to treat keloids on the earlobe and/or helix in 14 patients.[38] In 6 patients, RFTVR was the only treatment modality applied, while the rest received intralesional steroids with RFTVR throughout 1 to 7 sessions.[38] Satisfactory cosmetic results were achieved in 10 of 14 patients, whereas only 3 patients were refractory to treatment and 1 patient demonstrated disease progression despite treatment.[38] Ultimately, RFA is a relatively cheap and effective treatment for keloids when combined with another treatment modality.

CONCLUSION

The findings reveal that EBDs, including fractional CO2, Nd:YAG, diode fiber lasers, radiofrequency ablation, and PDLs, have shown varying degrees of efficacy in reducing the appearance of keloids. Nd:YAG lasers stand out as an effective option offering significant improvements in keloid thickness, erythema, and visual appearance with fewer adverse effects. Combination therapy, which pairs lasers with other modalities such as steroids, verapamil, or 5-FU, has demonstrated promising outcomes, often surpassing monotherapy. These findings suggest that combination therapy could be a beneficial approach to reduce recurrence rates and enhance keloid treatments.

Limitations to this review include heterogeneity of included study design, patient populations, and outcome measures. The decision to use laser-only or combination therapy should be made on a case-by-case basis, considering factors such as patient preferences, keloid characteristics, and available resources. Despite the promising results, further research is needed to establish a gold standard for laser monotherapy and to explore potential advancements in EBDs for keloid treatment.

DISCLOSURES

The authors have no conflict of interest to disclose.

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doi:10.36849/JDD.7826

November 2024 1003 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy of Topical Finasteride 0.25% With Minoxidil 5% vs Topical Minoxidil 5% Alone in Treatment of Male Pattern Androgenic Alopecia

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ABSTRACT

Background: Androgenetic alopecia (AGA) (male pattern hair loss) is the most common form of alopecia in men, affecting 30% of men by the age of 30 years and 50% by the age of 50 years.

Objective: To compare the efficacy of topical finasteride 0.25% with minoxidil 5% vs topical minoxidil 5% alone in the treatment of male pattern androgenic alopecia.

Methods: A total of 164 male patients aged between 30 and 60 years, presenting with androgenic alopecia of more than 2 months duration, were included in this single-blind study conducted at the Department of Dermatology, JPMC, Karachi. The patients were randomly divided into two groups: Group A (topical finasteride 0.25% with minoxidil 5%) and Group B (topical minoxidil 5% alone). Patients were followed up for 12 weeks, and hair regrowth was assessed at each visit.

Results: The mean age in Group A was 33.99±5.97 years, and in Group B it was 33.91±5.71 years. At baseline, the mean salt score was 1.8±0.7 in both groups. The efficacy of the treatment was significantly higher in Group A (86.7%) compared to Group B (69.1%; *P*=0.006).

Conclusion: The combination of topical finasteride 0.25% with minoxidil 5% provides superior efficacy in the treatment of male pattern androgenic alopecia compared to topical minoxidil 5% alone. These findings support the use of this combination therapy as a potential treatment option for patients with androgenic alopecia.

J Drugs Dermatol. 2024;23(11):1003-1008. doi:10.36849/JDD.7826

INTRODUCTION

Androgenic alopecia, commonly known as male pattern baldness, is a prevalent form of hair loss that primarily affects men. It is characterized by a combination of genetic and hormonal factors, particularly the hormone dihydrotestosterone (DHT).[1] DHT causes the hair follicles to shrink, leading to the production of thinner and shorter hair strands. Over time, this results in hair loss and baldness, typically starting at the temples and crown of the head.

The symptoms of androgenic alopecia in men include a receding hairline, thinning hair on the crown of the head, and overall hair loss on the scalp. The severity and progression of these symptoms can vary from person to person.

Several treatment options are available for androgenic alopecia in men. Medications such as minoxidil and finasteride are commonly used. Minoxidil is a topical solution or foam that is applied directly to the scalp to stimulate hair growth.[2] Finasteride, on the other hand, is a prescription medication that blocks the conversion of testosterone to DHT, thereby reducing DHT levels in the scalp and slowing down hair loss.[3]

Hair transplant surgery is another option for men with androgenic alopecia. This procedure involves moving hair follicles from areas of the scalp where hair is still growing to areas where hair loss has occurred.

It is important to note that while these treatments can be effective in slowing down hair loss and promoting hair growth, individual results may vary. It is recommended to consult with a healthcare provider or dermatologist to discuss treatment options and determine the most suitable approach.

The current study aims to evaluate the efficacy of topical finasteride 0.25% in combination with minoxidil 5% compared to topical minoxidil 5% alone in the treatment of male pattern

androgenic alopecia. Through an extensive literature search using various reputable sources, no studies exclusively focusing on a head-to-head comparison of these treatment regimens were found. This highlights the ongoing debate surrounding the clinical relevance of topical finasteride 0.25% with minoxidil 5%.[4] Therefore, this study seeks to provide valuable insights into the therapeutic efficacy and patient outcomes associated with these treatments. The findings from this study will contribute to generating local data and potentially guide future treatment strategies for patients with androgenic alopecia.

In terms of management, the FDA has approved 2 topical preparations for the treatment of baldness: minoxidil and finasteride. Both medications require a trial period of at least 4 to 6 months before any noticeable improvement is observed and must be used continuously to maintain results. Medication adherence can sometimes be challenging, and it is important to be aware that the initiation of these drugs may initially cause a shedding phase.[5] Combining finasteride and minoxidil has been shown to yield better results.[6] However, it is essential to discuss potential risks and benefits with a healthcare provider or dermatologist to make an informed decision.

Hair loss in androgenic alopecia follows a specific pattern and is influenced by intrinsic factors within each hair follicle. The self-regulation of hair follicles in response to androgens plays a role in the differences observed between balding and non-balding areas of the scalp. Hair transplantation experiments have demonstrated that occipital hairs retain their resistance to androgenic alopecia when transplanted to the vertex, while scalp hairs from the vertex transplanted to other areas miniaturize at the same rate as neighboring hairs. The affected areas in androgenic alopecia include the temples, vertex scalp, and mid-frontal scalp, each exhibiting a distinct pattern of hair loss.[7]

It was hypothesized that topical finasteride 0.25% with minoxidil 5% would demonstrate greater efficacy than topical minoxidil 5% alone in the treatment of male pattern androgenic alopecia. This study aimed to compare the effectiveness of a combination therapy of topical finasteride 0.25% with minoxidil 5% versus topical minoxidil 5% alone in the treatment of male pattern androgenic alopecia.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted at the Department of Dermatology, Jinnah Postgraduate Medical Centre (JPMC), Karachi, from July 2021 to January 2022.

Sample Size Calculation

The sample size was calculated using the WHO sample size calculator, considering the efficacy of topical finasteride 0.25% with minoxidil 5% versus topical minoxidil 5% as 85.6% and 69.4%, respectively, in the treatment of male pattern androgenic alopecia. The power of the test (1-β) was set at 80%, and the level of significance (α) was set at 5%. The estimated sample size was determined to be n=82 in each group.

SALT Score

The severity of hair loss was assessed using the Severity of Alopecia Tool (SALT). The scalp was divided into four areas: the vertex (40% of the scalp surface area), the right profile (18%), the left profile (18%), and the posterior aspect (24%). The percentage of hair loss in each area was calculated using the rule of thumb, where one thumb of the patient represented one percent. The SALT score was determined as follows: SALT score = (nv × 0.4) + (nr × 0.18) + (nl × 0.18) + (np × 0.24)

Hair Growth

The percentage of hair loss in each section was calculated, and the scores were summed to obtain the final percentage of hair loss using the SALT score. Hair growth was assessed by comparing baseline photographs with those taken at the last follow-up visit in responsive cases. The percentage change from baseline was recorded as hair growth, calculated as follows: (% Change = (SALT (baseline) – SALT final) × 100% / SALT (baseline)).

Inclusion Criteria

- Male patients aged between 30 and 60 years.
- Patients presenting with androgenic alopecia according to the operational definition.
- Duration of androgenic alopecia greater than 2 months.
- Patients who provided informed consent.

Exclusion Criteria

- Patients with androgenic alopecia who were already undergoing treatment.
- Patients with a history of bleeding disorders, taking anti-coagulant medications or having active local infections or keloidal tendencies.
- Patients with a history of psoriasis or lichen planus.
- Patients with hepatic or renal disease.
- Patients who underwent any therapy within the previous 3 months.
- Patients with a history of major medical illnesses.

Data Collection

The study was approved by the Research Department of the College of Physicians and Surgeons Pakistan. Male patients with androgenic alopecia visiting the Outpatient Department of Dermatology, JPMC, Karachi, who met the inclusion criteria, were enrolled in the study after obtaining informed consent. Clinical information, including gender, age, and disease duration before treatment initiation, was collected. The patients were randomly assigned to two groups (Group A and Group B)

using computer-generated sequential numbers placed in sealed envelopes, which were opened only before the start of the study. The study was conducted in a single-blind fashion. Group A received treatment with topical minoxidil 5% alone, while Group B received treatment with topical finasteride 0.25% with minoxidil 5%. Patients were advised to return for follow-up visits every 15 days for a period of 12 weeks. Hair regrowth was assessed and compared to baseline at each visit and at the 12-week mark. The outcome variable, efficacy, was assessed according to the operational definition after 12 weeks of treatment. The entire procedure was performed by the researcher herself under the supervision of a consultant with more than 5 years of experience. All data were recorded on a pre-designed proforma. Bias and confounding factors were controlled by strictly adhering to the inclusion criteria and conducting stratification.

Data Analysis

The data were analyzed using the statistical package for social science (SPSS Version 23.0). Mean ± SD was calculated for age, duration of disease, SALT score at baseline, and 3 months after treatment. Frequencies and percentages were calculated for the site of patchy alopecia (vertex, occipital, parietal, frontal) and efficacy. The chi-square test was applied to compare the efficacy between the two groups, with a two-sided P-value ≤ 0.05 considered statistically significant. Both groups were compared by age, SALT score at baseline, site of patchy alopecia, and duration of disease using appropriate chi-square or Fisher's exact tests to assess their impact on the outcome, with a two-sided *P*-value ≤0.05 considered significant.

RESULTS

A total of 164 patients were included in the study, with 82 patients in each group (Group A: topical finasteride 0.25% with minoxidil 5%, and Group B: topical minoxidil 5% alone). The objective of the study was to compare the efficacy of these treatments in the management of male pattern androgenic alopecia. The results were analyzed and presented as follows:

Age

The mean age in Group A was 33.99 years with a standard deviation (SD) of 5.97, and the mean age in Group B was 33.91 years with an SD of 5.71. The confidence intervals (CI) for the mean age in Group A and Group B were (32.67 - 35.30) and (32.65 - 35.16) years, respectively (Table 1). These findings indicate that the age distribution was similar between the two groups, with no significant difference in age.

Duration of Disease

The mean duration of disease in Group A was 7.72 months (SD = 2.51), while in Group B, it was 7.64 months (SD = 2.62). The CI for the mean duration of disease in Group A and Group B were (7.16 - 8.27) and (7.06 - 8.21) months, respectively (Table 2). These results suggest that the duration of disease was comparable between the 2 groups.

SALT Score at Baseline

The mean SALT score at baseline in both Group A and Group B was 1.8. In Group A, the SD was 0.7, and in Group B, it was 0.6. The CI for the SALT score at baseline in Group A and Group B were (1.64 - 1.95) and (1.66 - 1.93), respectively (Table 3). These findings indicate that the severity of alopecia at the beginning of the study was similar in both groups.

TABLE 1.

Descriptive Statistics of Age (n=164)							
Age [Years]		n	Minimum	Maximum	Mean	±SD	95% CI
Group	Group A	82	30	60	33.99	5.97	32.67–35.30
	Group B	82	30	60	33.91	5.71	32.65–35.16

TABLE 2.

Descriptive Statistics for Duration of Disease (n=164)							
Duration [Months]		n	Minimum	Maximum	Mean	±SD	95% CI
Group	Group A	82	3	12	7.72	2.51	7.16–8.27
	Group B	82	3	12	7.64	2.62	7.06–8.21

TABLE 3.

Descriptive Statistics of Salt Score at Baseline (n=164)							
Salt Score at Baseline		n	Minimum	Maximum	Mean	±SD	95% CI
Group	Group A	82	1.0	3.0	1.8	0.7	1.64–1.95
	Group B	82	1.0	3.0	1.8	0.6	1.66–1.93

TABLE 4.

Descriptive Statistics of Salt Score After 3 Months (n=164)							
Salt Score After 3 Months		n	Minimum	Maximum	Mean	±SD	95% CI
Group	Group A	82	1.0	6.0	2.9	1.3	2.61–3.18
	Group B	82	1.0	6.0	2.7	1.9	2.28–3.11

TABLE 5.

Distribution for Site of Patchy Alopecia (n=164)				
Groups	Site of Patchy Alopecia			
	Vertex	Occipital	Parietal	Frontal
Group A	18	16	20	29
	11.0%	9.8%	12.2%	17.7%
Group B	18	17	19	27
	11.0%	10.4%	11.6%	16.5%

TABLE 6.

Comparison of Efficacy Between Groups (n=164)			
Groups	Efficacy		*P*-Value
	Yes	No	
Group A (n=82)	72 (86.7%)	11 (13.3%)	0.006
Group B (n=82)	56 (69.1%)	25 (30.9%)	

TABLE 7.

Stratification of Age Group With Efficacy Between Groups (n=164)				
Age Group [In Years]		Efficacy		*P*-Value
		Yes	No	
30 – 35 (n=135)	Group A	58 (86.6%)	9 (13.4%)	0.015
	Group B	47 (69.1%)	21 (30.9%)	
>35 (n=29)	Group A	14 (87.5%)	2 (12.5%)	0.228
	Group B	9 (69.2%)	4 (30.8%)	

Applied *Chi* Square and Fisher's Exact test

TABLE 8.

Stratification of Salt Score at Baseline With Efficacy Between Groups (n=164)				
Salt Score At Baseline		Efficacy		*P*-Value
		Yes	No	
1 – 2 (n=111)	Group A	43 (81.1%)	10 (18.9%)	.017
	Group B	35 (60.3%)	23 (39.7%)	
>2 (n=53)	Group A	29 (96.7%)	2 (3.3%)	0.400
	Group B	21 (91.3%)	2 (8.7%)	

Applied *Chi* Square and Fisher's Exact test

SALT Score after 3 Months

After 3 months of treatment, the mean SALT score in Group A was 2.9 (SD = 1.3), and in Group B, it was 2.7 (SD = 1.9). The CI for the SALT score after 3 months in Group A and Group B were (2.61 - 3.18) and (2.28 - 3.11), respectively (Table 4). These results demonstrate that both treatment groups showed an improvement in the SALT score after 3 months, but the magnitude of improvement was slightly higher in Group A compared to Group B.

Site of Patchy Alopecia

In terms of the distribution of patchy alopecia across different sites, both groups had a similar pattern. In Group A, 18 (11.0%) patients had vertex involvement, 16 (9.8%) had occipital involvement, 20 (12.2%) had parietal involvement, and 29 (17.7%) had frontal involvement. In Group B, 18 (11.0%) had vertex involvement, 17 (10.4%) had occipital involvement, 19 (11.6%) had parietal involvement, and 27 (16.5%) had frontal involvement (Table 5). These results suggest that the distribution of patchy alopecia was comparable between the 2 treatment groups.

Efficacy Comparison

The efficacy of the treatments was assessed by comparing the percentage of patients showing improvement in each group. In Group A, 72 (86.7%) patients showed efficacy, indicating a significant improvement in hair growth. In Group B, 56 (69.1%) patients showed efficacy, demonstrating a relatively lower rate of improvement. The *P*-value for the comparison between the two groups was found to be significant (P=0.006) (Table 6). These findings suggest that the combination therapy of topical finasteride 0.25% with minoxidil 5% (Group A) was more effective in treating male pattern androgenic alopecia compared to topical minoxidil 5% alone (Group B).

TABLE 9.

Stratification for Site of Patchy Alopecia With Efficacy Between Groups (n=164)

Site of Patchy Alopecia		Efficacy		*P*-Value
		Yes	No	
Vertex (N=36)	Group A	18 (100.0%)	0 (0.0%)	0.001
	Group B	10 (55.6%)	8 (44.4%)	
Occpital (N=33)	Group A	16 (100.0%)	0 (0.0%)	0.005
	Group B	10 (58.8%)	7 (41.2%)	
Parietal (N=39)	Group A	18 (90.0%)	2 (10.0%)	0.678
	Group B	17 (89.5%)	2 (10.5%)	
Frontal (N=56)	Group A	20 (69.0%)	9 (31.0%)	0.909
	Group B	19 (70.4%)	8 (29.6%)	

Applied *Chi* Square and Fisher's Exact test

TABLE 10.

Stratification for Duration of Disease With Efficacy Between Groups (n=164)

Duration of Disease		Efficacy		*P*-Value
		Yes	No	
3 – 8 (n=106)	Group A	45 (84.9%)	8 (15.1%)	0.063
	Group B	37 (69.8%)	16 (30.2%)	
>8 (n=58)	Group A	27 (90.0%)	3 (10.0%)	.039
	Group B	19 (67.9%)	9 (32.1%)	

Applied *Chi* Square and Fisher's Exact test

Stratification Analysis

Further analysis was conducted to assess the impact of age group, SALT score at baseline, site of patchy alopecia, and duration of disease on the outcomes in both groups. Stratification by age group, SALT score at baseline, site of patchy alopecia, and duration of disease were performed (Tables 7-10). This analysis aimed to explore if these factors influenced the treatment response and to identify any significant differences between the groups based on these factors. The results of the stratification analysis provide a more detailed understanding of the impact of these variables on the treatment outcomes and can help guide future research and clinical decision-making.

DISCUSSION

Alopecia is a common problem in Pakistan, with a significant impact on the quality of life of those affected. Male pattern androgenic alopecia is a common condition affecting a significant number of individuals worldwide. Various treatment modalities have been explored to address this condition, including topical finasteride and minoxidil. In this study, we aimed to compare the efficacy of topical finasteride 0.25% with minoxidil 5% vs topical minoxidil 5% alone in the treatment of male pattern androgenic alopecia.

The results of our study demonstrated that the combination therapy of topical finasteride 0.25% with minoxidil 5% (Group A) showed superior efficacy compared to topical minoxidil 5% alone (Group B). The percentage of patients showing improvement was significantly higher in Group A (86.7%) compared to Group B (69.1%).[8] These findings are consistent with previous studies that have reported the effectiveness of combining finasteride and minoxidil in the treatment of androgenic alopecia.[9,10]

Topical finasteride, a 5-alpha-reductase inhibitor, acts by reducing the conversion of testosterone to dihydrotestosterone (DHT), the hormone responsible for the miniaturization of hair follicles in androgenic alopecia.[11] By inhibiting DHT production at the scalp level, finasteride helps to maintain hair growth and prevent further hair loss. Minoxidil, on the other hand, is a vasodilator that promotes hair growth by increasing blood flow to the hair follicles and prolonging the anagen phase of the hair cycle.[12]

Our study adds to the existing body of evidence supporting the efficacy of topical finasteride in combination with minoxidil for the treatment of male pattern androgenic alopecia. The combination therapy offers a synergistic approach by addressing both the hormonal aspect of hair loss through finasteride and the local blood flow and hair follicle stimulation through minoxidil.[13] Several studies have shown positive outcomes with the use of combination therapy, supporting our findings.[14,15]

Stratification analysis was performed to assess the impact of different factors on the treatment outcomes. Stratification by age group, SALT score at baseline, site of patchy alopecia, and duration of disease provided valuable insights into the influence of these variables. Although no significant differences were observed between the groups based on these factors, it is important to consider these variables when tailoring treatment approaches for individual patients.[16,17]

It is worth noting that our study has several limitations. Firstly, the study duration was limited to 12 weeks, and long-term follow-up data were not available. Future studies with extended follow-up periods are needed to evaluate the sustained efficacy and safety

of the combination therapy. Secondly, the study sample size was relatively small, which may limit the generalizability of the findings. Further studies with larger sample sizes are warranted to validate our results.[18,19]

Overall, the study results demonstrate that topical finasteride 0.25% combined with minoxidil 5% showed superior efficacy in the treatment of male pattern androgenic alopecia compared to topical minoxidil 5% alone. These findings support the hypothesis that the combination therapy would be more effective. The study contributes to the existing knowledge on the management of androgenic alopecia and provides valuable insights for clinicians and researchers in selecting the appropriate treatment approach for this condition.

CONCLUSION

In conclusion, our study provides evidence supporting the efficacy of topical finasteride 0.25% with minoxidil 5% in the treatment of male pattern androgenic alopecia. The combination therapy showed superior efficacy compared to topical minoxidil 5% alone. Clinicians should consider combination therapy as a potential treatment option for patients with androgenic alopecia. Further research and randomized controlled trials are necessary to establish the optimal dosage, treatment duration, and long-term outcomes of this combination therapy.[20,21]

DISCLOSURES

Consent was obtained or waived by all participants in this study. The authors of the study were actively involved in various aspects, including the study design, data collection, management, review, drafting of the article, and critically reviewing it. The authors have disclosed no conflicts of interest.

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doi:10.36849/JDD.7816R1

November 2024 1010 Volume 23 • Issue 11

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Biologic Use During Pregnancy and Breastfeeding in Dermatology: An Evidence-Based Review

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ABSTRACT

Biologic medications have revolutionized the treatment of many dermatologic conditions. However, their use during pregnancy and breastfeeding is a subject of ongoing concern due to limited data on their safety in these populations. As the course of many inflammatory skin conditions is unpredictable during pregnancy and may worsen, biologics are important therapeutic tools for disease stabilization in this patient population. In this review, we provide a comprehensive summary of the gestational safety profile of biologics commonly used in dermatology and provide recommendations during pre-conception, pregnancy, and post-partum periods. We also examine fertility data, placental transfer of biologics, and postpartum immunosuppression/immunomodulation data.

J Drugs Dermatol. 2024;23(11):1010-1015. doi:10.36849/JDD.7816R1

INTRODUCTION

Several classes of monoclonal antibody biologics medications are used in dermatology to treat inflammatory dermatoses, including inhibitors of tumor necrosis factor (TNF), interleukin-17 (IL-17), IL-23, IL13, IL4/13, IL-12/23 and CD20. Despite promising therapeutic potential, the safety data for biologic use in pregnant and breastfeeding patients is still limited, as randomized controlled trials are rare. However, data from case studies/series, pregnancy registries, and cohort studies can offer insights into the efficacy and safety profile of individual biologics for both the mother and fetus. Herein, we provide an evidence-based review of the safety of commonly used biologics in dermatology to guide the management of inflammatory skin diseases during pregnancy, breastfeeding, and vaccination administration. Overall recommendations for the preconception, peripartum, and postpartum periods are summarized in Table 1, in addition to the Food and Drug Administration (FDA) pregnancy category for each drug. Specific guidelines from the American College of Rheumatology (ACR) were included if available as they are based on the most comprehensive data available, with European Medicine Agency (EMA) or European Task Force on Atopic Dermatitis (ATFAD) guidelines being included if ACR guidelines were unavailable.

Fertility and Biologics

With the increasing widespread use of biologics, many women of childbearing years are receiving these medications for their dermatologic conditions. Thus, in patients wishing to conceive, it is important to examine the effect of these biologics on the reproductive potential of both men and women. Although the data on this topic is fairly limited, TNF inhibitors remain the most studied biologics in regard to fertility. A majority of studies do not show any decrease in male fertility with anti-TNF agent exposure.[2] One study examined the sperm quality in a group of 23 men with ankylosing spondylitis before and after receiving anti-TNF therapy (adalimumab, infliximab, etanercept). Sperm quality of men exposed to TNF inhibitors was found to be comparable to healthy controls, even after long-term treatment.[3] Another study in men with ankylosing spondylitis and psoriatic arthritis described multiple men who achieved pregnancy despite infliximab therapy.[4] Of note, some case reports noted a decrease in sperm quality, sperm motility, and abnormal morphology in male patients who received TNF inhibitors. However, these reports had several confounding factors, such as the severity of the disease and limitations.[5-8] There is currently a lack of publicly available human studies in dermatological conditions investigating the effects of biologics

TABLE 1.

Recommendations From the American College of Rheumatology (ACR), European Medicine Agency (EMA), and European Task Force on Atopic Dermatitis (ETFAD)

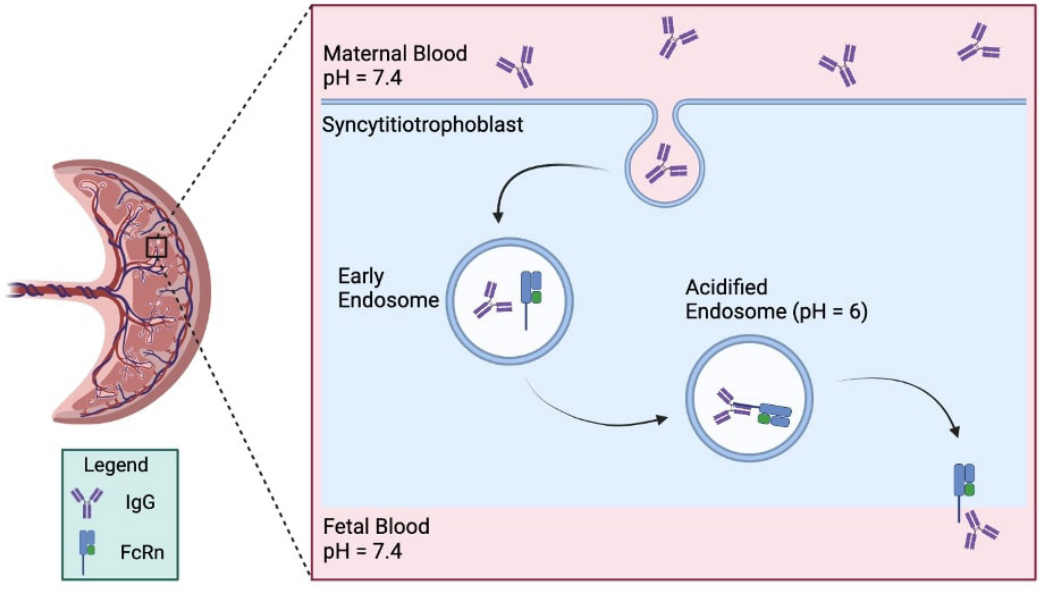
Biologic	Pre-conception	Pregnancy	Lactation	FDA Pregnancy Category
certolizumab (ACR)	Strongly recommended continuation	Strongly recommended continuation	Strongly recommended continuation	Not assigned
adalimumab (ACR)	Conditionally recommended continuation	Conditionally recommended continuation in 1st and 2nd trimesters and discontinuation in 3rd trimester	Strongly recommended continuation	B
etanercept (ACR)	Conditionally recommended continuation	Conditionally recommended continuation in 1st and 2nd trimesters and discontinuation in 3rd trimester	Strongly recommended continuation	B
infliximab (ACR)	Conditionally recommended continuation	Conditionally recommended continuation in 1st and 2nd trimesters and discontinuation in 3rd trimester	Strongly recommended continuation	B
Risankizumab (EMA)	Contraception is recommended until at least 21 weeks after the end of treatment (EOT)	Discontinue	Decision to continue breastfeeding/ treatment based on a risk/benefit analysis for the child and the mother (EMA)	Not assigned
tildrakizumab (EMA)	Contraception is recommended until at least 17 weeks after the EOT	Discontinue	Decision to continue breastfeeding/ treatment based on a risk/benefit analysis for the child and the mother	Not assigned
Guselkumab (EMA)	Contraception is recommended until at least 12 weeks after the EOT	Discontinue	Decision to continue breastfeeding/ treatment based on a risk/benefit analysis for the child and the mother	Not assigned
Ustekinumab (ACR)	Conditionally recommend discontinuation at conception	Conditionally recommend discontinuation during pregnancy	Expect minimal transfer due to large molecular size, but no available data	B
Secukinumab (ACR)	Conditionally recommend discontinuation at conception	Conditionally recommend discontinuation during pregnancy	Expect minimal transfer due to large molecular size, but no available data	B
Ixekizumab (EMA)	Contraception is recommended until at least 10 weeks after the EOT	Discontinue	Decision to continue breastfeeding/ treatment based on a risk/ benefit analysis for the child and the mother	B
rituximab (ACR)	Conditionally recommend discontinuation at conception	Conditionally recommend use ONLY for life/organ threatening disease	Strongly recommend use during lactation	C
dupilumab (ETFAD)	Discontinue at conception	Discontinue	Discontinue	Not assigned
tralokinumab (EMA)	N/A	Discontinue	Decision to continue breastfeeding/ treatment based on a risk/benefit analysis for the child and the mother	Not assigned

TABLE 2.

FDA Categories - Previous

Category	Type of Evidence
A	Adequate studies in pregnant women that have failed to demonstrate risk to the fetus.
B	Animal studies show no fetal risks, and there are no adequate human studies; or human studies show no fetal risk despite fetal risk in animal studies.
C	Animal studies show fetal risk, and there are no adequate human studies; or no animal and no human studies. Potential benefits may warrant use of the drug despite risks.
D	Positive evidence of fetal risk in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Positive evidence of fetal abnormalities in humans. Risks involved in use of the drug in pregnant women clearly outweigh potential benefits. Contraindicated.

FIGURE 1. Mechanism of neonatal Fc receptor-mediated active placental transfer of IgG.



on male and female fertility, particularly those beyond anti-TNFs, which are relatively new in use. Despite this, it is important to monitor the effects of biologics on fertility in both men and women, particularly in those who are of reproductive age and may wish to conceive.

Classification of Drugs in Pregnancy

The first set of drug labeling regulations developed by the United States (US) Food and Drug Administration (FDA) required drugs to be assigned to one of 5 pregnancy categories (A, B, C, D, and X; Table 2).[9] This classification system was criticized for oversimplification, the ambiguity of category C, and the fact that a drug with no animal or human data is included in the same category as a drug with adverse effects on animal fetuses. Given these issues, the FDA removed the pregnancy letter labeling as of June 2020 and instead required more detailed pregnancy categories with medication-specific risk summaries.

Placental Transfer of Biologics

Placental transfer of biologics refers to the passage of drugs or other biologically active substances from the mother's bloodstream through the placenta and into the bloodstream of the developing fetus. The extent of placental transfer of drugs depends on multiple factors, including the physicochemical properties of the drug and the stage of fetal development. The potential risks of placental transfer of biologics, specifically, depend on the specific drug and the stage of fetal development. Immunoglobulin G (IgG) and low levels of immunoglobulin A (IgA) are the only antibodies transferred from the mother to the fetus by the placenta, providing the infant with humoral immunity in early life. The active transplacental transport mechanism for IgG involves the binding of maternal IgG to the neonatal immunoglobulin constant fragment receptor (FcRn), with the transplacental transport of IgG1 being the most efficient and IgG2 being the least efficient.[10] This mechanism is detailed in Figure 1. This suggests that monoclonal antibodies with Fc domains will exhibit high transplacental transfer to the fetus, whereas antibodies lacking the Fc domain or those with less efficient subclasses such as IgG2 have lower transplacental transfer.

While most TNF inhibitors such as infliximab and adalimumab have IgG1 subclass, certolizumab pegol (CZP) is a unique biologic in that it is the only PEGylated anti-TNF-α agent without an Fc domain. Because of its unique structure and lack of Fc domain, certolizumab is not actively transported across the placenta during pregnancy. However, low levels may cross the placenta by alternative mechanisms. In a study of 31 women with Crohn's disease, infliximab and adalimumab demonstrated significant placental transfer, whereas CZP had only minimal placental transfer to the infant.[11] The CRIB study, a multicenter, prospective study, also found there was negligible to low placental transfer of CZP from mothers to infants.[12]

For other biologics that may result in placental transfer during the third trimester, such as adalimumab and infliximab, these antibodies are known to persist in the infant's serum for around six months after birth.[13] A prospective study in Spain of infants born to mothers treated with TNF inhibitors throughout pregnancy observed a decreased Treg cell frequency at birth

for these infants that inversely correlated with the mother's peripartum anti-TNF levels. They also reported a decreased response after mycobacterial challenge, which was used to test immune response in these infants, and some infants presented with atopy (predominantly atopic dermatitis) in the first year. Furthermore, some case reports suggest that TNF inhibitor exposure during pregnancy may be associated with neonatal neutropenia until around 8 to 14 weeks after birth.[14] Prior case reports have reported that these infants with third-trimester biologic exposure may be immunosuppressed after birth and unable to mount an appropriate immune response to infections or vaccines.[15,16] Further studies are needed in the future to assess the degree of postpartum-altered immune function in infants exposed to biologics in utero.

TNF Inhibitors

TNF inhibitors are the most studied biologics in relation to pregnancy. Animal studies in the past have shown that treatment with TNF inhibitors during pregnancy and lactation have little to no effect on the development and maturation of the offspring's immune system.[17,18] In addition to the effects on the fetus, it is also important to consider the pregnancy outcomes in human women exposed to biologics. The Organization of Teratology Information Specialists (OTIS) is a non-profit organization that established a collaborative research group in 1998 to study pregnancy outcomes following selected exposures. One prospective cohort study done by OTIS examined the birth outcomes of women who took adalimumab during pregnancy and found that the adalimumab-exposed pregnancies group was not associated with an increased risk for any of the adverse outcomes examined when compared with disease-matched-unexposed pregnancies group.[19] One retrospective study used the infliximab safety database to examine the pregnancy outcomes in women receiving infliximab for the treatment of Crohn's and rheumatoid arthritis. Of the 96 pregnancies with outcome data after infliximab exposure in the database, 67%, 14%, and 19% of the pregnancies resulted in live births, spontaneous miscarriages, and therapeutic miscarriages, respectively. These results were similar to the general population of pregnant women with Crohn's not exposed to infliximab.[20] Another study utilizing the Janssen's global safety surveillance database examined 1850 pregnancies with maternal infliximab exposure and found 82.5% resulted in live births, 12.1% resulted in spontaneous abortion/intrauterine death/ectopic pregnancy/molar pregnancy, 9.2% resulted in preterm births, 3.6% resulted in low birth weight infants, 2% congenital anomalies, and 1.2% infant infections. This frequency was consistent with the general population.[21] When considering the persistence of biologics in child blood after birth, certolizumab did not persist in child blood, whereas infliximab, adalimumab, and etanercept persisted for 7.3, 4, and 3 months, respectively.[22]

When examining the relevant outcomes within the first year of life, children born to mothers on certolizumab did not experience any reported abnormal growth or developmental changes. No serious adverse events were reported in the infliximab group, abnormal infant's immune response to BCG vaccine was reported in one case in the adalimumab group, and 17% of children experienced diarrhea and fever following the rotavirus vaccination in the etanercept group. The American College of Rheumatology (ACR) released guidelines on the management of rheumatologic diseases with biologics during pregnancy. The ACR strongly recommended continuation of certolizumab prior to, during, and after pregnancy due to the lack of FC chain and minimal placental transfer of the drug.[23] However, they only conditionally recommended the continuation of other TNF inhibitors such as infliximab, etanercept, or adalimumab during conception, first trimester, second trimester, and breastfeeding. They recommended the discontinuation of these other TNF inhibitors besides certolizumab during the third trimester if the patient's disease is under good control due to the risk of significant serum levels of the drug in the neonate for a period of time.

IL-23 Inhibitors

The data on the impact of IL-23 inhibitors on pregnancy and fetal outcomes is very limited; thus, we must rely on recommendations derived from mechanisms and clinical expertise. Per the EMA, contraception is recommended until at least 21, 17, and 12 weeks after the end of the treatment of Risankizumab, Tildrakizumab, and Guselkumab, respectively. They recommended the discontinuation of all IL-23 inhibitors during pregnancy and stated the decision to restart during breastfeeding should be based on a risk/benefit analysis on a case-by-case basis.[24]

IL-17 Inhibitors

Secukinumab and Ixekizumab are IgG1 monoclonal antibodies that bind to IL-17A. The data on the usage of IL-17 inhibitors during pregnancy is limited. One study used the Novartis global safety database to analyze outcomes of pregnancies with maternal or paternal Secukinumab exposure and did not find any evidence for increased rates of adverse pregnancy outcomes with Secukinumab. However, most patients discontinued Secukinumab in the first trimester, whereas Secukinumab is thought to be transferred through the placenta in the third trimester.[25] Per ACR guidelines, it is conditionally recommended to discontinue Ustekinumab and Secukinumab at conception and pregnancy. Per EMA guidelines, contraception should be used at least 10 weeks after stopping Ixekizumab and Ixekizumab should be discontinued during pregnancy. They state the decision to restart during breastfeeding should be decided on a risk analysis on a case-by-case basis. The EMA also recommends avoiding Secukinumab during pregnancy and suggests the use of appropriate contraception for at least 20 weeks after the last dose.[26]

IL-12/23 Inhibitors

Ustekinumab is an IgG1 monoclonal antibody that binds to p-40 subunit of both IL-12 and IL-23. One retrospective case series in the identified 10 pregnancies among 7 women with Ustekinumab exposure during conception and pregnancy in patients with chronic plaque psoriasis. Of the 10 pregnancies, 7 resulted in full-term delivery, 1 pre-term deliver due to unrelated maternal complications, and 2 miscarriages in 1 woman.[27] Per ACR guidelines, it is conditionally recommended to discontinue Ustekinumab at conception and pregnancy. Per EMA guidelines, contraception should be used at least 10 weeks after stopping.

Anti-CD-20

Rituximab is an anti-CD20 monoclonal antibody with scarce data on the use during pregnancy. However, one systematic review identified 102 pregnancies with rituximab use within 6 months of conception and noted 78 resulted in live births and 12 resulted in spontaneous abortions, with B-cell counts low in 39% of newborns and normalizing in 6 months.[28] The ACR conditionally recommends continuing rituximab while a woman is trying to conceive and during pregnancy if the disease warrants the use and strongly recommends continuing rituximab during breastfeeding.[23]

IL-4/13 and IL-13 Inhibitors

Dupilumab, an IgG4 monoclonal antibody that targets the alpha subunit of IL-4 and prevents IL-4 and IL-13 signaling is the only biologic used for atopic dermatitis. One study examined 36 reports related to dupilumab outcomes in pregnancy using the VigiBase database to evaluate the safety profile of dupilumab. They evaluated the following pregnancy, puerperium, and perinatal adverse events: abortion, induced abortion, spontaneous abortion, preeclampsia, ectopic pregnancy, heterotopic pregnancy, preterm premature rupture of membranes, and neonatal jaundice. They found that the odds ratio for most adverse events were lower in patients on dupilumab and concluded that dupilumab appears to be safe during pregnancy.[29] In addition, several published case reports of women on dupilumab before, during, and after pregnancy showed very successful outcomes with no adverse maternal or fetal outcomes.[30-33] Per the ETFAD, Dupilumab should be discontinued at conception and not used during pregnancy and breastfeeding.[34] However, the EMA reported no impairment on fertility with animal studies and stated that dupilumab should only be used if benefits outweigh the theoretical risk during pregnancy and breastfeeding.[22]

Biologics and Breastfeeding

Although biologics have low oral bioavailability, the neonatal Fc receptor can mediate the uptake of undigested immunoglobulins at the intestinal epithelial cells, which suggests biologics could be excreted into breastmilk and absorbed in infants. The Pregnancy in IBD and Neonatal Outcomes (PIANO) registry is a multicenter national prospective study for women with IBD that collected the 1-year post-partum follow-up of 824 women with 75% breastfeeding. One study found that less than 25% of 72 patients on biologics had measurable amounts of Adalimumab, Certolizumab, and Golimumab in collected breast milk samples.[35]

A Multicenter, Postmarketing Study Evaluating the Concentration of Cimzia® in Mature Breast Milk of Lactating Mothers (CRADLE) found that CZP had minimal transfer into breast milk.[36] It is thought that CZP is unlikely to cross into breastmilk to be absorbed by infants due to its large molecular size, low oral bioavailability, and lack Fc domain. The data for use of the other biologics classes during breastfeeding is limited. However, infant serum levels of the biologics after breastfeeding can depend on amount of breastmilk consumed, concentration of drug in the breastmilk, and absorption into the infant's gastrointestinal tract. Given the complexities of biologics and breastfeeding, individualized risks and benefits should be reviewed with each patient to promote shared decision making. Breastfeeding-compatible medications should also be discussed to help achieve disease control. In addition, dermatologists should be encouraged to collaborate with pediatricians on a case-by-case basis.

Vaccines in Infants Exposed to Biologics

Infants born to mothers exposed to biologics may be at an increased risk of infection, making it important to consider the types of vaccines given to these infants. The American Gastroenterological Association IBD Parenthood Project recommends that infants born to mothers exposed to any biologic therapy, except for certolizumab, should avoid receiving live vaccines during the first 6 months of their life as they may not be effective or could cause harm.[37] Live vaccines are those that contain weakened or attenuated live viruses, such as the rotavirus vaccine. The rotavirus vaccine is the only live vaccine administered before 6 months of age in the US. Therefore, it is important to avoid this vaccine in infants born to mothers who have been exposed to biologics, besides certolizumab, during pregnancy and/or breastfeeding. However, it is important to note that other non-live vaccines, such as the pneumococcal vaccine and the Haemophilus influenzae type b vaccine, are safe to administer to these infants.

After 6 months of age, the risk of infection is lower, and the infant's immune system may be more developed, allowing for live vaccines to be more safely administered. The MMRV (measles, mumps, rubella, and varicella) live vaccines are typically given to infants at one year of age and are appropriate to administer even if the infant is actively breastfeeding. Healthcare providers need to discuss vaccination options with mothers who have been exposed to biologics during pregnancy or breastfeeding.

CONCLUSION

TNF inhibitors have the most robust safety data for preconception, pregnancy, and breastfeeding periods. Current guidelines show certolizumab is the safest to use throughout the pregnancy. Current large studies and interim registry data show no increased adverse outcomes in women on biologics during pregnancy. However, given the limited data on use during pregnancy for other classes of biologics besides TNF inhibitors, the use of biologics from these other classes is not recommended during pregnancy if possible, and contraception is recommended concurrently. The avoidance of live vaccines, specifically the rotavirus vaccine, for the first 6 months of life is recommended for infants with mothers who had third-trimester biologic exposure, excluding certolizumab. As more biologics are being developed and those in the pipeline receive approval, more real life, registry, and trial data on this topic will be available. Thus, guidelines and recommendations for considering biologics during pregnancy and breastfeeding will need to be routinely updated. Overall, biologics should be considered on a case-by-case basis through shared decision-making when potential benefits outweigh the theoretical risk.

DISCLOSURES

VYS is on the board of directors for the Hidradenitis Suppurativa Foundation (HSF), is a stock shareholder of Learn Health and has served as an advisory board member, investigator, speaker, and/or received research funding from Sanofi Genzyme, Regeneron, AbbVie, Eli Lilly, Novartis, SUN Pharma, Genentech, LEO Pharma, Pfizer, Incyte, Boehringer Ingelheim, Aristea Therapeutics, Menlo Therapeutics, Dermira, Burt's Bees, Galderma, Kiniksa, UCB, Target-PharmaSolutions, Altus Lab/cQuell, MYOR, Polyfins Technology, GpSkin, Alumis, Skin Actives Scientific and the National Eczema Association. JLH is on the Board of Directors for the Hidradenitis Suppurativa Foundation, and has served as an advisor for Novartis, UCB, and Boehringer Ingelheim and as a speaker and advisor for AbbVie. Other authors have no conflicts to disclose.

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FORMULATION FOUNDATIONS:
A PEAK BEHIND THE DEVELOPMENT CURTAIN

Host: Dr. Adam Friedman | Guest: Dr. David Osborne

Finding the right formulation is not always a fun endeavor for the practitioner or patient, and can be the make or break for patient adherence. In fact, an active ingredient without a thoughtful, purposeful, clinically translatable vehicle is like peanut butter without jelly (though for us PB lovers who eat it from a spoon maybe that's not the best analogy). But how are we to think critically about the lotion or potion in which our cutting edge topical therapies are suspended/dissolved when this is not part of our training or CME? No need to answer because we've got the C.R.E.A.M. Joining podcast host Dr. Adam Friedman is formulation foreman Dr. David Osborne, Chief Technical Officer at Arcutis Therapeutics. Let's just say there is a really good chance you have prescribed something my man has invented over the past several decades. Uncap your knowledge gap and tune in to learn about key vehicle considerations to keep your form in check.

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This podcast is funded by Arcutis Therapeutics.

doi:10.36849/JDD.8639

November 2024 1017 Volume 23 • Issue 11

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Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel in Participants With Moderate-to-Severe Acne: The Patient Journey

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ABSTRACT

Introduction: Topical clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel is the only fixed-dose, triple-combination formulation approved for acne treatment. In 3 clinical studies of participants with moderate-to-severe acne, CAB demonstrated superior efficacy to vehicle and component dyads, with good safety and tolerability. Detailed efficacy/safety data from individual clinical study participants are presented.

Methods: In two phase 3 (NCT04214652, NCT04214639) randomized, double-blind, 12-week studies, participants aged at least 9 years with moderate-to-severe acne were randomized to once-daily CAB or vehicle gel. Descriptive data—including lesion count changes, treatment success (at least 2-grade reduction from baseline in Evaluator's Global Severity Score and clear/almost clear skin), compliance, treatment-emergent adverse events (AEs), and cutaneous safety/tolerance assessments—were summarized from 6 CAB-treated cases.

Results: By week 12, all cases achieved >70% lesion reductions, 4/6 achieved treatment success, and 1/6 achieved a 2-grade reduction in severity. All cases were compliant with CAB treatment. No cases reported serious AEs. Transient increases occurred on cutaneous safety and tolerability assessments, with scores generally decreasing back to/below baseline levels by week 12.

Conclusions: In two phase 3 clinical trials, fixed-dose, triple-combination CAB demonstrated good efficacy/safety. All 6 CAB-treated cases achieved substantial (>70%) lesion reductions, with 5/6 achieving treatment success or 2-grade reduction in severity by week 12. Transient cutaneous safety/tolerability severity increases generally resolved to baseline values by week 12. These clinical study cases reinforce the importance of patient education regarding adherence, expectations, and AEs.

J Drugs Dermatol. 2024;23(11):1017-1024. doi:10.36849/JDD.8639

INTRODUCTION

Treatment of acne vulgaris is difficult due to its chronicity, long treatment time course, and low patient adherence.[1,2] The main treatment goal is to clear lesions quickly to manage and/or mitigate persistent sequelae such as scarring and/or dyspigmentation.[3]

Topical clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB; Cabtreo®; Ortho Dermatologics) gel is the only fixed-dose, triple-combination formulation approved for acne treatment. In 3 clinical studies of participants with moderate-to-severe acne, CAB demonstrated superior efficacy to vehicle and component dyads, with good safety and tolerability.[4,5] As clinical data may provide a limited perspective on individual participant experiences, detailed efficacy and safety data from 6 clinical study participants with moderate-to-severe acne are presented here to document their treatment journey with CAB.

METHODS

Study Design and Participants

Details of the two phase 3 randomized, double-blind, vehicle-controlled, 12-week studies (NCT04214639; NCT04214652) have been published previously.[5] In brief, eligible participants aged ≥9 years with moderate-to-severe acne were randomized (2:1) to once-daily treatment with CAB or vehicle gel. These studies were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and were approved by institutional review board/ethics committees at all sites. All participants or their legal guardians provided written informed consent.

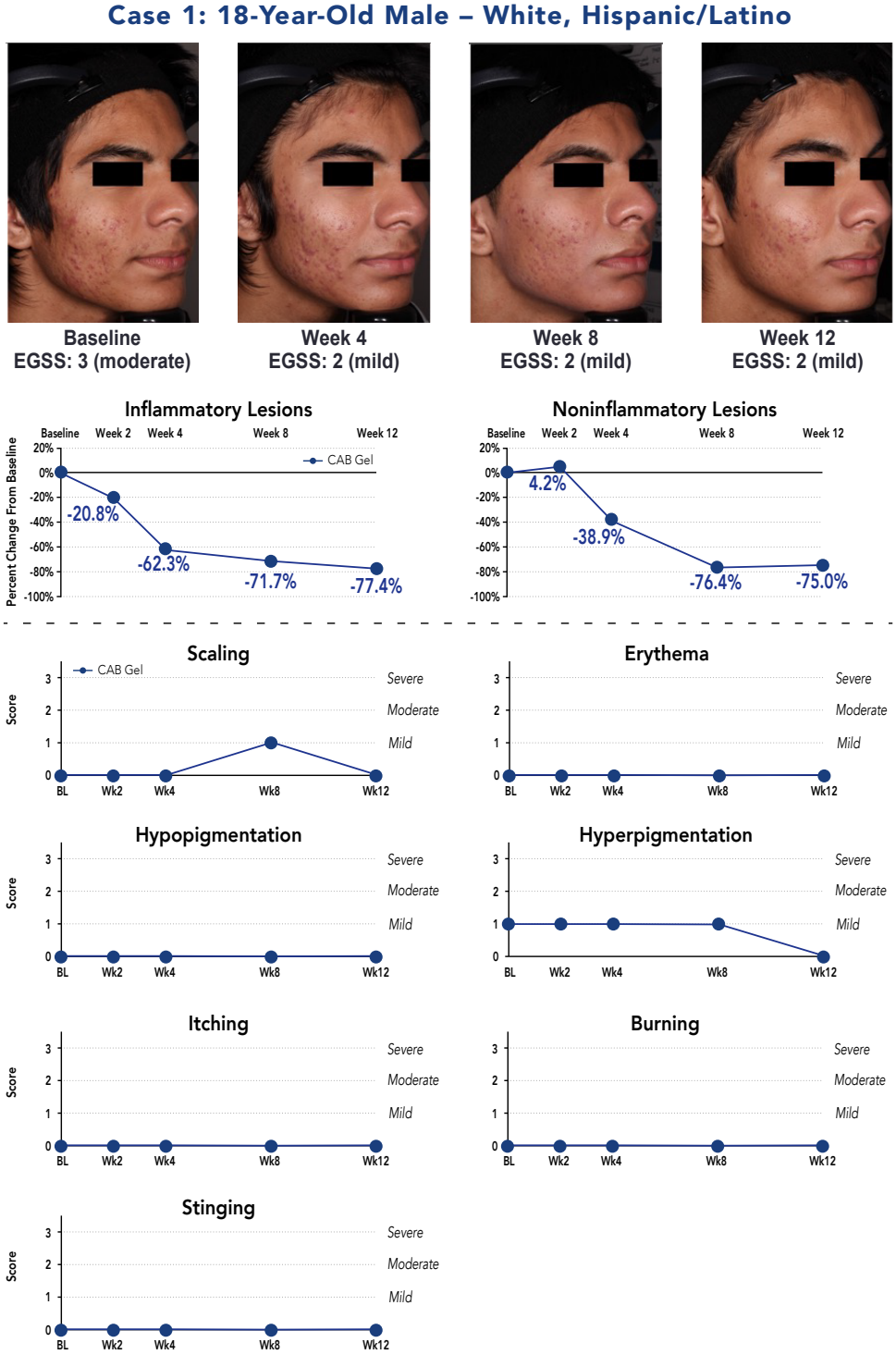
Study Assessments

Endpoints included percentage of participants achieving treatment success (≥2-grade reduction from baseline in Evaluator's Global Severity Score [EGSS] and clear/almost clear skin) and percent change from baseline in inflammatory/noninflamma-

tory lesion counts at week 12. Assessments occurred at baseline and weeks 2, 4, 8, and 12. Investigator-assessed cutaneous safety (scaling, erythema, hypopigmentation, hyperpigmentation) and participant-assessed tolerability (itching, burning, stinging) were scored using a 4-point scale (0=none to 3=severe). Treatment compliance was defined as participants not missing >5 consecutive days of dosing and applying 80%-120% of expected applications. Adverse events (AEs) were monitored throughout the studies.

Descriptive efficacy, safety, and tolerability data from selected cases who completed 12 weeks of CAB treatment are summarized.

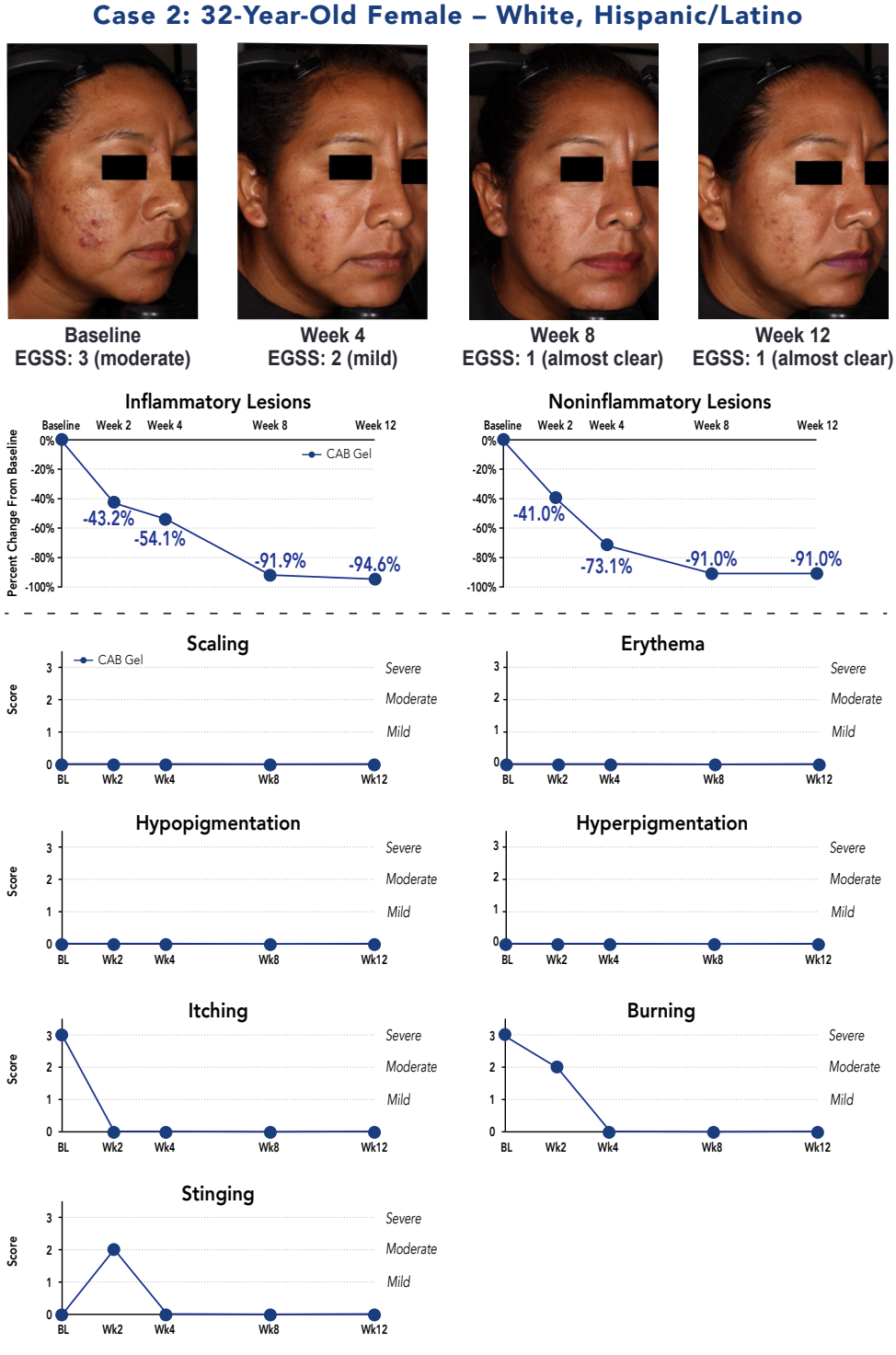
FIGURE 1. Photographs, acne severity, treatment efficacy, and cutaneous safety/tolerability by visit for 6 CAB-treated cases.



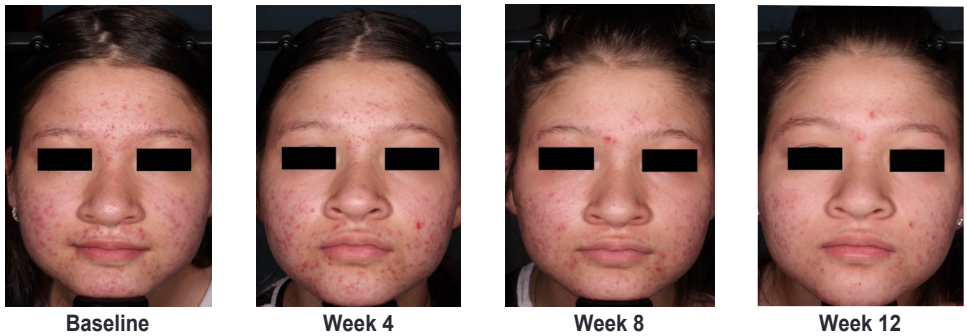
RESULTS

Photographs, efficacy results, and cutaneous safety/tolerability assessments are shown for 6 CAB-treated cases by visit in Figure 1. Demographic characteristics and EGSS are presented with photographs (none were taken at week 2). Three cases were female. Four cases self-identified as White, 2 as Asian, and 2 as Hispanic/Latino. Ages ranged from 13 to 32 years. All cases were compliant with CAB treatment (100%, n=4; 97.4%, n=1 [case 2]; 94.3%, n=1 [case 4]). By week 12, all cases achieved >70% acne lesion reductions, and 5/6 achieved either treatment success or a 2-grade reduction in acne severity.

One case (case 4) reported a treatment-related treatment-emergent AE (TEAE; mild application site dermatitis on treatment day 5 that resolved by day 77), and none reported serious AEs. While patterns in cutaneous safety/tolerability were



Case 3: 13-Year-Old Female – Asian, Non-Hispanic/Latino

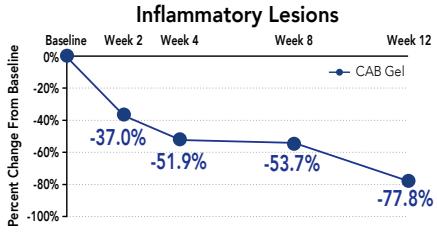


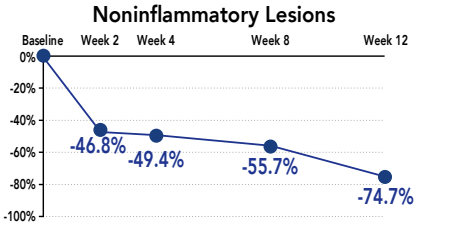
Baseline
EGSS: 4 (severe)

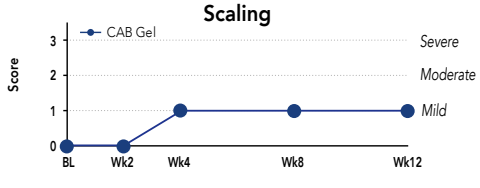
Week 4
EGSS: 3 (moderate)

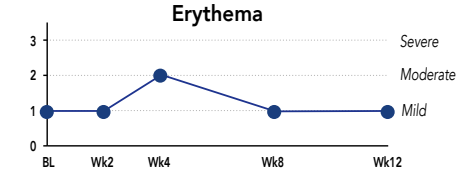
Week 8
EGSS: 3 (moderate)

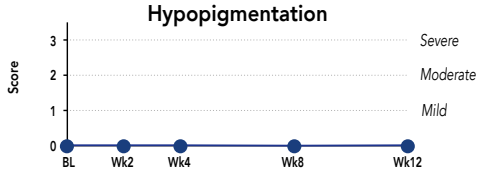
Week 12
EGSS: 2 (mild)

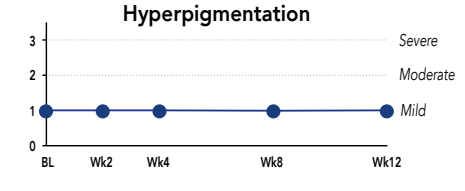


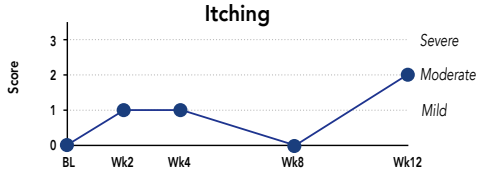


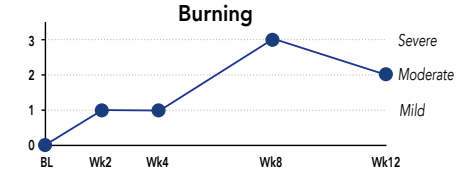


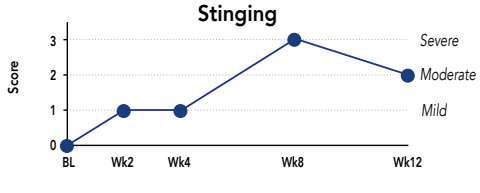




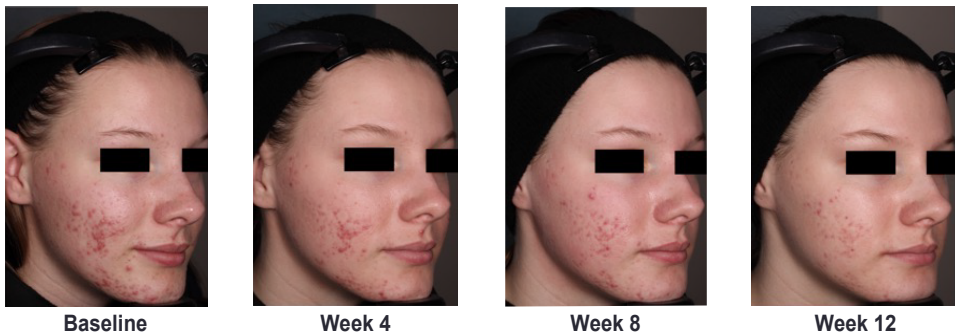








Case 4: 18-Year-Old Female – White, Non-Hispanic/Latino

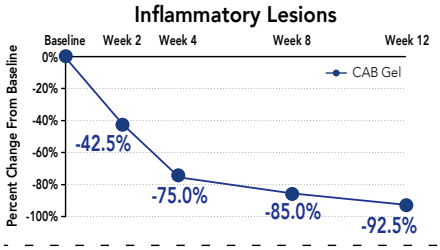


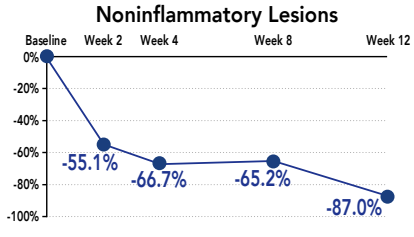
Baseline
EGSS: 3 (moderate)

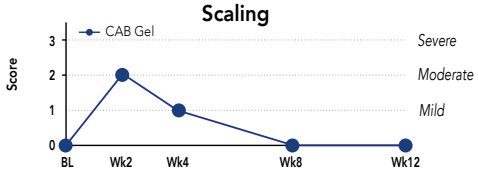
Week 4
EGSS: 3 (moderate)

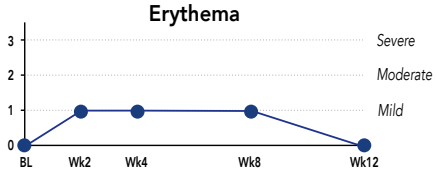
Week 8
EGSS: 2 (mild)

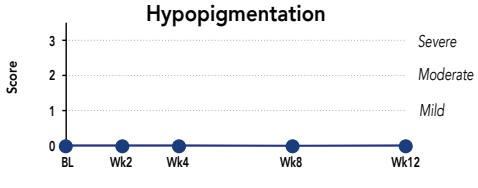
Week 12
EGSS: 1 (almost clear)

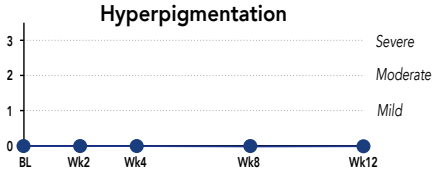


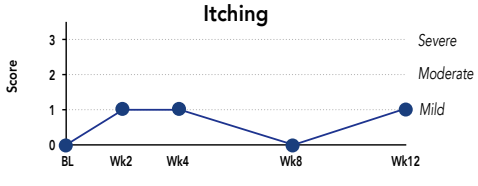


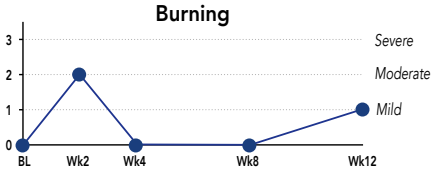


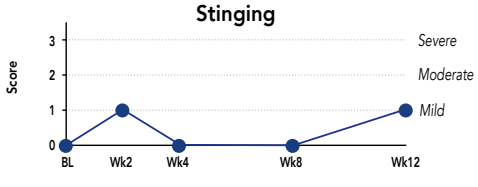




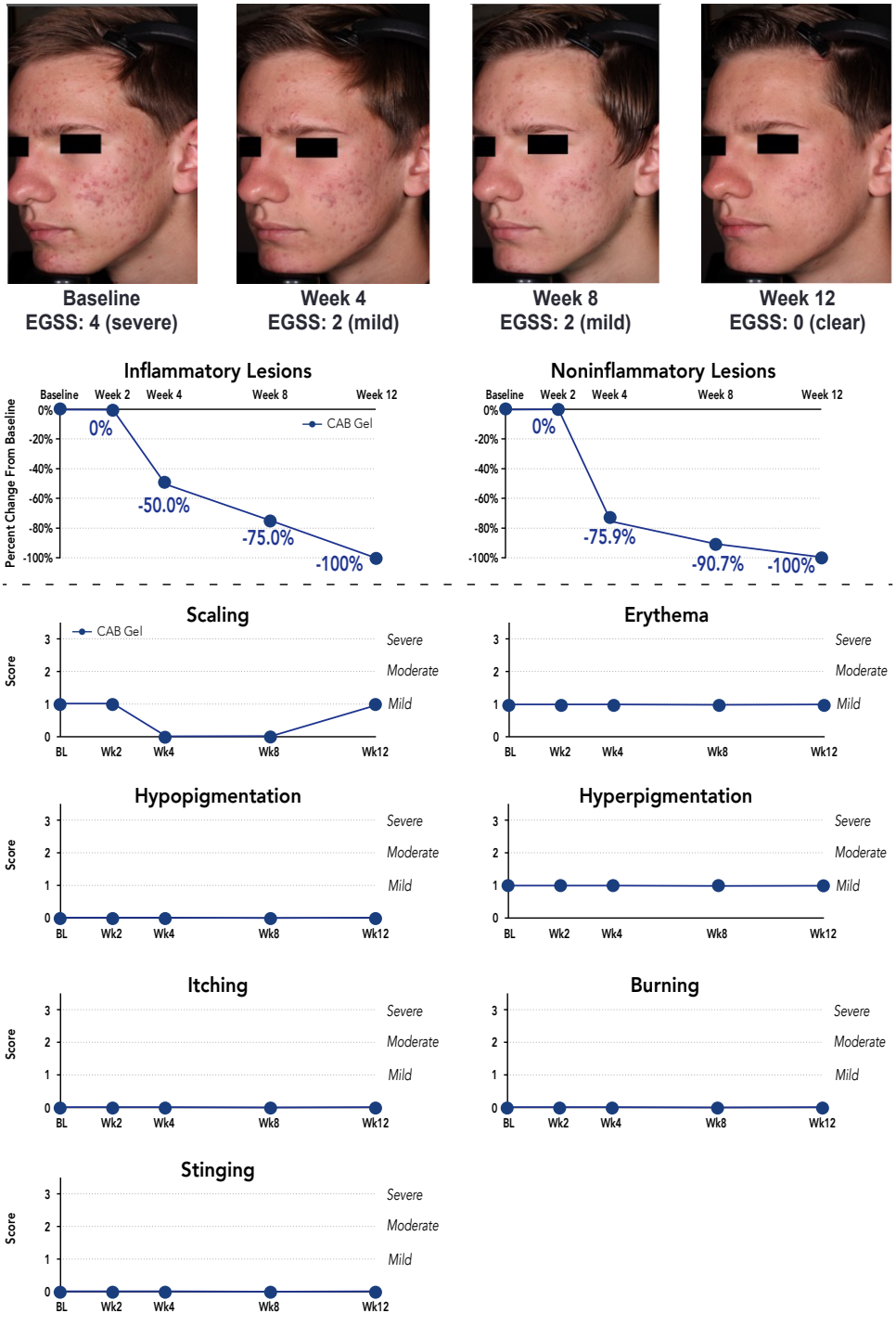








Case 5: 16-Year-Old Male – White, Non-Hispanic/Latino

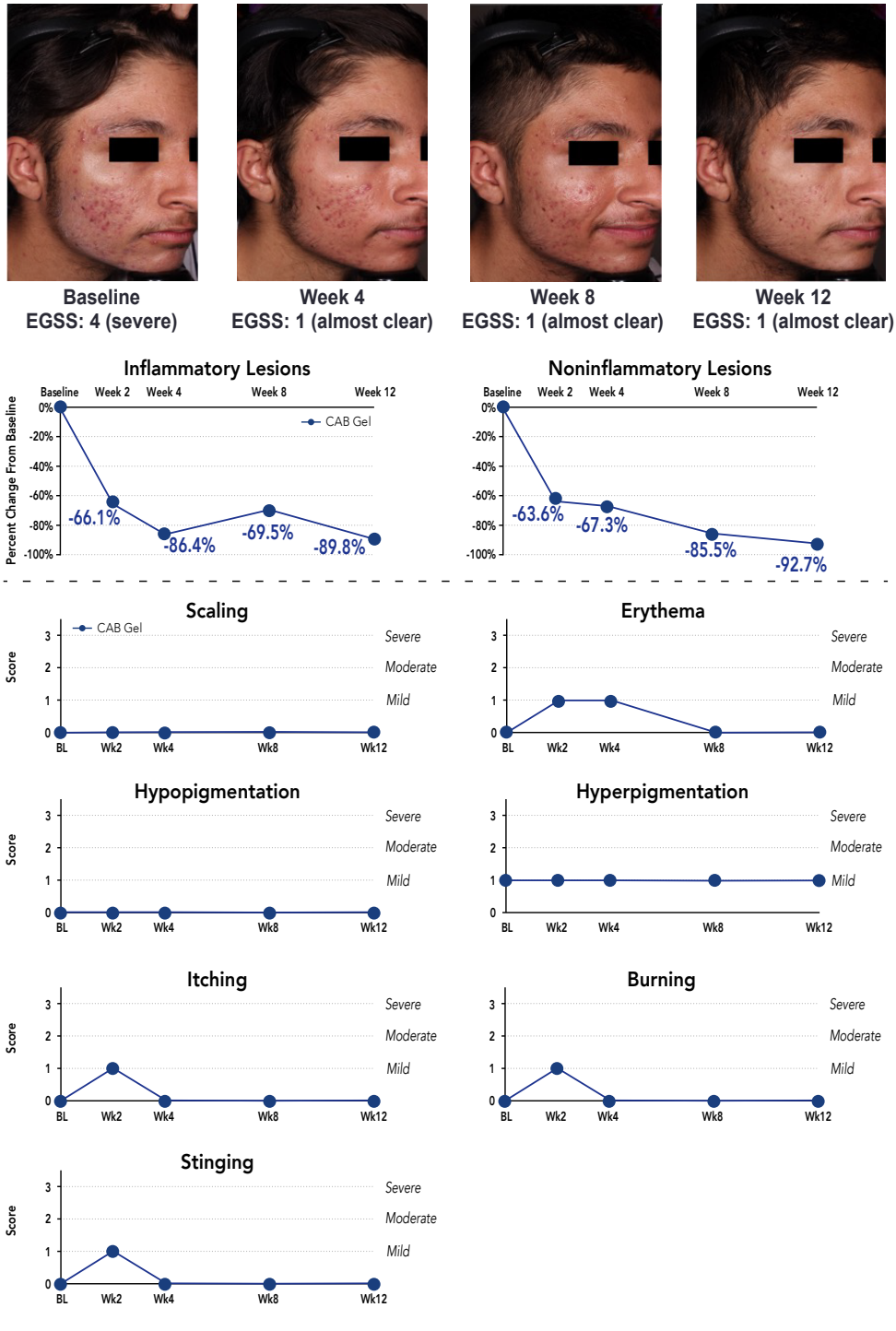


variable across cases, transient increases in cutaneous effects with CAB generally resolved to baseline values within 8 to 12 weeks of treatment.

DISCUSSION

Acne pathophysiology is a multifactorial process.[2] Clearing lesions rapidly to manage and/or mitigate persistent sequelae is the main treatment goal.[3] US guidelines recommend treatments

Case 6: 18-Year-Old Male – Asian, Non-Hispanic/Latino



Individual results may vary.
Photographic Images Copyright 2024.
BL, baseline; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel; EGSS, Evaluator's Global Severity Score; wk, week.

combining multiple mechanisms of action, with strong recommendations for topical retinoids, BPO, and/or antibiotics (antibiotic monotherapy is not recommended).[2] Unfortunately, treatment adherence is poor due to complex regimens, lack of efficacy, adverse effects, or unrealistic treatment expectations.[1,6] Simplifying topical regimens into a single fixed-dose, once-daily treatment may improve adherence.[1]

CAB, the only approved triple-combination topical for acne, addresses 3 of the 4 pathophysiologic acne processes.[2,7-9] Two recent meta-analyses determined that CAB and/or triple combinations like CAB that include BPO, a retinoid (topical), and an antibiotic (oral or topical) are among the most effective acne treatments.[10,11] In two phase 3 clinical studies, 50% of participants achieved treatment success with CAB, and all CAB-treated participants had >70% reductions in inflammatory/noninflammatory lesion counts at week 12.[5] CAB also rapidly and significantly reduced lesion counts from baseline versus vehicle as early as weeks 2 and 4.[12] All 6 CAB-treated cases achieved substantial (>70%) lesion reductions, with 5 of 6 achieving treatment success or a 2-grade reduction in acne severity by week 12. Additionally, 4 of 6 cases had >35% lesion reductions as early as week 2, and 2 of 6 achieved a ≥2-grade severity reduction by week 4.

When combining multiple active ingredients for acne treatment, there is the risk of increased AEs. CAB has demonstrated safety in the phase 3 studies, with most TEAEs being of mild-to-moderate severity and low discontinuation rates due to TEAEs (<4%).[5] One CAB-treated case shown here reported a TEAE, and none reported serious AEs. Although patterns in cutaneous safety/tolerability were variable across cases, severity increases were transient and generally returned to baseline values within 2 months of treatment, similar to what was observed in the phase 3 populations.[5] This may be due to the CAB polymeric emulsion delivering the active ingredients in a moisturizing aqueous formulation, which may reduce irritation.[13]

CONCLUSION

Once-daily CAB gel provided rapid lesion reductions and was safe and well tolerated over 12 weeks in 6 cases with moderate-to-severe acne. These clinical study cases reinforce the importance of patient education regarding acne treatments, including the importance of adherence, managing patient expectations, and the potential for increased, often transient, cutaneous effects.[3]

DISCLOSURES

Hilary Baldwin has served as advisor, served as investigator, and served on speakers bureaus for Almirall, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharma. Julie Harper has received honoraria from Almirall, Galderma, LaRoche-Posay, Ortho Dermatologics, and Sun Pharma. Joshua A Zeichner has served as advisor, consultant, or speaker for AbbVie, Allergan, Dermavant, Dermira, EPI Health, Galderma, Incyte, Johnson & Johnson, L'Oreal, Ortho Dermatologics, Pfizer, Procter & Gamble, Regeneron, Sun Pharma, UCB, Unilever, and Vyne. Zoe Draelos has received funding from Ortho Dermatologics. Lawrence Eichenfield has received honoraria for consulting services from AbbVie, BMS, Almirall, Amgen, Arcutis, Dermata, Dermira, Dermavant, Eli Lilly, Forte Pharma, Galderma, Incyte, Johnson & Johnson, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and Ortho Dermatologics and study support (to institution) from AbbVie, Amgen, Bausch Health, Dermata, Dermira, Eli Lilly, Galderma, Incyte, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme. Michael Gold has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharma, UCB, Arcutis, and Lilly. Leon Kircik has served as either a consultant, speaker, advisor, or an investigator for Allergan, Almirall, Epi Health, Galderma, Novartis, Ortho Dermatologics, and Sun Pharma.

ACKNOWLEDGMENTS

Medical writing and editorial support were provided by Lynn M. Anderson, PhD, of Prescott Medical Communications Group, a Citrus Health Group, Inc., company (Chicago, IL) with support from Ortho Dermatologics. Ortho Dermatologics is a division of Bausch Health US, LLC.

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November 2024 e181 Volume 23 • Issue 11

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Cost Analysis of Sunscreens Targeted Towards Skin of Color

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ABSTRACT

Skin cancer most commonly affects fair-skinned individuals[1]; however, it can appear in individuals of all skin tones. Photoprotective behaviors such as applying sunscreen should be practiced by all individuals regardless of skin tone. Herein, the authors discuss the cost and protection of popular sunscreens targeted towards patients with darker skin or skin of color (SOC), and suggest important considerations providers should take into account when advising about sunscreen recommendations for patients with skin of color.

J Drugs Dermatol. 2024;23(11): doi:10.36849/JDD.8710

INTRODUCTION

Skin cancer is the most common cancer diagnosis and there are several preventative measures aimed at reducing its prevalence such as photoprotection.[1] Photoprotective behaviors help prevent sunburns, skin cancer, and skin damage. However, individuals with skin of color (SOC) are less likely to use sunscreen due to misconceptions regarding its benefits and patients' susceptibilities to skin cancer and sunburns.[2] Further, cosmetic elegance and cost have been described as deterrents for patients with darker skin when deciding to use sunscreen.[3] Several studies have found that social media outlets and dermatologists recommend more expensive products to patients with SOC.[4]This discussion aims to analyze the cost and SPF level of sunscreens marketed toward patients with darker skin.

MATERIALS AND METHODS

Sunscreens were identified through a TikTok social media analysis following hashtags: "sunscreen for skin of color", and "sunscreen for dark skin." For each hashtag, the 10 most popular posts were selected, based on TikTok algorithms. Sixteen sunscreens were identified. Their price in U.S. Dollars, price per fluid ounce, and SPF were reported. Prices were obtained directly from the company's website for eleven out of sixteen sunscreens. For the remaining four sunscreens that could not be purchased directly from the company's website (CeraVe Hydrating Sunscreen Face Sheer Tint, EleVen Unrivaled Sun Serum, Mele No Shade Sunscreen Oil, and Neutrogena Purescreen Mineral UV Tint, and Biore UV Aqua Rich), the price was obtained from online retailers such as Target, Amazon, Credo Beauty, and Walmart. The lowest price available from an online retailer was used for these four sunscreens.

TABLE 1.

Price and SPF for popular sunscreens targeted towards skin of color

Sunscreen	Price (USD)	Price Per Fluid Ounce (USD/Fl Oz)	SPF
"Beauty of Joeseon Relief Sun: Rice + Probiotics"	$18.00	$10.65	50
Biore UV Aqua Rich	$15.99	$9.41	30
"Biossance Sheer Mineral Sunscreen"	$32.00	$18.82	30
Black Girl Sunscreen	$18.99	$6.33	30
"CeraVe Hydrating Sunscreen Face Sheer Tint"	$13.99	$8.23	30
Coola Mineral Sun Silk Stick	$26.00	$43.00	50
Dr. Dennis Gross Spot Sun Defense	$42.00	$24.70	30
"Dr. V InZincable SPF 50 Sunblock"	$34.00	$20.00	50
"EltaMD UV Clear Tinted Sunscreen"	$45.00	$26.47	46
"La Roche-Posay Anthelios Tinted Mineral Sunscreen"	$37.99	$22.35	50
Mele No Shade Sunscreen Oil	$16.99	$16.99	30
"Neutrogena Purescreen Mineral UV Tint"	$17.19	$15.63	30
Shishedo Stick	$32.00	$45.71	50
"Supergoop Unseen Sunscreen"	$38.00	$22.35	40

doi:10.36849/JDD.8710e

DISCUSSION

The average cost of sunscreens targeted toward patients with SOC was $31.20 ($24.92/fl oz), Prices ranged from $13.99 to $45.00 as highlighted in Table 1. SPF levels ranged from 30 to 50 which aligns with the AAD's recommendation to use sunscreen with an SPF of 30 or greater.[4] In comparison, one recent study found that the average cost of sunscreen targeted towards lighter skin tones was $11.32/fl oz.[4] This indicates that sunscreens targeted toward patients with skin of color appeared on average to be more expensive.[4] Although many of the sunscreens marketed toward individuals with darker skin are created by smaller businesses leading to higher prices, there need to be more affordable options to encourage photoprotection.

CONCLUSION

Awareness regarding photoprotection in patients with skin of color is increasing. The rise of dermatology in social media outlets, public awareness, and education regarding photoprotection has encouraged sunscreen usage. However, when counseling on photoprotection in individuals with skin of color, it is important to consider barriers to adherence such as cost. Sunscreen manufacturers have historically focused less on creating products for individuals with skin of color. As larger businesses expand their products, the average cost of sunscreen options for patients with skin of color will hopefully decrease. As awareness of this topic increases and new products are developed, providers should stay up to date on sunscreen options available to patients with skin of color.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.2024.NVRN1024

November 2024 1026 Volume 23 • Issue 11

FEATURED CONTENT

Journal of Drugs in Dermatology

NEWS, VIEWS, AND REVIEWS

GLP-1 Receptor Agonists for the Dermatologist: Uses and Considerations

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Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC

INTRODUCTION

The glucagon-like peptide-1 receptor agonists (GLP1RAs) are a widely popularized drug class due to their notable success in promoting weight loss. The GLP1RAs, dulaglutide, exenatide, semaglutide, liraglutide, tirzepatide, and lixisenatide are FDA-approved for use in the treatment of obesity and type 2 diabetes mellitus (DM), particularly to reduce cardiovascular risk and improve glycemic control.[1,2,3] GLP1RAs work by mimicking glucagon-like peptide-1 (GLP-1), an incretin, that functions to subdue appetite, delay gastric emptying, and regulate homeostasis of glucose. GLP1RAs also have anti-inflammatory effects; GLP-1 receptors are expressed in activated regulatory T cells and GLP-1 receptor agonists reduce proinflammatory cytokines through inhibition of tumor necrosis factor alpha (TNF-α), nuclear factor-kappa B (NF-κB), interleukin (IL)-23, IL-17, and IL-22.[1]

Despite their popular use in bariatrics, cardiology, and endocrinology, GLP1RAs should not be overlooked by dermatologists. While mounting evidence has shown the utility of GLP1RAs in the treatment of psoriasis, they have also proved useful in treating hidradenitis suppurativa (HS), acanthosis nigricans, Hailey-Hailey disease, and diabetic wounds. Additionally, dermatologists should be aware of lipo-cutaneous adverse reactions, as well as the dermatologic manifestations of rapid weight loss in patients using GLP1RAs.

Psoriasis

The anti-inflammatory effects of GLP1RAs have most extensively been used in the treatment of psoriasis, a prominently IL-17, IL-23-, and TNF-α-mediated condition. Reduction in psoriasis symptoms has been observed in patients taking GLP1RAs, and as an added benefit, these drugs simultaneously address comorbid obesity and DM.[4,5]

A recent meta-analysis including 63 patients who received liraglutide or exenatide subcutaneously revealed significant reductions in Psoriasis Area Severity Index (PASI) after treatment in patients with psoriasis alone (P=0.002) and in patients with psoriasis and comorbid DM (P=0.005). Overall, over one-third (35%) of patients showed 75% improvement in PASI from baseline after 6-12 weeks of treatment.[4] This study drew from results of a randomized-controlled trial (RCT) including 25 patients with psoriasis and DM taking liraglutide that showed improvements in PASI, Dermatology Life Quality Index (DLQI) (P<0.05), weight (P<0.001), body mass index (BMI) (P<0.001), and fasting blood glucose (P<0.001). In this RCT, the most common adverse events in the treatment group were nausea or vomiting (54.55%), and no serious adverse events occurred.[5] Notably, one case study has reported worsening of psoriatic lesions after two weeks of treatment with liraglutide, thought to be due to a cytokine imbalance.[6] These studies demonstrate current evidence for the efficacy of GLP1RAs in a multimodal treatment approach for patients with psoriasis and metabolic comorbidities, achieved through the drug's anti-inflammatory effects and promotion of weight loss and normoglycemia.

Hidradenitis Suppurativa

HS has well-established associations with metabolic syndrome and obesity, as weight gain not only predisposes to HS but exacerbates it.[1,7] Systemic inflammation in HS is modulated in part by IL-17, TNF-α, and NF-κB, targets of GLP1RAs. A recently published prospective cohort study including 14 patients with HS demonstrated that treatment with liraglutide led to significant decreases in BMI (P=0.0002), waist circumference (P=0.01), C-reactive protein (P=0.04), and homocysteine (P=0.005). Improvements in Hurley stage (P=0.002) and DLQI (P=0.04) were also observed.[8] While further evidence is warranted, the use of GLP1RAs as an adjunctive therapy in patients with HS and elevated BMIs can be considered.

Additional Applications in Dermatologic Conditions

Case-based evidence exists highlighting the use of GLP1RAs for a variety of dermatologic conditions. One report demonstrated the use of liraglutide in achieving improvements in the clinical appearance of acanthosis nigricans.[9] Hailey-Hailey disease, a genodermatosis with increased expression of IL-17, was successfully treated with liraglutide over a six-month period in one case of a previously treatment-refractory patient.[10] Additionally, in vitro and in vivo studies of liraglutide and exenatide, respectively, have shown efficacy in accelerating wound healing in DM patients.[11,12]

While concerns about liraglutide's association with skin cancer were cited during an early RCT, a recent cohort study did not find an association of liraglutide use with melanoma nor nonmelanoma skin cancer when compared to sulfonylureas. However, this result was not significant.[13] Additionally, some dermatologists have questioned the ethics of utilizing GLP1RAs for dermatologic conditions without long-term safety evidence and in light of the current drug supply shortages.[14]

This literature cumulatively demonstrates the creative ways in which GLP1RAs can be capitalized on, however, without additional efficacy and safety evidence, these drugs should be used with thoughtful consideration.

Cutaneous Adverse Events and Side Effects

Among the side effects of GLP1RAs are myriad cutaneous adverse events and side effects. A scoping review of semaglutide including 255 patients listed "altered skin sensations" as a side effect of orally dosed medication and "angioedema, bullous pemphigoid, dermal hypersensitivity, eosinophilic fasciitis, and leukocytoclastic vasculitis" from subcutaneous dosing.[2] These findings are consistent with a systematic literature review of 31 studies by Salazar et al. of GLP1RA-related cutaneous reactions, reporting "11 instances of dermal hypersensitivity reactions (33.3%), 10 eosinophilic panniculitis (30.3%), 3 bullous pemphigoid (9.1%),[2] morbilliform drug eruptions (6.1%), 2 angioedema (6.1%), and 7 other single instances of other cutaneous reactions."[3] Despite the reported association between GLP1RAs and bullous pemphigoid, a retrospective case-control cohort study did not find an association between the two.[15] Prompt recognition of and early intervention in cutaneous adverse events and side effects of GLP1RAs is the responsibility of all clinicians, especially the astute dermatologist.

Unintended Consequences

Despite the use of GLP1RAs in a variety of clinical contexts, unintended consequences of their use may be the context in which a patient presents to dermatology. "Ozempic Face" is a popularized colloquial term describing the rapid facial fat loss from GLP1RAs that can lead to the appearance of "wrinkles, sunken eyes, a hollowed appearance, sagging jowls…and alterations in the cheeks, lips, and chin," prompting patients to seek cosmetic procedures.[16] Ongoing discourse exists surrounding the effect of GLP1RAs on hair. Current hypotheses question how GLP1RA's effects on the hair growth cycle, hormonal pathways related to hair growth, nutritional deficiencies, and blood pressure may relate to the development of telogen effluvium and early-onset androgenetic alopecia. On the other hand, some hypotheses posit hair loss may be improved by increased insulin sensitivity and scalp blood flow.[17] Additionally, other dermatologic conditions may arise from GLP1RA use like erythema intertrigo from increased skin folds, nail changes from nutritional deficiencies, or striae from weight loss. These authors postulate that these unintended consequences may be prevented and/or treated by dermatologists.

CONCLUSION

GLP1RAs present a promising therapeutic option for patients with psoriasis and concomitant diabetes mellitus, as well as those with hidradenitis suppurativa. Given their popularity, dermatologists should remain vigilant in identifying potential adverse reactions, as well as managing the sequelae of rapid weight loss on the hair, skin, and nails. Education and appropriate counseling for patients on GLP1RAs may be warranted, especially if not addressed by prescribing clinicians. While dermatologists may not traditionally prescribe these medications, collaborating with prescribing clinicians is essential for optimizing treatment and ensuring comprehensive patient care.

DISCLOSURE

SIV's work is funded through an independent research grant from Galderma. NM's work is funded through independent research grants from Incyte and Johnson & Johnson.

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PHYSICIANS CONTINUING EDUCATION CORP/ JOURNAL OF DRUGS IN DERMATOLOGY	25376	15459616	9/12/2024
4. Issue Frequency	5. Number of Issues Published Annually		6. Annual Subscription Price *(if any)*
MONTHLY	12		$300.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)*
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Contact Person: Kelly Rosaaen
Telephone *(Include area code)*: (319) 536-1743 x5418

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