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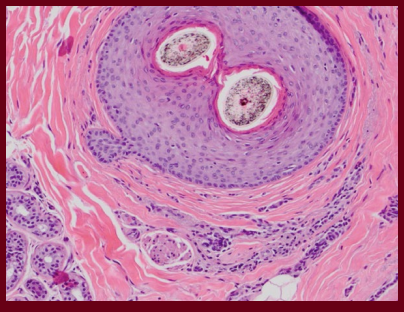
JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS



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SPECIAL FOCUS: SKIN OF COLOR

RESIDENT ROUNDS ◆ NEWS, VIEWS, & REVIEWS ◆ PIPELINE PREVIEWS ◆ CLINICAL TRIAL REVIEW

ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

For adults with plaque psoriasis

workingtogether

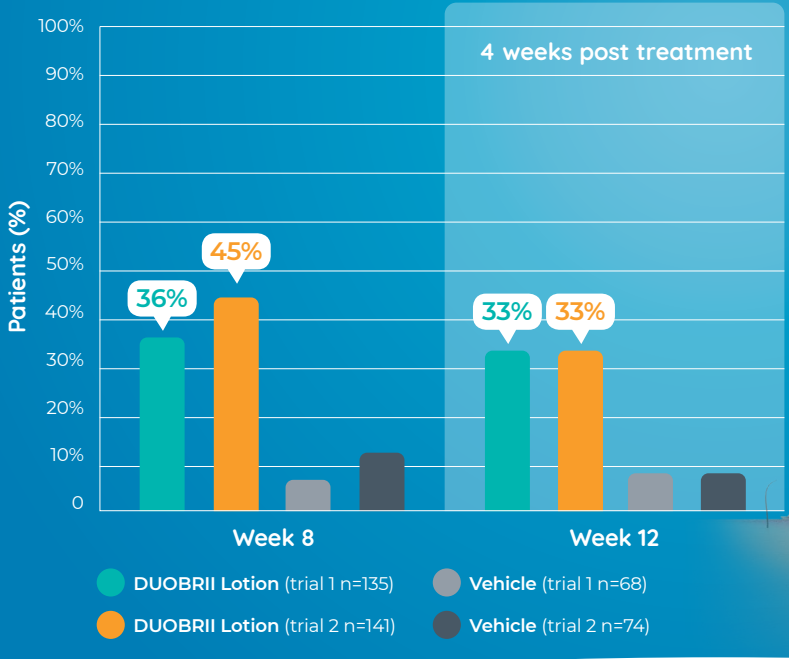
DUOBRII® (halobetasol propionate and tazarotene) Lotion 0.01% / 0.045%

DUOBRII Lotion is the only steroid/retinoid topical therapy. The AAD confirms that the combination of a steroid and a retinoid, such as **halobetasol** and **tazarotene**, may delay the relapse of plaque psoriasis and extend treatment duration.[1-3]

DUOBRII Lotion demonstrated extended remission 4 weeks post treatment[1]

2 phase 3 trials

Patients who achieved treatment success* with QD dosing (8 week primary endpoint)[1,4]



The only potent-to-superpotent steroid that has no time limits on use; use only until control is achieved.[1,5-9]

DUOBRII Lotion was studied in two 8-week clinical trials and a 1-year safety study. Discontinue treatment if atrophy, striae, telangiectasias, or folliculitis occurs.[1,10]

Indication

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

Important Safety Information

Contraindication

DUOBRII Lotion is contraindicated in pregnancy.

Warnings and Precautions

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

Adverse Events

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

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

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

AAD = American Academy of Dermatology
QD = once daily

*Treatment success was defined as at least a 2-grade improvement from baseline in Investigator's Global Assessment (IGA) score, and a score of "clear" or "almost clear" (primary endpoint at week 8).[1]

Study design: DUOBRII Lotion was assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 418 adult patients with psoriasis. Patients were treated with DUOBRII Lotion or vehicle, applied once daily and evaluated at 2, 4, 6, 8 weeks (primary endpoint), and post treatment at 12 weeks.[1]

References: 1. DUOBRII Lotion [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC. **2.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed February 12, 2020. **3.** Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643-659. **4.** Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: results of two phase 3 randomized controlled trials. *J Am Acad Dermatol*. 2018;79(2):287-293. **5.** Clobetasol propionate cream [prescribing information]. Lincolnton, NC: Cosette Pharmaceuticals, Inc. **6.** Diprolene lotion [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp. **7.** Enstilar foam [prescribing information]. Madison, NJ: LEO Pharma Inc. **8.** Halobetasol propionate cream [prescribing information]. South Plainfield, NJ: G&W Laboratories, Inc. **9.** Mometasone furoate cream [prescribing information]. South Plainfield, NJ: G&W Laboratories, Inc. **10.** Data on file.

Help your patients save at **DUOBRII.com**

Ortho Dermatologics

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Pregnancy

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

WARNINGS AND PRECAUTIONS

Embryofetal Risk

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

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

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

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

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

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

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

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

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

Local Adverse Reactions

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

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

Photosensitivity and Risk for Sunburn

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

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

Ophthalmic Adverse Reactions

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

Concomitant Skin Infections

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

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

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

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

Data

Human Data

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

Animal Data

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

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

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

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

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

Lactation

Risk Summary

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

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

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

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

Clinical Considerations

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions]*.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema *[see Warnings and Precautions]*.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

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

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

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

DUO.0039.USA.18 Based on 9645601

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Journal of Drugs in Dermatology

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JOURNAL OF DRUGS IN DERMATOLOGY

ORIGINAL ARTICLES

ORIGINAL ARTICLES (CONTD)

BRIEF COMMUNICATIONS

NEW!

ARAZLO™ (tazarotene) Lotion, 0.045%

REDEFINE WHAT'S POSSIBLE

FOR YOUR PATIENTS WITH ACNE VULGARIS

CRACK THE TAZAROTENE CODE

ARAZLO is the first and only tazarotene lotion, formulated with polymeric emulsion technology, to help deliver the clearance you expect and the tolerability you want[1-3]

- Treatment success* rates were 26% for ARAZLO Lotion vs 13% for vehicle in study 1 and 30% vs 17%, respectively, in study 2 ($P<0.001$ in both studies)[1,4†]
- Most common adverse events (≥1% of patients and greater than vehicle) at application site were pain (5%), dryness (4%), exfoliation (2%), erythema (2%), and pruritus (1%)[1†]

SEE WHAT'S POSSIBLE AT ARAZLO.COM

*Treatment success on the Evaluator's Global Severity Score (EGSS) was defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1).[1]

†**Phase 3 study design:** The safety and efficacy of ARAZLO Lotion were assessed in 2 multicenter, randomized, double-blind clinical trials of 1,614 subjects aged 9 years and older with facial acne vulgaris. Subjects had a score of moderate (3) or severe (4) on the EGSS, 20 to 50 inflammatory lesions, 25 to 100 noninflammatory lesions, and 2 or fewer facial nodules.[1]

Indication

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

Important Safety Information

ARAZLO Lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Contraindication

ARAZLO Lotion is contraindicated in pregnancy due to the potential harm to the fetus.

Warnings and Precautions

Embryofetal Risk Females of childbearing potential should be warned of the potential risk and should use adequate birth-control measures when ARAZLO Lotion is used. A negative result for pregnancy should be obtained within 2 weeks prior to ARAZLO Lotion therapy, and therapy begun during a menstrual period. If the patient becomes pregnant while using ARAZLO Lotion, treatment should be discontinued.

Skin Irritation Patients using ARAZLO Lotion may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity, adjust or interrupt dosing as needed, increasing or resuming treatment as tolerated. Avoid application of ARAZLO Lotion to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

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

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

Adverse Reactions The most common adverse reactions (in ≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

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

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

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

Ortho Dermatologics

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

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

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

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

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

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

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

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

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

Avoid application of ARAZLO to eczematous or sunburned skin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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CASE REPORTS

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DRUGS • DEVICES • METHODS

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Objective Evaluation of Skin Sensitivity Across Fitzpatrick Skin Types

Celina E. Dubin BA, Grace W. Kimmel MD, Peter W. Hashim MD, John K. Nia MD, Joshua A. Zeichner MD

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ABSTRACT

Context: Skin sensitivity may be best defined as self-reported intolerance to application of skincare products. It is commonly believed that individuals with darker skin are generally less sensitive, while those lighter skin are more sensitive. However, there is little objective data correlating sensitivity with skin type or with objective measures of sensitivity.

Objective: This study assessed Fitzpatrick skin type and self-reported perception of skin sensitivity.

Design: A single-blinded, lactic acid sting test was performed on the medial cheeks, where patients were randomized to receive room temperature 10% lactic acid on the left or right cheek with water applied to the contralateral cheek as a control.

Outcome Measures: Stinging was assessed 1 minute after application of test solution to one cheek using a visual analogue scale (VAS).

Results: There was a statistically significant difference in self-reported skin sensitivity in patients with Fitzpatrick skin types 1–3 vs 4–6 (73.6% vs 46.5%; P= 0.006). Patients who had higher perceived sensitivity were more likely to have objectively measured sensitivity as well, across all skin types (P<0.01). When stratified by skin type, a numerically higher percentage of subjects with Fitzpatrick skin types 1–3 experienced objective sensitivity compared to subjects with skin types 4–6 (45.6% vs 27.9; P=0.058).

Conclusions: Patients with self-perceived skin sensitivity were more likely to develop objective stinging compared to those who did not report sensitivity. Skin sensitivity can occur across all skin types, and patients should be asked about self-perceptions of sensitivity as it is likely an indicator of true sensitivity.

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INTRODUCTION

"Sensitive skin" is commonly reported by many patients and influences decision making in skincare routines. Skin sensitivity is generally accepted to be a reduced tolerance to cosmetics and other topical skin care products.[1] Based on consumer surveys, it is estimated that 40% of the population believes that they have sensitive skin, and this number appears to be increasing in recent years.[1,2] Typically lacking objective signs, skin sensitivity is usually a subjective finding by patients that is secondary to their own perceptions about their skin.[3,4] The correlation between perceived sensitivity and objectively sensitive skin has not previously been evaluated. Furthermore, there is limited understanding of which skin types more commonly believe that they have sensitive skin.

The biological basis of skin sensitivity is thought to be the result of many factors. A thin stratum corneum, increased blood flow, and neuronal activation are thought to be major contributing factors.[1,3,5] Studies looking at biophysical parameters of the skin reported trends towards increased transepidermal water loss and decreased capacitance in those with sensitive skin, indicating a possible barrier dysfunction.[4,6] Fitzpatrick skin type has also been thought to be associated with subjective perceptions of skin sensitivity objective measures.[7,8] One study assessing patients with skin responses to irritants found that 85% of affected patients were white.[9] Another study found differing symptomatology of skin sensitivity between ethnic groups, showing that Caucasian patients were significantly more likely to report visual effects (eg, redness), whereas African American patients were more likely to report sensory effects (eg, stinging).[1] However, other survey studies have shown similar rates of self-reported skin sensitivity across ethnic groups, and therefore the relationship between skin sensitivity and skin type remains unclear.[10,11] There is data to suggest that there are biophysical differences in the skin among skin types, and the skin of African American individuals has a thicker stratum corneum and increased lipid content.[11,12] Since there is limited research on the relationship between perceived skin sensitivity and skin type, it is unclear whether Fitzpatrick skin type truly plays a role in determining overall sensitivity.

A sting test using lactic acid solution (5% or 10%) is an effective way to create a non-damaging reaction on the face and is been widely accepted as a marker of skin sensitivity.[4] Previous studies have shown significantly higher stinging scores in response to lactic acid in patients with sensitive skin, and that

skin pH values increase significantly faster following lactic acid application in patients with sensitive skin than in those without.[3,4] Positive results on lactic acid sting tests have also been shown to correlate with self-reported skin sensitivity and with objective measures of stratum corneum function such as, transepidermal water loss.[6] The goal of this study is to examine the relationship between subjective skin sensitivity and objectively measured skin sensitivity using the lactic acid sting test, and evaluate whether skin sensitivity varies according to Fitzpatrick skin type.

METHODS

Participants

100 participants took part in the study following informed consent. These patients were recruited on a volunteer basis from our dermatology clinic and waiting room. Exclusion criteria included a diagnosed facial skin disorder that would interfere with evaluation, a known allergy to lactic acid, the use of a topical retinoid or hydroxy acid within two weeks, and pregnant women. Participants were not remunerated for their participation in any way. Of the 100 participants, 70% were female and 30% were male. 57% were Fitzpatrick skin types 1–3 and 43% were Fitzpatrick skin types 4–6. All participants were over the age of 18.

Procedure

Patient skin type was assessed on the Fitzpatrick skin type scale. Scores range from 1–6, with scores of 1 indicating the palest skin tone with no inherent melanin pigmentation, and 6 indicating the darkest skin tone with a significant amount of melanin.[8] Participants were then asked to report self-perceived skin sensitivity on a scale from 1 (none) to 5 (severe).

A single-blinded, lactic acid sting test was performed on the medial cheeks, where patients were randomized to receive room temperature 10% lactic acid on the left or right cheek with water applied to the contralateral cheek as a control using cotton tipped applicators. Static assessments of stinging were performed at 1 minute after application of test solution on the cheek using a visual analogue scale (VAS) (Appendix 1), on which participants were asked to indicate how much stinging they felt on a scale of 0 to 100. Solution was then rinsed off. The second solution was subsequently applied to the other cheek, after which the second stinging assessment was performed, using the same methods.

RESULTS

Of the 100 study participants, 62% reported having sensitive skin (defined as self-reported scores of 3–5), while 38% reported none or minimal sensitivity (self-reported scores of 1–2). Significantly more patients with Fitzpatrick skin types 1–3 reported sensitive skin, as compared to those with skin types 4–6 (73.6% vs 46.5%; P=0.006). Overall, on lactic acid assay, 38% of all participants demonstrated skin sensitivity. We defined objectivity sensitivity as stinging to the acid above the mean stinging of all participants to water. When stratified by skin type, a numerically higher percentage of subjects with Fitzpatrick skin types 1–3 experienced objective sensitivity to the lactic acid compared to subjects with skin types 4–6, although this was just under the threshold for statistical significance (45.6% vs 27.9; P=0.058). Additionally, those who had higher perceived sensitivity were more likely to exhibit objective sensitivity (P<0.01). No statistical differences were observed in perceived or objective sensitivity when stratified by gender or ethnicity.

DISCUSSION

This study aimed to examine the relationship between skin sensitivity and skin type. We specifically looked at the difference in perceived sensitivity between across skin types as well as a correlation between perceived and objective skin sensitivity. We found that perceived skin sensitivity was more common in lighter skin types (Fitzpatrick 1–3) as compared to darker skin types (4–6). Furthermore, we found that patients' prior perceptions of their own skin sensitivity reflected what they reported on lactic acid testing in the study. In clinical practice, this implies that simply asking patients about their perceived skin sensitivity may be useful in selecting appropriate therapeutics and treatment regimens. This approach optimizes patient outcomes and makes the care process inherently more efficient.

The results also showed that more patients with lighter skin tones experienced stinging following lactic acid application as compared to those with darker skin tones, although not statistically significant. Given our small sample size, it is unclear whether this difference is real, and larger studies will be needed for further evaluation. Regardless, it is important to note that both subjective and objective skin sensitivity occurs across all skin types, and we cannot make assumptions about sensitivity based solely on Fitzpatrick skin type. Moreover, this study helps dispel myths that women's skin is more sensitive than men's and that sensitivity is more common in specific ethnic groups.

Our study is limited by the small sample size of 100 patients, primarily comprised of female patients, which may impact responses. Despite these limitations, this study demonstrates that skin sensitivity is common, and while it may occur more often in light skinned patients, it should be considered in patients of all skin types.

DISCLOSURES

Dr. Joshua Zeichner is a consultant for Abbvie, Dermira, Galderma, Johnson and Johnson, L'Oreal, Menlo Therapeutics, Ortho Dermatologics, Pfizer, Procter and Gamble, Regeneron, Sanofi-Genzyme, Sun Pharma, and Unilever.

Celina Dubin has no conflict of interests to declare. Drs Kimmel, Hashim, and Nia have no conflicts of interest to declare.

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Appendix 1. Post-test VAS Questionnaire

Init:_____ ID # _____

Date: _____

Post-test Questionnaire

Draw a vertical line across the present line to represent the degree of stinging you experienced on each side of your face:

Stinging on the LEFT side:

Stinging on the RIGHT side:

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NEW EPISODE

What Women DON'T Want... Psoriasis
Drs. Deirdre Hooper and Adam Friedman

In this edition of the JDD Podcast, Dr. Adam Friedman is joined by Dr. Deirdre Hooper, Associate Clinical Professor in the Department of Dermatology at both Louisiana State University and Tulane University, to discuss her article "Impact of Psoriasis on Women" in the September 2019 issue of the JDD on the unique considerations for the adult female psoriasis patient. What questions should you be asking? What matters most when discussing therapeutic options? What is the best way to partner to ensure a long term relationship? If we could read minds this podcast would not be necessary but alas, it sorely is. Check it out!

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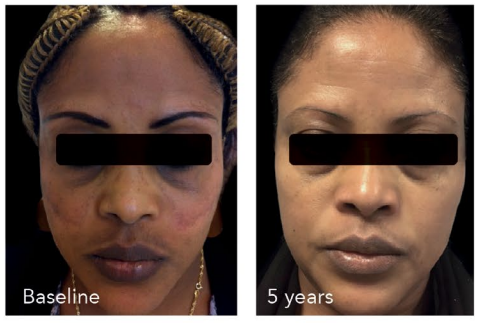

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Diagnosis and Management of Primary Hyperhidrosis: Practical Guidance and Current Therapy Update

Joe Gorelick MSN FNP-C[a] and Adam Friedman MD[b]

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ABSTRACT

Hyperhidrosis is a chronic medical condition characterized by excessive sweating beyond that which is necessary for thermoregulatory homeostasis. It is estimated to occur in 4.8% of the U.S. population (~15.3 million people) but is both underreported and underdiagnosed. With the busy practitioner and dermatology resident in mind, we provide here a disease state primer for hyperhidrosis, a topline review of the breadth of literature underscoring the overall burden of the disease, a practical guide to differential diagnosis, and an update on current treatment approaches, including for the most common form of the condition, primary axillary hyperhidrosis. In addition, a case study is presented to provide a real-life perspective from the clinic on the importance of early and effective management strategies for those suffering with hyperhidrosis.

J Drugs Dermatol. 2020;19(7):704-710. doi:10.36849/JDD.2020.5162

INTRODUCTION

In the most simplistic definition, hyperhidrosis is excessive sweating. However, it is largely misunderstood, often goes undiagnosed, and continues to be inadequately managed for many patients. Approximately half of those who self-identify as having excessive sweating do not discuss their symptoms with healthcare professionals despite the severe negative impact on their quality of life; reasons for this include the misconception that hyperhidrosis is not a medical condition and that no treatments exist.[1] In one study, only half of patients who reported their symptoms to a healthcare professional were ultimately diagnosed with primary hyperhidrosis, which may reflect a reality of widespread underdiagnosis of the condition.[1] In a survey conducted by the International Hyperhidrosis Society (IHhS), 48.9% of patients waited 10 or more years before seeking medical help for their excessive sweating.[2]

With the busy practitioner and dermatology resident in mind, here we provide a disease state primer for hyperhidrosis, a topline review of the breadth of literature underscoring the overall burden of the disease, a practical guide to differential diagnosis, and an update on current treatment approaches.[3,4] In addition, a case study in primary axillary (underarm) hyperhidrosis is presented to provide a real-life perspective from the clinic on the importance of early and effective management strategies for those suffering with hyperhidrosis.

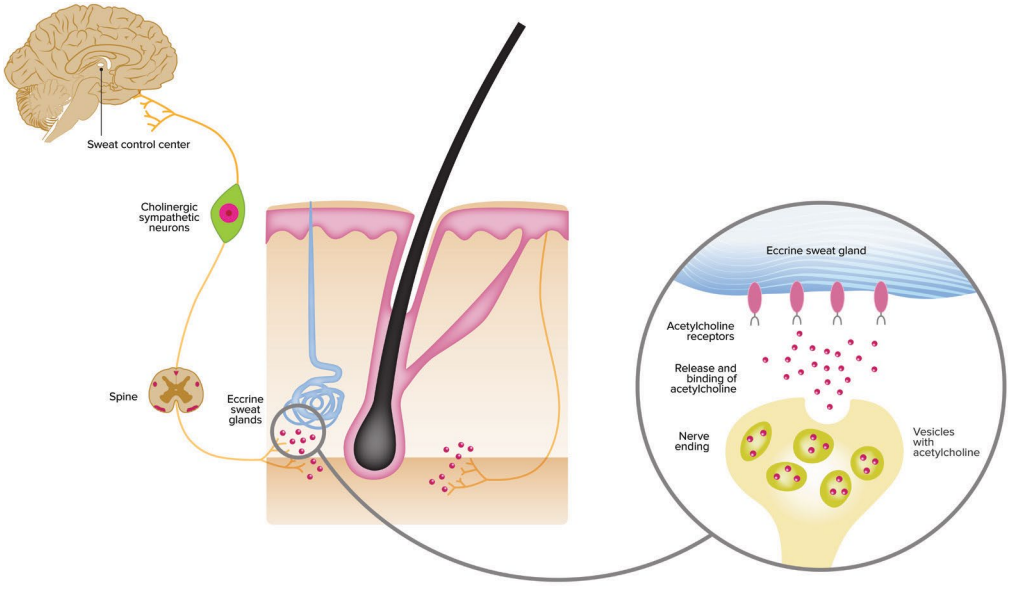
Hyperhidrosis Disease State Primer

Hyperhidrosis is a chronic medical condition characterized by excessive sweating beyond that which is necessary for thermoregulatory homeostasis.[1] The excessive sweating of hyperhidrosis is thought to be produced by eccrine sweat glands (Figure 1), which are highly abundant in axillae, palms, soles, and craniofacial areas.[4,5] Since no differences in histopathology, size, and number of eccrine sweat glands have been observed between patients with hyperhidrosis and those without the condition, it is thought that the disorder occurs due to abnormalities in the autonomic nervous system.[5,6] The nerves that innervate sweat glands are sympathetic and utilize acetylcholine as the primary neurotransmitter.[7] In hyperhidrosis, it is presumed that overstimulation of cholinergic receptors on eccrine sweat glands leads to overproduction of sweat.[8,9,10]

The condition is classified as either primary or secondary hyperhidrosis. Primary hyperhidrosis is idiopathic, tends to be concentrated in particular focal areas, often presents early in life, and is most often bilateral and symmetric in nature; patients with primary axillary hyperhidrosis do not typically experience excessive sweating while sleeping.[1,4,5,8] Primary hyperhidrosis may have underlying genetic factors, as 5.7% to 65% of patients have a family history of the condition.[2,11,12] Several genetic studies report primary hyperhidrosis inheritance as autosomal dominant or recessive, and identified loci for the condition on chromosome 2, 14, and 16; however, these results are heterogeneous and warrant further study to elucidate the disease etiology.[2,11,12]

Secondary hyperhidrosis occurs due to an underlying medical condition such as diabetes mellitus, hyperthyroidism, and lymphoma, or as a side effect of certain medications like some

FIGURE 1. Pathophysiology of hyperhidrosis: excessive cholinergic signaling. The nerves that innervate sweat glands are sympathetic and utilize acetylcholine as the primary neurotransmitter. Overstimulation of cholinergic receptors on eccrine sweat glands leads to overproduction of sweat.

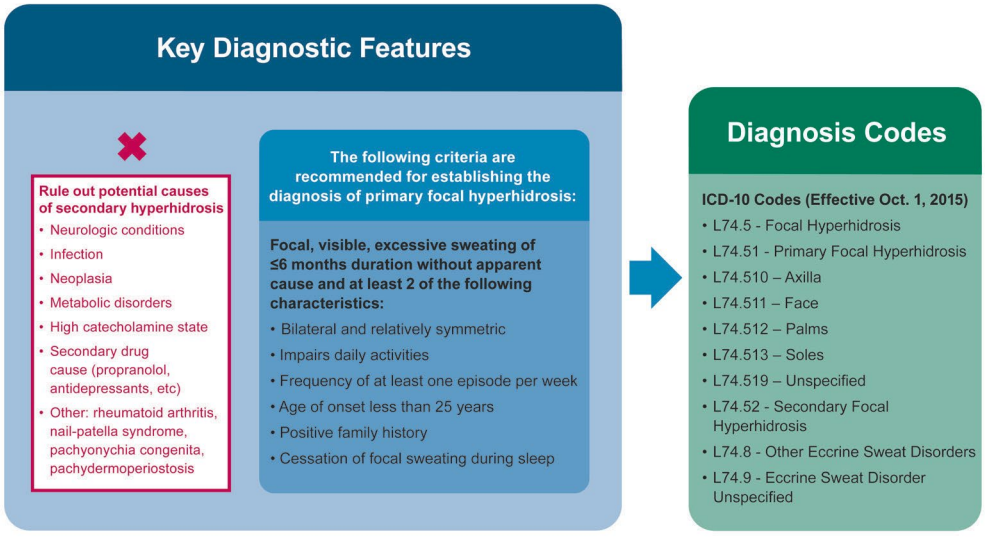


antidepressants, migraine medications (eg, sumatriptan), and asthma inhalers (eg, albuterol).[1,4,5,8,13] In contrast to primary hyperhidrosis, secondary hyperhidrosis is typically asymmetric, most often generalized throughout the body, presents later in life, and its symptoms often persist during sleep (Figure 2).[4,5,8]

Hyperhidrosis is estimated to occur in 4.8% of the U.S. population (~15.3 million people).[1] The disorder occurs equally in males and females, although females are more likely to discuss their symptoms with a healthcare professional.[14]There are limited real-world data that directly characterize treatment and diagnosis patterns with hyperhidrosis, and estimated prevalence rates may be low, given the tendency for hyperhidrosis to be both underreported and underdiagnosed.[1]

Focal points commonly affected by primary hyperhidrosis include axillae, palms, soles, and craniofacial areas. Of these, axillary hyperhidrosis is considered the most prevalent, as 51% to 68% of patients with hyperhidrosis report axillary sweating.[1,2,14] Approximately 80% of patients experience excess perspiration in more than one area, and nearly half of patients with axillary hyperhidrosis have 4 or more additional sites af-

FIGURE 2. Diagnosing focal primary hyperhidrosis. Content adapted from Hornberger et al 2004, www.sweathelp.org, and https://www.icd10data.com/ICD10CM/Codes.[16,40,41]



fected by the condition.[1,15] The onset of the disorder generally occurs before age 25.[4,16] In patients with an onset of hyperhidrosis before puberty, the condition most commonly presents as excessive perspiration in palmoplantar areas, whereas axillary hyperhidrosis is more commonly associated with onset after puberty.[17]

Burden of Disease

Hyperhidrosis patients suffer from decreased quality of life and experience social embarrassment, interference with intimacy, negative effects on emotional and mental health, and deleterious effects on daily activities and career.[1,2,18,19] In a national survey conducted by the IHhS, patients reported daily activity, clothing choices, and work/career as the top three areas negatively affected by the condition.[2] Anxiety and depression rates are significantly higher in patients with hyperhidrosis than those without the condition.[20] The adverse impact of hyperhidrosis on patients has been reported as similar to or greater than that of psoriasis or eczema.[21,22]

A number of studies have shown that these deleterious effects on quality of life extend to the younger patients experiencing hyperhidrosis.[23,24] An online survey showed that ~17.1% of U.S. teens experience excessive perspiration, and three quarters of those report major or moderate daily impairment due to their excessive sweating.[25] In pediatric patients, hyperhidrosis can interfere with school performance; the negative impact of the condition on psychological and social development can cause emotional and social distress.[26,27]

Diagnosis

The initial diagnostic goal for a patient reporting (or observed to have) excessive sweating is to distinguish between primary and secondary hyperhidrosis (Figure 2). Hornberger et al have provided specific, consensus recommendations for primary focal hyperhidrosis diagnostic criteria.[16] Based on these recommendations, a careful medical history should be performed, recording the location of excessive sweating, known triggers, how long the patient has experienced symptoms, family history of the condition, and a review of any medications being taken by the patient.[16,28,29,30] As noted, certain characteristics will strongly suggest a diagnosis of primary hyperhidrosis without additional testing beyond medical history and patient physical exam (Figure 2), including onset in otherwise healthy younger patients (childhood or adolescence) with a family history. Presentation of primary hyperhidrosis is usually bilateral, symmetric, and typically involves the palms, soles, and/or axillae (alone or in combination). In addition, patients with primary hyperhidrosis usually do not sweat during sleep.[31] When symptoms present asymmetrically, it is imperative to rule out the possibility of a neurological lesion or malignancy.[32] Blood, urine, and other lab tests can rule out other causes of secondary sweating, such as overactive thyroid or hypoglycemia.

Many health care providers would agree that an accurate diagnosis of primary hyperhidrosis can usually be made on the basis of history and ideally, observed excessive sweating. However, since hyperhidrosis is episodic, it is not always possible to observe excessive sweating events during office visits. For this reason, an assessment of the impact to quality of life and the level of impairment on daily activities can be confirmatory.[33] A recent review evaluated more than twenty disease severity, impact and quality of life tools that have been used in the assessment of patients with hyperhidrosis. Of these, the most commonly used were the Hyperhidrosis Disease Severity Scale (HDSS), the Dermatology Quality of Life Index (DQLI), and the Hyperhidrosis Quality-of-Life Questionnaire (HQLQ).

Though our focus here has been on practical guidance for accurately diagnosing primary focal hyperhidrosis, it is important to note that quantitative methods of measuring sweat (eg, gravimetric measurements, evaporimetry) exist but are of most value in an academic or research setting.[31,34] Although these tests can be powerful tools to quantitatively establish level of severity and treatment effect, they are not required for an accurate diagnosis and can be of limited utility in the clinic since sweating can be variable for a single patient, depending on factors such as emotional state, activity, or even time of day.[35]

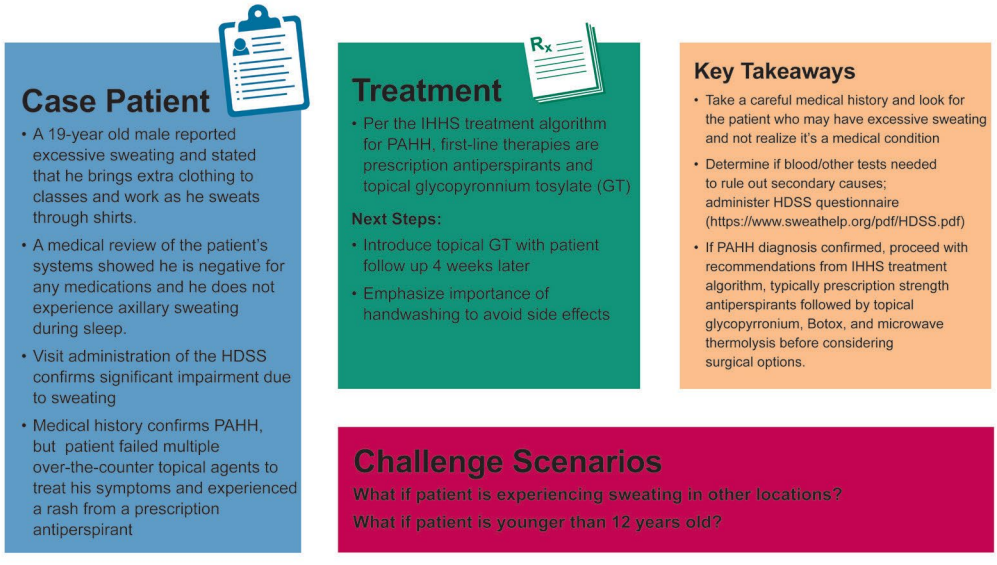
Dermatologists and health care providers within the dermatology field may often see patients with a primary complaint that does not involve excessive sweating. Even if primary hyperhidrosis is not a patient's chief complaint, practitioners should take care to not overlook the symptoms that may be right in front of them, particularly given the social burden carried by hyperhidrosis patients—and the availability of effective treatments to ease this burden.

Treatment

A wide range of techniques, devices, and medical treatments have been used to manage the symptoms of hyperhidrosis.[36] Solish et al provided treatment recommendations using response to the HDSS as a measure of treatment success.[37] The most recent treatment algorithms were developed with a panel of experts in conjunction with the IHhS (and can be accessed at www.sweathelp.org); these focus specifically on management decisions for primary axillary, palmar, plantar, and craniofacial hyperhidrosis as well as gustatory hyperhidrosis (Frey's Syndrome) and generalized hyperhidrosis (multiple focal areas).[38] Though these algorithms focus on devices and medical treatments, it should be noted that other management techniques, such as trigger avoidance and deliberate clothing choices may be useful in alleviating overall burden.[36]

Of note, the treatment algorithms recommend varying stepwise approaches based upon hyperhidrosis location; however, treatment options for primary hyperhidrosis can generally be

FIGURE 3. Primary axillary hyperhidrosis case study and key takeaways for clinical management.



placed into broad categories based upon method of administration as follows[39]:

1. Non-surgical (topical antiperspirants, iontophoresis, topical anticholinergics, thermal ablation with the miraDry® microwave device, systemic medication)

2. Minimally invasive (botulinum toxin injections): this category represents therapies that may be an important option for patients who fail to respond to more conservative treatment prior to resorting to surgery; it is important to note that in practice, fewer younger patients find the pain of botulinum toxin injections tolerable compared with adults[7]

3. Surgical (excision of axillary tissue, endoscopic thoracic sympathectomy): should be considered a last resort option

A summary of available treatment options within the hyperhidrosis field is included within Table 1 with an emphasis on practical, physician-to-physician guidance for optimizing management of primary hyperhidrosis. Hyperhidrosis type, along with intrinsic patient characteristics, including severity of the disease, will dictate initial treatment choices. For example, generalized hyperhidrosis may require systemic medication in order to manage symptoms despite a greater risk for adverse events, while primary axillary hyperhidrosis may be managed with topical agents.

In general, it is recommended to start with the least invasive treatment.[39] Practitioners should discuss combining treatment approaches with their patients with the goal of maximizing overall impact before considering more invasive options. There are not systematic and rigorous clinical data evaluating treatment combinations in hyperhidrosis, so any management decisions should factor in patient characteristics and an overall benefit-to-risk ratio and may require ongoing adjustments.

Topical anticholinergic agents are being studied as treatments for palmar and plantar hyperhidrosis (eg, NCT03404570, NCT03880266, NCT01930604) in addition to axillary hyperhidrosis. In general, to minimize side effects, a topical approach will remain first line therapy. Combinations of systemic, device, or injectable therapy along with topical agents may be considered. Surgical approaches are reserved for recalcitrant or very severe multifocal disease.

Perspective from the Clinic

As mentioned above, the IHhS provides detailed treatment algorithms for a number of different hyperhidrosis conditions. In reality, many patients may experience sweating at more than one of these focal locations, which can complicate overall management and treatment decisions if trying to apply these algorithms. Given that primary axillary hyperhidrosis is the most common form, we present in Figure 3 an instructive case study to illustrate how management in a hypothetical primary axillary hyperhidrosis patient may be optimized for the best patient outcome possible, including the important first step of an accurate diagnosis. The IHhS treatment algorithm for primary axillary hyperhidrosis can be applied across various patient circumstances and can guide different scenarios if initial treatment choices are unsuccessful. Some patient cases may be more challenging (eg, based on a particularly young or old age

TABLE 1.

Summary of Common Available Treatment Options for Hyperhidrosis

Treatment	Recommend Use in IHhS Matrix[a] ◯ = FDA Approved	Mode of Administration	Key Features	Practical Advice for Use
Non-prescription and prescription antiperspirants (eg, aluminum chloride hexahydrate)		Topical	• Over-the-counter formulations contain a maximum concentration of 12.5% aluminum chloride hexahydrate • Prescription formulations include 20% aluminum chloride in ethyl alcohol, 6.25% aluminum tetrachloride, and 12% aluminum chloride in sodium-carbonate–water • Blocks the lumen of distal eccrine sweat gland ducts	• Should be applied to dry skin before bedtime and stay on the skin for 6–8 hours prior to being washed off • Skin irritation is associated with higher aluminum chloride concen-trations
Glycopyrronium Tosylate (QBREXZA™ [glycopyrronium] cloth, 2.4%, for topical use]		Topical	• Approved in the U.S. for primary axillary hyperhidrosis in patients ≥9 years of age • Topical anticholinergic in individually packaged cloths (or wipes) that are to be used at home once daily • Blocks receptors responsible for sweat gland activation	• Most common side effects are dry mouth, erythema/area redness, and burning/stinging • Wash hands thoroughly after use to avoid inadvertent transfer of the drug from the hands to areas of the body such as the eyes
Iontophoresis		Topical (device)	• A medical device is used to pass a mild electrical current through water (usually using shallow pans for hands or feet or specific pads for other body areas) and through the skin's surface • No significant or serious side effects and the benefits are long-term, provided the maintenance schedule is adhered to (usually once per week)	• Drugs (aluminum chloride or an anticholinergic agent) can be added to the tap water to increase efficacy)
Microwave Device (miraDry®)		Topical (device)	• Cleared in the U.S. for severe axillary hyperhidrosis • Employs microwaves to thermally ablate sweat glands	• Performed in a physician's office with local anaesthesia (usually lidocaine injections) • Common and minor side effects of miraDry include underarm swelling, redness, and tenderness lasting for several days; numbness and tingling can occur in the upper arm or armpit and may last for about 5 weeks
Onabotulinum toxinA (BOTOX®)		Injection	• Approved in the U.S. for severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients • When injected intradermally, produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating	• Administered in physician's office • The most frequently reported adverse reactions following injection of BOTOX were injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome
Oral Anticholinergics (eg, glycopyrrolate, oxybutynin)		Oral	• Typically recommended when other treatments have failed for severe cases	• Adverse effects, including dry mouth, blurred vision, dry eyes, hyperthermia, orthostatic hypotension, gastrointestinal complaints, urinary retention, tachycardia, drowsiness, dizziness, and confusion lead to a high rate of discontinuation

[a]Based on IHhS Hyperhidrosis Treatment Matrix https://www.sweathelp.org/treatments-hcp/treatment-overview.html
Sites affected by hyperhidrosis include: Underarms (axillae) , Hands (palmar) , Feet (plantar) , Face/head (craniofacial)

of the patient or if multiple areas of the body are affected). In these cases, especially, it is important to take a stepwise approach to treatment decisions, working toward a treatment regimen that will result in the best balance for an individual patient in terms of effectiveness, convenience and cost.

Hyperhidrosis is a chronic, lifelong condition, but it is treatable—and should be prioritized when taking patient history, especially given the widespread social and emotional impact associated with the condition. Since there are effective and safe treatments available, there is no reason for patients to experience the burden of the disease—and early diagnosis will allow for earlier treatment interventions. We urge practitioners to take advantage of the information available on the IHhS website and to emphasize to their patients that it can serve as a helpful patient resource as well. The main IHhS website is organized such that patient-friendly resources appear on a main home page (https://www.sweathelp.org/index.php), while a more detailed provider-centric set of resources can be accessed at a different tab (https://www.sweathelp.org/medical-professional-resources.html). Among the many practical resources for both patients and their physicians on the IHhS website is helpful guidance and tools for navigating the complicated insurance and reimbursement system, including ready-to-use downloadable forms (https://www.sweathelp.org/insurance-tools/insurance-and-reimbursement.html). If coverage is initially denied, these available resources provide a roadmap that patients can take to advocate for themselves to get the treatments they need. The hyperhidrosis patient does have options, and clinicians should encourage and support their patients who need help, as they would with any other burdensome condition.

DISCLOSURES

J. Gorelick is a consultant and speaker for Dermira; A. Friedman is a consultant and speaker for Dermira and has had a financial agreement or affiliation with the following commercial interests as a consultant: Abbvie Pharmaceuticas, Celgene, Dermira, Lilly, Leo Pharma, Novartis Pharmaceuticals, Ortho Dermatologics, Pfizer, PruGen, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB; has served on Advisory/Speaker's Bureau for the following: Abbvie Pharmaceuticals, Dermira, Lilly, LEO Pharma, Novartis Pharmaceuticals, Ortho Dermatologics, Dermira, Pfizer, PruGen, Regeneron Pharmaceuticals, Sun Pharm, and UCB.

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ORIGINAL ARTICLE

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Impact of Iron-Oxide Containing Formulations Against Visible Light-Induced Skin Pigmentation in Skin of Color Individuals

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ABSTRACT

Visible light (400–700nm), which contributes to 45% of solar radiation, contributes to skin darkening and worsening of dyschromias, particularly in individuals with Fitzpatrick skin phototypes III and higher. Currently, sunscreens provide limited protection against that spectrum. Due to their capabilities in absorbing, scattering, and reflecting visible light, topical products containing pigments and/or metal oxides can provide additional photoprotection. In this study, the efficacy of two formulations containing iron oxide was evaluated in preventing visible light-induced pigmentation compared with a non-tinted mineral SPF 50+ sunscreen. Expert grading and colorimetry demonstrated that the iron-oxide containing formulations significantly protected against visible light-induced pigmentation compared to untreated skin or mineral SPF 50+ sunscreen in Fitzpatrick IV individuals. These results highlight that iron-oxide containing formulas in a foundation format have dual functions and can provide additional benefits in patients' daily routine by masking existing pigmentation and preventing the development of pigmentation triggered by sunlight exposure, extending protection beyond UV spectrum.

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INTRODUCTION

At the earth's surface, solar radiation comprises of 5–7% ultraviolet (UV), 45% visible light (VIS), and 48–50% infrared (IR) radiation.[1] Studies on the cutaneous impact of radiation have focused on UVB and UVA-mediated effects on the skin. Through different mechanisms, both UVA and UVB are shown to contribute to erythema, tanning, photoaging, and skin cancers.[2]

In recent years, VIS (400–700nm) was demonstrated to induce both immediate and persistent pigment darkening in subjects with skin phototype III and above.[3-5] It has been shown that long wavelength UVA1 (LUVA1) combined with VIS can result in erythema in skin phototype I–III, plus darker, persistent pigmentation and inflammation in subjects with skin phototype IV–VI.[6-8] Various protocols consisting of single or multiple exposures have been published to investigate the mechanism of VIS-induced skin darkening.[3-9] Growing evidence indicates that pigment formed at earlier time points after VIS irradiation is photo-oxidized melanin while, at later time points, new pigments are synthesized through neo-melanogenesis.[5] The proposed molecular mechanism for VIS-induced skin pigmentation is through the activation of Opsin 3, a photo-receptor, which mediates the expression and activity of the rate-limiting enzyme, tyrosinase, in melanocytes.[10,11]

Despite our growing understanding of the impact of VIS on human skin, commercially available sunscreens have a limited ability to extend protection beyond UV. Using a mini-zone back human model, Duteil el al. showed three products containing iron oxide (FeO), titanium dioxide (TiO2), and pigment, provided protection against VIS (400–700nm)-induced pigmentation following 24 hours after a series of four exposures each at a dose of 144 J/cm^2.[9] Another study has shown that topical application of a silicone in water emulsion containing 4.5% yellow FeO reduced VIS-induced pigmentation when compared to unprotected skin after 4 consecutive exposures of 150 J/cm^2.[12] Under real life conditions, daily application of a tinted sunscreen was demonstrated to reduce the appearance of cutaneous hyperchromias after 60 days.[13] Additionally, broad-spectrum sunscreens containing FeO alone or in combination with TiO2 and ZnO were shown to improve melasma lesions after 8 weeks, and to prevent relapses after 6 months.[14,15]

Due to their capabilities in absorbing, scattering, and reflecting visible light, topical products containing metal oxides can provide additional protection.[16] Using a similar exposure protocol as Duteil el al., we evaluated the efficacy of two tinted formulations containing a combination of FeO and TiO2 in comparison to a non-tinted mineral SPF 50+ sunscreen with ZnO and TiO2 for protection against visible light-induced pigmentation. The

mineral SPF 50+ sunscreen was included in the study to assess the efficacy of a UVA and UVB protection alone in blocking the mediated effects of visible light on the skin.

METHODS

Study Participants

The study was performed in accordance with Good Clinical Practices and the principles of the Declaration of Helsinki. The procedures used in this study were approved by IntegReview IRB (Austin, TX). Before any study procedure, the subjects received the necessary written and verbal information and signed an informed consent form. Eligibility was determined by physical examination and confirmation of all inclusion/exclusion criteria. Ten healthy women aged 18-50 years (mean age, 35 + 6 years) with Fitzpatrick skin phototype IV were included in this study. Subjects with planned UV exposure (sunlight or sunbeds) or who used laser or phototherapy to the back during the study; with a history of taking or planned on taking any photosensitizing, anti-inflammatory, immunosuppressive medications, or any medication known to cause abnormal responses to UV exposure; or having prior or current pathologies induced or aggravated by exposure to light, or having abnormal reactions to sunlight (eg, photosensitive dermatitis, skin cancers, solar urticaria), were excluded.

Study Design

The study was monocentric, randomized, and single-blinded. Following the screening visit, subjects were required to attend six evaluation visits as follows:

At baseline (day 0), five investigational zones of 2x2 cm were delineated on the middle section of each subject's back: one negative control zone (unexposed and un-irradiated), one positive control zone (only irradiated), and three pre-treated and irradiated zones. The three test products were applied (2 mg/cm^2) according to randomization plan.

On day 0, fifteen minutes after product application, the four test zones, excluding the negative control zone, were exposed to a single dose of VIS at 144 J/cm^2, equivalent to one hour of exposure at midday in summertime. Product application and VIS exposure were similarly repeated on day 1, day 2, and day 3.
Clinical grading for skin pigmentation, colorimetric measurements, and standardized photograph were performed before product application and VIS irradiation on day 0 to day 3, 24 hours post the last irradiation on day 4, and on day 14.

Test Materials

Test materials consisted of three currently marketed products: 1) Product A (mineral SPF 50+ sunscreen with ZnO and TiO_2); 2) Product B (FeO and TiO_2 formulation); and 3) Product C (FeO formulation). Figure 1A displays the concentrations of the metal oxides in each test products, and Figure 1B, their absorbance spectra within the UV and HEV range. Product B and C have wider absorption wavelength band extending in the HEV range, suggesting superior protection compared to Product A. All test products were applied in a randomized and single-blinded manner.

Solar Stimulator

An ORIEL solar simulator, model 94043A-SP01-1600W, was used (Stratford, CT, USA). Its artificial luminous source was composed of a 1600 Watts xenon arc lamp, giving a continuous spectrum covering ultraviolet (280nm) to infrared (1720nm). The light source was fitted with an AM 1.5G filter to generate the standard solar spectrum.

The Schott WG 400nm filter was used to eliminate UVR, allowing only VIS and IR spectra to pass through. A Schott KG3/2mm filter was then used to output mostly VIS and some IR-A emission (400–900nm) as illustrated in Figure 1C. The resulting spectral output, which will be referred to as visible light*, contained no UVB, 0.01% UVA (320–400nm), 88.2% VIS (400–750nm), 10.7% HEV (400–450nm), and 9.8% IRA (750–900nm). For each test zone, light intensity was measured just prior to exposure in order to deliver an accurate dose of 144 J/cm^2, with an average fluence rate of 50 mW/cm2.

Pigmentation Assessments

The intensity of the induced skin pigmentation was visually assessed by expert grading using an internally validated scale, ranging 0 (no pigmentation) to 13 (pronounced brown pigmentation). The scale is based on the visual comparison of the pigmentation of the test zone with that of the surrounding unexposed control skin. Scoring was performed by the same clinical expert throughout the study.

The instrumental measurements of skin color were performed before the subject inclusion and during the study, with a Chromameter® (Konica Minolta CR400), using the $L^*a^*b^*$ color system (CIE lab, 1976). The individual typology angle (ITA°) that defines skin fairness or darkness was calculated from L^* and b^* measurements, using the formula: $ITA° = [\text{arcTangent } (L^* - 50)/b^*)]\ 180\ /\pi$.

Skin color changes after irradiation were assessed by using the parameter $\Delta E = \sqrt{(\Delta L^2 + \Delta a^2 + \Delta b^2)}$, where ΔL is the difference between the L of exposed zone and the non-exposed zone. Similar calculations were performed for Δa and Δb.

Standardized photographs were taken using a Canon EOS Rebel T5 camera with standard cross polarized filters under the same source of artificial light.

Statistical Analysis

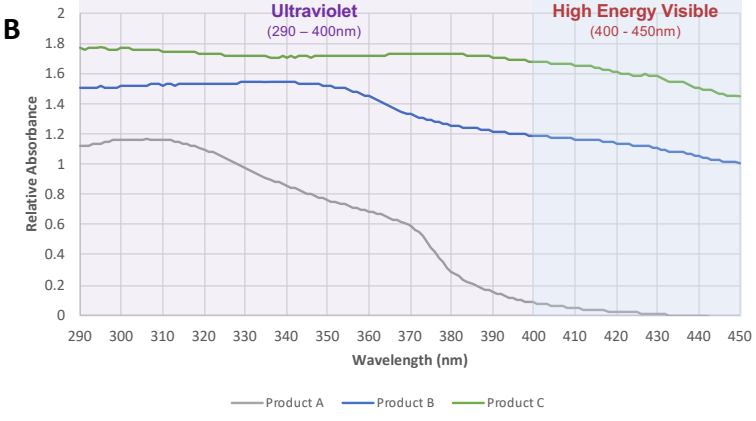
For pigmentation score, L^* value, a^* value, b^* value, ITA°, and Delta E, a Gaussian linear mixed model was used to analyze the mean difference in change from baseline between treatment with baseline, treatment, time, treatment-time interaction as

FIGURE 1. (A) Metal oxide content in the formulas; (B) UV and HEV absorption spectra of tested products; (C) Spectral irradiance of solar simulator between 250–1500nm with WG 400nm + KG3 filters.

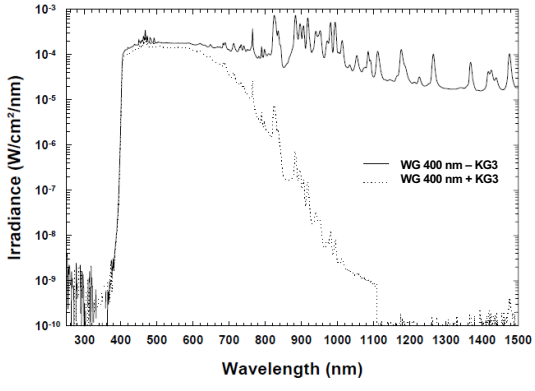
A

Products	ZnO	TiO_2	FeO
Product A (mineral SPF50+)	6.5%	4.5%	0%
Product B	0%	27%	4.85%
Product C	0%	0%	27.25%

B



C



fixed effects, and subject as random effect. *P*-values <0.05 were considered statistically significant.

For visible light protection factor (VL-PF), the slope from baseline to day 4 of estimated ITA° change from baseline was calculated, and the ratio between the mean slope for the VL-irritated bare skin over the mean slope of the VL-irritated skin treated with one of the products was obtained as the VL-PF. All calculations were performed using SAS ver 9.0.

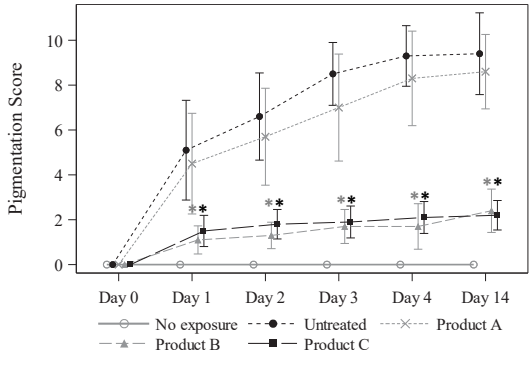
RESULTS

Clinical assessment for skin pigmentation, including statistical comparisons to baseline values, for each treatment from day 0 to day 14, are illustrated in Figure 2A. The untreated zone and the zone pre-treated with Product A showed a perceivable and statistically significant increase in pigmentation from day 0 to day 3, which was persistent to up to day 14. Pre-treatment with Products B and C demonstrated a statistically significant but less-pronounced increase in pigmentation, which was maintained at minimal level following the series of four consecutive exposures to visible light* and until day 14, as shown in Figure 2B.

The mean values of ΔL^* are shown in Figure 3A. In alignment with clinical assessment for skin pigmentation, untreated zone and Product A presented a statistically significant decrease in

FIGURE 2. (A) Clinical grading of pigmentation score for the 3 products and comparison to non-exposed control and untreated-VIS exposed control. *denotes *P*<.001 for Product B and C compared to untreated and Product A; (B) Representative images of visible light-induced pigmentation observed at indicated timepoints.

A



B

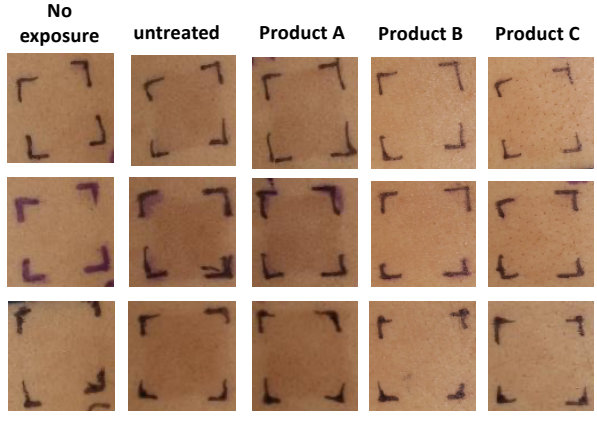


FIGURE 3. Change in efficacy parameters, (A) ΔL*, (B) ΔE, and (C) ΔITA° with comparisons from baseline. *denotes *P*<.001 for Product B and C from untreated and Product A.

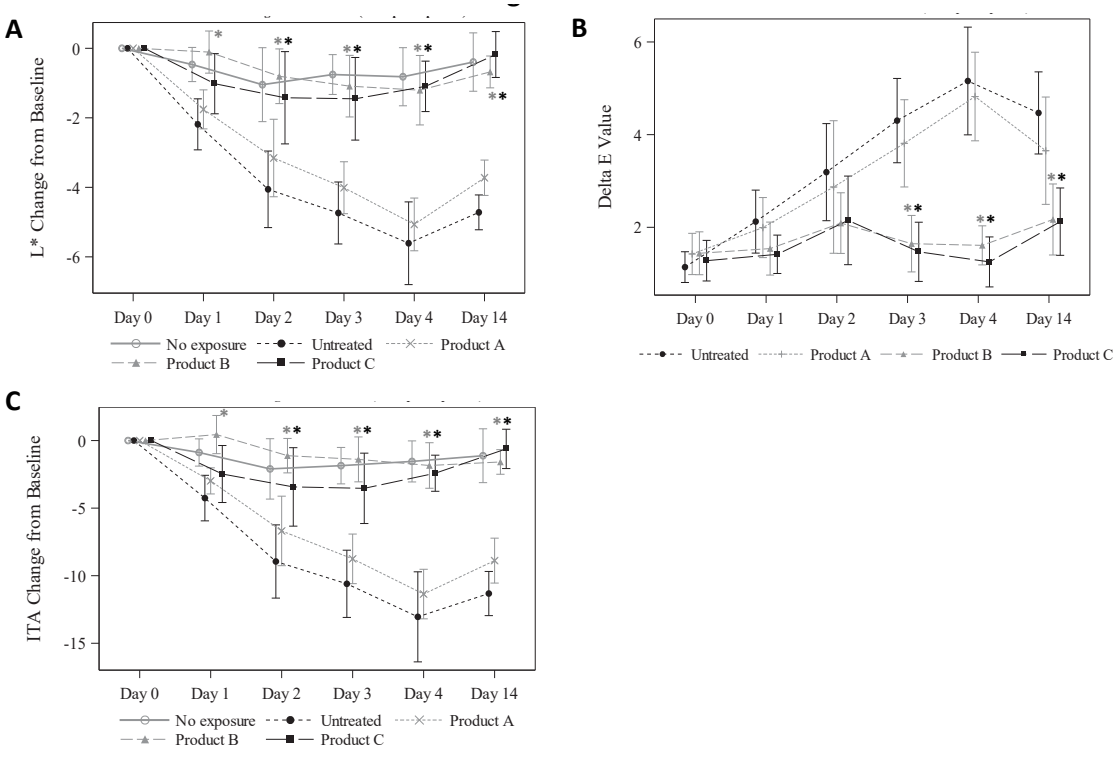


TABLE 1.

Pairwise comparisons between products. Statistical significance, *P*<0.05; trend towards statistical significance, *P*<0.1>0.05; ns, not significant.

Parameters	Comparisons	p values Day 1	p values Day 4	p values Day 14
Clinical Scoring	Untreated vs. Product A	ns	ns	ns
	Untreated vs. Product B	<0.001	<0.001	<0.001
	Untreated vs. Product C	<0.001	<0.001	<0.001
	Product A vs. B	<0.001	<0.001	<0.001
	Product A vs. C	<0.001	<0.001	<0.001
	Product B vs. C	ns	ns	ns
ΔL*	Untreated vs. Product A	ns	ns	0.035
	Untreated vs. Product B	<0.001	<0.001	<0.001
	Untreated vs. Product C	<0.001	<0.001	<0.001
	Product A vs. B	<0.001	<0.001	<0.001
	Product A vs. C	0.072	<0.001	<0.001
	Product B vs. C	0.064	ns	ns
ΔE	Untreated vs. Product A	ns	ns	ns
	Untreated vs. Product B	ns	<0.001	<0.001
	Untreated vs. Product C	ns	<0.001	<0.001
	Product A vs. B	ns	<0.001	0.005
	Product A vs. C	ns	<0.001	0.005
	Product B vs. C	ns	ns	ns
ΔITA°	Untreated vs. Product A	ns	ns	0.041
	Untreated vs. Product B	<0.001	<0.001	<0.001
	Untreated vs. Product C	ns	<0.001	<0.001
	Product A vs. B	<0.001	<0.001	<0.001
	Product A vs. C	ns	<0.001	<0.001
	Product B vs. C	0.015	ns	ns

ΔL* from day 0 to day 14 (indicating skin darkening); whereas, compared to baseline, both Product B and C showed a statistically significant, less-marked decrease in ΔL* at all timepoints except at day 1 and day 14 (indicating less skin darkening).

For clinical grading of pigmentation, pairwise comparisons between various zones presented in Table 1 illustrate no statistical difference between untreated zone and Product A on day 1 (after the 1st exposure), day 4 (24 hours after the last exposure), and day 14. Despite no significant difference between Product B and C, both showed statistically significant differences when compared to untreated zone and Product A at all timepoints.

For ΔL*, there was no statistical difference between untreated zone and Product A at day 1, day 3 (p value not shown), and day 4, and a statistical difference at day 14, favoring Product A. Product B demonstrated significant higher ΔL* compared to exposed zone and Product A at all-time points. Compared to untreated zone, Product C showed significant higher ΔL* at all-time points (less skin darkening), from day 2 (p value not shown) to day 14 when compared to Product A. These results suggest that both Products B and C were equally effective in blocking visible light*-induced skin pigmentation.

Similar results were observed for ΔE and ΔITA° parameters (Figure 3B, 3C, and Table 1). Product A was similar to untreated zone at all timepoints for ΔE, and same for ΔITA°, except at day 14. Both Products B and C were more effective in preventing skin color change compared to Product A from day 2 for ΔITA° and from day 3 for ΔE. No statistical differences in performance between Products B and C for ΔE, and same for ΔITA°, except a statistical difference at day 1, favoring Product B.

Skin redness (Δa*) and skin yellowness (Δb*) showed much smaller changes over time and inconsistent results for product performance distinction, indicating that the blocking of the visible light*-induced pigmentation by the products were specific for skin darkening (data not shown).

DISCUSSION

Originally believed to be harmless, it seems evident that VIS induces biological effects to human skin.[17] Combining LUVA1 and VIS cause an immediate erythema response in skin phototype I-III, while inducing inflammation and immediate pigment darkening in skin phototype IV-VI.[6-8] VIS alone or in combination with IR generates ROS, increases collagen degradation, and indirectly leads to DNA damage.[18,19] Since VIS and IR makeup a great proportion of solar radiation and due to the lack of sunscreens offering protection beyond UV, it is crucial that novel means of photoprotection against these longer wavelengths be developed and tested. Here, we demonstrate that FeO containing formulations were more effective in preventing visible light-induced pigmentation compared to a non-tinted mineral SPF50+ sunscreen.

Similar to UVA, VIS elicits immediate and persistent pigment darkening (PDD) in subjects with skin phototype III and above; processes that are mediated via the photo-oxidation of pre-existing melanin and de-novo melanogenesis, respectively.[4,20-22] The potential topical or oral use of antioxidants, molecules that scavenge free radicals, for VIS protection, has been proposed and tested by various research groups.[23-26] However, clinical studies evaluating the efficacy of antioxidants to protect against VIS-induced pigmentation are scarce. One study demonstrated that topical application of an antioxidant mixture reduced the immediate erythema and pigmentation responses followed by VIS+UVA1 exposure in subjects with skin phototypes I-III and IV-VI, respectively.[27] But, this protective trend was not observed at day 7, indicating that antioxidants may be more effective in reducing skin darkening mediated by melanin photo-oxidation, and less effective at preventing de-novo melanin synthesis, which constitutes the later phases of pigment formation. Our results show that both FeO-containing formulations tested efficiently prevented further skin darkening following each irradiation, which persisted up to 14 days, while the mineral SPF50+ sunscreen gave similar results as untreated skin. Due to their higher concentrations of metal oxides, particularly FeO, it is clear that these formulations provided a better physical barrier for the skin against VIS rays, defending against cumulative effects and inhibiting delayed tanning.

Interestingly, despite the difference in FeO and TiO2 levels (Figure 1A), there lacked statistically significant differences in performance between formulations B and C. This raises an important point concerning how to assess products photoprotective efficacy against VIS, as it is performed for UVB and UVA sunscreens under regulatory guidelines.[28-30] Several papers have suggested different in vivo methods to evaluate the VIS protection factor (VL-PF) of products.[9,12,31,32] For single dose exposure, the VL-PF is based on the minimal PPD of unprotected and protected skin, similar to the UVA protection factor method.[12] More recently, Kholi et al proposed to use the spectral signatures of the VIS+UVA1-induced skin pigmentation by obtaining the ratio of the area under the curve of the differential apparent absorbance of untreated skin from 400–700nm to that of treated skin at specific timepoints.[31] For multiple doses, Duteil et al determined the VL-PF by obtaining the ratio of the mean slope of the linear regression calculated between timepoints of the ΔITA° curves for untreated over treated.[9] Using similar method, the calculated VL-PF of Product A (mineral SPF 50+) was 1.48, while Product B and Product C had a VL-PF of 7.07 and 5.4. In alignment with prior studies, it appears that products with FeO pigments present higher VL-PF, as compared to products without pigment.[32] Despite the big differences in the FeO content between product B and C, in this study, we found both products demonstrated similar VL photoprotection. Future studies are needed to expand on the findings of this pilot study with bigger sample sizes, longer evaluation time beyond 14 days, determination of the minimal level of FeOs necessary for effective VIS

protection, and development of standardized guidelines for in vivo assessments of VL-PF and interpretation of this value.

CONCLUSION

In summary, our results show that products containing FeO protect the skin from VIS-induced pigmentation better than a mineral SPF50+ sunscreen containing TiO2 and ZnO. These findings highlight that FeO pigments-based foundation formulations can play a dual role by camouflaging existing pigmentation, as well as reducing the development of pigmentation triggered by sun exposure. The rising evidence that VIS and IR can induce long lasting biological responses in human skin has created the need to find non-traditional strategies for full spectrum photoprotection and beyond the UV range. Moreover, it is essential to identify different ways to bring clinically visible benefits that are compatible to daily routines of patients for minimizing the damaging effects of chronic sun exposure. The availability of topical products containing pigments and/or metal oxides, such as foundations in multiple shades and tones, can offer customized daily protection beyond UV for individuals of all skin phototypes.

DISCLOSURES

Pearl Grimes serves as a consultant for VT Cosmetics, Incyte and Dermaforce; as an investigator for Aclaris Therapeutics, Allergam, Pfizer, L'Oreal, Johnson & Johnson, Clinuvel, Thync Global Inc., VT Cosmetics and Incyte. All other authors are employees of L'Oreal Research & Innovation, USA.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Safety and Efficacy of Clobetasol Propionate 0.05% Emollient Foam for the Treatment of Central Centrifugal Cicatricial Alopecia

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ABSTRACT

Background: There is currently an unmet need for the treatment of women with central centrifugal cicatricial alopecia (CCCA).
Objective: To evaluate the safety and efficacy of Clobetasol propionate 0.05% emollient foam for the treatment of women with CCCA.
Methods: Adult women of African descent that presented with clinical evidence of early CCCA were enrolled (*N*=30). Clobetasol propionate 0.05% emollient foam was applied daily in an open-label fashion. Safety and efficacy assessments were performed at weeks 2, 6, 12, and 14.
Results: Subjects achieved substantial improvements in pruritus, pain, tenderness, erythema and scaling. Scalp biopsies revealed considerable improvements in severe inflammation and perifollicular edema. Overall, clobetasol propionate 0.05% emollient foam was well-tolerated.
Limitations: This was a nonrandomized, open-label study. Enrollment was limited to subjects with clinically mild CCCA.
Conclusion: Subjects with CCCA that applied topical clobetasol propionate 0.05% emollient foam to their scalp daily demonstrated continuous clinical improvement throughout the 14-week study.
ClinicalTrials.gov Identifier: NCT01111981

J Drugs Dermatol. 2020;19(7):719-724. doi:10.36849/JDD.2020.5201

INTRODUCTION

Central centrifugal cicatricial alopecia (CCCA) is a common cause of progressive, permanent, scarring alopecia. It is an inflammation-induced scarring type of hair loss that begins at the vertex of the scalp and progresses centrifugally. The etiology appears to be multifactorial. It occurs in all races but primarily among persons of African descent[1] and with a much greater frequency among women.[2,3] The prevalence is unknown, but may vary from 2.7% in South Africa to 5.6% in the United States within this population and increases with age.[2,4]

Pedigree analysis suggests an autosomal dominant mode of inheritance; however, hair grooming habits may markedly influence disease expression.[5] Recently, a PADI3 gene mutation has been identified in patients with CCCA.[6] The PADI3 gene is expressed in the inner root sheath, and encodes a protein that is necessary in the proper development of the hair shaft.[6,7] Abnormal inner root sheath desquamation has been linked to the pathogenesis of CCCA.[7] This finding may provide a causal relationship or increased susceptibility to hair loss in these individuals.[6] Although an association between CCCA and the use of hair grooming styles that cause traction such as sewn-in hair weaving and cornrow or braided hairstyles has been reported,[8,9] discontinuing these hair styles does not stop progressive hair loss. The results of a survey designed to determine risk factors for CCCA among African American women (*N*=326) revealed 59% had advanced central hair loss with clinical signs of scarring.[10] Among those with CCCA, the incidence of bacterial scalp infections and diabetes mellitus type 2 were significantly higher as were hair styles associated with traction.[10]

Early diagnosis and treatment are essential in stopping or slowing the progression of scarring and permanent hair loss. Dermoscopy and histologic evaluation may reveal early or late findings that can help establish the diagnosis.[11,12] Prompt and appropriate treatment is essential to help halt or slow disease progression.[13] As the likelihood of scarring is related to the extent of inflammation, anti-inflammatory medications are the mainstay of treatment, with topical and intralesional corticosteroids being first-line treatments for CCCA.[2,14–17] Other treatments include topical calcineurin inhibitors, oral antibiotics, hydroxychloroquine, and hair transplantation.[1,2,14,15,18–20] In addition to a discussion on camouflage techniques, patients should be counseled to avoid physical and chemical trauma to the scalp.[21]

Clobetasol propionate 0.05% emollient foam is an FDA-approved topical corticosteroid for the treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp, and for short-term (2 week) topical treatment of mild to moderate plaque-type psoriasis of non-scalp regions excluding the face and intertriginous areas.[22] Many studies have found the foam to be safe and effective, and a newer emollient formulation is less irritating than the original product.[23] A 24-week randomized, double-blind, placebo-controlled trial of clobetasol propionate 0.05% foam for the treatment of alopecia areata revealed it was efficacious and produced no significant modifications in cortisol or ACTH blood levels. It was well tolerated and had a good patient compliance profile.[24] The goal of this open-label prospective study was to evaluate the safety and efficacy of clobetasol propionate 0.05% emollient foam for the treatment of patients with CCCA. To our knowledge, the current study is the first to systematically assess the use of a drug therapy for the treatment of CCCA.[2,14,16,17]

METHODS

Study Subjects

Adult women of African descent that presented with clinical evidence of early CCCA were enrolled. The diagnosis was confirmed by medical history, scalp examination, and confirmatory scalp biopsy. Subjects completed the validated Central Scalp Alopecia Photographic Scale (CSAPS), which uses scores of 0 (no hair loss) to 5 (severe central scalp hair loss) on a six-point scale to assess baseline CCCA severity.[25] Enrolled subjects were required to have a score of 0–1, indicating early stage CCCA.

Exclusion criteria included male gender, women of non-African descent, history of hair transplantation, the use of anti-seborrheic dermatitis shampoo within 30 days of enrollment, the use of anti-inflammatory medications (steroids or NSAIDS) at the time of enrollment, the presence of other types of alopecia, pregnancy, and lactation. Women of child-bearing potential agreed to use a reliable form of contraception for the duration of the study.

Study Drug

The study medication was a topical emollient foam formulation containing clobetasol propionate 0.05% as its active ingredient (OLUX-E® [clobetasol propionate] Foam, 0.05%; Prestium Pharma, Inc., Newtown, PA. Provided by Stiefel Laboratories, Research Triangle Park, NC). The inactive ingredients included anhydrous citric acid, cetyl alcohol, cyclomethicone, isopropyl myristate, light mineral oil, polyoxyl 20 cetostearyl ether, potassium citrate monohydrate, propylene glycol, purified water, sorbitan monolaurate, white petrolatum and phenoxy ethanol as a preservative, pressurized with a propane/butane propellant.[26]

Study Procedures

Clinical photography of the scalp was performed at baseline and at week 14. Subjects completed a CSAPS and Hair Loss Questionnaire at the baseline visit. Subjects were instructed to apply a thin layer of clobetasol propionate 0.05% emollient foam to the scalp daily. Follow-up safety and efficacy assessments were performed at weeks 2, 6, 12, and 14.

Scalp biopsies were performed at baseline and week 12 and interpreted by the same dermatopathologist, who was blinded to the clinical status of the patient (pre- versus post-treatment). The diagnostic features used histologically to establish the diagnosis of CCCA were as follows: At the level of the deep dermis, some follicles showed premature desquamation of the inner root sheath. At the level of the upper isthmus and lower infundibulum, at least one follicle per specimen showed at least mild concentric lamellar fibroplasia, and a mild degree of perifollicular, chronic inflammation. Each specimen contained at least one naked hair shaft and/or follicular scar, evidence of prior follicular destruction. However, active inflammation was minimal, and sebaceous glands were present in each follicular unit. Clear-cut vacuolar interface alteration of the follicular epithelium was not observed and the epidermis was normal.

Each specimen was assessed for the following diagnostic features, and the degree of severity is defined as such:

1. Degrees of inflammation per follicle (in "most dense" zone of perifollicular inflammation) are defined as:
   a. None: 20 leucocytes or less per 400X power field
   b. Mild: 21–100 leucocytes or less per 400X power field
   c. Moderate: 101–500 leucocytes per 400X power field
   d. Severe: 501 or more leucocytes per 400X power field

2. Degrees of perifollicular edema, as defined by widened spaces between layers of perifollicular, concentric, lamellar fibroplasia, with increased pallor and decreased eosinophilia of perifollicular connective tissue. Assessed for the most severely affected follicle.
   a. None: no widening or no fibroplasia
   b. Mild
   c. Moderate
   d. Severe

The following photographs depict examples of the varying degrees of perifollicular edema, fibroplasia and inflammation (Figures 1–3).

Treatment compliance was established by weighing the container of study drug at each visit.

Efficacy End Points

The week 12 scalp biopsy was used to assess changes in scalp

FIGURE 1. Central Centrifugal Cicatricial Alopecia (CCCA). Mild fibroplasia and inflammation.

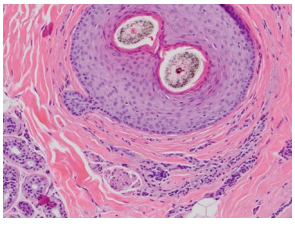


FIGURE 2. Central Centrifugal Cicatricial Alopecia (CCCA). Moderate fibroplasia and inflammation.

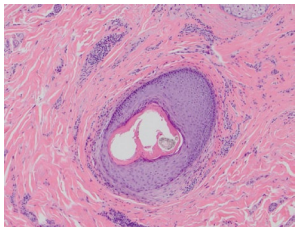
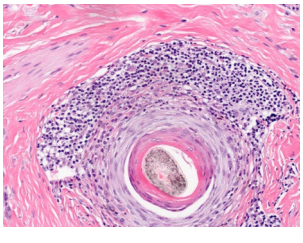


FIGURE 3. Central Centrifugal Cicatricial Alopecia (CCCA). Severe fibroplasia and inflammation.



inflammation. Subjective improvements in scalp symptoms (pruritus, tenderness, pain, and redness) were assessed at each visit. Investigators also performed scalp assessments rating the degree of erythema, scale, and hair loss at each visit. The primary efficacy endpoints were improvements in subject scalp symptoms, improvement in the investigator scalp assessments, and improvement in histologically observed inflammation. The CSAPS was used to assess changes in the clinical severity of CCCA.[25]

Safety

The scalp was examined by the Investigator at each visit and patient-reported adverse events (AEs) were recorded.

Ethics

The protocol, informed consent document and relevant supporting information were approved by a local institutional review board (Schulman Associates, Cincinnati, OH). The study was conducted in accordance with the regulations of the United States Food and Drug Administration as described in 21 CRF 50 and 56, the ethical principles that have their origin in the Declaration of Helsinki and was consistent with Good Clinical Practice and applicable regulatory requirements. Each enrolled subject provided written informed consent prior to participating in any study-related procedures. ClinicalTrials.gov Identifier: NCT01111981.

RESULTS

Thirty (30) female subjects with mean (SD) age of 44.7 years (8.7) (range, 28–72 years) were enrolled and were pre- (80%) or postmenopausal (20%). The 14-week study was completed by 25 subjects. Reasons for not completing the trial included lost to follow up (*N*=2), biopsy not revealing a diagnosis of CCCA (*N*=1), and withdrawal due to adverse events (*N*=2). Most subjects (86%) reported their most severe hair loss experienced to be ≤1B on the CSAPS and 57% responded that their hair loss had worsened during the 12 months prior to enrollment with 76% currently rating their hair loss as mild-to-moderate in severity.

A Hair Loss Questionnaire was utilized to examine participants' hair care practices, previous treatments utilized for their hair loss, subjective opinions of their hair loss when compared to standardized photographs, as well as comorbid medical conditions. Results of the Hair Loss Questionnaire revealed approximately 30% of subjects had received prior treatment for hair loss, including oral and topical antibiotics, topical antifungal treatments, topical minoxidil, and topical and intralesional steroids. In addition to the vertex, 57% of subjects reported experiencing hair loss on other parts of the scalp as well as a past medical history of adult acne (33%), hirsutism (47%), irregular menstrual cycle (30%), and vaginal yeast infections (43%). Most subjects reported some family history of hair loss (parents, maternal and paternal grandparents, sister). The questionnaire also captured hair care practices used by our subjects at the time of the study or prior to enrollment. Most (77%) reported using moisturizer on the scalp including oils (50%), ointments (37%), lotions (13%), and creams (13%). The majority of subjects also reported having used a relaxer with most using a lye-based relaxer (57%).

Efficacy

During the baseline visit, subjects complained of pruritus (80%), tenderness (59%), mild pain (13%), and scalp erythema (13%) (Table 1). At week 14, the frequency of symptoms decreased to mild pruritus (13%), tenderness (13%), mild pain (3%), and none complained of erythema. The baseline Investigator assessments revealed subjects with no erythema and no scale (63%), but mild erythema and mild scale at week 14 (10%). There was modest improvement among subjects with moderate hair loss at baseline.

Baseline and week 12 scalp biopsies assessed the degree of active inflammation of the terminal hairs, the degree of perifollicular edema, sebaceous gland loss in at least one follicle, and the presence of follicular scarring (Table 2). At baseline, a mean

TABLE 1.

Scalp Symptoms by Patient Examination					
Facial Area	**Day 0**	**Week 2**	**Week 6**	**Week 12**	**Week 14**
Pruritus, *N (%)*					
Not Done	0	0	2 (7)	6 (20)	6 (20)
None	6 (20)	10 (33)	12 (40)	16 (53)	20 (67)
Mild	13 (43)	15 (50)	13 (43)	7 (23)	4 (13)
Moderate	9 (30)	5 (17)	3 (10)	1 (3)	0
Severe	2 (7)	0	0	0	0
Tenderness, *N (%)*					
Not Done	0	0	2 (7)	6 (20)	6 (20)
None	12 (40)	22 (73)	22 (73)	19 (63)	20 (67)
Mild	13 (43)	6 (20)	6 (20)	3 (10)	3 (10)
Moderate	4 (13)	2 (7)	0	2 (7)	1 (3)
Severe	1 (3)	0	0	0	0
Pain, *N (%)*					
Not Done	0	0	2 (7)	6 (20)	6 (20)
None	26 (87)	29 (97)	28 (93)	23 (77)	23 (77)
Mild	4 (13)	0	0	1 (3)	1 (3)
Moderate	0	1 (3%)	0	0	0
Severe	0	0	0	0	0
Redness, *N (%)*					
Not Done	0	0	2 (7)	6 (20)	6 (20)
None	26 (87)	28 (93)	28 (93)	23 (77)	24 (80)
Mild	3 (10)	1 (3)	0	1 (3)	0
Moderate	1 (3)	1 (3)	0	0	0
Severe	0	0	0	0	0
Symptom-free, *N (%)*					
Not Done	0	0	2 (7)	6 (20)	6 (20)
None	27 (90)	23 (77)	19 (63)	12 (40)	8 (27)
Mild	3 (10)	7 (23)	9 (30)	12 (40)	16 (53)

of 3.4%, 2.9% and 2.7% of follicles showed mild, moderate and severe inflammation, respectively. At week 12, the number of follicles with mild and moderate degrees of inflammation remained stable, while follicles with severe inflammation decreased to 0.58%.

The number of hairs with no perifollicular edema increased from 9.85% at baseline to 10.24% at week 12 while mild perifollicular edema increased from 3.51% to 4.06%. This corresponded with decreases in mean number of follicles with moderate and severe edema. The appearance of the scalp epidermis showed no inflammation at baseline or week 12. Other improvements noted between baseline and week 12 included: premature desquamation of the inner root sheath (PDIRS) in ≥ 1 follicle decreased from 97% to 77%, sebaceous gland loss in ≥ 1 follicle decreased from 97% to 70%, and the percentage of follicular scarring decreased from 83% to 67%.

Safety

AEs determined to be definitely, probably, or possibly related to the study treatment were defined as biopsy site soreness/sensitivity/tenderness (*N*=4), dry/flaky scalp (*N*=4), mild headache (*N*=2), and burning sensation on scalp (*N*=2; same patient). All were mild to moderate in severity except burning sensation, which was reported to be severe. Other reported AEs included mild to moderate itching/pruritus (*N*=4), hair loss/thinning/breakage (*N*=4), steroid-induced acne (*N*=2), tooth extraction (*N*=1), hives (*N*=1) and white spots on scalp (*N*=1). There were

TABLE 2.

Biopsy Results		
	Day 0	Week 12
Total number of terminal hairs with active inflammation:[a]		
None, *N (%)*	28 (93)	23 (77)
Mean (SD)	21.1 (9.19)	25 (9.66)
Mild, N (%)	28 (93)	23 (77)
Mean (SD)	5.4 (3.35)	3.5 (3.06)
Moderate, N (%)	*28 (93)*	*23 (77)*
Mean (SD)	3.4 (2.9)	2 (2.17)
Severe, N (%)	28 (93)	23 (77)
Mean (SD)	1.4 (2.71)	0.2 (0.58)
Total number of hairs with perifollicular edema:[a]		
None, *N (%)*	28 (93)	23 (77)
Mean (SD)	*19.7 (9.85)*	*23.6 (10.24)*
Mild, *N (%)*	28 (93)	23 (77)
Mean (SD)	5.8 (3.51)	4.8 (4.06)
Moderate, *N (%)*	28 (93)	23 (77)
Mean (SD)	3.1 (2.72)	1.8 (2.35)
Severe, *N (%)*	28 (93)	23 (77)
Mean (SD)	*2.3 (2.62)*	*0.5 (1.04)*
Appearance of the epidermis:[b]		
Not done	1 (3)	7 (23)
Normal	29 (97)	23 (77)
Inflamed	0	0
Total number of Hairs:[a]		
N (%)	*28 (93)*	*23 (77)*
Mean (SD)	37.3 (11.49)	37.3 (11.12)
Terminal/Vellus Ratio:[c]		
N (%)	28 (93)	23 (77)
Mean (SD)	6.2 (4)	7.3 (5.01)
Telogen Count:[a]		
N (%)	28 (93)	23 (77)
Mean (SD)	1.5 (1.23)	1.2 (1.65)
PDIRS in at least one follicle:[b]		
Not Done	1 (3)	7 (23)
Present	29 (97)	23 (77)
Absent	0	0
Sebaceous gland loss in at least one follicle:[b]		
Not Done	1 (3)	7 (23)
Present	29 (97)	21 (70)
Absent	0	2 (7)
Follicular scarring:[b]		
Not Done	1 (3)	7 (23)
Present	25 (83)	20 (67)
Absent	4 (13)	3 (10)

[a]Results from both A and B biopsies are summed prior to computing the statistics for each visit; [b]Worst case from both biopsies; [c]Expressed as a fraction prior to averaging the two biopsies for each patient at each visit (eg, 17/2 = 8.5).

11 dose interruptions due to AEs and two AEs leading to study withdrawal (additional hair loss and scalp pruritus).

DISCUSSION

Alopecia of all types is associated with negative psychosocial sequelae, which are more significant for women.[27,28] This is especially true with permanent hair loss disorders such as CCCA. Among women with hair loss, those with scarring alopecia have significantly greater depression, anxiety, decreased self-esteem, and quality of life than those with non-scarring alopecia.[29,30] To date, the treatment of CCCA has been suboptimal, anecdotal, and challenging, and therefore stressing the need for published, controlled studies.[2,14,17]

Topical or intralesional corticosteroids and topical minoxidil have been suggested as a means of preventing additional scarring and encouraging regrowth of recovering follicles.[21] Hair transplantation has been shown to be successful for African American women with end-stage CCCA;[18] however, this type of intervention is not feasible for everyone. As CCCA has been associated with hair styles causing hair tension such as sewn-in hair weaving and cornrow or braided hairstyles with artificial hair extensions,[8] emphasis should be placed on the prevention of CCCA by avoiding these practices.[21]

Following the daily application of clobetasol propionate 0.05% emollient foam for 12 weeks, subjects achieved substantial subjective improvements in scalp pruritus, pain, and tenderness, as well as objective improvements in erythema and scaling. Scalp biopsies revealed considerable improvements in severe inflammation and perifollicular edema. Subjects demonstrated continuous improvement throughout the 14-week study suggesting additional improvement may be achieved with continued use.

Overall, the daily application of clobetasol propionate 0.05% emollient foam was well-tolerated. Although therapy was interrupted due to AEs in several subjects and two subjects withdrew from the study due to AEs, the overall incidence of AEs was very low.

CONCLUSION

Again, to our knowledge, this prospective study is the first to assess the use of a drug therapy for the treatment of CCCA.[2,14,16,17] Most subjects in this 12-week study demonstrated significant improvements in the signs and symptoms of central centrifugal cicatricial alopecia following once-daily treatment with clobetasol propionate 0.05% emollient foam. Importantly, physical and histological examination showed there was a significant decrease in scalp inflammation. The therapeutic benefit of this topical corticosteroid may prevent hair loss and eventual permanent scarring in patients with CCCA.

DISCLOSURES

Dr. Callender received a research grant from Stiefel Laboratories, Inc. Dr. Young received a research grant from Stiefel Laboratories, Inc. Drs. Kazemi, Chappell, and Sperling have no relevant conflicts of interest to declare.

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Rhofade® (oxymetazoline HCl) cream, 1%

Not an actual patient.

RHOFADE cream is the #1 prescribed topical treatment for persistent facial erythema associated with rosacea in adults*

See results with RHOFADE cream

At hours 3, 6, 9, and 12 on Day 29 of clinical trials, a ≥2-grade improvement in persistent facial erythema was seen in 12% to 18% of subjects using RHOFADE cream vs 5% to 9% using vehicle. The most common side effects at the application site include: dermatitis, worsening of rosacea pimples, itching, redness, and pain.[1] These are not all the possible side effects of RHOFADE cream. Individual results may vary.

Unretouched photos of clinical trial subject. Individual results may vary.

*Based on Symphony Health PHAST data recording the number of prescriptions written between July 2017 and October 2019.[2]

INDICATION

RHOFADE cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

IMPORTANT SAFETY INFORMATION AND WARNINGS

WARNINGS AND PRECAUTIONS

Potential Impacts on Cardiovascular Disease
Alpha-adrenergic agonists may impact blood pressure. **RHOFADE** cream should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

Potentiation of Vascular Insufficiency
RHOFADE cream should be used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

Risk of Angle Closure Glaucoma
RHOFADE cream may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

CONTRAINDICATIONS

There are no contraindications for **RHOFADE** cream.

ADVERSE REACTIONS

The most common adverse reactions ≥1% for **RHOFADE** cream were: application-site dermatitis 2%, worsening inflammatory lesions of rosacea 1%, application-site pruritus 1%, application-site erythema 1%, and application-site pain 1%.

For topical use only. Not for oral, ophthalmic, or intravaginal use.

Please see full Prescribing Information for RHOFADE cream at rhofadehcp.com and Brief Summary attached.

References: 1. RHOFADE® cream full Prescribing Information 2019.
2. Data on file. EPI Health, LLC.

RHO-JA2-0320

EPIHEALTH
Advancing Dermatology

RHOFADE® (oxymetazoline HCl) cream, 1%

BRIEF SUMMARY—PLEASE SEE THE RHOFADE® CREAM PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

RHOFADE cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

DOSAGE AND ADMINISTRATION

For topical use only. Not for oral, ophthalmic, or intravaginal use.

Prime the RHOFADE cream pump before using for the first time. To do so, with the pump in the upright position, repeatedly depress the actuator until cream is dispensed and then pump three times. Discard the cream from priming actuations. It is only necessary to prime the pump before the first dose.

RHOFADE cream tubes do not require priming.

Apply a pea-sized amount of RHOFADE cream, once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips. Wash hands immediately after applying RHOFADE cream.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. RHOFADE cream should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

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RHOFADE cream may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under 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.

A total of 489 subjects with persistent facial erythema associated with rosacea were treated with RHOFADE cream once daily for 4 weeks in 3 controlled clinical trials. An additional 440 subjects with persistent facial erythema associated with rosacea were also treated with RHOFADE cream once daily for up to one year in a long-term (open-label) clinical trial. Adverse reactions that occurred in at least 1% of subjects treated with RHOFADE cream through 4 weeks of treatment are presented in the table below:

Adverse Reactions Reported by ≥ 1% of Subjects Through 4 Weeks of Treatment in Controlled Clinical Trials

Adverse Reaction	Pooled Controlled Clinical Trials	
	RHOFADE Cream (N = 489)	Vehicle (N = 483)
Application-site dermatitis	9 (2%)	0
Worsening inflammatory lesions of rosacea	7 (1%)	1 (< 1%)
Application-site pruritus	5 (1%)	4 (1%)
Application-site erythema	5 (1%)	2 (< 1%)
Application-site pain	4 (1%)	1 (< 1%)

In the long-term (open-label) clinical trial, the rates of adverse reactions over a one-year treatment period were as follows: worsening inflammatory lesions of rosacea (3%), application-site dermatitis (3%), application-site pruritus (2%), application-site pain (2%), and application-site erythema (2%). Subjects with persistent erythema along with inflammatory lesions were allowed to use additional therapy for the inflammatory lesions of rosacea.

DRUG INTERACTIONS

Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha-1 adrenergic receptor antagonists such as in the treatment of cardiovascular disease, benign prostatic hypertrophy, or Raynaud's disease.

Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on RHOFADE cream use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. A literature article describing intranasal decongestant use in pregnant women identified a potential association between second-trimester exposure to oxymetazoline (with no decongestant exposure in the first trimester) and renal collecting system anomalies. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 3 times and 73 times, respectively, the exposure associated with the maximum recommended human dose (MRHD). The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Following repeated use of oxymetazoline hydrochloride solution nasal spray for the treatment of nasal congestion at a dose 5 times higher than recommended, one case of fetal distress was reported in a 41-week pregnant patient. The fetal distress resolved hours later, prior to the delivery of the healthy infant. The anticipated exposures for the case are 8- to 18-fold higher than plasma exposures after topical administration of RHOFADE cream.

Human Data

No adequate and well-controlled trials of RHOFADE cream have been conducted in pregnant women. Across all clinical trials of RHOFADE cream, two pregnancies were reported. One pregnancy resulted in the delivery of a healthy child. One pregnancy resulted in a spontaneous abortion, which was considered to be unrelated to the trial medication.

Lactation

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breast milk production, or to establish the level of oxymetazoline present in human breast milk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOFADE cream and any potential adverse effects on the breastfed child from RHOFADE cream or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness of RHOFADE cream have not been established in pediatric patients below the age of 18 years.

Geriatric Use

One hundred and ninety-three subjects aged 65 years and older received treatment with RHOFADE cream (n = 135) or vehicle (n = 58) in clinical trials. No overall differences in safety or effectiveness were observed between subjects ≥ 65 years of age and younger subjects, based on available data. Clinical studies of RHOFADE cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

OVERDOSAGE

RHOFADE cream is not for oral use. If oral ingestion occurs, seek medical advice. Monitor patient closely and administer appropriate supportive measures as necessary. Accidental ingestion of topical solutions (nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep RHOFADE cream out of reach of children.

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ORIGINAL ARTICLE

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Novel Polymeric Tazarotene 0.045% Lotion for Moderate-to-Severe Acne: Pooled Phase 3 Analysis by Race/Ethnicity

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ABSTRACT

Background: Acne vulgaris and inflammation-associated sequelae are highly prevalent in black and Hispanic populations. In a phase 2 study, a novel polymeric emulsion formulation of tazarotene 0.045% lotion had relatively fewer adverse events than tazarotene 0.1% cream, but with comparable efficacy. The objective was to evaluate tazarotene 0.045% lotion by race and ethnicity in the pivotal trials.

Methods: In two phase 3, double-blind, 12-week studies (NCT03168334; NCT03168321), participants with moderate-to-severe acne were randomized 1:1 to tazarotene 0.045% lotion or vehicle lotion (N=1,614). This pooled, post hoc analysis included subsets of participants that self-identified as white (n=1191) or black (n=262) and Hispanic (n=352) or non-Hispanic (n=1262). Coprimary endpoints were inflammatory/noninflammatory lesion counts and treatment success (defined as at least a 2-grade reduction from baseline in Evaluator's Global Severity Score and a score of 'clear' or 'almost clear'). Treatment-emergent adverse events (TEAEs) and cutaneous safety and tolerability were evaluated.

Results: At week 12, tazarotene 0.045% lotion led to significantly greater percent reductions in inflammatory and noninflammatory lesions compared with vehicle in white, Hispanic, and non-Hispanic participants ($P<0.05$, all). Black participants had significantly greater reductions in noninflammatory lesions following treatment with tazarotene 0.045% versus vehicle ($P<0.05$). Treatment success rates in all subpopulations were higher with tazarotene 0.045% lotion (29.4-34.1%) versus vehicle (16.4-23.1%). TEAE rates were similar across tazarotene-treated groups and most were mild-to-moderate in severity. The incidence of hyperpigmentation decreased in black tazarotene-treated participants from baseline to week 12.

Conclusions: Tazarotene 0.045% lotion demonstrated efficacy and was well tolerated across racial and ethnic subpopulations in this pooled analysis.

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INTRODUCTION

Acne vulgaris is one of the most common dermatologic conditions for which all patients seek treatment, including those with darker skin tones.[1] Given the growing non-white population, estimated to be nearly one-half of the United States population by 2050,[2] more information is needed regarding the effects of acne treatment in all skin types. Recent articles highlighting the treatment of acne in Asian patients,[3] Hispanic patients,[4] and women of color[5] have set the stage for understanding how race and ethnicity might affect treatment outcomes.

In all skin types, acne development has the same causes: follicular hyperkeratinization, increased sebum production, proliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) bacteria on the skin surface, and inflammation.[6,7] More highly pigmented skin can have properties that increase the risk of acne and inflammation-related sequalae.[6] These sequelae occur in 50%-75% of black women with acne and include dyspigmentation and scarring.[8,9] Post-inflammatory hyperpigmentation (PIH) can be associated with acne resolution or irritation from harsh treatments or skin care.[10-12] For many

patients with darker skin tones, PIH is cited as the reason for seeking dermatological care.[12]

In these particular patients, using aggressive, non-irritating treatment is the recommended strategy to treat acne while reducing the risk of PIH and keloid scarring.[10] The first line of treatment for mild-to-moderate acne in patients of color is topical retinoids[6,10]—these disrupt desquamation pathways and inhibit multiple inflammatory pathways, which is important for the prevention of secondary PIH.[13]

One challenge of traditional formulations of topical retinoids—such as tazarotene, adapalene, and tretinoin—has been achieving uniform and consistent application with low rates of irritation, which may preclude effectiveness in real-world settings.[14] The development of tazarotene 0.045% lotion formulation utilizing polymeric emulsion technology improves topical delivery of a drug by suspending the active agent(s) with a polymer in a hydrating emulsion of solvents, emollients, and humectants without using surfactants. This new formulation can thereby reduce irritation and uniformly distribute these microscopic droplets across the skin surface in an aesthetically pleasing, easily spreadable lotion.[15] The adaptation of this technology to topical retinoids has the potential to reduce skin irritation while maintaining efficacy at a lower dosage, which may have particular benefits for patients with darker skin tones.[12,15]

In a phase 2 trial in participants aged ≥12 years with moderate-to-severe acne, tazarotene 0.045% lotion provided numerically lower lesion counts and higher rates of treatment success compared with tazarotene 0.1% cream.[16] Promisingly, the incidence of treatment-emergent adverse events (TEAEs) was nearly 2-fold lower in the tazarotene 0.045% lotion group compared with the tazarotene 0.1% cream group.[16] Furthermore, two identical phase 3 double-blind, randomized, vehicle-controlled 12-week clinical studies demonstrated tazarotene 0.045% lotion was efficacious versus vehicle and well tolerated in participants with moderate-to-severe acne.[17] Pooled, post hoc analyses from these phase 3 studies were conducted to examine the potential effects of race and ethnicity on the efficacy and safety of tazarotene 0.045% lotion.

METHODS

Study Design and Participants

This pooled analysis includes data from NCT03168334 and NCT03168321, which were previously described.[17] Both trials were identical, multicenter, double-blind, randomized, vehicle-controlled, parallel-group phase 3 studies conducted at 89 study centers in the United States and Canada. Eligible participants were aged ≥9 years with Evaluator's Global Severity Score (EGSS) of 3 (moderate) or 4 (severe), and had facial acne inflammatory lesion counts between 20-50, facial acne noninflammatory lesion counts between 25-100, and ≤2 facial nodules. Participants were randomized (1:1) to tazarotene 0.045% lotion or vehicle lotion, applied to the face once daily for 12 weeks. Studies were conducted in accordance with the International Conference on Harmonization, the Declaration of Helsinki, Good Clinical Practice Guidelines, and local regulations. All participants or their legal guardians provided written informed consent. Studies were approved by relevant independent ethics committees or institutional review boards at each study site.

Study Assessments

Efficacy and safety assessments were performed at each study visit (baseline and at weeks 2, 4, 8, and 12). Blinded evaluators determined EGSS and measured the number of noninflammatory and inflammatory lesions as efficacy assessments. Treatment success was defined as the proportion of participants achieving ≥2-grade reduction from baseline in EGSS and a score of 'clear' (0) or 'almost clear' (1). Investigator-assessed cutaneous safety (scaling, erythema, hypopigmentation, hyperpigmentation) and participant-assessed tolerability (itching, burning, stinging) were evaluated using a 4-point scale where 0=none and 3=severe. Adverse events (AEs) and serious adverse events (SAEs) were also monitored throughout the study.

Statistical and Subgroup Analyses

The co-primary endpoints for the two phase 3 studies comprised absolute change from baseline to week 12 in mean inflammatory and noninflammatory lesion counts and the proportion of participants achieving treatment success at week 12. The intent-to-treat (ITT) population was defined as all participants who were randomized and received study drug. The safety population included all randomized participants who used study medication or vehicle at least once with a minimum of one post-baseline evaluation.

For this pooled post hoc analysis, data from a subset of participants were evaluated based upon self-reported race (white or black) and ethnicity (Hispanic or non-Hispanic). Race and ethnicity were not mutually exclusive. Least-squares (LS) mean percent changes from baseline in inflammatory and noninflammatory lesion counts at week 12 and treatment success at week 12 were analyzed for each subgroup.

An analysis of covariance (ANCOVA) was performed to test for superiority for lesion count data between treatment groups. Initial analyses of mean percent changes from baseline in noninflammatory and inflammatory lesion counts indicated significant skewness. To address this, a nonparametric method was used to rank transform data prior to performing ANCOVA, with factor of treatment and the respective baseline lesion count as a covariate. Logistic regressions (using Firth's Penalized Likelihood) were performed to analyze treatment success, with

factor of treatment group. Statistical significance was defined as P=0.05 determined using 2-tailed tests of the null hypothesis. Values were adjusted for multiple imputations. Missing efficacy data of lesion counts and EGSS data were estimated using the Markov Chain Monte Carlo method. All statistical analyses were performed in SAS® version 9.3 or later. Cutaneous safety and tolerability assessments were summarized using descriptive statistics. AEs were recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Imputations were not made for missing safety data.

RESULTS

Participants

The overall pooled study population in the phase 3 studies included 1614 participants who received tazarotene 0.045% lotion (n=799) or vehicle lotion (n=815).[17] In this post hoc analysis, the population was segmented by race (n=1191 white, n=262 black) and by ethnicity (n=352 Hispanic, n=1262 non-Hispanic; Table 1). The black subpopulation was, on average, slightly older and had a higher proportion of female participants compared with the white subpopulation. Disease characteristics were similar between the races, although a slightly higher proportion of white participants had an EGSS of 4 compared with black participants (10.0% versus 4.6%, respectively). The subpopulations defined by ethnicity were similar in age and sex. While the majority of both the Hispanic and non-Hispanic subgroups were white, the non-Hispanic subgroup had higher proportions of participants reporting black or Asian race (Table 1).

Efficacy

Inflammatory and noninflammatory lesion counts decreased over time across all racial and ethnic subpopulations. In white participants, LS mean percent change from baseline in inflammatory lesions was significantly greater in the tazarotene 0.045% lotion group compared with the vehicle group at week 12 (-57.6% vs -45.0%; P<0.001); significant improvements were also observed at week 8 (Figure 1). Tazarotene-treated black participants had a similar reduction in inflammatory lesions (-60.4%) to white participants at week 12, but with no significant differences relative to vehicle. For noninflammatory lesions, reductions from baseline were significantly greater with tazarotene 0.045% lotion than vehicle at week 12 for both race groups (P<0.001, white; P<0.05, black); significant improvements were observed as early as week 4 in white participants and week 8 in black participants (Figure 2).

In the subpopulations defined by ethnicity, LS mean percent change in inflammatory lesion counts were significantly greater with tazarotene 0.045% lotion versus vehicle at week 12 in the Hispanic and non-Hispanic groups (P<0.01, Hispanic; P<0.001, non-Hispanic; Figure 3). Similar trends were observed in noninflammatory lesion counts, with significant improvements following treatment with tazarotene 0.045% lotion versus vehicle at week 12 (P<0.01, Hispanic; P<0.001, non-Hispanic; Figure 4). In non-Hispanic participants, significant decreases were observed as early as week 4 for noninflammatory lesions and week 8 for inflammatory lesions.

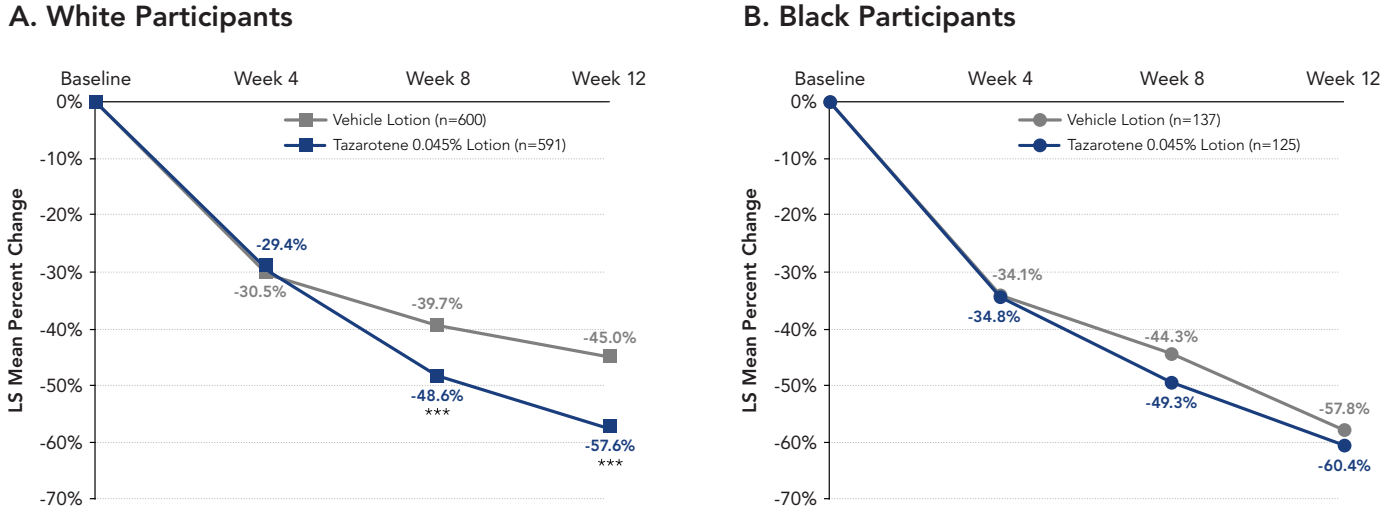
TABLE 1.

Participant Demographics and Baseline Characteristics (ITT Population, Pooled)

	Race		Ethnicity	
Characteristics	White (n=1191)	Black (n=262)	Hispanic (n=352)	Non-Hispanic (n=1262)
Age, mean (SD), y	19.6 (6.0)	24.0 (9.3)	20.7 (6.6)	20.4 (7.0)
Female, n (%)	753 (63.2)	205 (78.2)	225 (63.9)	839 (66.5)
Race, n (%)				
White	1191 (100)	0	307 (87.2)	884 (70.0)
Black/African American	0	262 (100)	15 (4.3)	247 (19.6)
Asian	0	0	2 (0.6)	76 (6.0)
Other[a]	0	0	28 (8.0)	55 (4.4)
Ethnicity, n (%)				
Non-Hispanic/Latino	884 (74.2)	247 (94.3)	0	1262 (100)
Hispanic/Latino	307 (25.8)	15 (5.7)	352 (100)	0
Inflammatory lesion count, mean (SD)	28.5 (7.3)	26.6 (6.0)	28.9 (7.8)	27.9 (6.9)
Noninflammatory lesion count, mean (SD)	40.9 (16.5)	40.6 (15.7)	41.3 (16.5)	41.0 (16.6)
Evaluator's Global Severity Score, n (%)				
3 – Moderate	1072 (90.0)	250 (95.4)	308 (87.5)	1159 (91.8)
4 – Severe	119 (10.0)	12 (4.6)	44 (12.5)	103 (8.2)

[a]Other comprises American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; and Other/Multiple.
ITT, intent to treat; SD, standard deviation.

FIGURE 1. Mean percent change in inflammatory lesion counts, by race (ITT population, pooled).



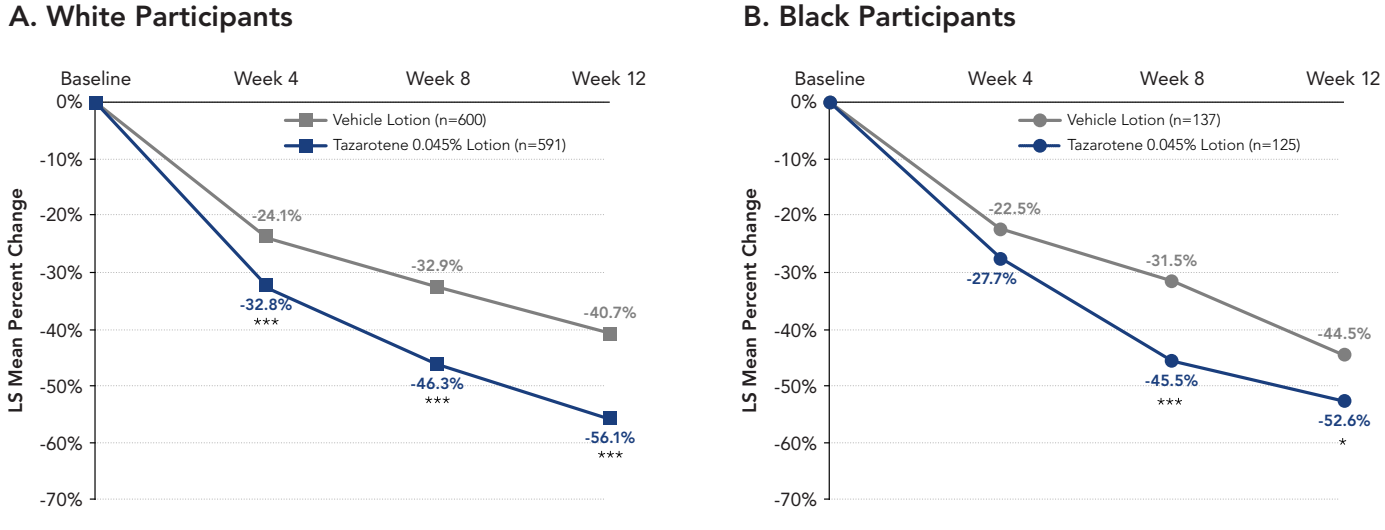
***P<0.001 versus vehicle.
ITT, intent to treat; LS, least squares.

Rates of treatment success were higher following treatment with tazarotene 0.045% lotion versus vehicle for all racial and ethnic subpopulations. At week 12, a significantly higher proportion of participants achieved treatment success with tazarotene 0.045% lotion compared with vehicle in the white, Hispanic, and non-Hispanic groups ($P<0.05$, all; Figure 5). Although a higher proportion of black participants achieved treatment success with tazarotene 0.045% lotion compared with vehicle, this difference was not significant. The size of black population subgroup may be responsible for the lack of statistical significance.

Safety

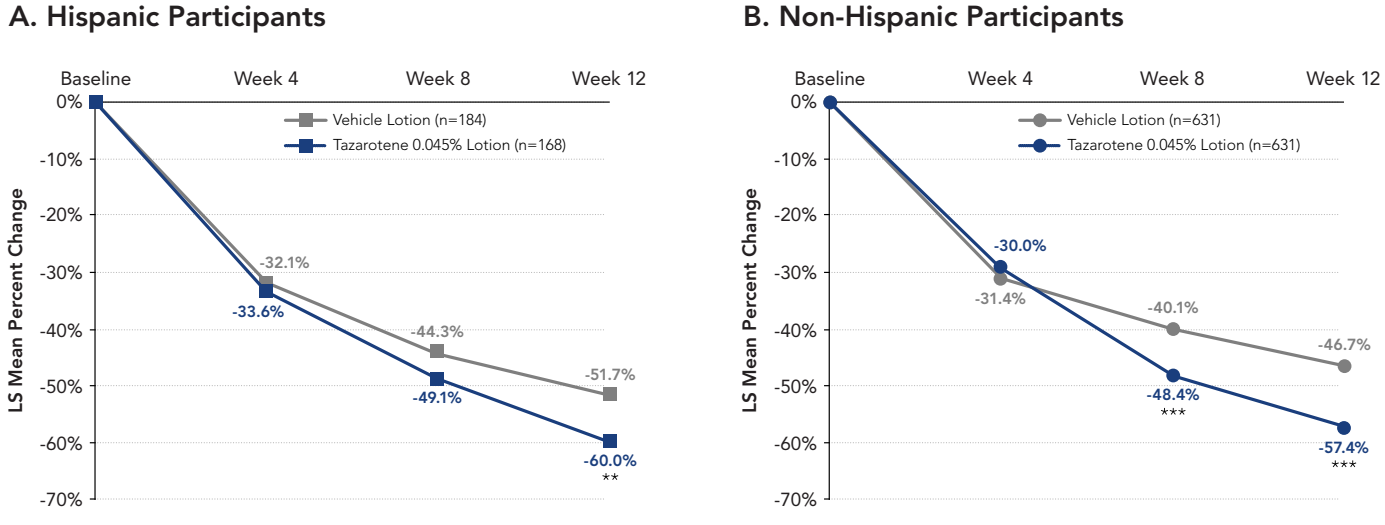
Rates of TEAEs were similar across the tazarotene 0.045% lotion-treated racial and ethnic subgroups (range, 20.2%–28.7%; Table 2). Overall, TEAE incidence was lower in the vehicle-treated groups compared with tazarotene. None of the SAEs were deemed related to treatment by study investigators. Most TEAEs were mild-moderate in severity; the incidence of moderate TEAEs was highest in white and the non-Hispanic subpopulations, regardless of treatment. The incidence of treatment-related TEAEs ranged from 9.8%–12.4% among the tazarotene 0.045% lotion-treated racial and ethnic subgroups.

FIGURE 2. Mean percent change in noninflammatory lesion counts, by race (ITT population, pooled).



*P<0.05 versus vehicle; ***P<0.001 versus vehicle.
ITT, intent to treat; LS, least squares.

FIGURE 3. Mean percent change in inflammatory lesion counts, by ethnicity (ITT population, pooled).

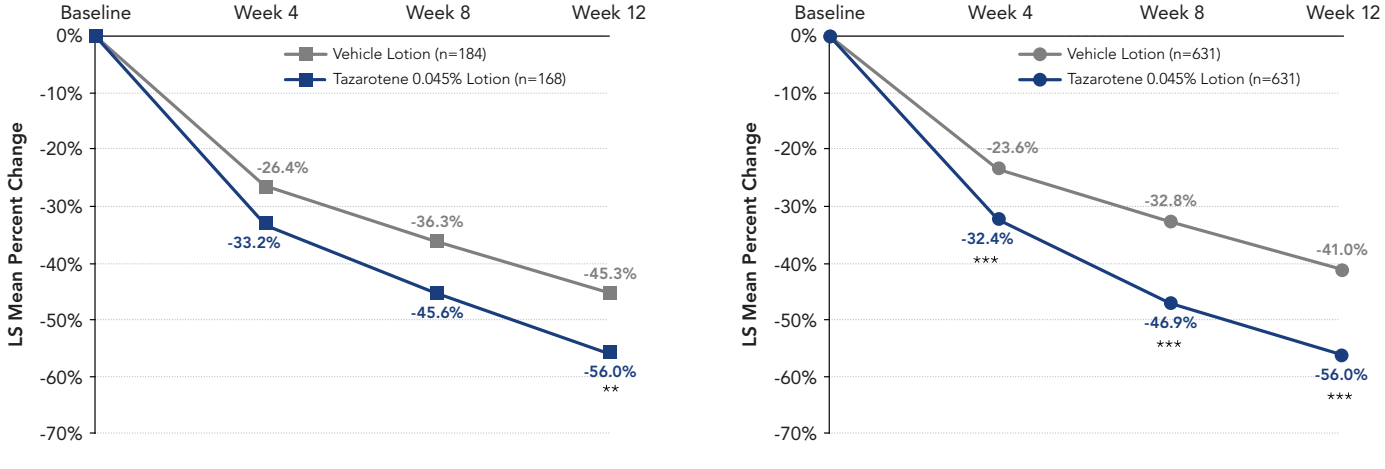


**P<0.01; ***P<0.001 versus vehicle.
ITT, intent to treat; LS, least squares.

The most common TEAEs were related to application site pain, dryness, and exfoliation (Table 2). Application site irritation was reported in ≤1.2% of each race and ethnic subgroup.

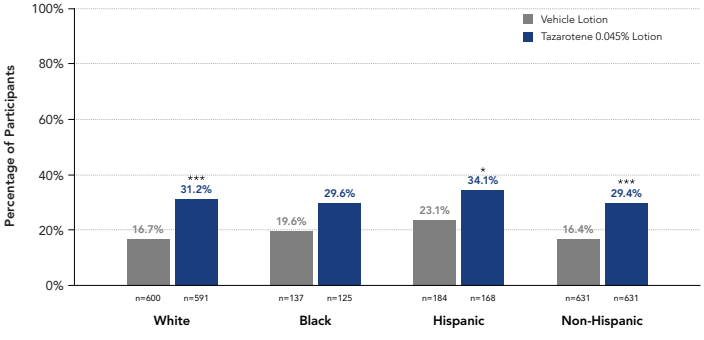
Among tazarotene-treated participants who had cutaneous safety and tolerability signs and symptoms, most had mild or moderate severity at baseline and week 12 (Figure 6). Across all tazarotene-treated subgroups, there were transient increases in severity (primarily mild or moderate) at weeks 2 or 4 relative to baseline for several of the cutaneous safety and tolerability evaluations (data not shown). Investigator-rated assessments indicated higher baseline rates (>20%) of hyperpigmentation in black participants and erythema in white, Hispanic, and non-Hispanic participants; however, all of these rates decreased by week 12. Patient-reported tolerability assessments of itching, burning, and stinging were generally low in all subgroups, with itching tending to decrease and burning/stinging tending to increase from baseline to week 12.

FIGURE 4. Mean percent change in noninflammatory lesion counts, by ethnicity (ITT population, pooled).



**P<0.01; ***P<0.001 versus vehicle.
ITT, intent to treat; LS, least squares.

FIGURE 5. Percentage of participants with treatment success at week 12, by race and ethnicity (ITT population, pooled).



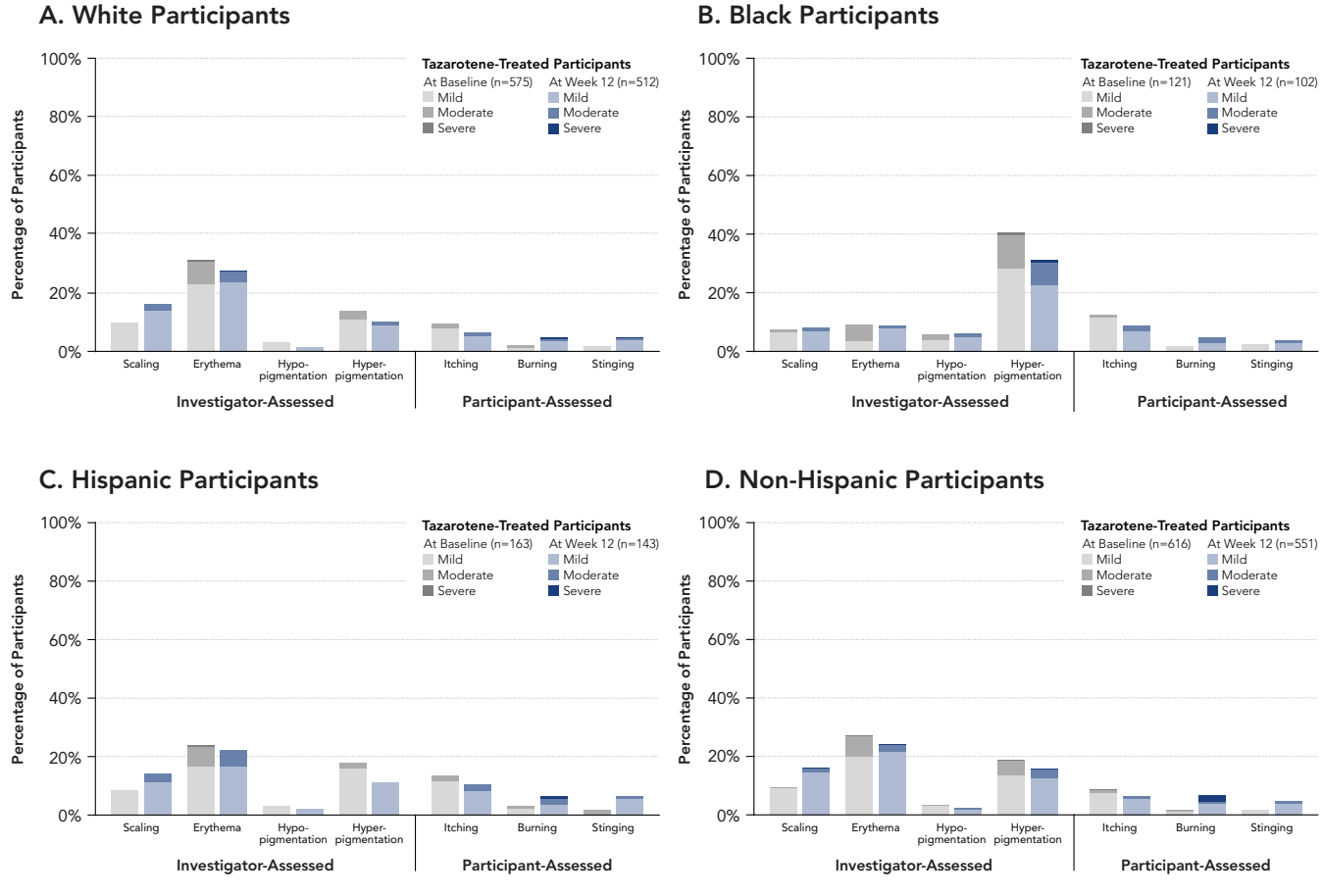
Treatment success = percentage of patients with at least a 2-grade reduction in EGSS relative to baseline and 'clear' or 'almost clear'.
*P<0.05 versus vehicle; ***P<0.001 versus vehicle.
EGSS, Evaluator's Global Severity Score; ITT, intent to treat.

DISCUSSION

This pooled, post hoc analysis of two phase 3 trials demonstrated that tazarotene 0.045% lotion applied once daily for 12 weeks improved acne symptoms and was well tolerated, regardless of race or ethnicity. Compared with vehicle lotion, treatment with tazarotene 0.045% lotion resulted in significant reductions in inflammatory and noninflammatory lesions and treatment success at week 12 in white, Hispanic, and non-Hispanic subpopulations. In black participants receiving tazarotene 0.045% lotion, there was a significant decrease in noninflammatory lesions compared with vehicle lotion. In all subpopulations, there were improvements in inflammation-associated sequelae of acne, including hyperpigmentation.

Clinical trials with topical retinoids have demonstrated efficacy for acne treatment in skin of color, but concerns remain on tolerability of some agents and formulations.[11,18,19] Our findings provide support for the use of tazarotene 0.045% lotion in the understudied setting of skin of color and concur with smaller

FIGURE 6. Cutaneous safety and tolerability assessments in tazarotene-treated participants, by race and ethnicity (safety population, pooled).



Data for "none" are not shown.

TABLE 2.

Treatment-Emergent and Related Adverse Events Through Week 12 (Safety Population, Pooled)

Adverse Events, n (%)	White		Black		Hispanic		Non-Hispanic	
	TAZ 0.045% Lotion (n=575)	Vehicle Lotion (n=584)	TAZ 0.045% Lotion (n=121)	Vehicle Lotion (n=132)	TAZ 0.045% Lotion (n=163)	Vehicle Lotion (n=178)	TAZ 0.045% Lotion (n=616)	Vehicle Lotion (n=613)
Any TEAE	165 (28.7)	118 (20.2)	30 (24.8)	17 (12.9)	33 (20.2)	17 (9.6)	176 (28.6)	134 (21.9)
Any SAE[a]	3 (0.5)	3 (0.5)	1 (0.8)	1 (0.8)	0	0	4 (0.6)	4 (0.7)
Severity of TEAEs								
Mild	103 (17.9)	63 (10.8)	22 (18.2)	8 (6.1)	21 (12.9)	10 (5.6)	115 (18.7)	73 (11.9)
Moderate	54 (9.4)	53 (9.1)	7 (5.8)	7 (5.3)	11 (6.7)	7 (3.9)	52 (8.4)	57 (9.3)
Severe	8 (1.4)	2 (0.3)	1 (0.8)	2 (1.5)	1 (0.6)	0	9 (1.5)	4 (0.7)
Relationship to study drug								
Related	68 (11.8)	8 (1.4)	15 (12.4)	1 (0.8)	16 (9.8)	0	72 (11.7)	9 (1.5)
Unrelated	97 (16.9)	110 (18.8)	15 (12.4)	16 (12.1)	17 (10.4)	17 (9.6)	104 (16.9)	125 (20.4)
Most common TEAEs[b]								
Application site pain	30 (5.2)	2 (0.3)	8 (6.6)	0	10 (6.1)	0	31 (5.0)	2 (0.3)
Application site dryness	24 (4.2)	1 (0.2)	4 (3.3)	0	4 (2.5)	0	26 (4.2)	1 (0.2)
Application site exfoliation	8 (1.4)	0	6 (5.0)	0	4 (2.5)	0	12 (1.9)	0
Viral upper respiratory tract infection[a]	25 (4.3)	25 (4.3)	6 (5.0)	2 (1.5)	1 (0.6)	2 (1.1)	35 (5.7)	29 (4.7)

[a]No instances were considered by the investigator to be treatment related.
[b]Reported in ≥3% of participants in any treatment arm across all subgroups.
SAE, serious adverse event; TAZ, tazarotene; TEAE, treatment-emergent adverse event.

studies conducted exclusively in patients with darker skin tones. For example, in a separate study of less than 80 participants, tazarotene 0.1% cream improved facial PIH compared with baseline in participants with Fitzpatrick skin type III–VI.[20] This benefit of tazarotene 0.045% lotion is not a universal effect of topical retinoids. A clinical trial comparing adapalene 0.1%, adapalene 0.3%, and tretinoin 0.05% found that 90 days of treatment with adapalene 0.3% or tretinoin 0.05% was associated with lower counts of noninflammatory and inflammatory acne lesions.[11] However, study participants receiving either treatment reported higher rates of PIH and overall adverse events compared with participants in the adapalene 0.1% arm.[11]

Despite the large number of participants in our pooled analysis overall, the small proportion of participants who self-identified as black may have limited our findings. Our analyses found trends for improvement but no significant differences between tazarotene 0.045% lotion and vehicle lotion groups for two efficacy assessments: change in inflammatory lesion counts and treatment success by week 12. The lack of a statistical difference between tazarotene and vehicle lotion in the reduction of inflammatory lesions is likely due to the high response rate to vehicle in black participants (Figure 1B), whereas the statistical analysis of treatment success may have been limited in part by the small sample size. Although the proportions of black participants in these phase 3 trials were similar to other clinical trials in dermatology, having larger sample sizes could have increased the ability to confirm numerically small differences.[21] Furthermore, racial identification does not necessarily reflect skin color or all skin characteristics.[22] Additional trials of tazarotene 0.045% lotion and other acne treatments in skin of color from all backgrounds could prove useful in developing evidence-based guidelines for the diverse skin types affected by this condition.

The tolerability of tazarotene 0.045% lotion in all subgroups analyzed here was consistent with the overall population of the pooled analysis.[17] The majority of TEAEs were mild or moderate in severity, and approximately 11% of TEAEs were considered related to tazarotene 0.045% lotion. Further, the incidence of application-site irritation was ≤1.2% in each group. Cutaneous irritation is a well-established adverse event associated with topical retinoids, and has been reported in 2-18% of patients for tazarotene 0.1%, 2-5.6% for various adapalene formulations, and 3.8-23.6% for various tretinoin formulations.[23] While irritation can reduce treatment compliance in any patient population,[14] it can also induce PIH in patients with skin of color.[12] Cutaneous safety and tolerability ratings from the current analysis suggest that the lower-dose tazarotene 0.045% lotion formulation produced benefits in terms of inflammation-associated sequelae such as hyperpigmentation and erythema.

CONCLUSIONS

Tazarotene 0.045% lotion using novel polymeric emulsion technology demonstrated efficacy in this pooled analysis of two

identical phase 3 trials, regardless of race and ethnicity, with fewer acne lesions and improved treatment success over a 12-week course of therapy. This new formulation of tazarotene had good tolerability compared with vehicle lotion as well as lower rates of irritation-related TEAEs compared with retinoid-based treatments. Tazarotene 0.045% lotion does not appear to induce post-inflammatory hyperpigmentation and may be an effective and well tolerated treatment option for patients with skin of color.

DISCLOSURES

Neal Bhatia has received honoraria and investigator grants from Bausch Health. Jonathan S. Weiss is a consultant, speaker, advisor, and/or researcher for Abbvie, Ortho Dermatologics/ Bausch Health US, Galderma, Foamix, Promius/Dr. Reddy's, LEO Pharma, Novartis, Sanofi/Regeneron, Aclaris, Endo International, Dermira, and Almirall. Neil Sadick has served on advisory boards, as a consultant, investigator, speaker, and/or other and has received honoraria and/or grants/research funding from Almirall, Actavis, Allergan, Anacor Pharmaceuticals, Auxilium Pharmaceuticals, Bausch Health, Bayer, Biorasi, BTG, Carma Laboratories, Cassiopea, Celgene Corporation, Cutera, Cynosure, DUSA Pharmaceuticals, Eclipse Medical, Eli Lilly and Company, Endo International, EndyMed Medical, Ferndale Laboratories, Galderma, Gerson Lehrman Group, Hydropeptide, Merz Aesthetics, Neostrata, Novartis, Nutraceutical Wellness, Palomar Medical Technologies, Prescriber's Choice, Regeneron, Roche Laboratories, Samumed, Solta Medical, Storz Medical AG, Suneva Medical, Vanda Pharmaceuticals, and Venus Concept. Fran E. Cook-Bolden has served as consultant, speaker, investigator for Galderma, LEO Pharma, Almirall, Cassiopea, Ortho Dermatologics, Investigators Encore, Foamix, Hovione, Aclaris, and Cutanea. Stephen K. Tyring has acted as an investigator for Ortho Dermatologics. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Anya Loncaric and Susan Harris are employees of Bausch Health US, LLC and may hold stock and/or stock options in its parent company. Bausch Health US, LLC is an affiliate of Bausch Health Companies Inc. Ortho Dermatologics is a division of Bausch Health US, LLC.

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ORIGINAL ARTICLE

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The Utility of Platelet-Rich Plasma for the Treatment of Alopecia

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ABSTRACT

Importance: Platelet-rich plasma (PRP) is a novel therapy for alopecia. Although the use of PRP remains under investigation, medical practitioners administer PRP for hair regrowth without quantitative evidence of clinical results.

Objective: Systematically review literature regarding PRP for alopecia.

Evidence Review: PRISMA guidelines were utilized to search the PubMed database in May 2019 with search terms "platelet rich plasma" and "hair", "hair loss", or "alopecia". Manuscripts were included if they were written in English and described PRP treatment in human subjects with alopecia.

Findings: Sixty-one articles discussed the use of PRP as monotherapy, or in combination with other medical modalities, for the treatment of androgenetic alopecia (AGA), alopecia areata (AA), and cicatricial alopecia, ranging from level Ib to IV evidence. PRP results in significant increase in hair density and hair shaft width in AGA patients, with high rates of patient satisfaction and minimal adverse events. Data heterogeneity and limited number of well-designed, large-scale clinical trials were limitations of this review.

Conclusions and Relevance: Preliminary results regarding the use of PRP for AGA, AA, and cicatricial alopecias are promising. Physicians should be aware that current studies often report qualitative, rather than quantitative, clinical outcomes and should counsel patients regarding PRP treatment efficacy accordingly.

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INTRODUCTION

Platelet-rich plasma (PRP) is an autologous blood product consisting of platelet-derived growth factors and concentrated platelets 1.6 to 8-fold times physiologic levels. Platelets may be "activated" to release growth-factor (GF)-rich granules using calcium-based compounds, thrombin, and components of extracellular matrix.[1] Due to PRP's purported regenerative, anti-inflammatory and anti-bacterial properties, it is utilized for various medical conditions. In dermatology, PRP is promising for skin rejuvenation, chronic ulcers, and alopecia.

The Mechanism of PRP for Hair Regrowth

The exact mechanism for PRP-induced hair regrowth is unknown. Platelet-derived GFs include platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), and insulin-like growth factor (IGF). It is unclear whether platelet activation is required, or if the injection process is enough for GF release as both preparations result in therapeutic response.

GFs bind receptors on hair follicle bulge stem cells – PDGF causes keratinocyte proliferation and prolongs the anagen phase in mouse models, IGF-1 prevents induction of the catagen phase, fibroblast growth factor (FGF) promotes dermal papilla cell (DPC) proliferation and hair shaft elongation, while VEGF is implicated in hair follicle revascularization.[2-5] Although it was hypothesized that PRP's effects are dependent on GF plasma concentration,[5,8] clinically significant results despite low GF concentrations contradict this theory.[9] For instance, a clinical trial demonstrated that although two, commercially available, calcium-activated PRP kits had similar GF concentrations, one kit resulted in superior hair growth.[1]

Calcium chloride-activated PRP causes upregulation of mitogen-activated protein kinase (MAPK) and protein kinase B (Akt) signaling, as well as downregulation of glycogen synthase kinase-3 and Wnt pathways, all playing a role in hair growth.[6,7] PRP increases expression of type I collagen and matrix metalloproteinase 1 mRNA in dermal fibroblasts. Upregulation of Bcl-2, an anti-apoptotic protein, allows for differentiation of hair follicle stem cells, while β-catenin and FGF-7 in dermal fibroblasts prolongs the anagen phase, and Ki-67 results in epidermal cell proliferation.[10] PRP also contains fibrin, fibronectin, thrombin, vitronectin and cytokines [interferon (IFN)-α, interleukins (ILs)-4, 5, 13, 17, tumor necrosis factor (TNF)]; their role in hair regeneration is unknown.[3]

PRP for the Treatment of Alopecia

A recent survey of 241 dermatologists revealed that 14% use PRP to treat male androgenetic alopecia (AGA), 20% for pre-menopausal female AGA, and 21% for post-menopausal female AGA, making it the sixth most commonly prescribed therapy after topical minoxidil, oral and topical 5α-reductase inhibitors, nutritional supplements, and spironolactone.[13] Commercially available PRP kits fall into two categories: pure (leukocyte-poor) platelet-rich fibrin (PRF) with a high-density fibrin network in which blood is centrifuged with the addition of an activator and a gel capable of size separation; or leukocyte-rich PRF or second-generation PRP with a high-density fibrin network in which blood is centrifuged without addition of anti-coagulant or platelet activator.[71] A standardized PRP protocol for alopecia is lacking with variations in volume of whole blood drawn and PRP obtained, spin methods (single versus double, speed and time of centrifugation), final platelet concentration, leukocyte content, total treatment sessions and duration between sessions, as well as frequency and interval of maintenance therapy.[1,4,5,8,14-70] Various alopecias may also require differing PRP regimens to obtain hair regrowth. We present a systematic review of the literature surrounding PRP as a therapeutic modality for alopecia.

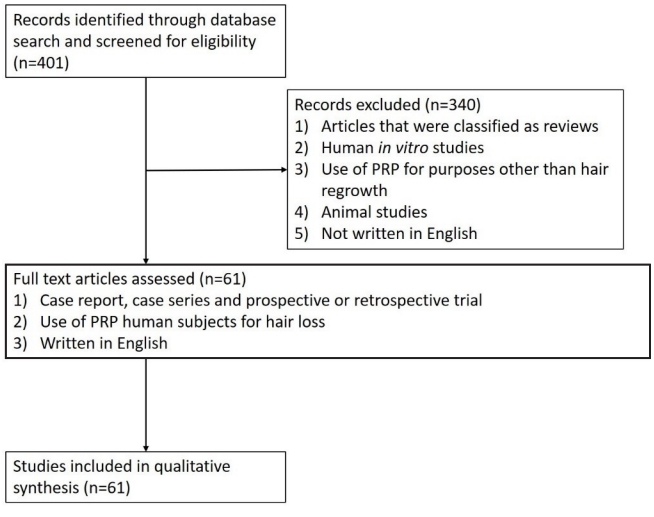
MATERIALS AND METHODS

An online PubMed database search was completed in May 2019 using PRISMA guidelines and included search terms "platelet rich plasma" and "hair", "hair loss", or "alopecia", without date limitation. Inclusion criteria were articles written in English discussing PRP for the treatment of non-scarring and scarring alopecias in human subjects including randomized-control trials (RCTs), prospective and retrospective studies, case series, and case reports. Exclusion criteria were articles published in a language other than English, using PRP for the treatment of other dermatologic conditions, and studies not completed in humans (Figure 1). Data was recorded on a standardized electronic data collection sheet and reviewed by author MJ. The level of evidence for each article was assessed using the Modified Oxford Centre for Evidence-Based Medicine Scale.

RESULTS

Initial search criteria yielded 401 manuscripts. After inclusion criteria and duplicate removal, 61 articles were reviewed (levels of evidence Ib to IV), with a total 1,980 patients. The most common alopecia treated was AGA [51 studies; n=1,738 (1,092 male, 588 female, 58 unknown; age range: 18 to 72 years)], then patch-type alopecia areata [AA; 5 studies; n=236 (88 male, 38 female, 110 unknown; age range, 10 to 41 years)] and cicatricial alopecia [5 studies; n=6 (1 male, 3 female, 2 unknown; age range, 24 to 70 years)]. PRP preparations included spin and double-spin methods, with or without activation using calcium, and platelet concentrations ranging from 1.6 to 6 times physiologic level. Adjunct therapies included topical minoxidil, oral finasteride, microneedling, follicular unit extraction (FUE), and low-level light therapy (LLLT), among others (Table 1).

FIGURE 1. Flow diagram depicting the PRISMA method to select appropriate clinical articles discussing PRP treatment of alopecia for review.



Androgenetic Alopecia

Treatment protocols included 1.5 to 12 mL of activated or non-activated PRP weekly to 3 months for 1 to 12 sessions, with maintenance injections every 3 to 6 months thereafter. Longitudinal follow-up to assess hair regrowth occurred for 6 weeks to 24 months after PRP injections. Clinical efficacy of PRP was compared to control/placebo [normal saline (NS), physiological solution (unknown composition), or no treatment; n=13], topical minoxidil (n=3), human follicle mesenchymal stem cell injection (HF-NSC; n=1), medical management (n=1), placental extract (n=1), and polydeoxyribonucleotide (PDRN; n=1). Several studies examined the use of PRP in conjunction with 1 to 1.25 mm microneedling (n=5), follicular unit extraction (FUE; n=2), topical minoxidil and microneedling (n=2), dalteparin and protamine (n=1), LLLT (n=1), oral finasteride only (n=1), PDRN (n=1), scalp lifting with suture embedding (n=1), stromal vascular fraction injection (n=1), and topical minoxidil and oral finasteride (n=1).[1,4,5,8,14,16-21,23-25,29-39,42-56,58-62,64-68,70]

Endpoints included global clinical improvement, decrease in hair pull test, quantitative trichoscopy, as well as patient-reported measures such as hair quality and satisfaction. Results were reported as comparisons to baseline or control (placebo or other AGA therapy), making it difficult to synthesize and compare results. Twenty-two studies reported a significant increase in hair density after PRP, while 8 reported a significant increase in hair shaft width; all other studies reported qualitative endpoints. When compared to topical minoxidil or oral finasteride, PRP was not inferior. Combining PRP with medical therapy often resulted in greater hair regrowth than either treatment alone, which is

TABLE 1.

A Summary of Hair Loss Disorders, Patients Treated and PRP Treatment Regimens Reviewed

Disease	Total Number of Studies (Level of evidence)	Study Type (n=number of studies)	Number of Patients	Age Range	PRP Treatment (n=number of studies)
AGA	51 (1b-4)	Prospective (including those that left part of the scalp untreated as control; n=25) Randomized trial (n=18) Retrospective (n=3) Case report/series (n=3) Cross-sectional survey (n=2)	1,738 (1092 M, 588 F, 58 unknown)	18-72 y/o	1.5 to 12 mL, q1 wk-3 mo x1-12 sessions, maintenance q3-6 mo Activated PRP (n=17) Adjunct Therapies 1 to 1.25 mm microneedling (n=5) Follicular unit extraction (n=2) Topical minoxidil and microneedling (n=2) Dalteparin and protamine (n=1) LLLT (n=1) Oral finasteride only (n=1) PDRN (n=1) Scalp lifting with suture embedding (n=1) Stromal vascular fraction injection (n=1) Topical minoxidil and oral finasteride (n=1)
AA	5 (1b-4)	Randomized trial (n=3) Prospective (n=1) Case report (n=1)	236 (88 M, 38 F, 110 unknown)	10-41 y/o	Up to 9 mL, q2-4 wk x3-6 sessions Activated PRP (n=1)
Cicatricial alopecia (LPP, CCCA)	5 (4)	Case report/series (n=5)	6 (1 M, 3 F, 2 unknown)	24-70 y/o	3-5 mL, q3-4 wk x3-4 sessions Activated PRP (n=1) Adjunct Therapies FUE+topical minoxidil 5% BID (n=1) LLLT (n=1)

consistent with the current approach to hair loss in which multiple therapies are used together to create a synergistic effect for greater clinical hair regrowth.[1,4,5,8,14,16-21,23-25,29-39,42-56,58-62,64-68,70]

Dermoscopy of the scalp after PRP demonstrated increased vellus and terminal hairs, thicker hair shafts, increased vascular structures, as well as disappearance of yellow dots, black dots, and perifollicular pigmentation.[43,61] Those studies using histologic analysis to determine PRP efficacy reported an increase in quantity of follicular bulge cells, Ki-67+ basal cells, epidermal thickness, and perifollicular angiogenesis.[1,19] The majority of patients were satisfied with PRP (>50%), in all studies that reported this outcome. Adverse events (AEs) were limited to minimal pain and pinpoint bleeding during injection, erythema, scalp edema, and self-resolving scalp sensitivity or headache post-treatment. No serious AEs were reported.

In addition to PRP injections, one study described a PRP spray formulation (3 to 5 times increase in platelet concentration containing VEGF, EGF, FGF-2, IGF-1, and TGF-β) applied to the scalp twice daily for 3 months resulting in "good" hair growth.[39] Although a blood draw is still necessary to prepare PRP, topical application is appealing as it disposes of multiple, painful scalp injections, and reduces consumables used by physicians.

Alopecia Areata

PRP regimens consisted of 4 mL to 9 mL of activated or non-activated PRP, every 2 to 4 weeks for 3 to 6 treatment sessions.[15,27,28,63,69] PRP (60% to 72.5% of trial patients with clinical response to treatment) was superior to intralesional triamcinolone (ILTAC) 2.5 mg/mL (27%), and equivalent to ILTAC 5 mg/mL every 2 weeks for 3 to 5 sessions (65%), or topical minoxidil 5% twice daily for 3 months (81%) in AA patients. PRP-induced hair regrowth was noted after 1 month, and clinical response was sustained for up to 6 months after 1 to 5 sessions of PRP. PRP resulted in significantly decreased relapse rates compared to ILTAC 2.5 and 5 mg/mL, with only 0% to 5% of patients experiencing relapse at 6 months and 31% at 12 (versus 25% to 38%, and 71%, respectively).[15,27,28,63,69] Given that only patch-type AA patients were treated, it is unlikely that we would expect

high relapse rates, unlike alopecia totalis or universalis. AEs of PRP included erythema, burning sensation during injection, and mild tenderness, which were similar to those reported for ILTAC.[15,27,28,63,69] It is difficult to determine significant clinical response to PRP therapy in AA patients as no studies used quantitative trichoscopy.

Cicatricial Alopecia

The use of PRP for the treatment of cicatricial alopecias, lichen planopilaris (LPP), and central centrifugal cicatricial alopecia (CCCA) is limited. PRP protocols included 3 mL to 5 mL of activated or non-activated PRP, every 3 to 4 weeks, for 3 to 4 treatment sessions. In addition to PRP, one case each of LPP was also treated with LLLT, and FUE from the unaffected to affected scalp with topical minoxidil 5% twice daily to the transplanted region. Although there was no use of longitudinal quantitative trichoscopy, all cases reported qualitative clinical improvement in scalp hair growth. In two cases, investigators described a decrease in perifollicular erythema and scale, suggesting PRP may have an anti-inflammatory effect. AEs, including worsening of disease, were not discussed in any of the reports.[22,26,40,41,57]

DISCUSSION

PRP is a novel alopecia therapy and can be used alone, or as an adjunct to "traditional" therapeutics such as topical minoxidil, oral finasteride or hair transplantation. Many studies use PRP to treat AGA, AA, and cicatricial alopecia with varying degrees of success. A recent meta-analysis of 7 RCTs using autologous PRP for male and female AGA determined that PRP caused a significant quantitative increase of scalp hairs compared to placebo (NS or distilled water).[72] Given the current evidence, PRP appears to be an effective treatment option for patients with AGA, AA and scarring alopecia, increasing both hair density and hair shaft diameter; however, further large-scale, well-controlled trials are needed to define exact treatment protocol(s) and make definitive statements regarding PRP's clinical efficacy for hair loss.

Results comparing PRP to placebo and/or controls for hair regrowth are promising with PRP outperforming placebo/control in almost all trials. However, when compared standard medical therapy (ie, topical minoxidil or oral finasteride in AGA, ILTAC 5 mg/mL in AA), PRP monotherapy was often only non-inferior. PRP has also been used in combination with topical minoxidil, oral finasteride, and FUE in AGA with evidence suggesting that combination therapy is superior to monotherapy. Combining PRP injections with finasteride, minoxidil, bioactive macromolecules, and/or other cell-based therapies (HF-MSC or placental extract) may prove beneficial for hair regrowth in the future.[73] Multiple sessions of monthly PRP may be equally as or more expensive than hair transplantation and is certainly more expensive than minoxidil or finasteride. Physicians should thoroughly discuss the pros and cons of each therapy with patients. Unlike hair transplantation, PRP can be completed in-office, in approximately half an hour versus a full-day procedure. Patients are also able to continue with their daily activities after PRP with little to no downtime.

Although AEs reported in this review were minimal,[2] it is important to note that patients with inflammatory, autoimmune skin conditions, may have serious AEs. In patients with cicatricial alopecia, clinicians may worry about disease progression (Koebnerization) after PRP-induced trauma. A case of a female patient with AA and Ménière's disease reported serum sickness (rash, arthralgia, fever) after PRP for skin rejuvenation of the face and neck. Resolution was achieved with high-dose systemic steroids and subsequent taper.[11] Rare cases exist in which inadvertent intra-arterial injection of a platelet plug or separation gel occurred along with PRP for periorbital rejuvenation, resulting in tissue necrosis and/or blindness.[74] Although rare, dermatologists administering PRP to the scalp for hair restoration should be especially vigilant regarding PRP impurities and placement of injections along the frontal hairline given the superficial supratrochlear and supraorbital vessels.

The use of PRP for hair regrowth in pregnant women has not been discussed in the literature. Autologous PRP for *in vitro* fertilization has been described with success suggesting its safety in women planning pregnancy or currently pregnant.[75-77] Although most injections of PRP are derived from an autologous source, clinicians should still be wary of treating women who are pregnant, planning pregnancy and nursing.

Future directions

PRP exerts its clinical effects at the hair follicle bulge located in the mid to deep dermis. Microneedling allows selective delivery of PRP to this level. Fractional photothermolysis may also be used to assist in PRP delivery at a uniform depth and distribution. A study used fractional CO2 therapy to deliver PRP or NS to the inner forearm for rhytides; PRP-treated forearms demonstrated rapid wound healing, with decreased erythema and healing time. Non-ablative wavelengths are suited to deliver PRP to the scalp, along with other topical solutions such as minoxidil, finasteride or bimatoprost.[3]

With evidence that PRP efficacy for hair growth may depend on specific GFs,[78] isolating GFs/peptides responsible for hair growth and applying these to the scalp may result in targeted hair follicle induction. A RCT of 40 women with chronic telogen effluvium (TE) treated with 10% IGF and EGF topical daily resulted in prolonged anagen phase. Sixty AA patients treated with a topical biomimetic peptide product (copper tripeptide-1, octapeptide-2, oligopeptide-20, acetyl decapeptide-3, lactoferrin, lactoglobulin, melatonin) twice weekly for 3 months demonstrated a mean SALT (Severity of Alopecia Tool Score, a validated scale to determine the degree of AA-associated hair

loss) improvement of 18.30 after 3 months, as compared to 9.49 in placebo.[79] Currently, the possibilities for PRP's utility in hair growth seem vast, and many therapeutic options still need exploring.

Limitations to this review include the inability to complete meta-analysis based on data heterogeneity. While inclusion of only well-designed, randomized-controlled trials reporting quantitative results would be ideal, we believe this would greatly limit our review's scope. PRP treatment protocols varied widely both in number of sessions, inter-treatment duration, activation of platelets, concentration of platelets and/or GFs, and final volume injected. Many studies did not employ quantitative measures, and qualitative clinical results were based on global improvement from digital photographs or physician/patient-reported outcomes.

CONCLUSION

PRP is a popular procedure for alopecia. Although studies demonstrate PRP's clinical efficacy in AGA, AA and cicatricial alopecia, this review highlights that current trials are limited by lack of standard protocol and qualitative conclusions. Although PRP may not be superior to medical therapy it may be a promising adjunct for alopecia patients without adequate clinical response. AEs after scalp PRP injections are minimal, including pain during the procedure. Future directions include PRP combination regimens using medical or cell-based treatment, topical application, laser-assisted delivery, and use of specific isolated GFs/peptides. Further large-scale, trials comparing PRP to standard hair loss therapies are needed to create standardized PRP treatment protocol(s) for all types of alopecia, assess for clinical efficacy, and determine PRP's long-term safety profile.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

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A Review of Vitamin D and Scarring: The Potential for New Therapeutics

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ABSTRACT

Introduction: Recent research on vitamin D has shown that the fat-soluble micronutrient has anti-microbial, anti-inflammatory, and anti-proliferative effects in cells and tissues. During wound healing, abnormal scarring may occur and lead to reduced mobility, disfigurement, and psychosocial concerns. The role of vitamin D in the pathogenesis and treatment of scarring has not been reviewed previously.
Methods: A literature search was performed on PubMed to identify articles on vitamin D and keloid, hypertrophic, or burn scars.
Results: Molecular, epidemiological, and human clinical studies are discussed. Overall, the evidence suggests lower levels of vitamin D precursors, the active metabolite, and receptor, are associated with increased risk of scar development and increased severity.
Conclusions: Scars are challenging to treat, and patients are increasingly interested in non-invasive treatment options. Although few human clinical studies have been reported, vitamin D may be beneficial as an adjunct therapy to current treatment options.

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INTRODUCTION

Vitamin D is a bioactive nutrient which can be obtained from the diet or synthesized in the skin from 7-dehydrocholesterol following exposure to UVB light.[1] Newly formed pre-vitamin D3 is converted to vitamin D3. Due to a higher concentration of melanin inhibiting UVB light, individuals with darkly pigmented skin have reduced vitamin D synthesis and are at increased risk for vitamin D deficiency.[1] In the liver, the 25-hydroxylase enzyme converts vitamin D3 into the prohormone 25-hydroxyvitamin D (25(OH) D), the biomarker of vitamin D status. Lower serum 25(OH) D levels have been associated with a variety of dermatologic conditions, such as atopic dermatitis,[2] psoriasis,[3] and systemic lupus erythematosus.[4] In the kidney, 25(OH)D is converted into its biologically active form 1,25-dihydroxyvitamin D (1,25(OH)2D) (also known as calcitriol) by 1-α-hydroxylase. Topical formulations of vitamin D analogs (calcipotriol and tacalcitol) have been proven effective for the treatment of plaque psoriasis.[5,6]

Through the vitamin D receptor (VDR), vitamin D is able to regulate genes containing vitamin D response elements (VDREs).[7] Various immune cells (T cells, B cells, natural killer (NK) cells, and monocytes) contain the VDR, so vitamin D is thought to regulate their function.[8] Inflammation is a critical step in wound healing, but can cause problems if prolonged or excessive. Researchers have shown that vitamin D inhibits pro-inflammatory cytokine production (Interleukin (IL)-6, IL-8, IL-17, IL-21, and interferon (IFN)-γ)[9,10] while increasing anti-inflammatory cytokines (IL-10)[11,12] in immune cells, epidermal cells, and fibroblast cell culture studies.

Following inflammation, the proliferative phase of wound healing proceeds and fibroblasts, keratinocytes, and endothelial cells aid in the formation of new tissue from collagen and other extracellular matrix (ECM) molecules.[13] Cathelicidin (LL-37), a human antimicrobial peptide, has a variety of roles in wound healing and is known to be upregulated by vitamin D.[14,15] In human dermal fibroblasts, cathelicidin inhibits collagen synthesis.[16] Cathelicidin has also been shown to activate the migration of human keratinocytes in vitro and increase the rate of re-epithelialization and granulation tissue formation in diabetic wounds in vivo.[17] More directly, VDR knockout mice display impaired epidermal stem cell migration, differentiation, and proliferation.[18]

Although scarring is a normal component of wound healing, sometimes an overgrowth of scar tissue occurs leading to the formation of hypertrophic scars or keloid scars. Unlike hypertrophic scars, keloids extend beyond the site of the original injury and involve adjacent normal skin.[19] Keloids are more common in individuals with darker skin and can be painful, itchy, and cause hyperesthesia.[20] In black patients with keloids, inflammatory signaling molecules such as serum IL-6, tumor necrosis factor (TNF)-α, and IFN-β were shown to be elevated in comparison to control subjects.[21] Numerous in vitro

studies have demonstrated anti-inflammatory,[22,23] and anti-proliferative[24,25] effects of calcitriol in human keratinocytes. However, the role of vitamin D in scarring is not well understood.

Vitamin D and Hypertrophic Scars

Data on the role of vitamin D therapy in hypertrophic scarring are mixed. In a 2009 double-blind, randomized controlled trial (RCT), researchers determined the effect of twice-daily topical calcipotriol (50 µg/g) on preventing and treating hypertrophic scars in 30 women who underwent bilateral reduction mammoplasty.[26] After 12 months, the study found no significant difference in hypertrophic scar incidence or thickness between the calcipotriol treatment group and placebo (Table 1).[26] In contrast, a 2019 supplementation study of 50 subjects who had 25(OH)D levels below 25 ng/mL and a post-surgery linear hypertrophic scar for at least 1 year demonstrated an effect of vitamin D.[27] Patients were randomized to 2,000 IU/day of oral vitamin D, surgical excision and suturing following 2,000 IU/day of vitamin D, or no treatment. Those who received oral vitamin D and subsequent surgical intervention had significantly reduced scar width after 12 months (Table 1), but no effect was seen in those who received oral vitamin D alone.[27] These results suggest oral vitamin D may be beneficial as an adjunct therapy for treating hypertrophic scars. However, the researchers did not examine the effect of surgery alone for comparison. A prospective study explored the relationship between vitamin D and hypertrophic scarring in 63 female patients.[28] The plasma 25(OH)D levels obtained prior to body contouring surgery were significantly lower in patients who developed hypertrophic scars 6 months post-surgery compared to those who formed normal scars.[28]

Vitamin D and Burn Scars

Limited data on vitamin D and burn scars exists. A 2004 case-control study collected skin biopsy samples from 12 children with burn scars undergoing reconstructive surgery and compared them to samples from 12 healthy infant and adult controls.[29] Significantly lower concentrations of vitamin D precursors (7-dehydrocholesterol and pre-vitamin D3) were measured in burn scar skin samples versus control samples.[29] In addition, the conversion of 7-dehydrocholesterol to pre-vitamin D3 following exposure to UVB light was significantly impaired in burn scar patients.[29] In a cross-sectional study of 492 male patients with burned body surface area (BSA) greater than 20%, lower 25(OH)D plasma levels were associated with significantly reduced distensibility and interstitial fluid movement suggestive of more rigid scars.[30] A subsequent cross-sectional study by Cho and colleagues was conducted in 486 men and women with burned BSA greater than 20%.[31] In addition to reduced scar elasticity, the researchers found that plasma 25(OH)D greater than 20 ng/ml was significantly associated with increased scar pigmentation, dryness, and reduced skin barrier function measured by trans-epidermal water loss.[31] Taken together, the results indicate vitamin D may play an important role in wound healing of burn scars.

Vitamin D and Keloids

To date, one clinical trial has been published on vitamin D supplementation and keloid scars. The 2017 study randomized 50 children with burn injury greater than 30% total body surface area to receive supplemental vitamin D based on kilograms of body weight.[32] All patients received 800 IU/L of vitamin D3 daily of a liquid multivitamin via tube feeding. In addition, patients were randomized to receive either vitamin D2 (range, 1,000–11,800 IU/d) or vitamin D3 (range, 980–7,300 IU/d).[32] The researchers observed lower 25(OH)D in patients who developed keloids (n=3) vs those who did not (n=47) after one year; however, this difference was not statistically significant and the study was under-powered (Table 1).[32]

In vitro studies have demonstrated mechanistic pathways through which vitamin D may impact keloid formation. A 2011 study obtained cultured keloid fibroblast from 7 Chinese patients who had undergone surgical excision.[33] Compared to normal skin fibroblasts from control subjects, the addition of calcitriol significantly reduced proliferating cell nuclear antigen (PCNA) in a dose-dependent manner, increased matrix metalloprotease (MMP)-9 activity, and suppressed transforming growth factor (TGF)-β1-induced fibronectin, α-smooth muscle actin, and collagen type I mRNA expression and protein levels in keloid

TABLE 1.

Summary of Clinical Data on Vitamin D Therapy and Scarring

Source[1]	Study Design	Sample Size	Mean Age	Vitamin D Therapy	Results (Treatment vs Control Group)
van der Veer 2009	RCT	30	35.1	Calcipotriol 50 µg/g	Scar incidence: 22% vs. 24% (P=0.83) Scar thickness: 1.7 mm vs. 1.6 mm (P=0.29)
Ince 2019	Randomized	50	29.9	Vitamin D 2,000 IU/d	Mean scar width: 1.7 cm (Group 1) vs. 1.8 cm (Group 2) vs. 1.2 cm (Group 3) P<0.05
Gottschlick 2017	Randomized, double-blind	50	7.2	Vitamin D[2] 100 IU/kg/d Vitamin D[3] 100 IU/kg/d	Mean 25(OH)D levels: 30.9 ng/mL vs. 45.6 ng/mL, P=0 .12

Randomized controlled trial: RCT, 25-hydroxyvitamin D: 25(OH)D, International units: IU.
[1]For full citations, see references
[2]In patients who underwent surgical excision

fibroblasts.[33] These data suggest an anti-proliferative and anti-fibrotic effect of vitamin D on keloids. Consistent with these results, an in vitro study of keloid fibroblasts obtained from 5 ears during cosmetic reconstruction showed a dose-dependent decrease in cellular proliferation following treatment with vitamin D3 (5–50 ng/mL).[34] In addition, the researchers showed a decrease in collagen I expression and B-cell lymphoma (Bcl)-2 in keloid fibroblasts treated with 20 ng/mL of vitamin D3 indicating reduced fibrosis and increased apoptosis.[34] Furthermore, a cross-sectional study of 32 keloid patients found a statistically significant negative correlation between serum 25(OH)D and keloid severity.[35]

Case-control studies have explored genetic variations in VDR underlying the association between vitamin D and keloid formation. In a 2013 study of 261 Chinese patients with keloid scars and 261 healthy controls, those with the CC TaqI genotype of VDR had 3.3 times greater odds of developing keloids compared to the TT genotype.[36] In addition, the CC genotype was associated with significantly lower concentrations of serum calcitriol compared to TT and CT genotypes.[36] In a separate case-control study, skin biopsies were obtained from 24 keloid scar patients and 24 controls following surgical excision.[37] VDR nuclear localization was significantly lower in black donors versus white donors, and localization was significantly higher in normal skin compared to keloid scars.[37] Consistent with these results, a 2017 study of 236 Chinese patients with keloids and 219 age- and sex-matched controls demonstrated significantly lower VDR mRNA expression in peripheral blood lymphocytes of keloid patients compared to controls.[38]

CONCLUSION

Vitamin D and its receptor have been implicated in the modulation of scarring. MMPs are important for the degradation of ECM components during healing, and their expression is altered in keloid and hypertrophic scars.[39,40] Vitamin D is thought to have an anti-fibrotic and anti-proliferative effect on keloid scars by increasing MMP activity, inhibiting TGF-β stimulation of fibroblasts, and inducing inhibition of apoptosis through upregulation of Bcl-2. The activity of vitamin D is dependent on the presence of the VDR in cells and tissues. As such, variation in VDR genotype and expression have been documented in skin biopsies from patients with keloid scars indicating a potential for a "personalized medicine" approach to scarring.

Epidemiological studies demonstrate that lower 25(OH)D serum levels are associated with greater incidence of hypertrophic scars, increased keloid severity, and the development of firmer and darker pigmented burn scars. However, these associations do not reflect causality and the biomarker may be a proxy for other underlying causes. Few clinical studies examining the therapeutic effect of vitamin D on scars have been reported, and the results are inconsistent. Oral vitamin D was shown to be beneficial as an adjunct therapy to surgical excision of hypertrophic scars in a small group of patients. Further research with larger study populations is needed to determine the effect of oral and topical formulations of vitamin D in the prevention and treatment of scars.

DISCLOSURES

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ORIGINAL ARTICLE

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An Analysis of Skin of Color Dermatology Related Content on Instagram

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ABSTRACT

Importance: Social media is making information about skin of color more readily available to those unfamiliar with ethnic skin and hair.

Objectives: To answer: 1) what skin of color-related dermatology content is being posted on Instagram? And 2) who is producing this content?

Design: Cross-sectional epidemiologic study analyzing the content of posts associated with 31 Instagram skin of color dermatology-related topics (hashtags).

Setting: Population-based

Participants: The Instagram accounts linked with the top 9 posts as generated by the Instagram algorithm associated with each search term.

Exposures: Instagram account holders.

Main Outcomes and Measures: [1] The number of posts associated with each skin of color dermatology hashtag search term. [2] Classification of posts as either educational or promotional. [3] Classification of posts as a photo or video. [4] Classification of Instagram accounts that produced the posts (American board-certified dermatologists, dermatology residents, foreign dermatologists, patients, medical interest groups, or other). [5] Quantification of the number of post likes and comments. [6] Comparison of number of educational and promotional posts between board-certified dermatologists and other Instagram users.

Results: The 31 sampled hashtags were associated with a total of 9,087,589 posts as of January 16, 2020. 219 of the 288 top posts generated from these queries met inclusion criteria. Board-certified dermatologists (26 posts) only generated 12% of top posts, whereas individuals not certified in dermatology produced 88% of top content. Of this group, social media influencers were the largest subcategory (37 posts). A majority of the top posts were promotional (135 posts, 61.6%) and formatted as photos (181 posts, 82.6%). While there was a significant difference in the number of likes for content posted by board-certified dermatologists vs non-dermatologists (P=0.027), these differences became non-significant after stratifying by the intention of the post (promotional P=0.13, educational P=0.17).

Conclusions and Relevance: Board-certified dermatologists are underrepresented among people generating top skin of color dermatology-related content on Instagram. Board-certified dermatologists should establish a more prominent presence on social media platforms so that patients have greater access to accurate, evidenced-based educational resources regarding dermatologic conditions, treatment options, and treatment risks from reliable sources.

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BACKGROUND

The population of the United States is becoming increasingly more diverse. The most recent US census showed that while non-Hispanic whites currently make up the majority of the population at 198 million, they remain the only segment of the US population in which deaths outpace the number of births. At the same time, other racial and ethnic groups are experiencing population growth.[1] In fact, it is projected that by 2050, over half the US population will be individuals of color.

While this rise in diversity has been reflected in many realms of society (eg, television, movies, and print media), there are

areas where diverse representation is lacking. For example, in the field of medicine, dermatology is one of the least diverse medical specialties. While blacks and Hispanics comprise 12.8% and 16.3% of the US population, only 3% and 4.2% of all US dermatologists are black and Hispanic, respectively.[2] The lack of dermatologists of color combined with the small percent of dermatologic education dedicated to patients with skin of color[3] has created racial disparity in the delivery of care to patients of color. Gorbatenko-Roth et al has confirmed that patients of color are concerned that race-discordant dermatologists do not have specific knowledge of their skin and hair conditions and/or routine skin and hair care regimens. Additionally, there is concern that these dermatologists do not offer individualized treatments for their disorders.[2]

Initiatives such as the Diversity Champion Initiative of the AAD's Diversity Task Force, aimed at diversifying dermatology and increasing exposure to skin of color dermatology during training, have been implemented but these changes are systemic and slower to take effect.[4] In the interim, patients are utilizing internet resources and social media to learn of dermatologic conditions and possible treatments. However, no studies about skin of color dermatology content available on different social media platforms have been done. Here, we sought to explore Instagram to identify skin of color-related dermatology content being posted, characterize the generators of this content, and compare the characteristics of content generated by board-certified dermatologists with other Instagram users.

METHODOLOGY

Data Collection

Data was collected from Instagram (https://www.instagram.com) social media accounts on January 16, 2020 by TW. Skin of color dermatology posts were identified using the hashtag search interface. A list of terms (Table 1) was generated using the list of common skin of color pathologies from the Skin of Color Society website (https://www.skinofcolorsociety.org) and entered into the hashtag search feature individually. The number of posts corresponding to each relevant search term was recorded.

Qualitative Analysis of Top Posts

The top nine most popular posts associated with each hashtag generated by the Instagram algorithm were qualitatively analyzed by three independent reviewers, who were in agreement. Posts were included in our analysis if they were relevant to dermatology (clinical photos, product advertisements, patient reviews, etc.) or were posted by a dermatologist. Duplicate posts and posts not relevant to dermatology were excluded. Each of the included posts from the top nine generated posts from each hashtag was classified by format (photo vs video) and intention (educational vs promotional). Posts were classified as promotional if they were self-promotion for the poster, promoted a specific product or brand, or promoted a specific service. The number of likes and comments on these posts was also recorded.

For each included top post, we analyzed the Instagram profile that produced the content and classified the content generator. Physicians were classified as board-certified dermatologists if they had received certification from the American Board of Dermatology, which was verified on https://www.certificationmatters.com and the American Academy of Dermatology website (https://www.aad.org). Dermatologists practicing outside of the US were designated as foreign dermatologists and their locations were recorded. Other types of physician status were verified on https://www.certificationmatters.org. Current dermatology residents were verified by checking their associated training program on their LinkedIn profiles and confirming on dermatology residency program websites. Nurse certifications were verified via the Nursys License Verification (https://www.nursys.com). Estheticians, hair stylists, and medical spas were verified by inspecting their services websites. Medical interest groups were verified by inspecting the organizations' websites. Patients were confirmed by inspecting the profiles for clinical photos. The profiles of Instagram users not falling into any of these categories (social media influencers, bloggers, basic science researchers, corporate brands, among others) were also inspected and classified.

Statistical Analysis

Three binary comparisons of collected top posts were considered based on our content generator classifications: 1) all board-certified dermatologists vs all other content generators ("Other"); 2) all physicians (including board-certified dermatologists, foreign dermatologists, current dermatology residents, and physicians from other specialties) vs "Other"; and 3) all mid-level providers (NP, RN-certified nursing staff) in addition to all physicians vs "Other". For each comparison, frequencies and proportions of posts by format (photo vs video) and intention (educational vs promotional) were tabulated and evaluated across categories by Pearson's Chi-squared test. A Wilcoxon rank-sum test assessed quantitative differences in overall content engagement, as measured by the total number of likes and comments received by posts in each content generator category. For all tests, statistical significance was defined as two-sided P-value <0.05.

RESULTS

The 31 skin-of-color hashtags searched produced a total of 9,087,589 posts (Table 1). The #acne search term generated the highest number of posts (5,224,299) and generated more posts than all other search terms combined. Conversely, searching for #folliculitispapillaris (0 posts) and #acnekeloidalis (15 posts) resulted in the least amount of content on Instagram.

TABLE 1.

Common Skin-of-Color Hashtags and Number of Related Posts for Each Hashtag Searched on January 16, 2020. The content generator category for each top-liked or top-commented post is shown.

Skin of Color Hashtag	Related Posts	Source of Top Liked Post	Likes	Source of Top Commented Post	Comments
#skinofcolor	9,622	Board-Certified Dermatologist	4,666	Board-Certified Dermatologist	306
#skinofcolordermatology	226	Board-Certified Dermatologist	293	Dermatology Resident	41
#skinofcolordermatologist	2,674	Foreign Dermatologist (Brazil)	6,658	Foreign Dermatologist (Brazil)	187
#ethnicdermatology	430	Foreign Dermatologist (Brazil)	1,387	Foreign Dermatologist (Brazil)	55
#acne	5,224,299	Influencer	36,781	Influencer	135
#postinflammatoryhyperpigmentation	1,521	Foreign Dermatologist (Australia)	4,259	Foreign Dermatologist (Australia)	2,580
#PIH	21,360	Esthetician	5,843	Esthetician	174
#pseudofolliculitisbarbae	312	Esthetician	203	Board-Certified Internist	19
#razorbumps	15,034	Influencer	24,045	Influencer	826
#melasma	1,286,202	Patient	4,894	Patient	207
#keloid	44,455	Foreign Dermatologist (Iran)	19,749	Foreign Dermatologist (Iran)	345
#centralcentrifugalcicatricialalopecia	304	Patient	241	Board-Certified Dermatologist	43
#CCCA	12,217	Actress	29,399	Actress	230
#tractionalopecia	13,093	Hairstylist	9,829	Hairstylist	481
#eczema	1,731,261	Influencer	1,424	Influencer	181
#vitiligo	364,813	Model	5,010	Influencer	292
#acnekeloidalis	15	Medical Spa	86	Board-Certified Dermatologist	10
#folliculitispapillaris	0	N/A		N/A	
#dermatosispapulosanigra	469	Dermatology Resident	347	Influencer	27
#dpn	18,835	Foreign Dermatologist (Brazil)	109	Foreign Dermatologist (Brazil)	3
#dissectingcellulitis	26	Board-Certified Dermatologist	1,269	Board-Certified Dermatologist	64
#melanoma	172,232	Influencer	31,341	Patient	1,399
#nonmelanomaskincancer	211	Dermatology Resident	143	Board-Certified Dermatologist	11
#NMSC	4,612	N/A		N/A	
#psoraisis	1,837	Influencer	626	Influencer	163
#sarcoidosis	39,866	N/A		N/A	
#seborrheicdermatitis	6,889	Journalist	2,630	Journalist	374
#dandruff	94,121	Beauty Influencer	11,614	Beauty Influencer	132
#trichorrhexisnodosa	26	Board-Certified Dermatologist	229	Board-Certified Dermatologist	49
#hairbreakage	20,244	Influencer	6,269	Influencer	300
#tineacapitis	383	Medical Interest Group	1,234	Microbiologist	13
Total	9,087,589	**Total**	210,578	**Total**	8,647

Of the 288 top posts collected for the 31 queried skin of color hashtags, 219 met inclusion criteria. Board-certified dermatologists (26 posts) only generated 12% of top posts, whereas individuals not certified in dermatology produced 88% (Figure 1 and Table 2). Of this group, social media influencers were the largest subcategory (37 posts). A majority of the top posts were promotional (135 posts, 61.6%) as opposed to educational (84 posts, 38.3%), and were formatted as photos (181 posts, 82.6%) as opposed to videos (38 posts, 17.4%). To compare engagement between categories, the nonparametric Wilcoxon rank-sum test was appropriate due to distribution skewness driven by a small number of "viral" posts with much higher numbers of likes and comments relative to other posts, as seen in the log-scaled boxplots in Figure 2. For example, the most-liked top post (#acne, Instagram influencer) received 36,781 likes and 135 comments, while the most-commented top post (#postinflammatoryhyperpigmentation, foreign dermatologist) received 4,259 likes and 2,580 comments (Table 1). There was a significant difference in the number of total likes (P=0.027) but not in the number of comments (P=0.48) for content posted by board certified dermatologists vs non-dermatologists. Similar findings were observed when comparing all physicians and mid-level providers vs "other" (likes P=0.010, comments P=0.097), but not for all physicians vs "other" (likes P=0.052, comments P=0.35) where the p-value for likes does not quite reach significance. Content generator category did not generally influence the proportions of post formats or intention, except for "Other" category content generators being significantly more likely to post promotional material (Chi-squared, P=0.038 vs all physicians, P=0.00054 vs all physicians and mid-level providers). Notably, when repeating comparisons of engagement after stratification by post intention (Table 3), significant differences were only observed in the higher number of likes for educational posts generated by "Other" relative to the physicians and mid-level providers category (educational post likes P=0.0074).

TABLE 2.

Characteristics of Top Posts Generated by Board-Certified Dermatologists, Physicians, and Mid-Level Providers Compared to Other Instagram Content Generators

	Board-Certified Dermatologists	Other	
Number of Posts (%)	26 (11.9)	193 (88.1)	
Total Likes (row %)	16,402 (3.4)	417,918 (96.6)	p = 0.02695 (Wilcoxon)
Total Comments (row %)	1,296 (10.2)	16,460 (89.8)	p = 0.4762 (Wilcoxon)
Educational (%)	12 (46.2)	72 (37.3)	p = 0.5117 (χ2)
Promotional (%)	14 (53.8)	121 (62.7)	
Photo (%)	24 (92.3)	157 (81.3)	p = 0.2672 (χ2)
Video (%)	2 (7.7)	36 (18.7)	
	Physicians	**Other**	
Number of Posts (%)	62 (28.3)	157 (71.7)	
Total Likes (row %)	70,956 (16.3)	363,364 (83.7)	p = 0.05224 (Wilcoxon)
Total Comments (row %)	5,424 (30.5)	12,332 (69.5)	p = 0.3459 (Wilcoxon)
Educational (%)	31 (50.0)	53 (33.8)	p = 0.0382 (χ2)
Promotional (%)	31 (50.0)	104 (66.2)	
Photo (%)	54 (87.1)	127 (80.9)	p = 0.3711 (χ2)
Video (%)	8 (12.9)	30 (19.1)	
	Physicians and Mid-Level Providers	**Other**	
Number of Posts (%)	66 (30.1)	153 (69.8)	
Total Likes (row %)	71,261 (16.4)	363,059 (83.6)	p = 0.01019 (Wilcoxon)
Total Comments (row %)	5,434 (30.6)	12,322 (69.4)	p = 0.09668 (Wilcoxon)
Educational (%)	35 (53.0)	49 (32.0)	p = 0.005407 (χ2)
Promotional (%)	31 (47.0)	104 (68.0)	
Photo (%)	58 (87.9)	123 (80.4)	p = 0.251 (χ2)
Video (%)	8 (12.1)	30 (19.6)	

FIGURE 1. Number of skin-of-color dermatology-related top Instagram posts by content generator category. Board-certified dermatologists were underrepresented amongst those posting top content to Instagram.

FIGURE 2. Boxplots showing distributions of likes and comments for each comparison category. Summary statistics including median, interquartile range (IQR), minimum (Q1 - 1.5*IQR), and maximum (Q3 + 1.5*IQR) are shown on each plot. The y-axis was log transformed due to distribution skewness and multiple outliers.

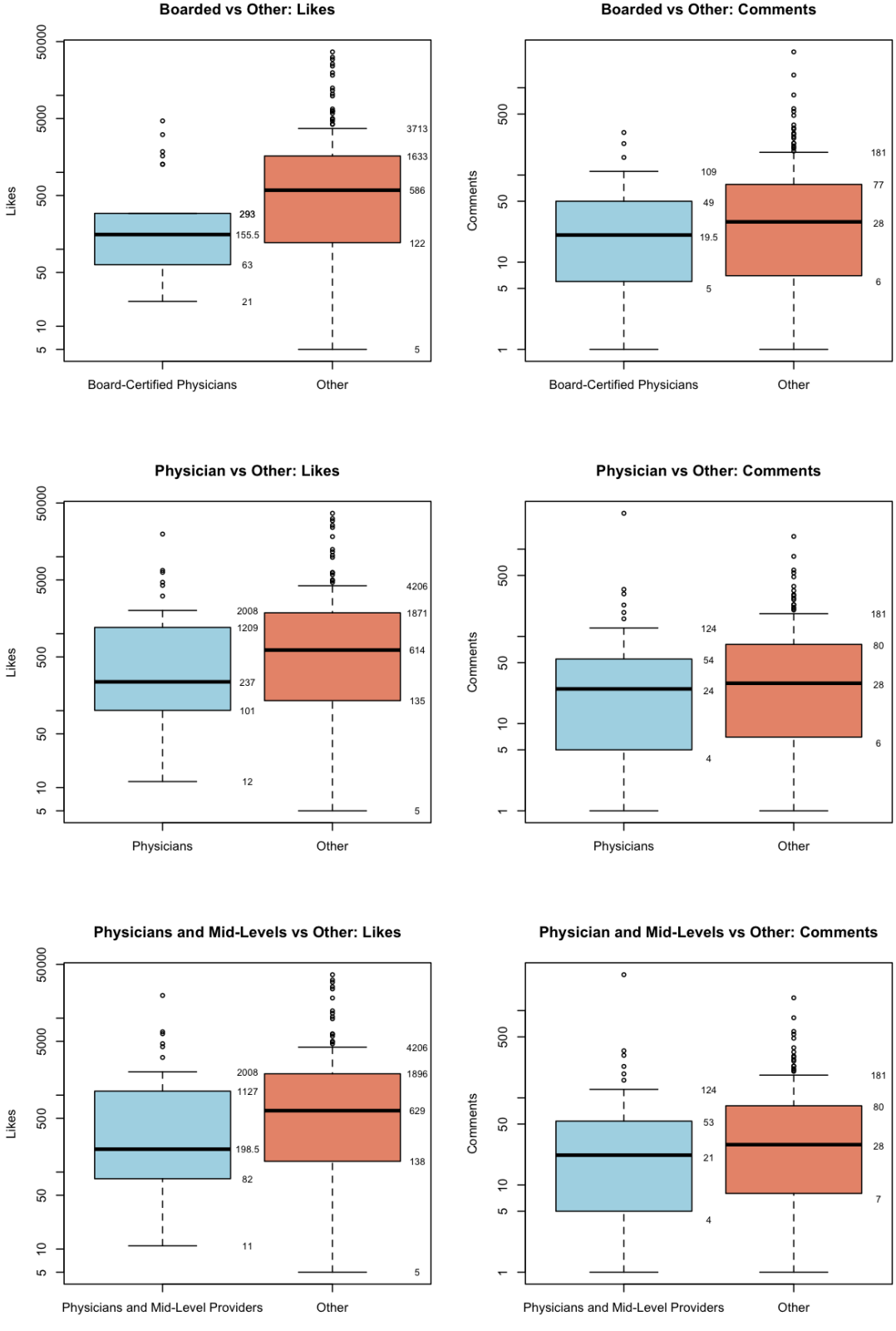

TABLE 3.

Comparisons of Engagement by Post Intention and Content Generator Category

Type of Post	Promotional		Educational	
Source of Post	Board-Certified Dermatologists	Other	Board-Certified Dermatologists	Other
Posts (%)	14 (10.3)	121 (89.6)	12 (14.3)	72 (85.7)
Likes Total (%)	11,791 (3.9)	286,736 (96.1)	4,611 (3.4)	131,182 (96.6)
Likes Mean	842	2,370	384	1822
Likes Median	132	614	159	534
Likes SD	1,412	5,992	571	3699
Likes Wilcoxon	p = 0.1269		p = 0.1674	
Comments Total (%)	786 (6.2)	11991 (93.8)	510 (10.2)	4,469 (89.8)
Comments Mean	56	99	43	62
Comments Median	15	34	21	18
Comments SD	87	261	61	170
Comments Wilcoxon	p = 0.2407		p = 0.5867	
	Physicians	Other	Physicians	Other
Posts (%)	31 (23.0)	104 (77.0)	31 (36.9)	53 (63.1)
Likes Total (%)	50,468 (16.9)	248,059 (83.1)	20,488 (15.1)	115,305 (84.9)
Likes Mean	1,628	2,385	661	2176
Likes Median	276	620	229	551
Likes SD	3,722	6,180	1192	4180
Likes Wilcoxon	p = 0.4011		p = 0.06853	
Comments Total (%)	4,288 (33.6)	8,489 (66.4)	1,136 (22.8)	3,843 (77.2)
Comments Mean	138	82	37	73
Comments Median	25	32	21	18
Comments SD	461	133	47	196
Comments Wilcoxon	p = 0.4897		p = 0.7915	
	Physicians and Mid-Level Providers	Other	Physicians and Mid-Level Providers	Other
Posts (%)	31 (23.0)	104 (77.0)	35 (41.7)	49 (58.3)
Likes Total (%)	50,468 (16.9)	248,059 (83.1)	20,793 (15.3)	115,000 (84.7)
Likes Mean	1,628	2,385	594	2347
Likes Median	276	620	167	808
Likes SD	3,722	6,180	1,136	4,305
Likes Wilcoxon	p = 0.4011		p = 0.007438	
Comments Total (%)	4,288 (33.6)	8,489 (66.4)	1,146 (23.0)	3,833 (77.0)
Comments Mean	138	82	33	78
Comments Median	25	32	18	22
Comments SD	461	133	46	203
Comments Wilcoxon	p = 0.4897		p = 0.2005	

DISCUSSION

Instagram and Board-Certified Dermatologists

In the field of dermatology, professional organizations such as the American Academy of Dermatology and the Dermatologist are found to have a large presence on social media outlets.[5] Resources produced by these organizations afford individuals greater access to information regarding skin disease. It is estimated that 80% of the adult population uses the internet to search for health information and can therefore easily access dermatologic proposed treatment online from these associations.[6] Organizations of dermatologists are well represented on such platforms as Facebook and Twitter, but the presence of individual board-certified dermatologists is minimal.

The individual board-certified dermatologist has the opportunity to cultivate patient relationships and participate in professional development opportunities via social media.[7] Regarding engagement between board-certified dermatologists and 'other', there was a statistically significant difference (P=0.027) in the number of likes that posts receive, but this difference became non-significant when adding physicians in other specialties, which means that other physicians and non-medical professionals generate more engagement. A possible explanation is that there are so few top posts (N = 26) provided by board-certified dermatologists content, they post relatively infrequently, or they have too few followers to generate the same attention that other users may garner. It is no surprise

that most outlier "viral" content with high numbers of likes or comments was posted by social media influencers and other non-providers with large Instagram followers. Promisingly, this difference in engagement became non-significant when stratifying by the intention of the post, but the overall numbers of top posts by board-certified dermatologists are still exceedingly small, especially for educational posts (N = 12). Board-certified dermatologists may therefore be missing a valuable opportunity to advocate for the specialty, disseminate educational resources about skin disease, and potentially discover collaborations with individuals with similar research interests. Moving forward, board-certified dermatologists should recognize there is an incredible paucity of users providing educational content regarding skin of color. This gap provides opportunity for board-certified dermatologists to provide evidence based skin of color education or those who already have a significant following.

Instagram and Non-Medical Professionals

Aestheticians and hair stylists are two professions that regularly come into contact with skin and hair of skin of color individuals. According to the Associated Skin Care Professionals (ASCP), aestheticians' scope of practice includes improving and maintaining the appearance of skin through various treatments. Examples of such treatments include cosmeceutical application, hair waxing, skin cleansing, chemical/mechanical exfoliation, or facial steaming. However, evidence supporting many of these therapies and/or procedures is limited. Notably, the ASCP excludes diagnosis and management of skin conditions in their scope.[8]

Hair stylists are also an important tool in hair care and education. While not typically incorporated into dermatologic practice, as aestheticians are, hair stylists see an incredible volume of individuals, of which, many are bound to present with dermatologic disease. Similar to aestheticians, hair stylists can play an important role in the early detection of skin and hair disease in addition to the recommendations of hair-specific cosmeceuticals.

Aestheticians can play a role in the management of acne vulgaris and rosacea.[8] Similarly, hair stylists may contribute to the prevention and early detection of dermatologic conditions common in skin of color such as hair breakage, scalp itching, seborrheic dermatitis, and alopecia.[9] Further, there is a paucity of evidence-based data regarding the utilized therapies or cosmeceuticals and more studies are necessary to elucidate their roles in dermatologic care.

Despite their respective contributions to the field of dermatology, it is essential that their scope of practice is strictly defined to prevent the spread of misinformation. That said, there is still a paucity of evidence-based data regarding their respective treatments.

Social Media and Dermatoethics

The increasing commonality of social media usage among healthcare providers has caused many new important ethical questions to be considered. The American Medical Association has recognized the increasing presence of physicians on these social media platforms and made their stance on appropriate behavior in these settings in a clearly outlined set of guidelines. The AMA recommends that physicians (1) apply ethical principles for preserving the relationship, confidentiality, privacy, and respect for person to online settings and communications, (2) maintain boundaries between social and professional spheres of life online, (3) only correspond electronically with patients that have establish physician-patient relationships and include all correspondence in the patient's medical record, (4) self-audit periodically to assess accuracy of information about them available online and (5) be aware of the potential future professional implications of online postings.[10] Dermatologists have been placed at the forefront of addressing these questions due to the compatibility of social media and the visual nature of dermatology.[11] However, it is important to not only evaluate the composition of posts generated by board-certified dermatologists, but to explore the ethical implications behind both types of content.

With social media providing an avenue for physicians to educate patients, certain professional standards need to be considered, including patient privacy and differentiation between fact and opinion.[13,14] It is common for dermatologists to use patient cases or images on social media to educate the public and other physicians. However, there is a high risk of breaching patient confidentiality in this field due to the existence of distinct markings and tattoos. Great precaution should be taken to avoid sharing images that contain these possible identifiers.[14] Additionally, because facts and opinions posted to dermatologists' social media accounts may have significant impact on their followers, physicians should be diligent in citing sources of information and potential conflicts of interests.[11]

Social media marketing has been found to be significantly more influential than traditional forms of advertisement (print media and television) as evidenced by rise in popularity of brands consulting "influencers" for collaborative advertising opportunities.[15] Many physicians have started to utilize social media as a marketing tool for specific products or services they provide, especially aesthetic dermatologists and plastic surgeons. Though social media can be an important tool for branding and promotion of dermatologic services, physicians have a responsibility to act in the best interest of potential patients when promoting medications, products or procedures on their accounts. When using social media for the purpose of promotion, physicians should heavily consider the impressionability of their audiences, disclose all potential conflicts of interest, and educate their audiences about the

range of potential clinical outcome as result of treatment.[15]

Spread of Misinformation

Another growing concern with the rising popularity of social media to consider is the rampant spread of health-related misinformation. The largest appeal of social media, the ease of accessibility and ability to create content, may be a pitfall when it comes to medically related information available on these platforms. Medical information is often unreferenced or informal, and generated by people who are unknown or identified by limited information.[16,17] Additionally, the interactive nature of social media allows for the proliferation of medical information that may not be scientific in nature and is more likely than not anecdotal medicine based on individual user experiences.[12]

Essentially, social media platforms lack internal controls to help users navigate the sea of information provided and identify who is creating the content, their credentials, and whether the information being shared is evidence-based or anecdotal in nature. This is a pervasive problem on the internet in general as evidenced by a campaign led by the World Health Organization to the Internet Corporation for Assigned Names and Numbers. Under their initiative, a strictly monitored process would be used to establish a new domain suffix for websites providing validated health information. Search engines would also prioritize these domain addresses when providing results in responses to health-related inquiries.[18]

A similar measure could counter the spread of medical misinformation on social media platforms. While certain platforms (Twitter, Instagram) have verification procedures which users can undergo to verify their identity, these processes are often reserved for celebrity users. If social media platforms implemented a credential verification process for users generating medically related content and promoted posts by these verified accounts in relation to health-related search queries, it could be easier for users of color to readily identify reliable, relevant, dermatology- related information.

Future Uses

The further integration of social media and medicine has been met with mixed reviews from physicians. In a 2019 study conducted by Sedrak et al, physicians expressed lack of time and experience, uncertainty of patient benefit, and muddling of personal and professional boundaries as reasons not to engage with patients via social media under professional pretenses. However, their presence and engagement with the public on these platforms is necessary to make evidence-based health information available to the public and combat the slew of misinformation shared in these spaces.[20]

Limitations

The use of hashtag queries to discover dermatology-related content may have been limited due to the high specificity of hashtag terms. Because they are so specific, it is difficult to account for posts tagged with misspelled terms or shortened, colloquial terms for pathologies with longer names. Another limitation was the inability to search multiple hashtag terms simultaneously. As it stands, the current search interface of Instagram only allows users to make one query at a time. The ability to search multiple hashtag terms simultaneously could have possibly assisted in narrowing the scope of each query to dermatology specific content and reduced the number of excluded posts. Finally, social media is extremely fast paced and popular content changes almost every second of the day. While this study provided a snapshot analysis of skin of color dermatology content on Instagram, it would be interesting to see this content characterized in a similar manner over a longer period of time. Such an analysis could provide a more holistic examination of skin of color dermatology related content on Instagram.

CONCLUSION

Board certified dermatologists are notably underrepresented among Instagram accounts that produce popular skin of color-related dermatology content. The vast majority of these top posts are for promotional purposes. Additionally, non-medically trained individuals are promoting dermatologic treatments and attempting to educate prospective patients about common dermatologic conditions. These findings present a significant cause for concern due to the volume of dermatology advertisements by non-dermatologists and the ensuing risk they pose to patient safety and outcomes. It is critical that board-certified dermatologists establish a more prominent presence on social media platforms like Instagram so that SOC patients can be better educated about dermatologic conditions, treatment options, and treatment risks, from reliable sources.

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Cutaneous Photoaging: A Notable Pattern of Distribution of Lentigines on the Face

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ABSTRACT

Importance: Facial lentigines are a common patient complaint encountered in general and cosmetic dermatology practices. Lentigines are a marker of photoaging and understanding their distribution will provide insight into the aging process in order to better counsel patients.

Objectives: To compare the relative distribution of lentigines in facial cosmetic subunits.

Methods: We reviewed clinical photographs of patients receiving Alexandrite laser treatment for facial lentigines during the time period 11/1/2017–12/1/2018. Individual lentigines were plotted for each patient into one of 21 aesthetic units. A "heat map" was created to compare the relative density of these lesions.

Results: Grouped peripheral cosmetic subunits contained more lentigines compared to grouped central cosmetic units. The mean number of lentigines in the central units was 0.60 and in the peripheral units was 0.85. This finding was statistically significant with a p value of 0.0001.

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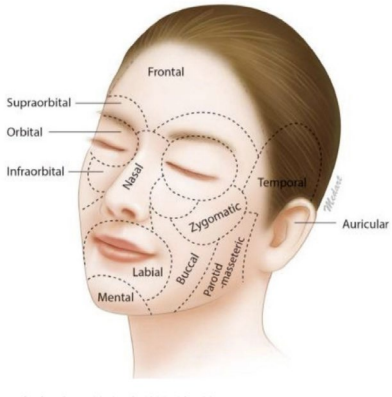
INTRODUCTION

Facial lentigines are a common patient complaint in dermatology practices. Lentigines are a marker of photoaging and understanding their distribution will provide insight into the aging process. The goal of our study was to determine the distribution of lentigines on the face and to determine if distribution of lentigines corresponds to published cutaneous UV damage and skin cancer distributions.

METHODS

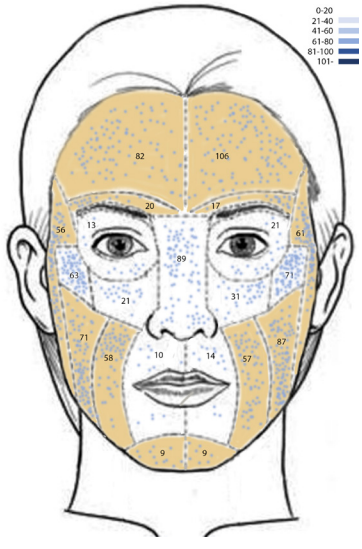
We performed an IRB-approved retrospective chart review at SkinCare Physicians in Chestnut Hill, MA. Eligible patients were identified by screening the electronic health record (EHR) for patients who had procedure codes for short-pulsed Alexandrite during the time period of 11/1/2017–12/1/2018. Patients who were 25–80 years-old and received Alexandrite laser treatment for facial lentigines were included. Patients were excluded if they did not have a series of high-quality photographs of the entire face. Photographs were reviewed and each patient's lentigines were plotted on a diagram of the face divided into aesthetic units based on a modified Gonzalez-Ulloa distribution (previously used to perform studies evaluating skin cancer distribution[1]) (Figure 1). There was a total of 21 aesthetic units.

FIGURE 1. Modified Gonzalez-Ulloa cosmetic facial subunits used to record facial lentigines from photograph review *(Used with permission).* *Auricular unit was not included in our evaluation as photos did not capture this site and the study focused on assessing lentigines on the face. **The nasal unit remained as a single unit given its central location on the face and difficulty in determining laterality for lentigines on the dorsum of nose. ***Modified to include laterality for a left-right comparison.



Arch Plast Surg. 2013 Jul; 40(4): 387–391.

FIGURE 2. Lentigines Distribution. Peripheral units are shaded yellow.



RESULTS

A total of 191 patients' charts were screened and 62 met the criteria. The patient cohort had a mean and median age of 57 with a range of 27–78. Of the 62 patients evaluated, there were 52 women and 7 men. Approximately 10% of the cohort had a prior history of a non-melanoma skin cancer. With respect to Fitzpatrick skin types, 3% were skin type I (n=2), 40% skin type II (n=25), 44% skin type III (n=27), and 13% skin type IV (n=8).

The number of facial lentigines in each of 21 units were recorded. A heat map schematic was created by manually plotting each individual lentigo into each of the aforementioned units. (Figure 2).

With regards to individual units, the frontal unit had the greatest number of lentigines with 106 on the left-side and 82 on the right-side (total 188 lentigines). This was followed by the parotid-masseteric unit with 87 on the left-side and 71 on the right-side (total 158 lentigines). The nasal unit had 89 lentigines. Other areas that were noted to have relatively high numbers of lentigines included the temporal, zygomatic, and buccal units (Table 1). The Wilcoxon rank-sum test was applied to assess for a difference in laterality and found the average number of facial lentigines was 7.7 for left facial units and 6.5 on right facial units, however, this was not statistically significant (P=0.20).

TABLE 1.

Average Lentigines Count by Facial Aesthetic Unit			
	Left	Right	Total
Supraorbital	0.27	0.32	0.59
Orbital	0.34	0.21	0.55
Temporal	0.98	0.9	1.88
Zygomatic	1.15	1.02	2.17
Infraorbital	0.5	0.34	0.84
Parotid-masseteric	1.4	1.15	2.55
Buccal	0.92	0.94	1.86
Labial	0.23	0.16	0.39
Mental	0.15	0.15	0.3
Frontal	1.71	1.32	3.03
Nasal	N/A	N/A	N/A
Total	7.65	6.51	14.16

Finally, in order to compare the distribution of lentigines as central or peripheral, subunits were categorized as follows: central (nasal, labial, zygomatic, infraorbital, and orbital) and peripheral (frontal, supraorbital, temporal, parotid-masseteric, buccal, and mental). A Wilcoxon-rank sum test was performed to evaluate for a difference between lentigo distribution within the designated central and peripheral subunits. The mean number of lentigines in the central units was 0.60 and in the peripheral units was 0.85. This finding was statistically significant with a P value of 0.0001.

DISCUSSION

The comparisons were analyzed using a Wilcoxon rank-sum given the non-normal distribution of the collected data. Our findings were notable in several key ways. First, in this cohort of patients, lentigines were noted to be more prevalent in the grouped peripheral units than the grouped central facial units (0.85 vs 0.6; P<0.0001). Additionally, it is important to note that although the frontal subunits had the highest absolute number of lentigines, the density appears to be highest in the temporal, zygomatic, and parotid-masseteric units. This is explained by the high number of lentigines in these units, which have small surface areas (especially when compared to frontal subunit, which has the largest surface area). We hypothesize that the reason that lateral facial compartments have more lentigines than central ones is related to sun exposure and behavior. For the most part, unless trying to actively tan, one tends to look away and not directly at the sun. Thus, the lateral face gets more sun exposure that the central face and could explain the difference. Several studies have shown that the most common aesthetic units affected by skin cancer are the nasal, buccal, and temple units.[1,2,3,4] In this subset of patients, there was a statistically significant difference in distribution of lentigines with more lentigines in the peripheral cosmetic units. This may be attributed to a number of reasons including differences in biology between lentigines and skin cancer, site-specific biology, and patient behavior. This information is helpful when counseling patients regarding sun protection and prevention of lentigines. Recently published data has shown the rates of skin cancer development on different parts of the face are not associated with the amount of sun exposure as some of the least exposed units (ie, under eyebrow, eyelids, nasolabial folds, and the medial/lateral canthus) had higher rates of skin cancer development than more exposed units (ie, forehead, chin, temple, jaw).[2]

The predilection for photoaging and skin cancer development to occur more frequently on the left side of the face has been the subject of several hypotheses, with one of the leading hypotheses linking drivers in right-hand-drive cars to greater sun exposure on the left side of the face. Our data did not show a statistically significant difference for lentigines on the left side of the face, which is a distribution pattern that has been previously observed with facial skin cancer distribution.[5] This is likely due to the small sample size of the study.

Our study had several limitations. The distribution of the lentigines was plotted by the cosmetic unit, which may result in a loss of information as some subunits covered large surface areas. This was addressed by using a heat map that demonstrated the density in each unit by mapping each individual lentigo. Second, the results of this study were limited to a small population at a single practice in a Boston suburb. The geographic location may result in different sun exposures factors, both with respect to the environment and the patients. As a result, the findings may not be generalizable. Additionally, each lentigo recorded was plotted equally and we did not account for size or degree of pigment of each lentigo.

CONCLUSION

In this study, lentigines, a marker of photodamage, tended to be peripherally distributed in the cohort of patients. This data provides insight into how lentigines are distributed and can help when counseling patients on sun protective practices such as sun avoidance, paying particular attention to sunscreen application on the lateral part of the face, and wearing a broad-brimmed hat as opposed to shorter brims, or a baseball cap to get more lateral coverage of the face.

DISCLOSURES

The authors have no conflicts to report.

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ORIGINAL ARTICLE

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The Use of Botanical Extracts in East Asia for Treatment of Hyperpigmentation: An Evidenced-Based Review

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ABSTRACT

Recent years have seen a growth in the Asian cosmeceutical industry and an expanding worldwide marketplace with increasing consumer use of plant-based skin care products. The rising prevalence of Asian cosmeceuticals has led to research studies assessing the safety and efficacy of these products. We seek to review current evidence on safety and efficacy of key ingredients used in Asian cosmeceuticals to treat disorders of hyperpigmentation. A comprehensive search on PubMed was conducted to identify hyperpigmentation-related research studies on eight popular ingredients used in Asian cosmeceuticals: green tea, soy, orchid, licorice, rice water, ginseng, bamboo, and aloe. Both in vitro studies and clinical trials involving human subjects were included. Of the ingredients reviewed, soy and licorice had the most clinical evidence supporting their efficacy, while all other ingredients were supported by in vitro studies. More research is needed to further evaluate the safety and efficacy of Asian cosmeceutical ingredients in treatment of hyperpigmentation.

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INTRODUCTION

Cosmeceuticals, topical skin products containing bioactive ingredients purported to have medical benefits, are the fastest growing beauty industry in the world with an estimated $42.8 billion worth of sales in 2018.[1] The cosmeceutical industry is particularly robust in Asia, where skin lightening takes on cultural significance. This strive for aesthetic beauty has led to the formulation of naturally-based skin care products targeted at hyperpigmentation. Korea has been at the forefront of generating the newest and most innovative cosmeceutical products. Some of the most popular ingredients used in these cosmeceuticals include green tea, soy, orchid, licorice, rice water, ginseng, bamboo, and aloe. Since the rising popularity of Asian cosmeceuticals, there has been an increasing world-wide demand for skin care products utilizing exotic plant-based ingredients. Scientists have been conducting research studies on these plant extracts, their unique properties, and their evidence-based use in the current beauty industry. With increasing consumer use of cosmeceutical products, it is imperative that physicians understand the properties of these extracts and the scientific basis of their efficacy in order to better inform patients and ensure their safety. Few research articles have explored the effectiveness of plant-based Asian cosmeceuticals in treating hyperpigmentation, and even fewer have assessed the clinical evidence behind their efficacy. In this review, we seek to incorporate the most recent scientific literature to critically appraise in vitro studies and clinical trials investigating the natural ingredients found in Asian cosmeceuticals.

MATERIALS AND METHODS

A comprehensive review of the literature on natural ingredients most frequently used in Korean cosmeceuticals to treat hyperpigmentation was conducted on PubMed (U.S. National Library of Medicine). The search terms "green tea," "soy," "orchid," "licorice," "rice water," "ginseng," "bamboo," and "aloe vera" were input into the advanced search tool to identify all articles discussing hyperpigmentation or pigmentary disorders from both in vitro and in vivo studies with publications up to April 2019. Non-English language articles were excluded. A total of 50 studies were included for this study.

Studies Categorized by Active Ingredients

Aloe Vera

Aloe Vera is a popular succulent plant that has long been used for many dermatologic conditions such as eczema, burn wounds, skin infections, and acne vulgaris.[2] Inside the leaves of the aloe vera plant is copious amounts of gel that can be squeezed out and directly applied to the skin.[3] This gel has been used for its anti-bacterial and anti-inflammatory properties as well as to decrease hyperpigmentation of the skin. Aloesin, a natural hydroxymethyl chromone compound and the active ingredient in the aloe vera plant, competitively inhibits dihydroxyphenylalanine (DOPA) oxidation and non-competitively inhibits tyrosine hydroxylase activity.[4] Melanin is synthesized through tyrosine hydroxylase and oxidation of DOPA.[5] Thus inhibition of these steps in melanin biosynthesis has the potential to prevent overproduction of melanin and skin hyperpigmentation. A prior

study showed that the topical application of aloesin following ultraviolet (UV)-irradiation (210 mJ) on the inner forearm provided pigmentation suppression in a dose-dependent manner.[6] Another in vitro study showed that aloesin induced melanin aggregation in isolated tail melanophores of tadpoles, *B. melanostictus*, which lead to lightening of the skin.[7] More recently, aloe vera was tested in a double-blinded randomized clinical trial aimed at determining the clinical efficacy of a topical liposome-encapsulated aloe vera in the treatment of melasma in pregnant women. Researchers were able to show that this drug carrier system along with aloe vera decreased the severity of melasma in pregnancy when compared to aloe vera gel extract alone, as demonstrated by a 32% improvement in MASI scores in the treatment group compared to a 10% improvement in the control group.[2] When used topically, aloe vera is generally considered safe; however, some case reports of skin irritation and hypersensitivity to Aloe products have been reported.[8]

Bamboo

Bamboo is a type of flowering plant that belongs to the *Bambusoideae* subfamily and has been used as a healing treatment by Asian cultures for centuries.9 In vitro studies have shown bamboo to be an effective lightening agent. Water extract from bamboo shavings (WEBS) has demonstrated potent inhibitory effects against the activity of melanin-synthesizing enzyme, tyrosinase, in malignant melanoma B-16 cells of mice.[10] In this study, the effects were dose dependent and melanin content was significantly inhibited (65.05%) at 16 mg/ml with an inhibitory concentration (IC50) of 6 mg/ml. The application of the topical formulation was shown to be non-toxic and non-irritating to the skin. Another study examined the effects of bamboo extract on UVB-induced cell damage. Human keratinocytes were exposed to UVB in the presence of bamboo extract at varying concentrations and changes in cell viability were determined.[11] Bamboo extract diminished the generation of reactive oxygen species, inhibited matrix metalloproteinase 1 expression, and enhanced UVB-exposed cell survivability, as measured by apoptotic assays. These results suggest that bamboo extract may have the ability to attenuate the process of skin photoaging. Few clinical trials on human subjects have been conducted on bamboo extract. The only clinical trial to date utilized a skin cream formulated with flavonoids and extracts from bamboo leaves.[12] Results showed that addition of 1.5% topical bamboo extract resulted in sun screening efficacy and protection against UVB damage as indicated by an SPF of 1.27. A UV Index reading of 0 to 2 indicates low risk of harm from unprotected sun exposure for the average person. No irritation was reported by participants with topical application to the skin.

Ginseng

Ginseng has been used for centuries in Asian traditional medicine to treat many chronic diseases.[13] The popularity of the ingredient has led to its formulation in high-end Asian skin care products. In vitro studies demonstrate that P-coumaric acid extracted from the fresh leaves of Panax ginseng inhibits tyrosinase activity and melanin content in B16 melanoma cells, suggesting that this ingredient may be an effective skin lightening agent.[14] Furthermore, ethanol extract from ginseng seeds reduced melanin production in melan-a-cells (melanoctyes originating from mice) by 35.1% without cytotoxicity.[15] Among the active metabolites isolated, picrionoside A was shown to be effective in reducing body pigmentation in zebrafish in addition to decreasing the rate of melanin synthesis in melan-a-cells by 17.1% without cytotoxicity.[16] These in vitro studies suggest that different active ingredients in ginseng may be efficacious skin lightening agents. No clinical trials have studied the effects of topical application of ginseng. However, one study evaluated the effectiveness of oral administration of ginseng on patients with melasma. A cohort of 25 female patients consumed 3 grams of Korean red ginseng powder over a 24 week period.[17] Skin pigmentation was assessed using the melasma area and severity index (MASI), melasma quality of life scale (MELASQoL), and patient/investigator-rated improvement scales. After 24 weeks, the MASI score decreased from 8.8 to 5.6, and the MELASQoL showed improvement in 91% of patients ($P<0.05$). The mean level of pigmentation decreased from 184.3 to 159.7 and erythema levels decreased from 253.6 to 216.4 ($P<0.05$). The regimen showed good tolerability overall with minimal adverse events.

Green Tea

Green tea is known for its potent antioxidant and anti-inflammatory properties.[18] Among the many polyphenols in green tea extract, epigallo-catechin-3-gallate (ECGC) is the primary active ingredient.[19] One study using immortalized melanocytes showed that camellia sinensis water extracts containing green tea inhibited melanogenesis and tyrosinase activity in a concentration-dependent manner.[20] The skin lightening effects of green tea may be due to chelating properties at the active site of tyrosinase.[21] In a randomized controlled trial, 60 women with melasma were treated with a 2% analogue of green tea in a hydrophilic cream.[22] Hyperpigmentation lesions were significantly reduced in 60% of the experimental group relative to the control group as measured by a reduction of mean number of hyperpigmented lesions, as determined by dermatologic and photographic evaluations. In addition to treating melasma, green tea extracts were shown to reduce skin pigmentation in healthy Asian subjects.[23] The lightening effects of green tea may be due to the prevention of sun damage accumulated over time. The skin of normal volunteers was treated with green tea or one of its main ingredients.[24] After thirty minutes, the treated areas were exposed to solar-simulated UV radiation and subsequent UV-induced erythema was monitored. Skin areas with green tea extract showed a dose-dependent inhibition of erythema response caused by UV radiation. Further histology showed that areas of skin treated with green tea extract had a reduced num-

ber of sunburn cells and epidermal Langerhans cells damaged by UV radiation. With the emerging popularity of green tea extract-formulated skin care products, more clinical trials are needed to evaluate the lightening effects of green tea on human skin.

Licorice

Licorice, also known as Glycyrrhiza glabra, has long been used for its medicinal value and anti-inflammatory components.[25,26,27] However, licorice also contains the active ingredient Glabridin that may have value in reducing pigmentation. Glabridin works by inhibiting UVB-induced pigmentation and tyrosinase, thus disrupting the pathway of pigment production.[28] In vitro studies have shown that Glabridin has 16 times the skin lightening effects of hydroquinone, a known skin lightening agent.[28,29] In line with this, in a single-center, double-blind clinical study of 18 subjects comparing the efficacy of a hydroquinone-free formula, containing Glabridin, there was a significant reductions in ultraviolet-induced hyperpigmentation when compared to both the negative control as well as 4% hydroquinone cream.[30] Furthermore, in a single-blinded study comparing the efficacy of belides, embilica, and licorice 7% to 2% hydroquinone in the treatment of melasma, the degree of depigmentation in both groups was not statistically different.[31] Another active ingredient present in licorice, liquirtrin, has also demonstrated depigmention properties. In fact, in one double-blind, split-face study of 20 subjects comparing 2% and 4% liquirtin to 4% hydroquinone for the management of melasma, both concentrations of liquirtin were significantly more effective in decreasing pigmentation when compared to hydroquinone.[32]

Orchid

Orchid extract contains plant pigments called anthocyanins, a group of phytochemicals known for their antioxidant and anti-inflammatory properties.[33] These flavonoids combat reactive oxygen species (ROS) and are capable of soothing and enhancing skin tone while minimizing oxidative stress.[33,34] In vitro studies suggest that orchid extract is effective in suppressing WNT1 expression by downregulating a transcriptional activator of the gene.[35] Increased expression of WNT1 stimulates melanocyte stem cell differentiation. A double-bind, comparative, split-face clinical trial in 48 female patients with melasma and/or solar lentigines to evaluate the in vivo efficacy of a cosmetic formulation containing orchid extract compared to 3% vitamin C derivative.[36] After 8 weeks of topical use, the orchid extract group showed similar efficacy as vitamin C group in lightening melasma and lentigines by colorimetric measurements and subjective questionnaire. Importantly, the study found little risk associated with the use of topical orchid extract. No instances of contact dermatitis, pruritis, or irritation were reported during the 8 weeks of treatment.

Rice Water

Rice (*Oryza sativa*) extract is a key ingredient in many Asian hair and skin treatments.[37] It contains high levels of bioactive phenolic compounds (p-coumaric, ferulic, and caffeic acids) that display anti-tyrosinase and photoprotective properties.[38] The anti-melanogenic peptides found in rice bran protein were shown to significantly inhibit melanogenesis in mouse B16 melanoma cells without causing cytotoxity.[39]The suppression of melanogenesis can be attributed to its anti-tyrosinase and TRP-2 inhibitory effects, which protect the cell from oxidative stress in a dose-dependent manner. It is proposed that the potent skin lightening effects of the extract result from the synergistic activities of the active phenolic ingredients.[38] A double-blind randomized control trial of 24 volunteers demonstrated that rice extract cream (0.1% or 0.2%) resulted in a significant decrease in melanin index ($P< 0.001$) post-treatment (28 days) compared to baseline.[38] Furthermore, no subjects reported adverse effects over the study period. To confirm the safety of the topical treatment, patch testing in a separate cohort of 25 healthy subjects showed no signs of skin irritation on exposure to rice extract cream. Another clinical trial using semi-purified rice bran extract entrapped in niosomes formations demonstrated skin lightening in 30 human subjects within a 28-day period.[40] Both gel and cream formulations resulted in a sustained skin lightening effect post-treatment even after continued application was forgone for 7 days. No skin irritation was noted in this clinical study.

Soy

Soybean is a legume commonly grown in East Asia.[41] It consists of many biologically active ingredients including isoflavones.[42] There are a number of in vitro studies attesting to the pigment-reducing properties of soybean extract.[42,43,44] Equally significant is the large amount of clinical trials supporting its efficacy as skin lightening agent. A 16-week, double-blind, placebo-controlled clinical study of African-American, Hispanic, and Asian patients with Fitzpatrick skin types III–V showed that a soy-containing topical formulation resulted in a reduction in post-inflammatory hyperpigmentation caused by acne. Assessments of acne severity and hyperpigmentation were measured by expert clinical evaluations, global acne asessments, and spectroscopic measurements evaluating changes in redness and melanin over time.[46] Another double-blind, vehicle-controlled study enrolled 65 women with facial photodamage and monitored their skin condition over a 12-week period with the use of a soy extract-containing moisturizer.[47] Using colorimetric measurements, digital photography, and clinical evaluation, the soy moisturizer was significantly more efficacious in reducing mottled pigmentation blotchiness and overall skin tone compared to the vehicle. No adverse events were reported. In a study of 16 Hispanic women with melasma, subjects applied a stabilized soy extract once daily for 3 months to areas of dyspigmentation with untreated dyspigmented areas serving as controls.[47,48] Fourteen of the sixteen subjects had a 12% reduction in hyperpigmentation as measured by colorimetric evaluations. No side effects were noted. In fair-complexioned men of Celtic origin,

TABLE 1.

Comparison of Properties of Active Ingredients in Asian Topicals

Name of Topical	Evidence Behind Use	Skin Condition(s) Treated	Dosing & Formulation*	Mechanism of Action	Adverse Events**	Market Availability in U.S.***
Aloe Vera	Double-blinded RCT2,6-7	PIH, melasma, eczema, burn wounds, skin infections, acne vulgaris	Liposome-encapsulated leaf gel extract (0.5 wt % concentration)	Competitive inhibition of DOPA oxidation, non-competitive inhibition of tyrosine hydroxylase	Skin irritation, hypersensitivity, hives	Yes
Bamboo	Uncontrolled observational study[12]	Hyperpigmentation, UVB-damaged skin, photoprotection	Cream formulation with 1.5% mass fraction of bamboo leaf extract	Dose-dependent inhibition of tyrosinase activity	No reported incidences of skin irritation	Yes
Ginseng	Uncontrolled observational study[17]	Melasma, hyperpigmentation	Oral formulation w/1 gram red ginseng powder	Inhibition of tyrosinase activity	No reported cutaneous effects with oral administration	Yes
Green Tea	Multiple RCTs[21-24]	Melasma, hyperpigmentation, photoprotection	2-5% green tea extract in hydrophilic cream	Concentration-dependent Inhibition of tyrosinase activity via chelation at active site	No reported incidences of skin irritation	Yes
Licorice	Single and double-blind clinical studies[28-32]	Hyperpigmentation, melasma	Topical formulation of 7% licorice extract or 2-4% liquiritin	Inhibition of tyrosinase	No reported incidences of skin irritation	Yes
Orchid	Double-blind comparative split-face clinical trial[36]	Melasma, solar lentigines	5% orchid extract cosmetic formulation or serum	Reduction of reactive oxygen species (ROS), downregulation of transcriptional activity of WNT1 gene	No adverse events including irritation, itching and contact dermatitis	Yes
Rice Water	Several double-blind RCTs[38,40]	Hyperpigmentation	0.1-3% rice bran in oil-based cream or niosomal dispersion	Dose-dependent inhibition of tyrosinase and TRP-2, photoprotective properties	No reported incidences of skin irritation	Yes
Soy	Multiple RCTs[46-48,50]	PIH, photodamage, melasma, facial hypermelanosis	Active moisturizer with stabilized soy extracts	Inhibition of melanosome phagocytosis by keratinocytes via protease-activated receptor 2 (PAR-2)	No reported incidences of skin irritation	Yes

PIH = post-inflammatory hyperpigmentation; RCT = randomized control trial
*Dosing and formulation based on efficacious activity of the topical(s) with observable results and definable endpoints.
**Adverse events as reported in current scientific literature. More studies are needed to further elucidate adverse events and appraise the long-term side effects of these topical formulations.
***Market availability in U.S includes but is not limited to over-the-counter products and cosmeceuticals available in stores or online platforms.

soybean extract had a skin lightening effect in treating facial hypermelanosis in 44 individuals.[50] Overall, promising results from multiple randomized-control trials and the well-tolerability of soy extract supports the use of soybean extract in treating hyperpigmentation.

DISCUSSION

Asian cosmeceuticals containing natural plant-derived ingredients are increasing in popularity in the U.S. and worldwide. As the market for these skin care products continue to grow, consumers will increasingly seek advice from dermatologists regarding their efficacy. The scientific and clinical evidence supporting some of the most popular ingredients formulated in Asian skincare products used to treat hyperpigmentation, as reviewed here have shown them to overall be safe and well-tolerated. Although, well-controlled, robust clinical studies evaluating the safety and efficacy of plant extracts for treatment of hyperpigmentation are continuing to evolve, as reviewed

here, soy and licorice had the most clinical evidence to date. Nonetheless, all the ingredients have been substantiated to some degree by scientific research, through in vitro and/or in vivo studies, and appear to be well-tolerated.

With the mounting popularity of Asian skin care products, we anticipate an increasing number of clinical studies in the future to further evaluate the efficacy and safety of these ingredients in human subjects, allowing clinicians to better understand and counsel patients, and perhaps offer alternative, non-hydroquinone based topical lightening therapy to their patients.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

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Randomized Controlled Trial Comparing the Efficacy and Safety of Two Injection Techniques of IncobotulinumtoxinA for Axillary Hyperhidrosis

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ABSTRACT

Background: Botulinum toxin A (BoNT-A) is an effective treatment for axillary hyperhidrosis (AH) typically applied by multiple injection punctures.

Objective: To compare the efficacy and safety of two BoNT-A injection techniques for AH.

Methods: Randomized, evaluator-blinded trial, in which each axilla of the same patient received 50 U of incobotulinumtoxin A (IncoA; Xeomin), one injected intradermally using multiple punctures, the other subcutaneously by radial approach. Follow-up visits occurred after 30, 120, 180, and 270 days. Outcomes included procedure duration and pain, gravimetry and starch-iodine tests and safety.

Results: Twenty-four patients with severe hyperhidrosis were included; 67% were female and mean age was 34.7 years. Radial injection was faster applied than multiple punctures (P<0.001) but showed higher pain scores (P=0.001). Pre- and post-treatment gravimetric measures showed that IncoA led to a significant sweat reduction, by both techniques, with 95% of responders (≥50% reduction from baseline) after 30 days of treatment. Similarly, Minor's test showed an excellent response (90-100% reduction) by most patients regardless of the technique used, after 30 days and sustained for at least 270 days. At most time points, there were no significant differences between the two techniques; however, multiple punctures showed a higher reduction of gravimetric measures at days 30 and 180, and of Minor's test at day 270. Treatment was well tolerated.

Conclusions: IncoA is an effective and safe treatment for AH irrespective to the technique used for injection. Our study suggests that multiple punctures injection may confer better outcomes at some time points.

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INTRODUCTION

Primary hyperhidrosis (PH) is an idiopathic, chronic disorder characterized by uncontrolled sweat production exceeding that required for homeostasis maintenance.[1] Typically in a bilateral and symmetrical pattern, PH can affect different areas of the body, most commonly axillae, palms, soles, and face, with affected patients often sweating from one or two areas of the body.[2] The prevalence of PH is widely variable in the literature. In the U.S., a survey with 150,000 households estimated a national prevalence of 2.8%,[3] while a more recent study reported the prevalence of hyperhidrosis at 4.8%.[4] Of the affected population, more than half of the patients have axillary hyperhidrosis (AH).[3,4]

AH affects both genders, and symptoms usually manifest during puberty or adolescence.[5] It is an emotionally, physically and socially distressing condition that interferes with everyday activities and exerts a negative impact on patients' quality of life.[6,7] Given the burden of excessive sweating, reduction of sweat production is an important goal of management and treatment of AH.[8]

Botulinum toxin A (BoNT-A) has proven to be an effective and safe treatment for primary AH, promoting high levels of satisfaction among patients.[9-11] This treatment can temporarily inhibit excessive sweating by blocking the release of the neurotransmitter acetylcholine, producing efficient chemical gland denervation. It is a minimally invasive procedure that can be administered in outpatient facilities under topical, local, or locoregional anesthesia. Incobotulinumtoxin A (IncoA, Xeomin®, Merz Pharma) was shown to have similar efficacy and safety profiles as onabotulinumtoxin A (Botox®, Allergan).[12]

For AH, BoNT-A is typically applied by multiple (usually 10 to 20) intradermal injections of small doses per point, spaced 1–2cm apart, to cover the affected area.[8,11] Overall, it is an easy, simple and well tolerated procedure. An alternative injection technique involving the use of a more diluted solution (Dr. Rosa Flores, Mexico, personal communication based on Odderson[13]) injected subcutaneously in a radial manner through two points of entrance has been proposed with the aim of reducing procedure duration. However, its efficacy and safety have not

been compared with those of the multiple-puncture technique. The aim of this study was to confirm the efficacy of IncoA and compare both techniques of injection in the treatment of AH.

METHODS

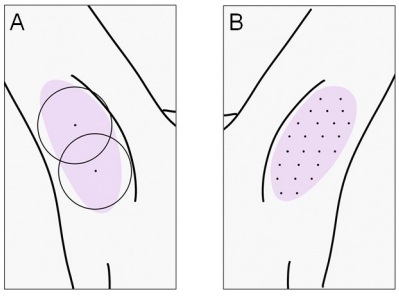
Study Design and Patients

This study was a randomized trial, conducted between May 2017 and December 2018 at the Dermatology outpatient unit of the Hospital do Servidor Público Municipal de São Paulo (São Paulo, Brazil). The study was open-label to treating physicians and patients, but the clinical evaluator in charge of the main efficacy analysis was blinded in relation to the injection technique used for each axilla.

Inclusion criteria comprised patients with clinical diagnosis of primary AH, of both genders, ≥18 years old, without any botulinum toxin treatment in the previous year, with baseline gravimetrically measured sweat production ≥50 mg/5 minutes in each axilla, bilateral positivity in the Minor's starch-iodine test, and an Hyperhidrosis Disease Severity Scale (HDSS) grade ≥2 (4-point scale; HDSS grade 2= sweating is tolerable but sometimes interferes with my daily activities; grade 3= sweating is barely tolerable and frequently interferes with daily activities; grade 4= sweating is intolerable and always interferes with daily activities). HDSS evaluation was performed using a version translated to Portuguese and validated in a Brazilian sample of patients.[14,15] Main exclusion criteria were prior surgical procedure or ongoing systemic treatment for AH, clinically significant abnormality in the local area (axilla), myasthenia gravis or Lambert-Eaton syndrome, and known hypersensitivity to any botulinum toxin product. Female patients who were pregnant or breastfeeding were also excluded. The study protocol was approved by the institutional Research Ethics Committee and registered at the Plataforma Brasil (CAAE number: 65536117.1.0000.5442); all patients provided written informed consent.

Each eligible patient received a single treatment with 50 U of IncoA (Xeomin®, Merz Pharma, Germany) per axilla, serving as his/her own control as both axillae were treated on the same day using a different injection technique (multiple-puncture or radial; Figure 1), as defined by randomization using sealed envelopes previously prepared by a statistician. Follow-up assessments were performed at 30, 120, 180, and 270 days after treatment. A safety visit was performed 48 hours after the treatment only to assess side effects such bruising. Participants were requested to not use antiperspirants for at least 24 hours before each visit.

FIGURE 1. Radial diffusion (A) and multiple punctures (B) techniques for injection.



IncobotulinumtoxinA Preparation and Techniques Used for Injection

Prior to injection, each 100 U vial of lyophilized incobotulinumtoxinA (Xeomin®, Merz Pharma) was reconstituted using a 22 G needle with 2 mL of sterile, preservative-free 0.9% saline solution, providing a final concentration of 50 U/mL. One axilla received 50 U as multiple intradermal punctures equally distributed in the hyperhidrosis area identified by the starch-iodine test and delimited with a marker pen. Injections (25/2 U each) were performed using 30 G sterile needles, distributed 1.5 cm apart, within the affected area. The remaining 50 U of the vial were further diluted by adding 4 mL of sterile 0.9% saline solution, and the 50 U/5 mL final solution was injected subcutaneously in the contralateral axilla, using 22 G sterile needles, in a radial approach in two entry points 5 cm apart. Before treatment, both sides were cleaned with an antimicrobial solution. No anesthetics were used at the site of injection.

Efficacy and Safety Assessments

For each injection technique, treatment duration (time between the first injection and the end of the procedure); pain intensity, as reported by the patient according to the visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain); and adverse events were assessed. Efficacy and safety of the procedures were evaluated at 30, 120, 180, and 270 days after treatment. Follow-up assessments included clinical examination, adverse events, gravimetry and iodine-starch tests. For the gravimetry, a filter paper (Melitta) was weighed on a high precision laboratory scale before and after being placed in the armpits for 5 minutes, and the rate of sweat production was calculated in mg per 5 minutes.[16] The Minor's starch-iodine test was used both to identify the hyperhidrotic area before treatment and to quantify the sweating area change during the study.[10,11,17] For this test, each axilla was dried with absorbent paper, then 3% iodine alcohol solution was applied using wet gauzes and then the starch was applied using a shaving brush. Following the test, a transparent millimetric grid was used to measure the affected area and the results were registered using photographs. Both tests were performed after the patient had rested for 15 minutes in a sitting position at room temperature of 22° C to 25° C.[16]

The treatment effect in sweating production was assessed by a blinded evaluator comparing pre-treatment and post-treatment gravimetric measurements and photographs. The two techniques for injection were compared in relation to the percentage of reduction in sweating production achieved at

each post-treatment time point as well as the number of patients who achieved a reduction of 0-25%, 25-49%, 50-74%, or 75-100% in relation to the baseline values. Likewise, the reduction or elimination of the sweating area identified by the Minor's starch-iodine test was quantified and the injection techniques were compared regarding the percentage of reduction achieved to assess treatment effect in the affected area extension. Responses were then classified as 'excellent', 'very good', 'good', 'poor', or 'no response' based on a percentage of reduction of the affected area compared to baseline of 90–100%, 75–89%, 51–74%, 25–50%, 0–24%, respectively. An adverse event was defined as any event registered after the patient had signed the informed consent form. The event intensity and its relation to the treatment were determined by the investigator.

Statistical Analysis

No formal sample-size calculation was performed; 50 patients were screened. The primary outcome of the study was the relative sweat reduction, computed as the percentage difference between baseline (pretreatment) and post-treatment sweat rates, as previously described.[9] The Shapiro Wilks-test was used to confirm whether the data and model residues were normally distributed. For continuous variables, data were summarized using ranges, means, standard deviations (SD), 95% confidence intervals (95% CI) for means, and medians. Comparisons between groups were conducted using paired t-tests or Wilcoxon signed-rank tests, as appropriate. For categorical data, percentages were calculated, and the chi-square test was applied for comparisons between groups. All statistical analyses were conducted by a contract research organization and performed using XLSTAT 2019 software. Two-sided *P* values <0.05 were considered significant.

RESULTS

Patient Characteristics at Study Entry

Of the 50 screened patients, 26 were excluded due to important bilateral asymmetry in sweat production/distribution between the two axillae, age under 18 years old or botulinum toxin application or anticholinergic medication use in the previous year. A total of 24 patients were included. Most patients were female (67%), and the mean age was 34.7 years, ranging from 20 to 50 years. Co-morbidities were reported by two patients, one case of epilepsy and one of rheumatoid arthritis. Regarding hyperhidrosis severity at study entry, seven patients (29%) had an HDSS grade of 3 while 17 (71%) graded 4, meaning all had severe disease. Gravimetrically measured sweat rates ranged from 50 to 1010 mg per 5 minutes (mean, 231.7 ± 236.4; median, 110 mg). The mean sweat rates at baseline were 253.3 ± 233.1 mg for the multiple puncture technique treated axilla and 245.7 ± 255.1 mg for the radial injection technique.

Procedure Duration and Pain Intensity

Table 1 displays procedure duration and pain intensity data.

TABLE 1.

Procedure Duration and Pain			
	Multiple punctures	Radial	*P*-value
Duration of application, in seconds	*N=24*	*N=24*	--
Range	70 to 239	31 to 155	--
Mean ± SD	131.5 ± 39.0	70.7 ± 26.4	<0.001*
Median	121	69	--
CI 95% of the Mean	[115.0; 147.9]	[59.5; 81.8]	--
Pain during the procedure (VAS)	*N=24*	*N=24*	--
Range	1 to 10	2 to 10	
Mean ± SD	4.4 ± 2.0	5.9 ± 2.1	0.001**
Median	5	6	
CI 95% of the mean	[3.6; 5.3]	[5.0; 6.8]	
Number (%) of patients who reported VAS score > 5	6 (25%)	13 (54.2)	

*Wilcoxon signed-rank test
**Student's t-test for paired samples
VAS, visual analogue scale

Time between initiation and the end of the multiple-puncture procedure ranged from 70 to 239 seconds, while the radial approach duration lasted a minimum of 31 and a maximum of 155 seconds. Mean duration times were 131.5 and 70.7 seconds, respectively, confirming that the radial technique reduces the procedure duration (*P*<0.001). Pain intensity was significantly higher for the radial technique when compared to the multiple-puncture method (*P*=0.001), as mean VAS scores were 5.9 ± 2.1 and 4.4 ± 2.0, respectively. Pain intensity ranged from 1 to 10 and 2 to 10, respectively. Figure 2 shows patient distribution according to VAS scores reported for each injection technique. Pain intensity higher than 5 (between 6 and 10) was reported by 25% and 54% of patients treated with multiple-puncture and radial injection techniques, respectively, again showing a higher

FIGURE 2. Distribution of patients according to pain intensity during the procedure, assessed using the VAS and according to the technique used for treatment application.

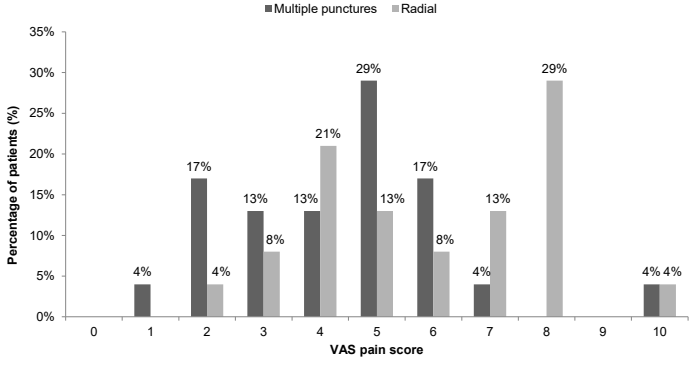


FIGURE 3. Distribution of patients according to the percent reduction in the gravimetric assessment, application technique (MP=Multiples punctures; RAD=Radial) and follow-up visit.

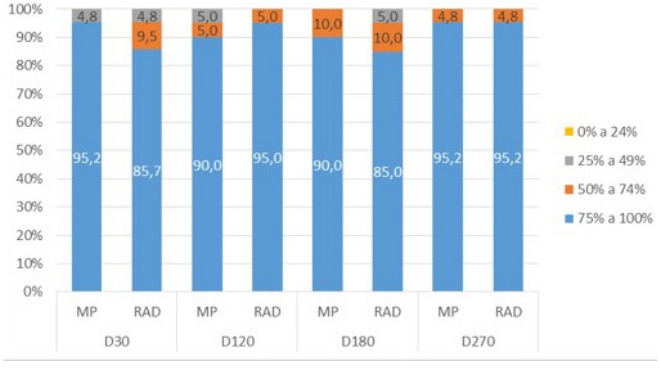
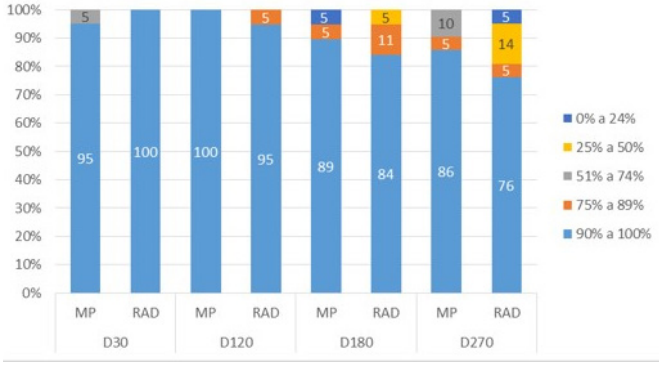


FIGURE 4. Distribution of patients according to the percent reduction in the starch-iodine assessment, application technique (MP=Multiples punctures; RAD=Radial) and follow-up visit.



pain level with the latter. For each technique, one different patient reported a pain score of 10.

Efficacy and Safety Analyses

Three patients were lost to follow-up after treatment and were excluded from the efficacy analyses. Injection of IncoA led to a drastic reduction of baseline sweat gravimetric values, with the vast majority of patients showing a reduction of 75% to 100%, as shown in Figure 3. This favorable effect was observed for both application techniques and was observed 30 days after treatment and sustained until the last follow-up visit (270 days). Comparison between the two techniques for each time point did not show statistically significant differences regarding the distribution of patients in the four categories of reduction (chi-square test; $P\text{-value}_{D30}$=0.349; $P\text{-value}_{D120}$=0.598; $P\text{-value}_{D180}$=0.598; $P\text{-value}_{D270}$=1.000). The percentage of reduction was also analyzed as a continuous variable, as shown in Table 2. For the side that received treatment through multiple punctures, the percent reduction ranged from 37.5% to 100%, with mean and median values of 93.1% and 98.4% at 30 days after treatment, respectively, and from 72.2% to 100%, with mean and median values of 93.3% and 97.1% after 270 days of treatment. Similarly, for the axillae that was treated through radial injection, the percent reduction ranged from 25% to 100%, with mean and median values of 89% and 96.7%, at 30 days after treatment, respectively, and from 64.3% to 100% with mean and median values of 91.7% and 91.8% after 270 days of treatment. Comparison between the two application techniques showed a significant difference at days 30 (P=0.039) and 180 (P=0.010), with a higher reduction obtained with multiple-punctures. No significant differences were observed for the other two time points.

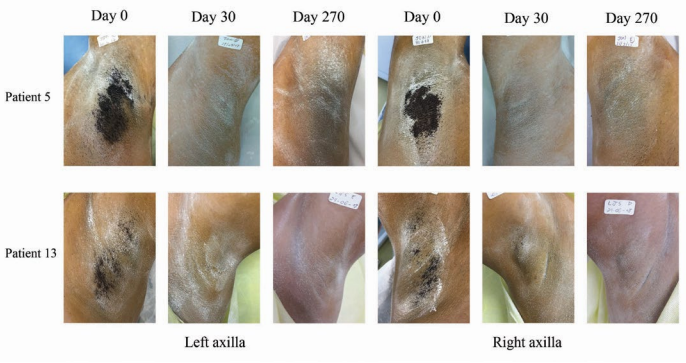
As shown in Figure 4, Minor's starch-iodine test showed an excellent response for the majority of patients, with a reduction between 90% to 100% of the initial area, regardless of the

TABLE 2.

Relative Reduction in Sweating Production Assessed by Gravimetric and Minor's Starch-Iodine Test								
	D30		D120		D180		D270	
	Multiple punctures	Radial	Multiple punctures	Radial	Multiple punctures	Radial	Multiple punctures	Radial
Reduction in the gravimetric test in relation to baseline, %	*N=21*	*N=21*	*N=20*	*N=20*	*N=20*	*N=20*	*N=21*	*N=21*
Range	37.5 to 100	25.0 to 100.0	44.4 to 100.0	63.6 to 100.0	54.1 to 100.0	37.5 to 100.0	72.2 to 100.0	64.3 to 100.0
Mean ± SD	93.1 ± 14.1	89.0 ± 17.7	90.4 ± 14.5	93.9 ± 10.0	91.7 ± 13.6	86.1 ± 18.8	93.3 ± 9.2	91.7 ± 9.6
Median	98.4	96.7	96.8	100.0	99.3	93.1	97.1	91.8
P-values*	**P=0.039**	--	**P=0.120**	--	**P=0.010**	--	**P=0.286**	--
Starch-iodine test	*N=24*	*N=24*	*N=24*	*N=24*	*N=24*	*N=24*	*N=24*	*N=24*
Range	72.1 to 100	94.4 to 100	100.0 to 100	79.7 to 100	-22.0 to 100	31.1 to 100	63.1 to 100	23.0 to 100
Mean ± SD	98.3 ± 6.3	99.5 ± 1.5	100.0 ± 0.0	98.9 ± 4.7	92.6 ± 28.0	94.3 ± 16.5	95.2 ± 10.6	87.7 ± 24.7
Median	100	100	100	100	100	100	100	100
P-values*	**P=0.789**	--	**P=1.000**	--	**P=1.000**	--	**P=0.036**	--

*P-values comparing the two techniques at each time point using the Wilcoxon signed-rank test

FIGURE 5. Minor's test in two different patients at baseline and after 30 and 270 days of treatment with botulinum toxin injected by multiple punctures (left axilla) and radial techniques (right axilla).



technique used. Frequency of excellent responses at 30 and 270 days of treatment were 95.2% and 85.7% for multiple punctures, and 100% and 76.2% for the radial approach. The percent reduction was also analyzed as a continuous variable (Table 2). For both techniques and at all time points, the median percent reduction was 100%. Comparison between the two techniques showed no significant difference at days 30 (P=0.789), 120 (P=1.000), and 180 (P=1.000); however, a significant difference was observed at the end of the study (270 days), with a higher reduction obtained with the multiple-puncture technique (P=0.036). Figure 5 depicts the positive results achieved with both techniques after 30 and 270 days of treatment with IncoA in two of the study patients.

Safety

During the 270 days of follow-up after injection, no adverse events were associated with treatment with IncoA. Adverse events were reported for five patients (three with radial and two with multiple-puncture techniques), all classified as ecchymosis of mild severity with no need of treatment, and not related or unlikely related to the study drug. These adverse events were temporary and considered to be mostly caused/related to the injection technique.

DISCUSSION

This study showed that injection of 50 U of IncoA effectively reduced sweat production in patients with AH at all time points and using both injection techniques. Relative reduction of the sweat production assessed by gravimetry showed mean and median percent reduction >90% for the axilla treated with multiple punctures and >85% for the axilla treated with the radial approach at all time points. These findings are consistent with previous studies showing that most patients obtain excellent results with more than 80% efficacy.[5,8-10] A randomized trial conducted in 320 patients, comparing the effects of injection of 50 U of another formulation of BoNT-A and placebo, found a percentage of responders, defined as patients with ≥50% reduction from baseline in sweat production, of 94% and 82% at 4 and 16 weeks after treatment with the toxin, respectively.[10] Adopting this definition of responders and a longer follow-up (270 days instead of 16 weeks), this trial demonstrated similarly favorable results, with 95% of responders 30 days after treatment using both injection techniques with responses lasting for at least 270 days in most cases. Minor's starch-iodine test also revealed that the percent reduction was excellent, defined as reduction of 90%-100%, in most cases treated regardless of the injection technique.

Comparisons between the two injection techniques showed that the radial technique reduced the procedure duration (median values of 69 vs 121 seconds for multiple punctures), but enhanced discomfort as pain was significantly higher (>50% of patients reported pain score of 6 or higher in VAS). Overall, no significant differences were observed between the two techniques regarding the efficacy outcomes in most time points analyzed. However, the multiple punctures technique conferred some advantages in the long run. One possible explanation could be that with this technique the product is injected closer to the glands and more evenly distributed.

Adverse events and complications associated with botulinum toxin therapy are rare and temporary, commonly resolving without sequelae[8] similar to what occurred in this trial: few patients reported mild ecchymosis with both techniques.

Previous studies have shown that the onset of action of BoNT-A occurs rapidly, within 2 to 4 days, and the therapeutic effect is long-lasting, being sustained for approximately 6 to 9 months.[10,11] No differences in onset of action, duration, efficacy or side effects were found in a study comparing injection of 50 U of Inco A and 50 U of onabotulinumtoxinA for AH.[12] A retrospective study of 83 patients treated with BoNT-A for AH found a statistically significant difference between the median duration of efficacy of the first and the last injection (5.5 vs 8.5 months; P=0.0002), indicating that duration of efficacy increases with the repetition.[18] In our study, a long duration of treatment effect was achieved with a single injection of IncoA, as 95% of patients continued to exhibit a 75–100% reduction in sweat production after 9 months, regardless of injection technique used.

In this randomized, evaluator-blinded study, female patients represented nearly two-thirds of the sample. A higher frequency of female patients is commonly reported in hyperhidrosis clinical trials probably because male patients are less likely to seek treatment, despite being equally affected by the disease.[5] Other limitations of our study include the relatively small number of patients of a single institution, and the lack of evaluation regarding patients' satisfaction with both procedures. On the other hand, the side-by-side design and the blinded evaluation for the efficacy assessments are important strengths.

In conclusion, regardless of the technique used for injection,

IncoA provided an effective, long-lasting and safe strategy for sweating reduction in patients with severe AH. Although the radial injection technique provided a reduction in procedure duration and similarly high rates of sweat reduction at most analyzed time points, patients reported a higher level of pain during this procedure in comparison with the classical multiple punctures technique.

DISCLOSURES

Ada Regina Trindade de Almeida is a speaker, consultant and researcher for Merz and Allergan. Drs Noriega, Bechelli, and Suárez have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Recommendations for Dermatology Office Reopening in the Era of COVID-19

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ABSTRACT

The COVID-19 pandemic, originating in Wuhan, China, has become a major public health and economic challenge for countries around the world. As of May 08, 2020, there are over 3 million COVID-19 cases, and 250,000 COVID-19- associated deaths in 215 countries. As more data is collected, updated infection control measures are continuously released and published by government, public health authorities, and physician specialty associations. Across the globe, dermatological practices have had to limit their operations to varying degrees to facilitate disease control, but as the pandemic subsides, they will broaden their operations. In light of the uncertainty surrounding safe and effective practice of medical and aesthetic dermatology in the era of COVID-19, fourteen international experts in the field contributed to recommendations for effective infection control protocols and practice management modifications. While guidance from the world health organization and local public health officials comes first, these recommendations are crafted as a starting point for dermatologists worldwide to commence either reopening their doors to patients or expanding available service offerings. This can help ensure that patients receive needed care in the short term and improve long term practice viability.

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INTRODUCTION

On March 11, 2020, the coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO).[1] The incubation period of the virus varies from a few days up to two weeks until presentation of reported symptoms that include fever, cough, nasal congestion, fatigue, breathing difficulty, sore throat, diarrhea, vomiting, and loss of taste or smell.[2] In severe cases, the disease can progress to Acute Respiratory Distress Syndrome (ARDS), septic shock, acidosis resulting in severe metabolic alterations, coagulation deficiency, and multiple organ failure can occur.[3] The pandemic has placed significant stress on healthcare providers and their patients, both due to critical resource shortages and delays in care. Because clear dermatological diagnoses can rarely be done from a distance larger than 20 cm, and close face-to-face contact is required for a plethora of dermatologic procedures, both medical and aesthetic, even routine dermatologic care poses a significant risk of viral transmission between patient and providers. In the early stages of the pandemic, response varied by country: from the American Academy of Dermatology recommendation to cease all but the most urgent dermatological care to preserve critical personal protective equipment (PPE) for hospital COVID units to the German Federal Ministry of Health requirement that dermatology practices remain open to keep dermatologic care out of emergency units. These variations were based in part upon population density, availability of PPE, and hospital capacity in different countries. Despite these differences, dermatologists

around the globe face similar challenges as they face the 'new normal' of evaluating and treating patients in the time of COVID. Indeed, as lockdowns are lifted, social distancing measures are relaxed, and patients' demand for both standard dermatologic care and aesthetic treatments returns, dermatologists worldwide recognize they will need to resume a new operational modus operandi, one in which preparedness and emergency policies are hardened against known and new biological risks. As practices open, fully new, as yet unknown, issues around liability and other legal and public health obligations may arise. While guidance is an evolving scenario that is updated by local ministries of health to reflect new information and considerations, there is a dire need for a roadmap dermatologists can follow as they resume operations, to safely and effectively treat their patients without compromising clinical outcomes, overutilize precious resources, or suffer additional financial losses. Medical associations around the world have provided "physician practice guides for reopening" on their websites. Multispecialty groups of physicians and surgeons have recently published some recommendations specific to aesthetic specialties and procedures.[4-6]

In recognition of this gap of knowledge for dermatologists and taking into consideration that COVID-19 government responses around the world have been nuanced, a group of international experts was assembled to formulate guidance and best-practices for resuming dermatology practices in a COVID-19 era. Participants included individuals from Europe, North America, Latin America, and Asia, with a balanced spectrum of professional seniority and expertise. Experts convened via videoconferencing on three separate occasions and collectively designed an outline describing new guidelines, policies, and protocols that may be utilized to resume practice with a completely revised operational standard. Each member contributed to the recommendations, which were backed up by the best available research evidence identified by PubMed searches with MeSH terms. The recommendations include considerations for new organizational policies and practical guidelines for dermatology practices as the corona pandemic continues. A personal perspective of each experts' experience from different countries of origin is also included. The recommendations are not to replace federal, state or local government laws, which have to be obeyed.

Pre-Opening Planning

Digital Footprint: Website, Social Media, etc.

All online avenues of the dermatology practice (website, newsblasts, social media) need to be harnessed and have their messaging adjusted in an informative yet positive manner. Communication should the unique ability of specialty dermatology practices to provide the safest environment for their dermatologic needs. It is important to prepare patients for each clinic's new standards of practice in response to the COVID-19 outbreak. Clear instructions should be sent prior to arrival and include the relevant details of the clinic practice preparedness plan including expectations for patient behavior – utilizing hand washing stations, required mask wearing, and others, and what to expect regarding practice flow through the office and physician and staff PPE. Understanding the clinic regulations and their own responsibility in this setting can both reduce patient anxiety upon entry and aid staff to maintain stringent infection control. All the new policy and protocols should be clearly displayed at office entry, throughout common areas, treatment rooms, and in bathroom. Clearly visible and easily understandable visual images are particularly helpful for these posted protocols.

Telemedicine

Consider integrating telemedicine in your practice. While this may not be an answer for every practice, it has proven to be successful in various settings.[7] "Telemedicine" is a term that covers any use of electronic communication technology to convey medical information. While previously promoted as an opportunity to expand healthcare access rural and underserved populations, telemedicine has been aggressively adopted as a safer means to provide medical care during the COVID-19 pandemic. In addition to minimizing office traffic and contact time and, thereby, reduce the potential risk of infectious disease transmission, telemedicine has been shown to achieve similar health outcomes compared with in-person patient visits in several studies and can have additional benefits including reducing travel costs and time away from work. The contact time in the office can then be limited to what is needed for examinations and procedures that may not be done virtually. In the USA, the government has temporarily waived compliance with strict patient privacy regulations to increase accessibility of telemedicine during the COVID-19 pandemic. Prior to using publicly available applications such as FaceTime, Skype, and Zoom, or specific electronic health portals, to provide telehealth remote communications with patients, physicians should check their country's applicable government regulations. The ability to collect payment from patients for these visits and the relevant coding and documentation needed must also be checked with national healthcare agencies.[8-10]

Necessary for successful telemedicine integration may include an electronic medical record system infrastructure, audiovisual platforms, necessary hardware, coding/billing integration, and information technology (IT) support. Training on both the side of the physician (providers, assistants, schedulers, and billers) and the patient (patient and/or caregiver) is also critical to allow adequate visibility during each virtual examination. In some cases, a small investment by the patient in a home device such as a simplified Bluetooth dermatoscope and home diagnostic lab kits may be required. The most easily integrated telemedicine visits are:

- E-visits, for digital evaluation and medication management. For these visit patients must be established, enrolled, and active in the patient portal and have had an appointment in the past one year.
- Evaluation of recorded video and/or images submitted by an established patient that includes interpretation with follow-up with the patient within 24 business hours. This visit is unrelated to services provided within the previous 7 days and does not lead to an e-visit or in person visit within the next week.
- Virtual consultations for new medical or cosmetic dermatology patients are also an option for some practices. Practices may wish to allow time for a second shorter in-office evaluation immediately before performing an aesthetic procedure on any patient seen only virtually.
- Patients should be advised that virtual visits do not replace the need for an in-office appointment at a time when safety standards allow.

In the experts' experience, onboarding patients and even physicians on telemedicine platforms has a steep learning curve, which can frustrate patients and support staff. However, minimal training is required to use it for straight forward medical follow ups and counseling. Before the visit, which lasts an average of 15 minutes, medical information and photographs are sent to the physician. After the interaction, the patient chart is completed as it would be during an in-person visit with history, evaluation, assessment, and plan. While telemedicine is currently built as a physician platform, it can also be used by nursing staff within the telemedicine model to mimic a standard in-person encounter. Aesthetic consultations may also be conducted virtually in this manner. Collectively, the experts feel that being an early adopter of telemedicine may have long-term benefits for patients who find it physically difficult to attend routine appointments due to health or distance, and for the practice's ability to increase the number of patients served. Effective implementation requires clinician and patient enthusiasm and organization but can be leveraged as an effective channel for patient care during this challenging time.

Forms and Questionnaires

Forms and questionnaires including preregistration data collection, health information, preoperative instructions, and informed consent, must be updated to include pertinent information relating to the SARS-CoV-2 virus. In order to avoid unnecessary patient anxiety, these forms should be kept as simple, clear, and concise as possible. Important screening information such as a diagnosis of COVID-19, the presence of COVID-19-like symptoms, recent travel, and the health of contacts is easily captured through simple verbal or written questionnaire and can be used to determine whether a patient can be seen in-office, must reschedule at a later date, or should be switched to a virtual visit (Table 1). These screening questions are generally based upon standard World Health Organization definitions and should be updated with additional signs and symptoms as new knowledge arises.

TABLE 1.

Example Preregistration Form		
	Yes	No
In the past 14 days have you or a household member traveled in areas with known cases of COVID-19. If so which location		
In the past 14 days have you or a household member had contact with a known COVID-19 patient?		
Have you had a history fever in the past 14 days?		
Have you had any cold or flu-like symptoms in the last 14 days or any of the following: loss of taste or smell, cough, sore throat, respiratory illness, difficulty breathing		

TABLE 2.

Scoring System Patient Risk Level for Contraction of Severe COVID-19 Disease	
Extreme Risk	Above 70 years old + 3 risk factors
High Risk	Above 70 50-69 years old + 2 risk factors 0-49 years old + 4 risk factors
Risk Factors	
Smoking	
Diabetes	
Cardiovascular condition	
BMI above 30	
Hospital admission in past 3 years	

Per one expert, the Israel health ministry released a "patient risk score scale" to be used prior to scheduling healthcare visits to determine the patient's risk of morbidity or mortality with a COVID-19 infection. However, such a measure has not been adopted internationally, and some of the experts feel this is an issue that should be determined by the individual patient and his or her general medicine physician, not dermatologist (Table 2). Certainly, any patient known to be COVID-10 positive or recently exposed to a COVID-19 positive patient, should be rescheduled. However, even asymptomatic and 'risk-free' patients should be approached as though they could be COVID-19 positive, just as with other universal precautions.

Physical/Equipment Considerations

SARS-CoV-2 is transmitted through microdroplets and aerosol: its diffusion occurs through coughing, sneezing, and saliva, and infection entry points are the mouth, nose, and eyes.[11] Because both asymptomatic patients in the incubation phase and healthy carriers can transmit the virus, even pre-screened

in-office patient contacts should be approached as potentially infectious.[12] The virus can remain viable and infectious in aerosols for hours and on surfaces up to several days (depending on the inoculum shed and surface material).[13] Exposure distance less than 6 feet, duration greater than 15 minutes, and/or contact with a contaminated surface or airborne particles presents high risk for infection. Given these facts, physical space needs to be redesigned to reduce the risk of contamination and contact for both staff and patients. Prior to the pandemic, the modern medical office had transformed from the traditional cold, clinical setting to a warm, welcoming environment where patients were encouraged to relax prior to the visit, with refreshments, samples, and reading materials at their disposal. In the COVID-19 era however, the physical space must be stripped from anything redundant and separated into clearly demarcated areas:

- Barriers, such as glass or acrylic 'sneeze shields' may be placed to protect reception staff from incoming and outgoing patients.
- Hand sanitizers should be prominently placed for patient use on office entry and throughout the office including utilized areas of the waiting room, lavatories, and treatment rooms. Hands-free units (electronic or foot pedal) are ideal to avoid cross contamination.
- Remove magazines, pens, blankets, pillows, toys, promotional or any reading materials, and skincare samples, and block off refreshment areas and coat closets to discourage contamination by patient contact.
- Patient waiting areas should be closed, or, if in use, provide seating separated by standards of physical distancing.
- All workstations must be rearranged to provide safe physical distance between staff members.
- Adding an air circulation and filtering system such as one including HEPA filters and UVC irradiation in current HVAC systems or adding portable devices may be useful in some environments.
- Decontamination and disinfection supplies should be accessible in every room to facilitate sanitizing surfaces before and after each patient visit. Lipid solvents such as ether, 75% ethanol, and disinfectants containing chlorine (hypochlorous acid), peracetic acid, and chloroform are recommended to inactivate and destroy pathogens from any surface. A list of disinfectants approved against SARS-CoV-2 can be found online in each countries environmental protection agency website.[14]
- Treatment room contents must be minimized. Remove brochures, extra pillows, blankets, and other non-essential items that cannot be stored within a closed cabinet or drawer. These materials may be brought into the room on an as needed basis for individual patients. If office space is limited, disposable covers are an option to protect equipment not in use.
- Invest in smoke evacuator units for procedures that produce a plume such as electrocauterization, laser (including ablative and non-ablative resurfacing, laser hair removal, tattoo removal). The smoke capture device should be held less than 1 inch away from the treatment site to achieve efficient evacuation.
- Provide no-touch waste containers with disposable liners in all reception, waiting, patient care, and restroom areas. All waste receptacles should be clearly labeled as biohazard or regular per government regulations.

PPE Staff/Physician Considerations

The type of PPE (masks, gloves, goggles, shoe covers, face shields, jackets, or other body coverings) required for each staff member will depend on the anticipated risk of exposure while performing their job responsibilities. In the USA, every office must have written Occupational Safety and Health Administration (OSHA) regulations and document employee training. Employees may use a higher level of protection but cannot use less than the minimum required to prevent occupational exposure to transmissible pathogens.[15] In the USA, the American Society of Testing and Materials (ASTM) rating system is a useful guide to face mask selection and use.[16] Government health agencies should be used as a guide in other areas.

- Surgical masks (SMs) can filter particles of 0.04–1.3 μm and are commonly used to physically block particles such as droplets. Their principal limitation is due to poor quality of face fit and the consequent possibility of aerosol aspiration. However, these can be worn by support staff or in all eventualities where there is contact between the patient and other people less than 2 meters away and for more than 15 minutes. These may also be worn by patients to avoid their contaminating environment. The level mask used and whether a 'home made' cloth mask is sufficient must be determined based upon the employees' responsibilities
- Filtering-face piece respirators (FFP) such as N95 (USA), KN95 (ASIA), and SPP3 (EUROPE) have filtration efficiencies ranging from 80%–99% and are the most appropriate barriers against aerosol because they provide a tight seal to the facial skin. Staff working in close proximity to or over long duration at the patient's side need to wear an FFP mask as a minimum. If patient is not wearing a mask because of the treatment performed, the additional use of single use gowns or washable upper body coverage, gloves, and full coverage goggles or a plastic full-face shield is recommended.

Disinfection routines must be rigorously followed including handwashing and changing of contaminated PPE and thorough cleansing of equipment as well as all high-touch areas (bed, chair, tables, door handles, light switches, etc) before and after direct contact with a patient, before any aseptic procedure, after potential exposure to body fluids, and after direct contact to potentially contaminated items or surfaces. In addition to PPE, it is recommended that surgical scrubs or other dedicated office uniforms be worn by all providers and staff in close proximity to

patients, to avoid the risk of clothing as a transmission vector.

Office Operations and Management

Under normal circumstances, maintaining a smooth-running dermatology practice is not an easy task. There are constant challenges for which professionals need to be prepared to provide quality care for their patients. With the COVID-19 pandemic, even long-standing, successful policies may need to be altered or completely rewritten from patient scheduling, to visit-day details, and all associated alterations needed to staffing and supplies.

Personnel

- In order to maintain social distancing, it is recommended that only essential staff be onsite. In some offices, receptionists and billing staff may be able to work remotely if compliant with country and local privacy regulations.
- Staff must be educated on policies and practices to recognize symptoms and minimize chance of exposure to respiratory pathogens including SARS-CoV-2 and how and to whom to report concerns.
- Policies that promptly alert key staff about known suspected COVID-19 patients need to be implemented. Follow up of positive or suspected cases of COVID-19 must be done per department of health directives.
- Institute a plan of action in case of office staff illness, absences, and/or quarantine. All such plans should be in compliance with government department of health regulation and local labor laws.
- Where possible, it may be useful to cross-train staff for all essential office and medical functions.
- In multi-provider offices, staff may be divided into teams working in different areas and/or at staggered schedules. In that way, only the team exposed to a COVID-19 patient will require quarantine, not the full office staff.
- Monitor staff compliance with standard precautions and provide mechanisms for improvement as needed.

PPE Supply and Cleaning Procedures

- Review proper office and medical cleaning routines. Patient rooms must be sanitized before and after each patient visit. Always allow fresh air in between one patient and another.
- Identify PPE supplies required for care to be delivered during an outbreak or pandemic, and suitable suppliers.[17]
- Anticipate delays in shipping and delivery and stock up on commonly used products in advance.
- Service all equipment and keep their service inspections up to date.
- Professional office cleaning services used daily or more frequently must be evaluated for their use of appropriate cleansers and PPE while in the office

Scheduling and Triage of Patients

- Depending on the size of the clinic, limit the number of patients seen per day in order to maintain safe distancing in all public spaces.
- Consider scheduling high risk patients (elderly) at specific times of day to avoid their contact with other patients.
- Add an extra 15–30 minutes between patient appointments to allow treatment rooms and equipment to be sanitized and patients to enter and exit separately.
- Practices may need to extend daily office hours and the days of the week offered to allow more patients.
- In order to minimize multiple points of exposure, if possible, patients should be taken upon arrival to a single treatment room in which preparation (including topical anesthesia if needed), treatment, and post treatment acts are performed. This coordination must be determined prior to the patient arrival and may affect the number of treatments that can be performed during one visit.
- A final confirmation of the patient appointment that includes triage regarding potential COVID-19 related symptoms should be done 24–48 hours prior.
- Schedule telemedicine visits if patient does not require procedure.

Pre-Consulting

The experts discussed how a day-to-day life will look like in this new COVID-19 era. This will vary depending on the size of the practice, the number of office locations, the office space, and the type of patients providers see. The end goal however is to keep in-office appointments as short as possible and minimize the patients contact touchpoints in the clinic.

- All providers, staff, and patients are screened for COVID-19 symptoms at the entrance of practices and given a temperature check with a "no-touch" thermometer.
- System is in place either for communication between office staff and patients to time patient entrance into the clinic. In either case, the patient will wait either in their car or curbside until they have been told to enter.
- Unless necessary for medical reasons (disability, health impairment, a minor), each patient must enter the clinic unaccompanied by friends, family members, or children.
- Patients will be instructed to sanitize hands prior to or upon entering the office and those without a mask will have one left for them outside the door along with shoe covers.
- All incoming patients are directed to an additional hand sanitizer or to the bathroom to wash their hands prior to their visit.
- One nurse/medical assistant is assigned per patient.
- Patients must wear a mask throughout their time in the clinic except when the face is specifically evaluated or treated. A clean mask is applied immediately after.
- Depending upon the office layout, payment and follow up scheduling may be done online, in the treatment room, or with contactless payment at reception desk.
- Patient room is sanitized/cleaned before and after each visit:

- o All disposable sheets are removed, and surfaces are disinfected (treatment bed, as well as everything touched by the patient: eg, hand mirror, chair, desk, pen used for signature of the consent form).
- o Disposable bed sheets/pillowcase are changed and underlying examination table and manual controls sanitized.
- o Doorknobs, light switches, tray tables, mayo stands, patient chairs, and all other potential surface areas of contact are sanitized (these areas are sanitized/disinfected – they are not sterilized).
- o Surfaces of equipment such as energy-based device surfaces are disinfected.
- o All contaminated PPE must be properly removed, cleaned, or disposed of properly with office biohazardous waste and labelled accordingly.
- o Rigorous hand hygiene must be performed after glove removal.
- o The dermatologic surgery theater is disinfected and air is allowed to circulate.
- o Staff change uniforms each day (or protective cover/gown).

Dermatologic Treatments and Risk Tiering

As practices resume operations, the question arises whether dermatologists will be able to provide their full offering of medical and aesthetic care safely and effectively. These offerings must now be perceived through a new lens: the risk of COVID-19. High risk procedures are any aerosol-generating procedures (AGPs), such as those that involve breach of mucosa, and laser-generated plume.[18] Until new safety protocols have become smooth, practices may wish to defer procedures that involve the oropharyngeal and nasopharyngeal area, since this is the main route of COVID19 transmission from patient to provider.[19] For procedures involving the nasal and/or oral cavity, pre-procedural irrigation with an oral disinfectant solution (1.5% hydrogen peroxide, 0.2% povidone iodine or hypochlorous acid) is advised.[20] All providers and staff present during those procedures should be wearing the highest level of PPE described above. In high risk or longer procedures, it might be wise to ask patients to get tested for COVID-19. Some institutions are requiring patients have two negative COVID-19 tests within 24 hours immediately prior to such procedures.

Conclusion and Dermatologic Insights from Around the World

As the pandemic subsides, dermatologists like the rest of society face resumption of previously usual routines now in the most unusual of circumstances. Since the situation will continue to be fluid with ongoing publication of new regulations and guidance from professional societies, federal, state, and local authorities, it is crucial that dermatologists remain alert in order to protect their patients, staff and practice. We must not become over-confident: only time will tell if these safeguards are sufficient. However, experts feel optimistic that overcoming the current challenges will provide the safe and efficient environment our patients expect for dermatologic care. Preparation now will also serve us and our communities if we are every faced with similar circumstances in the future.

United States, Beverly Hills, CA – Ava Shamban

Patients are screened by telephone for prior exposure and any risk factors. A telemedicine appointment is conducted to ascertain exact nature of visit and consents are sent electronically.

Patient arrives and notifies front desk by text or phone call. When patient arrives at the door thermal thermometer is used, hands sanitized, mask is given if not already on. Patients are escorted immediately to their room. Visit is conducted with both patient and provider wearing masks except when perioral area is treated. Checkout, payment, product sales, and future appointment are made in the exam room. Patient departs. Staff is properly screened as described in other protocols. PPE includes cloth hair bonnet, safety googles, N95, scrubs, and disposable shoe coverings. Clothing is removed at the end of the workday and taken home to be laundered. Disposable bed and pillow covers are in place. Medical grade air purifiers are in rooms with appropriate filter and air recirculation frequency. Building to provide superior air filters in building air conditioner. At the end of the visit, Lysol wipes or equivalent are used. Hypochlorous mouth wash is used before perioral injectables. Smoke evacuation to be used with every ablative or fractionated ablative procedure.

United States, New York, NY – Neil Sadick

Sadick Dermatology has two ground-floor clinics and research centers in Manhattan. Since NYC is the US epicenter of the COVID-19 outbreak in the US, many guidelines and restrictions have been put into place by our state officials. Our focus is to support NYC healthcare and our patients that do not have COVID-19 but still need dermatologic care. For example, complicated cases of psoriasis, infections, and skin cancers with health risks still need in person visits, so we operate with a skeleton staff to serve them. We take safety seriously and follow the OSHA standards to sanitize and clean our offices during the day and between patients. Our staff are up-to-date with the latest guidelines published by the local public health authorities. On a day-to-day basis, patients are swiftly taken to the treatment rooms and they spend minimal, if any, time in the waiting room. We limit the number of patients in the practice, and direct patients to the bathroom to wash hands prior to their visit. Masks are required at all times in the office. We've ensured a supply of PPE for our vendors, so we can keep our doors open to our patients that need care. For all other patients, we offer telemedicine consultations, which has been a great success as our patients can make appointments, and get advice and prescriptions filled without coming into the office. Our research group also continues to be busy; we abide to the FDA COVID-19 guidance document for the conduct of clinical trials and keep moving forward by having close communication with our study monitors and sponsors.

We are providing our enrolled subjects the option of conducting virtual or phone visits if subjects are unable to come on-site visits. This is a challenging time, but I am confident we will emerge with bulletproof protocols against any future adversity and equipped to as never before.

United States, Nanuet, NY – Heidi A. Waldorf
New York State, and in particular the southern part of the state, which includes my office, is the epicenter of COVID-19 cases in the USA. The state closed non-essential workplaces including medical offices in mid-March. Opening of strictly aesthetic practices like mine is expected in June. My office does not use electronic medical records or telemedicine. Currently, staff are working from home except when absolutely necessary to enter the office. Anyone entering office throughout the closure wears a mask. Staff will be brought back into the office, most likely on staggered schedules, the two weeks prior to the start of patient hours. The week prior to reopening, all staff will be present for OSHA training including training in the use of PPE for their contact-risk level and review of new Standard Operating Procedure guidelines and job definitions and new workstation assignments to provide physical distancing. The office will be 'decluttered' of all nonessential items that could risk contamination. Patients will be sent instructions, updated forms, and a link to a video explaining what to expect during their visit. Prescreening for COVID-19 risks will be done prior to arrival and repeated prior to entry. Front staff and patient will communicate by text or call to coordinate their entry into the office, hand sanitizing, and receiving a mask if they do not have one, and then have temperature taken, and be brought directly into the exam room by a nurse. In the room, the patient mask will be removed for face photos and then replaced so that the initial discussion may be done utilizing photos. Face masks will be removed for facial treatment and a new mask placed. In addition to PPE and room/equipment sanitizing, all procedures that may produce a smoke plume will be performed using a filtered smoke evacuator and in the presence of an air circulation, filtration, and UVC device. Check out will be done at reception, with only one patient present at any given time to ensure that recommended follow-up appointments are made prior to leaving.

Kuwait, Salmiya – Sahar Ghannam
All clinics have been under mandatory closure since the middle of March and are hoping to reopen by the beginning of June. When opening, we plan to instruct patients to come on time, prepare paperwork before entering the office, and use the stairs instead of the elevator. Temperature checks will be done upon arrival. We will consolidate treatments and checkout to be complete in one room. We will require patients and staff to wear masks. Teledermatology is not common in our area and we don't utilize such platforms.

Brazil, Porto Alegre – Doris Hexsel
In Porto Alegre, the social distancing recommendations started by the end of March, but by then, 50% of the physicians reopened their clinics adopting many measures in order to prevent COVID infections and avoid potential contaminated patients. By the end of April, some industries and other businesses were allowed to return to work. Some of the measures in our clinic, which has been open since April 15, include:

Staff measures: frequent handwashing, no jewelry, protective clothing, surgical masks and shield masks, scheduling of patients to avoid more than 2 patients in the waiting room and to keep distance between them; one exclusive room for risk patients (older people, under cancer treatment, etc). Avoidance of patients coming from other countries and states of Brazil, or those presenting with symptoms or living with patients who had COVID in the last 15 days.

Patient measures: we only admit patients using masks. We give them special disposable clothing, cover shoes and caps, as well as a clean plastic bag to bring handbags and clothing from outside. Alcohol-gel and hand moisturizing is available all rooms.

Brazil, São Paulo – Suleima Arruda
São Paulo is the most affected area in Brazil with the highest number of COVID-19 cases in the country. Partial lockdown started on March 16 and we are still respecting it till the present moment. If a medical consultation can´t be rescheduled for a later date, it must happen following the local safety guidelines. It's important to note that telemedicine till now was not allowed in Brazil. It just started now with all the Covid19 adaptations, and it seems it will be here for good. Dermatologists in Brazil should continue to abide with the Brazilian local regulations.

Germany, Darmstadt – Sonja Sattler
Germany had a little different approach how to deal with COVID-19: Depending on the state we were living in, and the hot spot centers of the COVID19 infections, we had a full or partial lockdown of the cities and area. In our state, Hessen, which always showed moderate numbers, we were asked to stay home, but were allowed to move more or less free outside. We never closed fully our clinic or our little satellite offices and have been available for emergencies (which were few) all the time. We saw between 4–8 patients per day. We separated all staff into 2 groups, which are now working 1 week and stay home 1 week, so if any infection of COVID-19 appears, only half of the staff must go into quarantine and be tested. Doctors and all staff in my clinic take all precautions: with PPE and disinfection, single use gowns (we now added multi-use cotton gowns, which will be washed every day, and can be sterilized if needed), etc, and consider that no matter what the patient tells us, each patient can be COVID-19 positive. So, we do not score our patients. We do not do temperature checks, since it does not give us more information. We do trust our patients, but even when they declare they feel well, we consult them as if they are COVID-19 positive. Patients and staff are always wearing masks. Staff working

close or longer at the patients' side need to wear an FFP2 mask, especially when the patient cannot wear a mask because of the treatment performed. In addition, the staff wears single-use gowns plus gloves in my clinic, and also plastic full-face shields, if possible. On May 4th, 2020 we were able to start working again for medical indications as well as cosmetic treatments and surgeries in Hessen, Germany. My staff is well educated and highly motivated. With all the precautions in place, we started quite good, trying to keep up with the patient flow and all rules. Limiting the number of patients per day becomes essential and is the most difficult task at this point. Each of our doctors sees 1 patient in 45 minutes–1 hour for a consultation including, eg, cosmetic filler treatment, which is 20-30 minutes longer than scheduled before COVID-19. Every patient only goes into 1 consultation room, everything is performed in this one room consultation – photography, treatment, and payment.

Philippines, Manila – Cristina Puyat
We have been on total lockdown since March 15 until the present time. Our lockdown might be lifted May 15. In our country, there are 2 kinds of quarantine namely Enhanced Community Quarantine (ECQ), which is where we fall now. Stringent measures are observed, public transportation system is suspended, and only essential businesses are allowed to operate. While the ECQ is in effect, telemedicine and teledermatology has been implemented. Consent form is sent to the patient electronically prior online consultation in accordance with the 2012 data privacy act of the Philippines. We assure that everything we discuss, and all pictures sent, are kept confidential. Wearing of mask in public is required. General Community Quarantine (GCQ) might be implemented May 15. This is the only time that our private clinics will be able to operate putting all the safety guidelines into place. The new protocols for re-opening clinics post-COVID-19 quarantine will be discussed with the patient who will be going to the clinic physically as these protocols will be strictly implemented. Public transportation in reduced capacity will be allowed, as well as reopening of selected establishments, subject to health standards enforced by the local government.

Malaysia, Kuala Lumpur – Tingsong Lim
Malaysia started implementing Movement Control Order (MCO) March 18 when localized clusters began to emerge. All businesses were closed except for essential services. The restriction was then eased since early May, allowing certain degree of business as usual. However, aesthetic practice was not one of them. Currently, for those who started off seeing medical patients, teams are divided into 2, with shifts and rotation to avoid possible chances of infections among the work force. We also implemented screening of patients before they come for appointments. One patient, one room, one time, is being implemented as well, with minimal human to human contact. We encouraged our staff to get tested before starting work and also to retest if any possibility of getting infected. Vigilant screening is done, and the workplace is being disinfected very frequently.

Israel, Tel Aviv – Ofir Artzi
We were closed for 5 weeks. Before resuming activity, we undertook many measures and changes in all office spaces to allow physical distancing and to minimize possible virus transmission. A reminder call and a screening to identify potential infection is performed prior to patient arrival. In this call, we exclude any symptoms, exposures, or recent travel. The patient should fill and sign a disclosure form. High-risk patients and procedures are delayed at the moment. In this call, all protective measures taken are conveyed to the patient. We elaborate on the new protocol and the expected behavior – we remind the need to arrive on time and alone. We leave the accompanying person in the car outside unless special circumstances. No one enters the office spontaneously without an appointment. We measure temperature in the entrance and provide gloves and mask upon entry. We limit greetings to a smile, wave, and other non-contact gestures. The patients are taken upon arrival to a single treatment room. All supplies and relevant energy-based devices are prepared before patient entry. If possible, only one provider will be with the patient. We allow no more than one medical assistant in the room. Doors are closed – no going out and in when the patient is in. All pretreatment, treatment, and post treatment actions including payment are performed in this room. Payment (if not done) and scheduling of follow-up visit are made later by telephone. Between patients, we disinfect beds, chairs, surfaces, instruments, tables, doors handle, etc. Up to two weeks post procedure, we follow our patients (videoconference or telephone) both to monitor progress and to verify that no COVID-19 symptoms developed. Before treatment, the patient signs an appendix to the consent form. Whenever possible for all non-treatment interaction, telemedicine is used. We schedule 10–15 minutes per patient for first consultation. All existing data, medical records, pictures taken by the patient, are sent prior to this virtual meeting. A temporary summary of the conversation is documented. It is emphasized to the patient and in writing that the recommendations are based on a virtual appointment and thus are can be amended (including the cost) when meeting the patient in person. We reduced the number of patients by 20% but did not experience decrease in income because consultations are made in different time frame to save time.

South Korea, Seoul – Hosung Choi
South Korea had already experienced MERS five years ago, in 2015. During that crisis, we learned how to do epidemiological investigations of an epidemic, how to treat it, and how to prevent it. After MERS outbreak, South Korean CDC realized that persistent patient tracking and the transparency to the public are very important for a high level of quarantine. These preparations appear to have paid off and we were somewhat prepared for the new virus. The preventative measures being taken in South Korea have so far involved no lockdowns, no roadblocks, and no restriction on movement, only social distancing was recommended by the government. Therefore, I've never closed my clinic and only reduced my working hours for two months vol-

untarily. I think that early patient detection with accurate tests followed by isolation can lower the mortality and prevent the virus from spreading.

Appointments with allotted timeslot to allow disinfection of consult and treatment rooms in between. We are disinfecting regularly the entire clinic using proper disinfectants three times a day. All doctors and staff wear masks all the time when facing patients. (when consulting patients who are suspected of being infected with the COVID-19, N95 mask must be worn, otherwise wearing a dental mask is enough). We are measuring body temperature of every single patient who visits the clinic in order to protect not only patients, but also medical staff. We are actively informing our patients of our efforts to prevent the infection through text messaging or online media. There are thermal imaging cameras in the entrances to most major buildings in South Korea. Bottles of hand sanitizers have been placed in every lift.

Italy, Modena – Elena Rossi

In Italy, the lockdown started on March 8. Working both in the national health system and in private practice, I faced two very different scenarios. In our private practice, I continued to do urgent procedures in the first 2 weeks of March (ie, post-surgical follow-up, urgent consultations, no cosmetic). Then we closed until May 4. I managed contact with my patients mainly via WhatsApp, telephone, and emails. It was very important to try to keep a virtual relationship with more sensitive patients, not only to care for them medically but to reassure them about the general situation and help them not feel abandoned (mainly the eldest). Whatsapp was also a very nice tool also to follow up with some COVID-19-positive patients who showed signs of cutaneous rash. Now we resumed operations and we conduct non-urgent procedures (cosmetic included), but we increase time between patients and keep up with all the precautions (PPE, social distancing, disinfection).

Within the national healthcare system, we could continue to perform urgent consultations and surgical operations. Since the number of surgical sessions was reduced both for inpatient and outpatient, surgery was highly selective for melanoma, high risk squamous cell carcinoma, and rapidly growing nodular lesions. The situation in the OR has been changing day by day regarding the different protocols and safety measures. At first, there was a lack in PPE. Then depending on the anatomical areas and type of anesthesia (ie, general anesthesia procedures have high risk for contamination) we adopt different safety protocols and PPE: for inpatient going under general anesthesia the protocol the patient is tested in preadmission with blood test, chest-x-ray, and nasal swab before surgery. For outpatients, when the tumor is located on the face and the patient cannot keep the mask during surgery, the surgeon is recommended to keep both the N95 mask and the surgical mask on top of it. I also had the chance to work once a week supporting the coronavirus unit on the territory of my city.

DISCLOSURES

The authors have no conflicts of interest.

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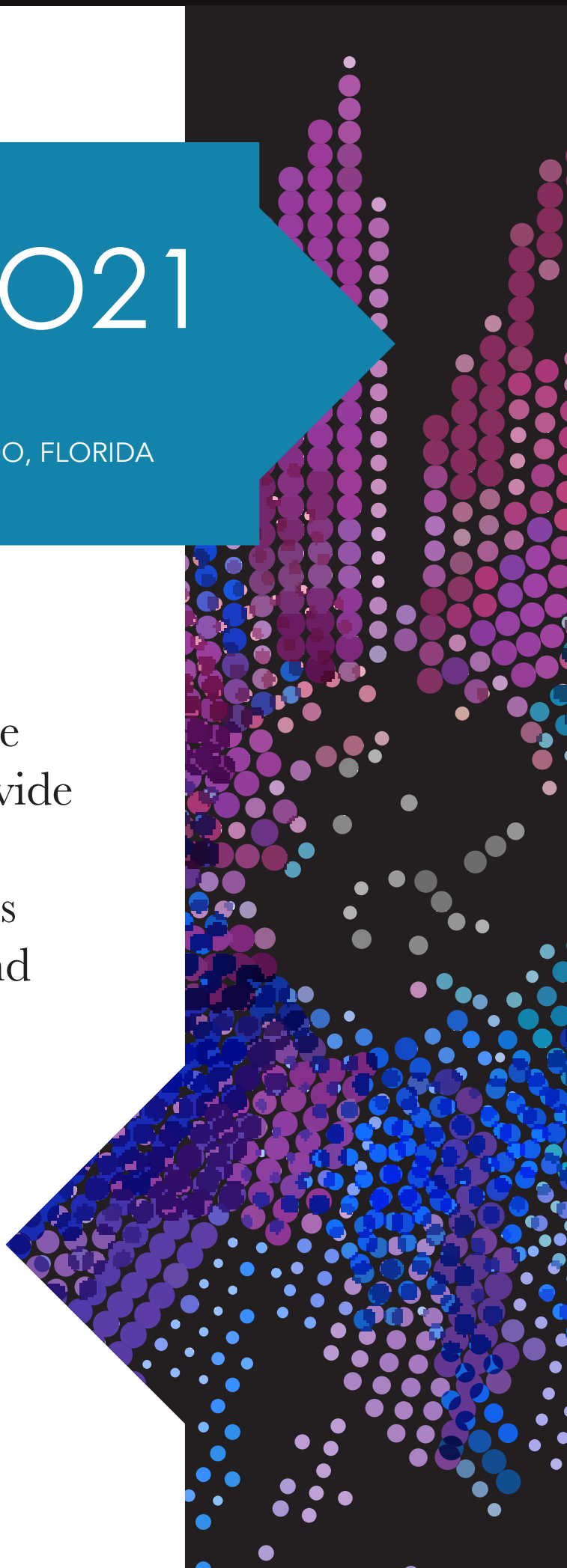

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Use of Beauty Products Among African American Women: Potential Health Disparities and Clinical Implications

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ABSTRACT

Skin and hair care products may be a potential source of toxic chemical exposure that disproportionately affects skin of color patients. African American women may have increased exposure to endocrine-disrupting chemicals, as they are more likely to use personal care products such as chemical straighteners and relaxers. While studies on the association between beauty product use and certain diseases have shown variable findings, recent research has highlighted the potential increased risk of breast cancer among women who use certain hair products. The potential toxicity of beauty product-related chemicals has led women's health providers to issue a call to action to identify and reduce patient exposure to these agents. We call for further research to better characterize the potential systemic effects of beauty products, especially those targeted toward skin of color individuals.

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INTRODUCTION

Skin and hair care products may be a potential source of toxic chemical exposure that disproportionately affects skin of color patients.[1] Recently, much debate has focused on the "clean beauty" movement, which promotes the use of so-called natural or organic ingredients, and avoidance of suspected or proven toxic compounds.[2] Concurrently, there has been a shift towards embracing more natural hair styles in the African American (AA) community. Sales of hair relaxers marketed to black women decreased by 40% between 2008 and 2015.[3] Conversely, the sales of shampoo, conditioner, and styling products marketed for natural hair are increasing. Between 2013 and 2015 alone, sales of natural hair styling products increased by 27%, now compromising 35% of the AA hair care market.[3] Although this is believed to be a positive shift in the AA beauty market, this brief communication highlights that there is a paucity of research on potential toxicities of beauty products, and how increased exposure among AA may contribute to health-related disparities.

African Americans comprise 13% of the U.S. population yet they yield significant spending power, accounting for 22% of the $42 billion personal care products market annually.[1] AA women aged 18–34 are considered "heavy buyers," purchasing more than ten types of beauty products per year.[1] Research has demonstrated that AA women have higher levels of parabens and phthalates, common preservatives found in beauty products, in their bodies compared to Caucasian women.[3] Additionally, AA children have been found to have five times the urinary paraben level compared to their Caucasian counterparts.[3] The use of endocrine-disrupting chemical containing beauty products such as chemical relaxers in AA girls begins as early as age 4-8, and has been proposed as a risk factor for premature sexual development.[1] Despite these correlations, definitive conclusions cannot be made about the systemic absorption and effects of topical beauty product use.

Increased chemical exposure from ethnic skin and hair care products may be driven partially by targeted marketing, which has created vulnerable consumerism among the historically underserved AA population.[1] Targeted marketing exploits European beauty norms to influence AA consumers.[1] This type of targeted racial marketing is reminiscent of the marketing of methanol cigarettes that occurred in low-income inner city AA neighborhoods, which created a racialized geography of tobacco-related health disparities.[1] The influence of marketing on the sales of hair straighteners and skin lighteners has been evaluated.[1] In a study that analyzed the marketing of skin lighteners in Harlem, researchers concluded that advertisers associated lighter skin tone with greater educational attainment and employment earnings.[1] This societal pressure also exists in the workplace, as AA women are twice as likely as Caucasian women to experience work-related pressure to straighten their

hair.[1] Historically, the U.S. army banned several hairstyles used by AA women such as twists and braids, in favor of styles that encouraged straightening.[1]

The influence of societal discrimination on beauty product use in the AA population may contribute to health disparities.[1] AA women, who are more likely to use chemical straighteners and relaxers, may be exposed to endocrine-disrupting chemicals in hair products.[1,3] Data has demonstrated in vitro estrogenic and anti-estrogenic activity of these products, but further studies are warranted to investigate in vivo activity.[3] Previous studies on the association between hair product use and breast cancer have shown inconsistent results; however, a large national prospective cohort study recently yielded significant results.[1,3,4] The study enrolled 50,888 participants with no history of breast cancer but had a sister with breast cancer.[4] The association between hair dye and chemical relaxer/straightener use and breast cancer risk was examined by ethnicity.[4] Permanent hair dye use was associated with a 45% higher breast cancer risk in black women and a 7% higher risk in white women.[4] Hair straightener use was associated with breast cancer, with higher risk associated with increased frequency.[4] Frequency varied by ethnicity with 74.1% of black women reporting any use, compared to only 3.0% of non-Hispanic white women.[4] These findings contrast with the null association observed in the Black Women's Health Study in the 1990s.[5] However, this discrepancy may reflect changes in targeted marketing and chemical composition in beauty products.[5] The potential toxicity of beauty product-related chemicals has led women's health providers to issue a call to action to identify and reduce patient exposure to these agents.[1]

Despite the popularity and widespread use of hair care and beauty products, inaccurate and inconsistent labeling of ingredients is common due to laxity of regulations.[3] Federal cosmetic regulations have not been updated since 1938, when the Federal Food, Drug, and Cosmetic Act was passed.[6] Since then, beauty products have been under the regulation of the U.S. Food and Drug Administration (FDA), but do not necessarily require FDA approval to be on the market.[3] However, the market is still rapidly evolving. There have been multiple attempts to modernize regulations to keep up with this beauty evolution, but none have proven successful.[6] For example, the Occupational Safety and Health Administration issued a hazard alert on formaldehyde containing hair products, but the hazard alert is not a regulation nor does it create new legal obligations.[7] Dermatologists can be advocates for patients by pushing for adequate safety laws for beauty products.

We recommend that dermatologists remain mindful of potential toxicities of beauty product use. This awareness is especially important with vulnerable populations, such as AA women who may be at a higher risk of endocrine-disrupting chemical exposure from the use of ethnic skin and hair care products. Dermatologists may practice culturally competent care by incorporating the discussion of beauty products into their clinical practice and inquire about current skin and hair care regimens. Dermatologists may counsel patients on potential safety concerns. Further research is warranted to understand and better characterize the systemic effects of beauty products, especially those targeted toward AA. Dermatologists and industry should work together to ensure safer beauty products are developed for skin of color. By understanding the effects of topical beauty products, dermatologists may aid in closing the gap in health disparities between racial and ethnic groups.[1,7]

DISCLOSURES

The authors declare that they have no relevant conflicts of interest to disclose.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The Obesity Epidemic and the Rise of Acanthosis Nigricans – A Case for Lifestyle Medicine

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INTRODUCTION

The prevalence of obesity in the United States, defined as a body mass index BMI>30, has steadily increased over the last three decades. Approximately 43 million people are considered obese with the prevalence being higher in non-Hispanic Blacks and Hispanic adults.[2-4] Obesity is a multifactorial disease leading to multiple adverse health outcomes affecting several organ systems. As the number of obese individuals increases, so does the prevalence of acanthosis nigricans (AN), with approximately 74% of obese individuals having this condition, making it one of the most common skin findings seen in these patients.[5,6] AN most commonly presents as velvety, hyperpigmented plaques on the neck, groin, and axillae, and less commonly can involve the face. Native Americans and African Americans are the most commonly affected with AN, followed by Hispanics, Asians, and less often, Caucasians.[3]

Obesity in Skin of Color

Studies have found racial and ethnic health disparities related to obesity. Specifically, darker skin types have been shown to be positively associated with higher risks of obesity, hypertension, and diabetes, especially among Blacks and Hispanics.[2] It is estimated that African American women have the highest rates of obesity compared to other ethnic groups in the United States, and that 4 of 5 African American women are overweight or obese.[7] Racial and ethnic differences in lifestyle and socioeconomic status, along with environmental factors, all play a significant role in the disproportionate prevalence of obesity in the skin of color population.

Childhood Obesity and Acanthosis Nigricans

The onset of AN has been observed in younger populations due to the paralleled increase in obesity prevalence.[3,8-10] Published data from 2017 suggests that the prevalence of childhood obesity in the United States was as high as 18.5%, affecting 13.7 million children and adolescents.[7] From 1980 to 2010, obesity has increased from 7% to 18% in children 6–11 years old. When looking specifically at racially and ethnically diverse populations, the incidence of AN alone rises to 28%.[3] AN is significantly associated with insulin resistance in children, and is oftentimes present before the diagnosis of diabetes mellitus.[3] Therefore, diagnosis and appropriate diabetes screening is critical in this population. Brickman et al assessed children in community pediatric offices to determine the prevalence of comorbidities in patients presenting with AN.[11] This study found that 25% of overweight children had AN and 29% of those with acanthosis nigricans had abnormal glucose homeostasis.[11] Another study examined the association of AN and metabolic syndrome and concluded that early intervention in children with AN can be beneficial in decreasing future health complications.[12] AN in childhood is associated with an increased risk of obesity, hypertension, hyperinsulinemia, insulin resistance, and type II diabetes.[9]

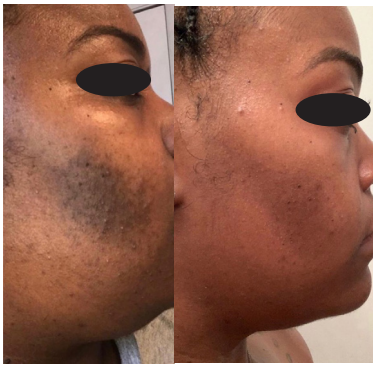
Impact of Lifestyle Changes on Acanthosis Nigricans

The role of lifestyle changes has been underutilized for the treatment of AN in dermatology. Successful treatment of AN must target the etiology of the disease, and since most cases are associated with obesity, weight loss often leads to resolution. Diet, exercise, and counseling are the key pillars of obesity management.[8] Emotional, physical, and economic stress are contributing factors to obesity, oftentimes making it challenging to address in a typical office visit. At the same time, not addressing this causative factor in AN is a disservice to our patients. Dermatologists have the opportunity to encourage patients to sustain healthy lifestyle changes for the treatment of their skin conditions.

AN presents an ideal example of how lifestyle changes can treat one of the most commonly seen skin conditions. Anecdotally, in practice, we see noticeable improvement in AN in gastric bypass patients. In one study of 37 obese patients undergoing gastric bypass surgery, 23 patients also had AN. In this study, all 23 patients had noticeable improvement in AN at a 3-month follow up, likely due to improved insulin resistance and fat loss.[13]

We present a case of a 33-year-old African American woman who presented with a chief complaint of dark discoloration on her face. Physical exam revealed dark brown symmetric velvety thin plaques on the bilateral cheeks consistent with AN. The patient was advised to use topical cosmeceuticals and the importance of weight loss was discussed with an emphasis on healthy lifestyle changes. The topical regimen included cosmeceuticals with kojic acid, arbutin, licorice, and retinol. At

FIGURE 1. Patient before, and at 5-month follow-up.



5-month follow up, the patient reported a 30-pound weight loss and almost complete resolution of the hyperpigmented plaques and an overall improvement in her skin tone and texture.

CONCLUSION

Acanthosis nigricans, a skin condition more common in skin of color, is an ideal example of how lifestyle interventions can dramatically improve obesity related dermatologic diseases. As dermatologists, we need to acknowledge and embrace lifestyle interventions for the prevention and treatment of certain skin conditions. Although challenging, weight-loss needs to be addressed in obesity-related skin diseases including AN, intertrigo, hidradenitis suppurativa, and psoriasis, in addition to topical therapies. Additionally, this case highlights the importance of considering the diagnosis of AN for facial hyperpigmentation as it is often misdiagnosed and treated as melasma or another pigmentary disorder. Dermatologists need to recognize this common condition in obese patients and emphasize the importance of weight loss and healthy lifestyle changes as treatment options.

DISCLOSURES

The authors report no conflicts of interest.

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CASE REPORT

Journal of Drugs in Dermatology

Dupilumab Improves Atopic Dermatitis and Post-Inflammatory Hyperpigmentation in Patient With Skin of Color

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ABSTRACT

Atopic dermatitis, a chronic inflammatory condition, accounts for numerous dermatology visits for patients with skin of color. The inflammatory process often leads to post-inflammatory hyperpigmentation, especially in patients with skin of color, which may negatively impact quality of life. We present a case that demonstrates clinical improvement of atopic dermatitis, post inflammatory hyperpigmentation, and lightening of pigmentation in clinically non-lesional areas after initiation of dupilumab. Lightening of the patient's skin even in areas that previously appeared clinically normal supports the scientific evidence that non-lesional skin in those with atopic dermatitis is often subclinically involved. For skin of color patients, aggressive treatment with duplimab may accelerate the return of the patient's overall normal skin tone.

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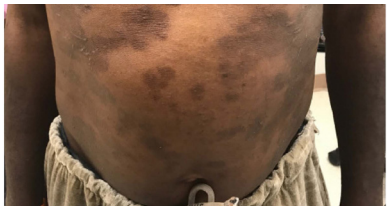
INTRODUCTION

Atopic dermatitis is a chronic inflammatory skin condition that affects up to one fifth of the population in developed countries.[1] It is characterized by relapsing pruritic patches and plaques with exudation, crusting, scaling, fissures, and lichenification in later stages.[2] Atopic dermatitis lesions may be intensely itchy and elicit discomfort. African Americans are disproportionately affected by atopic dermatitis compared to their Caucasian counterparts, 19.3% and 16.1%, respectively.[3] Additionally, atopic dermatitis may be more severe in patients with skin of color and for non-Hispanic black and Hispanic children, is more likely to persist into adulthood.[4] Atopic dermatitis in skin of color patients may be particularly distressing due to post-inflammatory hyperpigmentation, which often leads to psychosocial effects and negative impacts on quality of life and productivity.[5] In vivo, atopic dermatitis is active in both lesional and non-lesional skin.[6] We highlight a case in which treating atopic dermatitis aggressively in a patient of African descent not only leads to clinically improved areas of atopic dermatitis and post-inflammatory hyperpigmentation, but also improves hyperpigmentation in non-lesional skin.

CASE PRESENTATION

A 53-year-old male of African-descent presented with a 1-year history of worsening pruritic rash. He was applying petroleum jelly without relief. Past medical history was significant for deafness and iron deficiency. On physical exam, there were multiple hyperpigmented plaques, hyperpigmented lichenified plaques, and hyperpigmented patches on the trunk, extremities, buttocks, neck, and face. The patient was diagnosed with moderate-severe atopic dermatitis. Triamcinolone ointment 0.1%, tacrolimus 1% and cetirizine 20 mg po daily were prescribed. Gentle skin care and soak and smear technique were reviewed. Two months later, the patient received 600 mg loading dose of dupilumab. Two weeks later, the patient's atopic dermatitis and pruritus were improved (Figure 1). The patient continued 200 mg subcutaneous every 2 weeks resulting in continued improvement of atopic dermatitis, post-inflammatory hyperpigmentation, and apparent hyperpigmentation in non-lesional areas (Figures 2 and 3). Gentle skin care routine emphasized with intermittent use of topical triamcinolone 0.1% ointment or tacrolimus 1% ointment as needed for pruritus. After completion of the fifth

FIGURE 1. Improvement of atopic dermatitis two weeks following initiation of dupilumab.



FIGURES 2 AND 3. Continued improvement of atopic dermatitis, post-inflammatory hyperpigmentation and apparent hyperpigmentation in non-lesional areas.

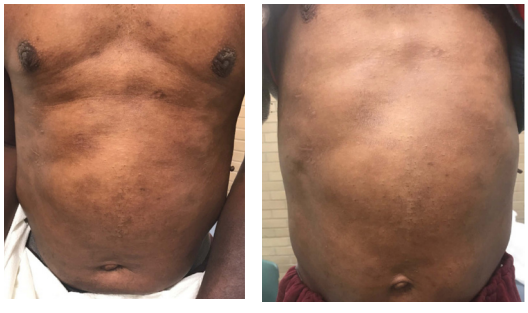
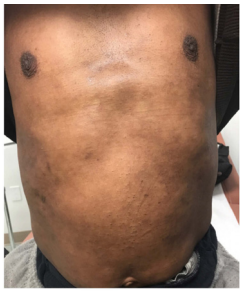


FIGURE 4. Resolution of atopic dermatitis flare and improved post-inflammatory hyperpigmentation.



month, his next 200 mg injection was performed at the 3-week mark instead of the 2-week mark. His atopic dermatitis flared during this time with pruritus. Dupilumab frequency was re-instated at every 2 weeks. The atopic dermatitis flare resolved, and post-inflammatory hyperpigmentation improved (Figure 4).

DISCUSSION

Atopic dermatitis and post-inflammatory hyperpigmentation are among the top five most common chief complaints seen by dermatologists in skin of color patients. A study conducted on patients that presented to the Skin of Color Center at St. Luke's-Roosevelt Hospital Center in New York, NY found dyschromias, including post-inflammatory hyperpigmentation, to be the second most common diagnosis in African-American patients, while it was not even among the top ten diagnoses in Caucasian patients.[7] Atopic dermatitis often leads to post-inflammatory pigment alteration, most commonly post-inflammatory hyperpigmentation, in those with skin of color.[8] Chronic inflammation results in increased melanocyte density, hyperplasia, and hypertrophy.[9] This strongly suggests increased function of melanocytes and explains why inflammatory conditions such as atopic dermatitis cause hyperpigmentation. Post-inflammatory hyperpigmentation tends to be more persistent and clinically visible in patients with darker skin tones.[10]

Dupilumab is a monoclonal antibody that blocks the IL-4 alpha receptor and therefore inhibits IL-4 and IL-13 signaling, preventing the release of type 2 cytokines that promote inflammation in atopic dermatitis.[11] A randomized control trial of 54 patients treated with dupilumab resulted in reduced cellular infiltrates and significant clinical improvement.[11] After 16 weeks of treatment, researchers observed reversal of lesional atopic dermatitis phenotype.[11]

In this case, the post-inflammatory hyperpigmentation was quite severe. After initiation of dupilumab, clinical improvement of the post-inflammatory hyperpigmentation, and lightening of overall skin tone was noted. Suarez et al. compared chronic atopic dermatitis lesional skin, non-lesional skin, and normal skin biopsies and found that non-lesional skin has cutaneous T-cell expansion.[6] Non-lesional and lesional skin differ from normal skin in regards to keratinocyte terminal differentiation and inflammatory pathways.[6]The abnormalities seen in lesional atopic dermatitis skin are also seen in non-lesional skin, which suggests that the total body surface area of skin in patients with atopic dermatitis is abnormal, even if it appears normal clinically.[6] This is especially important in skin of color patients who are more prone to residual effects of atopic dermatitis such as post-inflammatory hyperpigmentation.

Systemically treating moderate-severe atopic dermatitis with dupilumab in skin of color patients with significant, distressing hyperpigmentation should be considered. Reducing hyperpigmentation in non-clinically apparent areas of atopic dermatitis and evident post-inflammatory hyperpigmentation areas may contribute positively to quality of life. For skin of color patients, aggressive treatment with duplimab may accelerate the return of the patient's overall normal skin tone.

Post-inflammatory hyperpigmentation often comes with psychosocial impairments. A study assessing quality of life found that patients with atopic dermatitis reported significantly more mood and sleep disorders compared to controls.[5] These patients had significantly reduced health related quality of life on physical and mental domains.[5] In a study of 419 patients, those with post-inflammatory hyperpigmentation had higher scores on the Dermatology Life Quality Index (DLQI) survey, which indicates poorer quality of life, when compared to patients with other disorders of hyperpigmentation.[12] Additionally, the study demonstrated that DLQI scores were higher in women and those younger than 35 years of age. Having a graduate level education was associated with significantly lower DLQI scores, showing that patients with lower education level had a more negative impact on quality of life.[12] Atopic dermatitis is a systemic disease. Dupilumab's impact on post-inflammatory hyperpigmentation and apparent hyperpigmentation in non-lesional skin emphasizes the scientific data of atopic dermatitis activity in lesional and non-lesional skin. When considering whether to treat atopic dermatitis aggressively, it is essential to consider the overall

impact of the disease including the psychosocial burden, subsequent post-inflammatory hyperpigmentation and in some cases overall skin hyperpigmentation. Patients with atopic dermatitis experience higher rates of anxiety, depression, sleep disorders, and decreased work productivity.[5] Additionally, the resulting post-inflammatory hyperpigmentation can negatively impact quality of life. The burden of atopic dermatitis in patients with skin of color goes way beyond pruritus. In our case, aggressive treatment with dupilumab resulted in improvement of the apparent hyperpigmentation in clinically non-lesional skin (but likely scientifically lesional skin), post-inflammatory hyperpigmentation and atopic dermatitis.

DISCLOSURES

There are no potential perceived conflicts of interest and/or support, financial interests, or patents for Ciara Grayson.

Dr. Heath is a consultant for Sanofi-Regeneron and Pfizer.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Pityriasis Rosea-Like Rash as a Cutaneous Marker for COVID-19 Infection

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INTRODUCTION

Severe acute respiratory syndrome corona virus2 (SARS-CoV-2) is the most recently identified member of the zoonotic pathogens of corona viruses. It started by causing an outbreak of pneumonia in December 2019 in Wuhan, China.[1] Among all related acute respiratory syndromes (SARS-CoV, MERS CoV), SARS-CoV-2 remains to be the most infectious with the highest potential for human transmission and can eventually end up in acute respiratory distress syndrome (ARDS).[2,3]

Only 15% of COVID-19 cases progress to pneumonia and about 5% develop ARDS, septic shock, and/or multiple organ failure. The majority of cases only exhibit mild to moderate symptoms.[4,5] A wide array of skin manifestations in COVID-19 infection were reported including maculopapular eruptions, morbilliform rashes, urticaria, chickenpox like lesions, livedo reticularis, covid toe, erythema multiforme, and pityriasis rosea, and several other patterns.[6]

Different speculations regarding cutaneous manifestations in COVID-19 emerged to explain their pathogenesis. Symptoms mimicking viral exanthems were thought to be an immune mediated response to the viral nucleotides while other cutaneous eruptions such as vasculitis and thrombophlebitis were recognized as a secondary systemic consequence to COVID-19 infection.[7]

Pityriasis rosea (PR) is a relatively common, self-limited papulo-squamous dermatosis of unknown origin, which mainly appears in adolescents and young adults (10–35 years) and is slightly more common in females.[8] It has a sudden onset, and in its typical presentation, the eruption is preceded by a solitary patch termed "herald patch", mainly located on the trunk. A few days later, secondary eruption appears, with small pink, oval macules, with a grayish peripheral scaling collarette around them. The secondary lesions adopt a characteristic distribution along the cleavage lines of the trunk, with a configuration of a "Christmas tree".[9]

CASE

A 33-year-old female patient presented to the dermatology clinic with fever and a pruritic skin rash. The patient was fatigued and gave a history of cervical lymphadenopathy and shortness of breath. Upon skin examination, a rash consisting of oval-shaped salmon-colored patches and papules, up to 2cm in diameter, surrounded by light white scales located on her, chest, back thighs and upper limbs was noticed (Figures 1–2) She described that the lesions erupted 10 days before showing up to clinic. It started by an erythematous and scaly annular plaque that appeared on the left forearm and was accompanied by a low-grade fever and bouts of gastroenteritis that she was not concerned about. Several days later, the lesions continued to disseminate and became pruritic until she attended the clinic. Her oral and ocular mucosae were free of any presentations. The patient used a "mometasone furoate 0.1%" cream, which was prescribed to her by a local pharmacist with no response before attending clinic. No relevant medical history was given by the patient. Laboratory investigations showed lymphopenia. Chest x-ray and a positive nasopharyngeal smear test were consistent with COVID-19 infection. The patient confirmed that to her knowledge she had not been exposed to anyone who was diagnosed with COVID-19, however she works as a local seller in a traditional market with exposure to hundreds of people every day.

FIGURE 1. Disseminated popular eruptions with collarette of scales on the trunk.

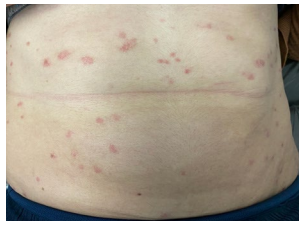
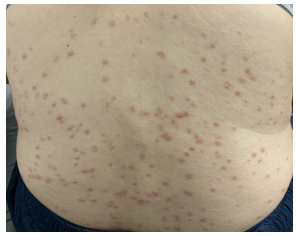


FIGURE 2. Multiple, erythemato-squamous, oval lesions with a peripheral collarette scale distributed along the back.



DISCUSSION

The exact cause of PR remains to be unknown. A number of studies significantly associated human herpesvirus 6 and 7 (HHV-6 and HHV-7) with PR. However, this remains to be controversial and a number of pathogens including bacteria, fungi, vaccines, and most notably, viruses, were speculated to play a causative role.[10] Ehsani et al reported a case of pityriasis rosea in a 27-year-old otherwise healthy male who was later diagnosed to have COVID-19.[11]

It was confirmed that COVID-19 infection is accompanied by a reduction in lymphocytes, monocytes, and eosinophils, along with a significant reduction of CD4/CD8 T cells, B cells, and natural killer (NK) cells. It was further revealed that non-survivor COVID-19 patients continued to show a decrease in lymphocyte count along the course of their disease until death.[12-15]

Diminished levels of natural killer (NK) cells and B-cells activity in the lesions of PR have been observed.[16]This suggests the role of a T-cell mediated immunity. Besides, increased amounts of CD4 T cells and Langerhans cells have been found in the dermis, which possibly points towards viral antigen processing and presentation. However, this matter is still debated since some individuals are infected with HHV 6–7 and do not develop the disease.[17]

New information and cutaneous manifestations possibly related to COVID-19 are emerging every day. Further studies are needed to evaluate whether these lesions are associated with the virus or not. Careful documentation and robust reporting of cutaneous manifestations associated with COVID-19 are needed to augment our understanding of disease presentation and epidemiology.

DISCLOSURES

The authors have no relevant conflicts to report.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The Relevance of Vitamin D Supplementation for People of Color in the Era of COVID-19

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INTRODUCTION

African Americans (AA) and other people of color are dying at highly disproportionate rates from COVID-19. The statistics are staggering: in New York City alone, per 100,000 population, death rates in AA were 92.3, and in Hispanics 74.3, compared to 45.2 in Whites and 34.5 in Asians.[1] Similar numbers have been reported in other cities and are presumed underestimations, given limited racial/ethnic reporting. In the states currently releasing the number of COVID-19 deaths by race and ethnicity, Blacks make up roughly 13 percent of the population, but 27 percent of the deaths. According to the American Public Media Research Lab, the rate of COVID-19 deaths nationally for Blacks has been reported as twice the rate of deaths of Asians and Latinos in the US and more than 2.5 times the rate for White residents.

Socio-economic reasons, pre-existing comorbidities, work circumstances, inconsistent healthcare access, stress, and decreased immunity, amongst other factors, have been posited as reasons for this shocking disparity. People of color, in particular AA and Hispanics, are more likely to be uninsured and to be frontline workers during the COVID-19 pandemic. This is compounded by the fact that comorbidities such as hypertension, diabetes, asthma, obesity, and cardiovascular disease are more common in AA and are also associated with higher COVID-19 mortality rates. Emerging evidence suggests that Vitamin D deficiency may represent another risk factor for poor outcomes from COVID-19.

Relevance of Vitamin D

Vitamin D is a secosteroid hormone synthesized in the skin following exposure to UVB ultraviolet radiation where it mediates the conversion of 7-dehydrocholesterol to pre-Vitamin D3. Following transport to the liver, it is hydroxylated to 25(OH)D, the primary circulating form typically used to measure serum Vitamin D levels. 25(OH)D is subsequently converted to the biologically active form 1,25, dihydroxy vitamin D in the kidneys by 1-alpha hydrolase. This active form binds to its nuclear Vitamin D receptor to induce the transcription of over 200 genes, affecting a wide range of physiologic functions.

Multiple studies have documented significant Vitamin D deficiency in people of color, especially in AA. Heavily melanized skin retards the synthesis of Vitamin D and necessitates longer periods of sun exposure for adequate synthesis of Vitamin D. Ginde et al. assessed demographic differences and trends of Vitamin D insufficiency in a US population.[2] Serum 25(OH)D levels were compared over two time periods (1988–1994 and 2001–2004) from the Third National Health and Nutrition Examination Survey (NHANES III) data base including two large populations (n=18,883 and n=13,369, respectively). Non-Hispanic Blacks had a significantly higher prevalence of Vitamin D deficiency, increasing in severity in the later data base. Recent NHANES data from 2011–2014 further documented the high risk of deficiency in non-Hispanic Blacks. In a recent prospective cohort study of 14,319 subjects, an estimated 65.4% of non-Hispanic Blacks were deficient in Vitamin D, compared to 29% of Hispanics and 14% of non-Hispanic Whites.[3]

Vitamin D deficiency has been shown to be a risk factor for many of the comorbidities that disproportionately plague AA including diabetes, hypertension, cardiovascular disease, autoimmune diseases such as lupus erythematosus, as well as aggressive forms of breast and prostate cancer.[4] While the classic role of Vitamin D involves calcium and phosphorus homeostasis for healthy bone metabolism, it exerts a spectrum of pleotropic effects impacting cell growth, differentiation, inflammation, and immune regulation. Healthy levels of Vitamin D have been linked to significantly reduced mortality and improved health outcomes. Numerous investigations document the prolific role of Vitamin D in antimicrobial defense and modulation of the innate and adaptive immune responses. It mediates the induction of key antimicrobial peptides in the respiratory epithelium including cathelicidin (LL37) and beta defensins, which destroy invading organisms. In addition, Vitamin D inhibits the production of pro-inflammatory cytokines including IL-2, IFN-γ, TNF-α, and IL-6, while promoting Th2 responses by increasing IL-4, IL-5, and IL-10 production, hence skewing T cell responses to a down regulated, anti-inflammatory state.[4]

For the general population, the US Institutes of Medicine (IOM) recommends Vitamin D supplementation at doses that vary according to age and are based primarily on bone health. Current IOM supplementation recommendations are 400 IU (10ug) for infants, 600 IU/d (15ug) for children, adolescents, and adults,

TABLE 1.

Recommended Supplementation for Patients With Laboratory Confirmed Vitamin D Deficiency (25(OH)D Level <20 ng/mL)	
Age	**Recommended Dosing**
Neonates (<1 month of age)	1000 IU/d (25 µg/d)
Infants >1 month and toddlers	2000-3000 IU/d (50–75 µg/d)
Children and adolescents (1–18 years of age)	3000-5000 IU/d (75–125 µg/d)
Adults and elderly	7000-10,000 IU/d (175–250 µg/d) or 50,000 IU/week (1250 µg/week)

*Ranges are based on body weight.
Reference: P. Pludowski et al. *J Steroid Biochem.* 2018;175:125–135.

and 800 IU/d (20ug) for adults aged over 70 years to maintain a 25(OH)D concentration of 20ng/mL or higher. However, in individuals who are deficient in Vitamin D (25(OH)D level <20 ng/mL), of which patients with skin of color are at a higher risk, supplementation is considerably higher. These recommendations are summarized summarized in Table 1.[5]

Numerous studies have addressed the relationship between Vitamin D and respiratory tract infections. A recent meta-analysis incorporating data from 21,000 patients showed that subjects with Vitamin D levels less than 20 ng/mL had a 64% increased risk of community-acquired pneumonia.[6] An additional meta-analysis of data from 10,933 subjects from 25 randomized controlled trials documented an overall protective effect of Vitamin D supplementation against acute respiratory tract infection. Protective effects were observed in those receiving daily or weekly dosing of Vitamin D and were strongest in patients with baseline levels less than 25nmol/L than in those with baseline levels greater than 25nmol/L.[7]

Recent investigations suggest a potential relationship between Vitamin D levels and COVID-19 mortality rates. A retrospective multicenter study of 212 hospitalized patients with laboratory confirmed COVID-19 infection reported an increased odds of having a critical disease outcome when serum 25(OH)D decreased.[8] The serum 25(OH)D level was lowest in critical cases, but highest in mild cases. Laird et al conducted a literature search of Vitamin D status in European countries, which were selected based on the severity of COVID-19 infection. Low Vitamin D concentrations were associated with increased mortality. Countries with a formal Vitamin D fortification policy appeared to have the lowest rates of infection while countries with no policy and highest deficiency rates appeared to be more adversely affected.[9]

Daneshkhah et al analyzed data from hospitals and clinics in Europe, Asia, and the United States. They noted that patients from countries with high COVID mortality rates had lower vitamin D levels compared to countries that were not as severely affected. There was a strong correlation between Vitamin D deficiency and cytokine storm characterized by a hyperinflammatory, overactive immune response common in patients with COVID-19.[10]

CONCLUSIONS

Vitamin D deficiency has been well documented in people of color, in particular AA. The aforementioned data suggest a relationship between low Vitamin D status and COVID-19 mortality rates. While myriad socioeconomic and health care disparities may be contributing factors, we must indeed consider key biological variables, including Vitamin D status, that may impact these observations. Future prospective studies are necessary to confirm these findings. As there is currently no readily available treatment or vaccine for COVID-19, treating physicians should be cognizant of the higher prevalence of Vitamin D deficiency in skin of color populations and its emerging potential role in COVID-19 outcomes. Given the devastating statistics of COVID-19 among minority communities and the multifaceted role of Vitamin D in skin and systemic health, dermatologists are essential partners in decreasing health care disparities by initiating the vitamin D dialogue. As such, we can play an invaluable role in improving the health outcomes of our patients, particularly people of color, during and beyond the COVID-19 pandemic.

DISCLOSURES

The authors have no relevant conflicts to report.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Disparities in the Utilization of Dermatologists for Primary Cicatricial Alopecias

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INTRODUCTION

Early intervention in cicatricial alopecias is critical to prevent permanent damage to the hair follicles. Previous literature, however, has suggested that individuals who are black are less likely to visit dermatologists than individuals who are white.[1]

METHODS

In order to assess if there are disparities in the utilization of dermatologists for scarring alopecias, we performed a retrospective chart review of treatment naive individuals seeking care for the first time from a dermatologist, for the most common forms of primary cicatricial alopecias. We then quantified the degree of hair loss at presentation from clinical photographs using the Severity of Alopecia Tool (SALT) II score.[1] Statistical analyses were performed using the chi-squared and *t*-tests (Stata, version 14.2, StataCorp, College Station, TX). The George Washington University institutional review board approved this study.

RESULTS

In total, we identified 86 treatment naive individuals (98% women) with clinically diagnosed primary cicatricial alopecias. In this cohort, subjects who were identified as black by the investigators presented to dermatology on average 45.6 months after the self-reported onset of hair loss compared to 16.8 months after the self-reported onset of hair loss in subjects were identified as white (P=0.002). Additionally, black subjects presented to dermatology with more severe alopecia—having lost an average of 37.7% of their scalp hair compared to 20.3% lost at presentation in white patients (P<.001). In regard to retention in care, black subjects also followed up for shorter periods of time (mean, 8.2 months) compared to white subjects (mean, 15.7 months; P=0.016). These results are depicted in Table 1.

In our cohort, subjects who were black were more likely to have Medicaid insurance than subjects who were white. However, when Medicaid enrollees of all races were compared to individuals with private insurance of all races, no significant differences in the duration (P=0.24) or severity (P=0.17) of hair loss at presentation were observed, suggesting that the disparities observed here are not related insurance status.

DISCUSSION

In this cohort, black subjects with primary scarring alopecias presented to dermatologists later after the self-reported onset of hair loss, with more severe hair loss, and followed up for shorter periods of time, compared to white subjects. We could not, however, assess the impact of race-discordance on these results given the previous lack of diversity within our department, and dermatology in general—the second least diverse specialty

TABLE 1.

Disparities in Primary Cicatricial Alopecias

	Black	White	*P* value
Characteristic	Value, %(n)	Value, %(n)	--
Sex	--	--	0.034
Female	59(100)	25 (93)	--
Male	--	2 (7)	--
Age, years	--	--	0.834
Average (range)	51.7 (22-79)	52.4 (24-75)	--
Primary Cicatricial Alopecia	--	--	<.001
CCCA	54 (92)	--	--
LPP	5 (8)	18 (67)	--
FFA	--	8 (30)	--
GLS	--	1 (4)	--
Insurance	--	--	0.042
Private	36 (61)	23 (85)	--
Medicaid	15 (25)	1 (4)	--
Medicare	8 (14)	3 (11)	--
Burning or pruritus at presentation	36 (61)	13 (52)	0.263
Duration of alopecia at presentation, months	--	--	0.002
Average (range)	45.6 (1-240)	16.8 (1-60)	
Median	24	12	
Initial Severity of Alopecia Tool II Score, %	--	--	<.001
Average (range)	37.7 (4-94)	20.3 (6-38)	--
Median	34	18	
Final Severity of Alopecia Tool II Score, %	--	--	0.131
Average (range)	32.3 (5-72)	16.8 (12-21)	--
Median	25	17	
Length of follow up, months	--	--	0.016
Average (range)	8.2 (0-57)	15.7 (0-59)	--
Median	4	12	

Abbreviations: CCCA=central centrifugal cicatricial alopecia; LPP=lichen planopilaris; FFA=frontal fibrosing alopecia; GLS=Graham Little syndrome

in medicine.[2] Previous literature has demonstrated that 71% of black patients prefer to see a black (or race-concordant) dermatologist, and that black men are more likely to consent to influenza vaccinations and cardiovascular disease screenings from physicians who are black than from physicians who are white.[3,4] Our findings further emphasize the need for increasing racial diversity within the dermatology workforce and even more importantly, ensuring all trainees receive adequate training, both of which will potentially increase utilization of dermatologists for scarring alopecias. Additionally, educational campaigns highlighting the importance of early dermatologic interventions in cicatricial alopecias—targeting the affected patient populations and referring physicians—may prompt patients to obtain treatment earlier in the disease course.[5] It is also unclear if the perception of scalp and hair symptoms differs between racial or ethnic groups, or if the lack of familiarity with ethnic hair amongst dermatologists, are contributing to the study results.

This study is limited by several factors. Firstly, the lack of histopathologic confirmation of the cicatricial alopecia diagnoses, as we uncommonly perform scalp biopsies for these conditions because of the largely overlapping treatment modalities. Supporting the scarring nature of the alopecias, there were only minimal improvements in SALT II scores at study completion. A more important limitation is that this study was a retrospective chart review and unfortunately investigators were not able to ask patients to categorize themselves or identify their race. The designations used were the perceptions of the investigators and therefore are inherently biased. Race is truly subjective and it is no longer acceptable to place our implicit biases on others by categorizing them as how we perceive them. Future studies are necessary to assess if there are racial differences in the perception of hair loss and to better identify barriers to obtaining dermatology specialist care for cicatricial alopecias.

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LETTERS TO THE EDITOR

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Culturally Competent Care for LGBT Patients in Dermatology Clinics

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Lesbian, gay, bisexual, and transgender (LGBT) patients face unique health disparities.[1] Routine collection of sexual orientation and gender identity (SOGI) data can optimize patient-provider interactions.[2] Gender-neutral bathrooms promote inclusivity for LGBT patients.[3] There is limited data on the extent to which dermatology practices make use of such features to deliver culturally competent care to LGBT patients.

We developed an anonymous, online survey to investigate dermatology practice characteristics relevant to LGBT patients. IRB approval was obtained prior to distributing the survey via a listserv of board-certified dermatologists available on the American Academy of Dermatology's website. Bivariate associations were explored using Monte Carlo estimation for the Fisher's exact test and chi-square. Multivariable logistic regression was performed to evaluate the associations between provider demographic, practice variables, and likelihood of routine patient intake form use.

891 board-certified dermatologists received the survey link. 81 dermatologists completed the survey. Of providers surveyed, most were female (63%), heterosexual (80%), practiced in urban environments (53%), and in private practice settings (64%) (Table 1). Most practices reported seeing less than 5 transgender patients annually (54%), though 21% of practices reported seeing more than 10 transgender patients annually. 79% of practices surveyed reported making using of gender-neutral bathrooms. Of 71 respondents with knowledge of their intake forms, 15 (21%) reported routine collection of patient sexual orientation and 14 (20%) reported their forms asked about patients' preferred gender pronouns, in addition to gender identity. Intake form administration did not vary significantly by provider sexual orientation (P=0.43) or practice setting (P=0.10). Of 13 dermatologists not using intake forms, 7/13 (54%) cited administrative burden, 2/13 (15%) reported intake forms were not in the scope of their practice, and 1/13 (7%) cited a lack of data for patient benefit.

TABLE 1.

Survey Respondent Demographics and Practice Characteristics			
Variable		Count	Percentage
Gender	Male	30	37.5%
	Female	50	62.5%
Age	Mean ± SD (years)	45 ± 11	
Sexual Orientation	Bisexual	3	3.7%
	Lesbian or gay	13	16.1%
	Straight or heterosexual	65	80.2%
Practice Area	Rural	7	8.6%
	Suburban	31	38.2%
	Urban	43	53.1%
Practice Setting	Academic	23	28.4%
	Both	6	7.4%
	Private	52	64.2%

Based on our survey results, we hypothesize that the frequency of gender-neutral bathrooms in dermatology practices is increasing in comparison to past decades. However, our results suggest that routine SOGI data collection using intake forms is less common. In oncology, it has been shown that patients have favorable perceptions regarding gender, sex-at-birth, pronoun, and sexual orientation questions regardless of demographic characteristics.[4] Routine SOGI data collection is important to provide medically appropriate and culturally sensitive care, especially as the volume of transgender patients seen by dermatologists increases. Interestingly, our results suggest that neither provider demographic variables nor practice variables such as location or practice setting affect likelihood of routine SOGI data collection. Our study highlights the need for further research to investigate additional barriers to the implementation of routine SOGI data collection in dermatology clinics.

Limitations of our study include the small sample size, low response rate, and risk of response bias. Private practice dermatologists were also overrepresented in our sample. Nonetheless, we believe our data suggest the need for greater investigation of this issue and validation of our results with larger, more highly controlled studies.

DISCLOSURES

The authors have no conflicts of interest to declare.

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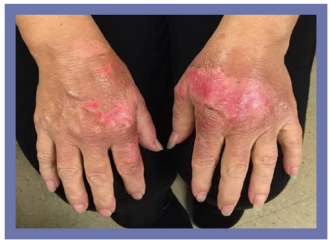

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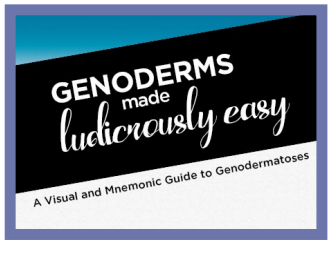

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Analysis of Geographical Density of Dermatologists Compared to Dermatology Physician Assistants

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In the past decade, the number of dermatologists in the United States (US) has increased, but distribution is skewed, with higher concentrations in academic centers and urban areas, resulting in a shortage in dermatological care.[1,2] Non-physician practitioners, including, physician assistants (PAs), may fill this need, however, they are also unevenly situated.[3] Therefore, our goals were to examine the distribution and ratio of dermatologists to dermatology PAs across the US.

Dermatologists, dermatology residents, and fellows' locations based on state licenses were acquired from Doctordatabases Media Company (October 19, 2019). Members of the Society of Dermatological Physician Assistants (SDPA) and their practice locations were obtained (November 19, 2019). The dermatologist to dermatology PA ratio was calculated based on zip codes.

The analysis included 15020 dermatologists and 2695 dermatology PAs in 566 zip codes. There was a 1.8% annual growth rate in SPDA memberships from 2016 to 2019. The growth rates for dermatologists and the US population in 2017 were 1.8% and 0.8%, respectively.[3] On average, there were 6 dermatologists per PA. In 12 (2.1%) zip codes, there were 0.5 dermatologists or fewer per PA, in 44 (7.8%), there were more than 0.5 and up to 1 dermatologist per PA (Table 1).

The ratio of dermatologists to dermatology PAs were unevenly distributed across the US (Figure 1). In general, more rural areas had lower dermatologist to dermatology PA ratios.[1,2] Areas with fewer dermatologists were most impacted by the increased dermatology PA presence. While PAs may expand dermatology scope of practice, they are not meant to be permanent solutions to the dermatology shortage. For example, PAs and dermatologists biopsied 39.4 and 25.0 pigmented lesions, respectively, to diagnose one melanoma case.[4] In addition, PAs are significantly less likely to diagnose melanoma in situ compared to dermatologists.[4] Therefore, areas with low dermatology/dermatology PA ratios will likely lead to higher rates of missed diagnoses. Dermatology PA training consists of 100 hours of online modules and on the job training by supervising physicians.[5] In 9.9% of zip codes, there was 1 or fewer dermatologist per PA, which translates to patients having an equal likelihood of being treated by a PA or dermatologist. Also, in those dermatologist sparse areas, PAs are most likely to be taught by only one dermatologist. In contrast, dermatology residents are instructed by a broad range of dermatologists with different subspecialties.

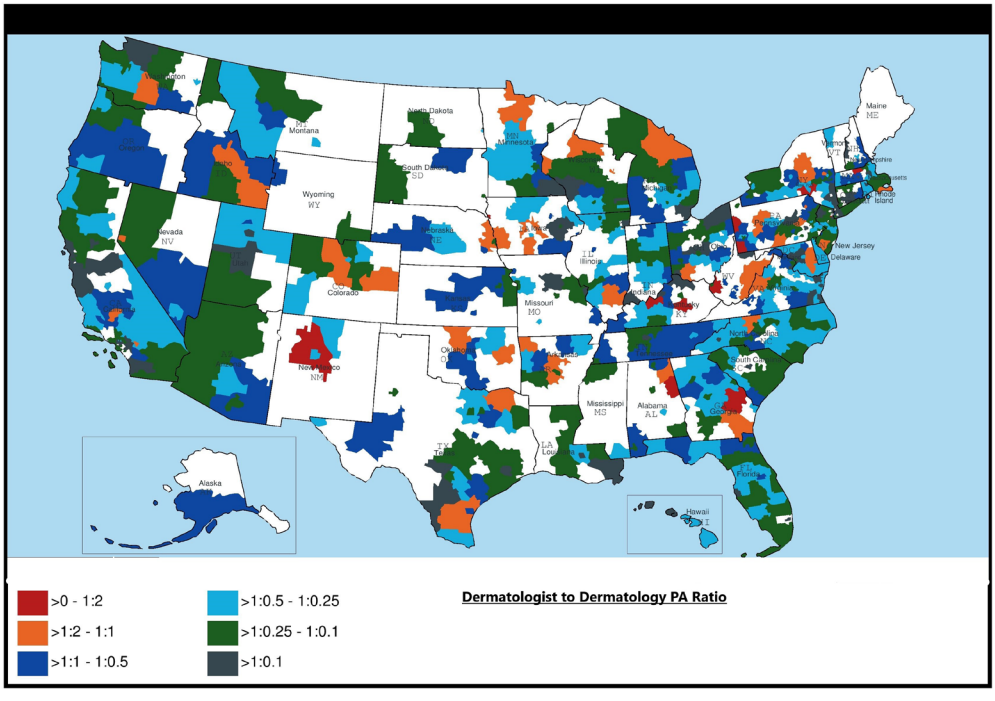
This study is subject to several limitations. The SDPA does not include all dermatology PAs and dermatology nurse practitioner (NP) data was not analyzed. However, had all dermatology PA/NPs been included, the dermatologist to dermatology PA/NP ratio would be even lower.

TABLE 1.

Top 10 Zip Codes With Lowest Dermatologist to Dermatology PA Ratios. Zip codes with the same number of dermatologists to dermatology PA were given the same rank.

Rank	3 Digit Zip Code	Location	Number of Dermatologist to Dermatology PA
1	014	Fitchburg, MA	1/4
2	404	Lexington, KY	1/3
3	153	Washington, PA	1/2.5
4	137	Binghamton, PA	1/2
4	161	New Castle, PA	1/2
4	255	Huntington, WV	1/2
4	304	Swainsboro, GA	1/2
4	362	Anniston, FL	1/2
4	401	Louisville, KY	1/2
4	511	Sioux City, IA	1/2
4	870	Albuquerque, NM	1/2
5	502	Des Moines, IA	1/2
6	804	Golden, CO	1/1.75
7	497	Mackinaw City, MI`	1/1.67
8	933	Bakersfield, CA	1/1.6
9	851	Phoenix, AZ (Vicinity)	1/1.5
10	185	Scranton, PA	1/1.33
10	543	Green Bay, WI	1/1.33
10	989	Yakima, WA	1/1.33

FIGURE 1. United States map showing the ratios of dermatologists to dermatology PA in each 3-digit zip code. Colors are identified by the legend below. Zip codes without a dermatology PA are left are shown in white.



In conclusion, rural areas have lower dermatologist to dermatology PA ratios compared to urban areas. Lower dermatologist/dermatology PA ratios may result in insufficient PA supervision and increased mortality. More dermatology residency positions are necessary to address the undersupply of dermatologists in the US, with incentives given to encourage board certified dermatologists to practice in underserved areas.

DISCLOSURES

Yu Wang and Dr. Lipner have no conflicts of interest relevant to the content.

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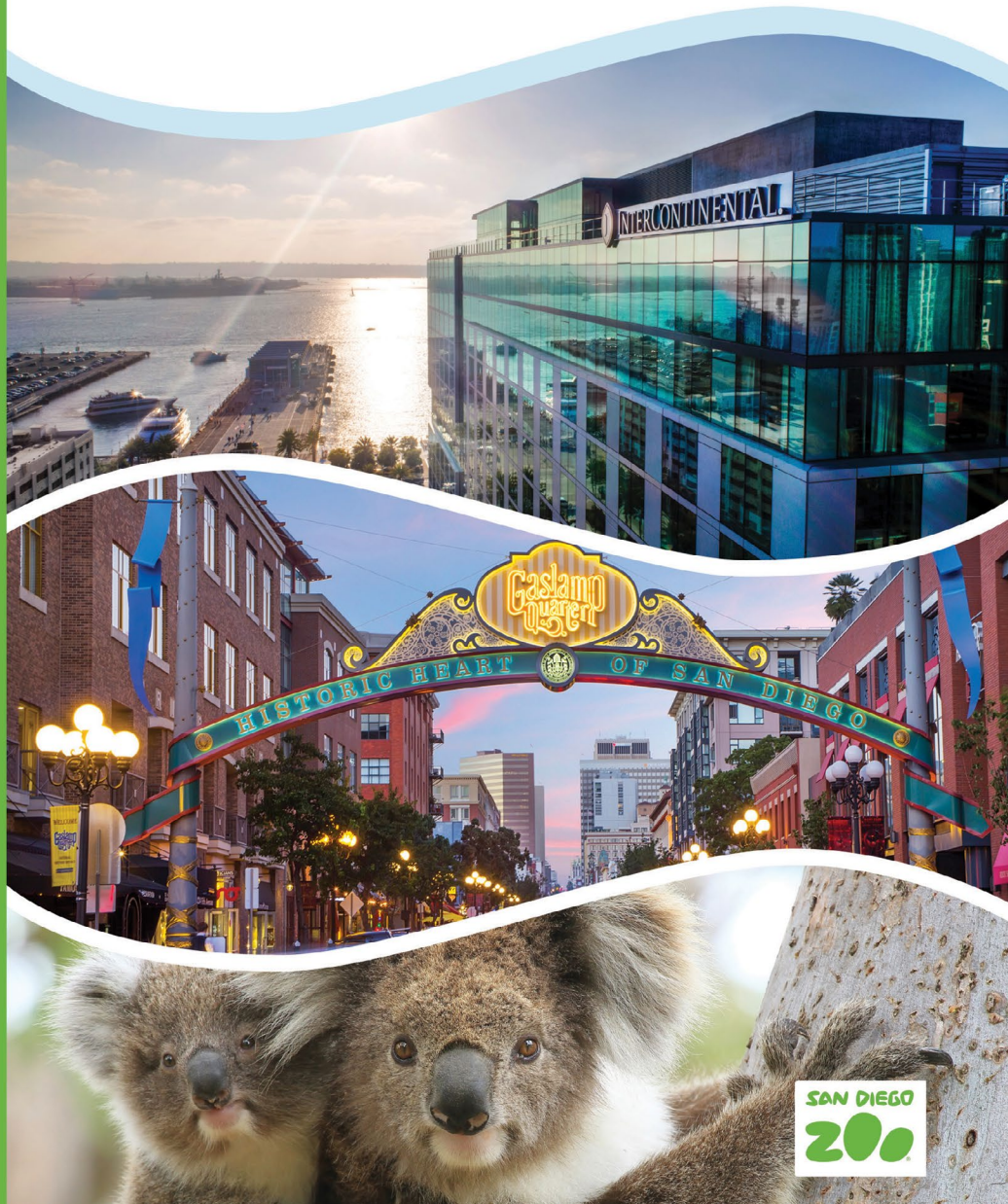

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CASE REPORT

Journal of Drugs in Dermatology

Ocular Dermoid in Patient With Basal Cell Nevus Syndrome

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Laser and Skin Surgery Center of Indiana, Indianapolis, IN

CASE

A 47-year-old women presented for Mohs Micrographic Surgery for a biopsy proven basal cell carcinoma involving the right nasal ala. The patient had a history of basal cell nevus syndrome (BCNS) and previous history of multiple basal cell carcinomas.

On initial examination, the patient was noted to have a few scattered pearly molluscoid papules on the head and neck, which were suspicious for early basal cell carcinomas. The patient was also noted to have a 1 cm dome shaped nodule on the lateral corneal-scleral junction of the right upper eyelid (Figures 1 and 2). On palpation, the lesion was firm and rubbery but was not fluctuant. The patient was a poor historian, however, on further questioning, the patient noted decreased visual acuity in the right eye and stated that she had had the lesion for many years. She had last seen an ophthalmologist over 20 years ago and was unsure if she had the eyelid lesion at that time. There was no lymphadenopathy on exam and the patient stated that she otherwise felt well.

On obtaining previous records, it was discovered that the patient had the lesion at least since the age of one year. The lesion was biopsied by a pediatric ophthalmologist and found to be an oculardermoid. No further treatment was recommended at that time as the lesion was not obstructing vision. The lesion subsequently grew and began to obstruct vision; however, no surgical treatment was performed.

Ocular dermoids are uncommon tumors, which are rarely seen by dermatologists. They represent the misplacement of dermal tissues and are frequently associated with cutaneous auricular appendages and first branchial arch anomalies.[1] The most commonly associated auricular appendages are accessory tragi and preauricular sinuses.[2] Definitive treatment of dermoids can be achieved by surgical resection, however, determining which lesions should be surgically removed is a topic of debate. A case series published in 2015 recommended that all dermoids affecting the visual axis, dome shaped, or causing conjunctival injection/irritation, be surgically removed.[3] Additionally, patients who were undergoing removal of auricular appendages or had parents who desired cosmetic removal, could also be considered for removal. Due to the risk of general anesthesia, every effort should be made to schedule removal concurrently with any other necessary surgeries.[3]

Although a rarely encountered entity by dermatologists, they should be aware of this condition and its associated management. Delay in treatment can lead to significant lifelong impairment of visual acuity. Additionally, ocular dermoids are commonly associated with preauricular sinuses and accessory tragi. Therefore, patients presenting to dermatology with preauricular sinuses or accessory tragi should be considered for ocular exam. Interestingly, our patient also had a history of BCNS. Based on the authors' review of the literature, there are no published reports of ocular dermoid tumors in association with BCNS, however, there is one report of a midline nasal dermoid cyst in association with BCNS.[4] Larger population-based studies or additional case reports should be reported to better assess any possible link between BCNS and dermoid cysts.

FIGURE 1. Direct view of bilateral eyes with ocular dermoid involving approximately 50% of right ocular surface.

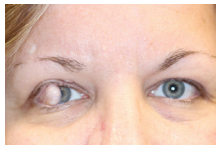
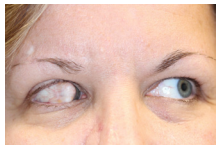


FIGURE 2. Far medial deviation of right eye showing ocular dermoid with direct connection to corneal surface.



DISCLOSURES

The authors have no conflict of interest to declare.

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CASE REPORT

Journal of Drugs in Dermatology

Frontal Fibrosing Alopecia Presenting as Androgenetic Alopecia in an African American Woman

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ABSTRACT

Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia that is currently regarded as a variant of lichen planopilaris. FFA has historically been considered rare in black patients, in whom traction alopecia, central centrifugal cicatricial alopecia, and androgenetic alopecia are frequently assumed to be more common. We describe a case of FFA in a black woman that both clinically resembled androgenetic alopecia and lacked many of the physical exam and dermoscopic findings associated with FFA. In doing so, we highlight the need for physicians to have a high index of suspicion for FFA in any black patient who presents with frontotemporal alopecia.

J Drugs Dermatol. 2020;19(7):794-795. doi:10.36849/JDD.2020.4682

REPORT OF A CASE

A 53-year-old African American woman presented with a 6-month history of asymptomatic, moderately severe hair loss along the frontal hairline, which had not stabilized or improved with minoxidil 2% solution BID. Physical exam revealed decreased hair density affecting the frontal scalp, suggestive of androgenetic alopecia (Figure1). Dermoscopic examination showed decreased follicular ostia without perifollicular scaling or erythema. Eyebrow alopecia, facial papules, and glabellar red dots were absent, and there was no associated loss of body hair. A 4-mm punch biopsy sent for histopathologic examination revealed dense, chronic, perifollicular inflammation affecting the mid and upper portions of the follicles, with loss of associated sebaceous glands. Involved hairs demonstrated vacuolar interface disruption of the basilar and epibasilar layers at the level of the isthmus and infundibulum, with prominent exocytosis of lymphocytes into the outer root sheath. There was no miniaturization, dermal mucin, or inflammation affecting the epidermis, arrector pili muscles, and eccrine glands (Figure 2).

A diagnosis of FFA was confirmed by these findings. Our patient was managed with intralesional triamcinolone acetonide (10mg/cc) injections, clobetasol 0.05% ointment BID, hydroxychloroquine 200 mg PO BID, and minoxidil 5 mg PO daily. Unfortunately, her alopecia did not stabilize with these measures.

FIGURE 1. Clinical presentation. Moderately decreased hair density in a band-like distribution along the frontotemporal hairline. Note the absence of follicular erythema, scale, and lateral eyebrow alopecia.

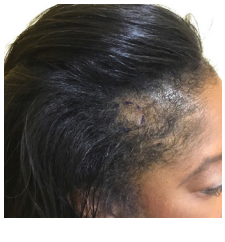
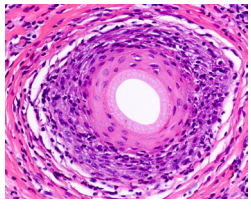


FIGURE 2. Histopathologic image of frontal fibrosing alopecia. Perifollicular inflammation at the level of the isthmus and infundibulum. Vacuolar interface alteration disrupting the basilar and epibasilar layers, with exocytosis of lymphocytes into the outer root sheath (original magnification x200).



DISCUSSION

FFA is a primary lymphocytic cicatricial alopecia that is currently regarded as a variant of lichen planopilaris. It is characterized by band-like frontotemporal hairline recession, often with associated eyebrow alopecia, perifollicular erythema, and scaling. Clinical findings are frequently accompanied by pruritus and burning of the affected scalp. Since it was first described in 1994,[1] FFA has largely been viewed as an alopecia of post-menopausal Caucasian women. This archetype has been maintained by patient demographics of subsequent published case series.[2,3] FFA may thus be underdiagnosed in black women, in whom traction alopecia, central centrifugal cicatricial alopecia, and androgenetic alopecia are assumed to be more common. Furthermore,

FFA can manifest uniquely in black women, who may be premenopausal[4,5] and asymptomatic[4] at the time of presentation. Classic signs of FFA may be subtle or absent among black patients, as increased pigmentation may render erythema difficult to appreciate, while oils and hair care products may diminish the appearance of scale.

It is important for dermatologists to both recognize that FFA is not uncommon in the black population,[4,5] and to acknowledge how it initially came to be regarded as a disease of post-menopausal white women. Several of the larger published series come from geographic areas that lack a substantial skin of color population.[2,3] There are also socioeconomic factors to consider. One series comprised exclusively of Caucasian women found their patients to be more affluent, which was speculated to be a surrogate marker for an unknown risk factor associated with the development of FFA.[3] What these authors did not discuss, however, is that affluence enables access to specialty medical care. Affluence affects insurance status, which has been shown to vary widely among racial groups.[6] Insurance status in turn bears upon who has access to dermatologic care, and who is ultimately included in a case series.

Although there are no universal treatment guidelines for FFA, the goal of management is to halt progression of the disease before follicles are irrevocably lost to fibrosis. Initiation of appropriate treatment requires a correct diagnosis, which is contingent upon a clinician's willingness to consider certain conditions in patients who do not fit the paradigm that they have been taught. FFA must be considered in any black patient who presents with frontotemporal alopecia.

DISCLOSURES

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

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