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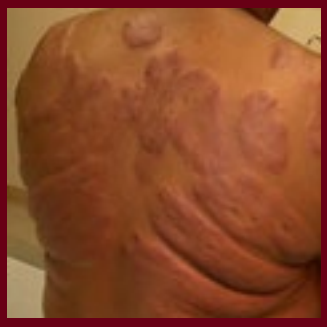

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SPECIAL FOCUS: BRIDGING THE GAP IN DERMATOLOGY

ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

Skyrizi®
risankizumab-rzaa

#1
PRESCRIBED BIOLOGIC
BY DERMATOLOGISTS FOR PATIENTS WITH PSORIATIC DISEASE

#1 PRESCRIPTION ANALYSIS CALCULATED BY COMBINED PRESCRIPTION DATA ACROSS Ps AND PsA

For patients with psoriatic disease, defined as those with plaque psoriasis or psoriatic arthritis. Source of data: Integrated Symphony Health (PatientSource) as of 8/2022.[1]

An IL-23 inhibitor for adults with moderate to severe plaque psoriasis (Ps) and for adults with active psoriatic arthritis (PsA)[2]

NOTHING IS EVERYTHING

Nothing less than the opportunity to reach for their treatment goals.
For your patients, that's everything.

UltIMMa-1 & 2 STUDY DESIGN[3]

UltIMMa-1 (N=506) and **UltIMMa-2** (N=491) were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and 16, and every 12 weeks thereafter. Co-primary endpoints were PASI 90 and sPGA 0/1 at Week 16 vs placebo in each study (assessed by non-responder imputation).

KEEPsAKE-1 & 2 STUDY DESIGN[2,4,5]

KEEPsAKE-1 and **KEEPsAKE-2** were phase 3, multicenter, randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of SKYRIZI in adults with active PsA. **KEEPsAKE-1** included patients who had an inadequate response or intolerance to at least 1 DMARD. **KEEPsAKE-2** included patients who had an inadequate response or intolerance to biologic therapy and/or DMARDs (mixed population of bio-naïve and bio-experienced). Patients were randomized to SKYRIZI 150 mg or placebo followed by SKYRIZI 150 mg at Week 28. The primary endpoint for both studies was the proportion of patients who achieved ACR20 at Week 24.

ACR20=American College of Rheumatology 20% improvement criteria; DMARD=Disease-Modifying Antirheumatic Drug.

abbvie

 US-SKZD-230086 April 2023

SKYRIZI GIVES YOUR PATIENTS THE OPPORTUNITY FOR...

DURABLE, RAPID & CLEAR SKIN

In **Ps**, most patients achieved co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16, including response 4 weeks after 1st dose. Most patients who achieved PASI 90 at Week 16 maintained it at Week 52.[2,3]

PASI 100 was achieved by many patients at Week 16 and by a majority at Week 52.[2]

POWERFUL JOINT SYMPTOM RELIEF

In **PsA**, a majority of patients achieved the primary endpoint of ACR20 at Week 24, experiencing improvement in joint symptoms including patient-reported pain data.[2]

4 INJECTIONS A YEAR

Reliable quarterly dosing after 2 initiation doses at Weeks 0 and 4 (150 mg/dose) for **Ps** and **PsA**.[2]

Safety data up to ~8 years in Ps clinical trials and ~3 years in PsA clinical trials.
Safety profile observed in PsA is generally consistent to Ps (PsA Week 24, Ps Week 16).[2,6,7]

LEARN MORE AT SKYRIZIHCP.COM

INDICATIONS[2]

Plaque Psoriasis: SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis: SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

IMPORTANT SAFETY INFORMATION[2]

Hypersensitivity Reactions

SKYRIZI® (risankizumab-rzaa) is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately.

Infection

SKYRIZI may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Tuberculosis (TB)

Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age appropriate vaccinations according to current immunization guidelines.

Adverse Reactions

Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.

In psoriatic arthritis phase 3 trials, the incidence of hepatic events was higher with SKYRIZI compared to placebo.

SKYRIZI is available in a 150 mg/mL prefilled syringe and pen.

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

References: 1. Data on file, AbbVie Inc. PatientSource/IQVIA data. 2022. **2.** SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **3.** Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650-661. **4.** Kristensen LE, Papp K, White D, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 100-week results from the KEEPsAKE 1 and KEEPsAKE 2 trials. Poster presented at: American College of Rheumatology Convergence; November 10-14, 2022; Philadelphia, Pennsylvania. **5.** Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. *Ann Rheum Dis.* 2022;81(2):225-231. **6.** Gordon KB, Blauvelt A, Coates LC, et al. Risankizumab long-term safety in patients with psoriatic disease: integrated analyses of data from psoriasis and psoriatic arthritis clinical trials. Poster presented at: 31st Congress of the European Academy of Dermatology and Venerology (EADV 2022); September 7-10, 2022; Milan, Italy. **7.** Data on file, ABVRRTI73417. AbbVie Inc.

SKYRIZI® (sky-RIZZ-ee) (risankizumab-rzaa) injection, for subcutaneous or intravenous use

150 mg/mL single-dose pen and prefilled syringe
600 mg/10 mL single-dose vial for intravenous infusion
180 mg/1.2 mL single-dose prefilled cartridge with on-body injector
360 mg/2.4 mL single-dose prefilled cartridge with on-body injector

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Plaque Psoriasis

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis

SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

Crohn's Disease

SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

CONTRAINDICATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately *[see Adverse Reactions]*.

Infections

SKYRIZI may increase the risk of infections *[see Adverse Reactions]*.

Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the PsO-3 study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Hepatotoxicity in Treatment of Crohn's Disease

A serious adverse reaction of drug-induced liver injury in conjunction with a rash that required hospitalization was reported in a patient with Crohn's disease (ALT 54x ULN, AST 30x ULN, and total bilirubin 2.2x ULN) following two 600 mg intravenous doses of SKYRIZI. The liver test abnormalities resolved following administration of steroids. SKYRIZI was subsequently discontinued.

For the treatment of Crohn's disease, evaluate liver enzymes and bilirubin at baseline, and during induction at least up to 12 weeks of treatment. Monitor thereafter according to routine patient management.

Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Tuberculosis *[see Warnings and Precautions]*
- Hepatotoxicity in Treatment of Crohn's Disease *[see Warnings and Precautions]*

Clinical Trials Experience

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

Plaque Psoriasis

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared with 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In Studies PsO-1 and PsO-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Psoriatic Arthritis

The overall safety profile observed in subjects with psoriatic arthritis treated with SKYRIZI is generally consistent with the safety profile in subjects with plaque psoriasis. Additionally, in the Phase 3 placebo-controlled trials the incidence of hepatic events was higher in the SKYRIZI group (5.4%, 16.7 events per 100 patient years) compared to the placebo group (3.9%, 12.6 events per 100 patient years). Of these, the most common events that were reported more frequently in both the placebo group and the SKYRIZI group were ALT increased (placebo: n=12 (1.7%); SKYRIZI: n=16 (2.3%)), AST increased (placebo: n=9 (1.3%); SKYRIZI: n=13 (1.8%)), and GGT increased (placebo: n=5 (0.7%); SKYRIZI: n=8 (1.1%)). There were no serious hepatic events reported. The incidence of hypersensitivity reactions was higher in the SKYRIZI group (n=16, 2.3%) compared to the placebo group (n=9, 1.3%). In the Phase 3 placebo-controlled trials, hypersensitivity reactions reported at a higher rate in the SKYRIZI group included rash (placebo: n=4 (0.6%); SKYRIZI: n=5 (0.7%), allergic rhinitis (placebo: n=1 (0.1%); SKYRIZI: n=2 (0.3%), and facial swelling (placebo: n=0 (0.0%); SKYRIZI n=1 (0.1%). One case of anaphylaxis was reported in a subject who received SKYRIZI in the Phase 2 clinical trial.

Crohn's Disease

SKYRIZI was studied up to 12 weeks in subjects with moderately to severely active Crohn's disease in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2) and a randomized, double-blind, placebo-controlled, dose-finding study (CD-4; NCT02031276). Long-term safety up to 52 weeks was evaluated in subjects who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3).

In the two induction studies (CD-1, CD-2) and the dose finding study (CD-4), 620 subjects received the SKYRIZI intravenous induction regimen at Weeks 0, 4 and 8. In the maintenance study (CD-3), 297 subjects who achieved clinical response, defined as a reduction in CDAI of at least 100 points from baseline after 12 weeks of induction treatment with intravenous SKYRIZI in studies CD-1 and CD-2, received a maintenance regimen of SKYRIZI either 180 mg or 360 mg subcutaneously at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks.

Adverse reactions reported in > 3% of subjects in induction studies and at a higher rate than placebo are shown in Table 2.

Table 2. Adverse Drug Reactions Reported in > 3% of Subjects with Crohn's Disease Treated with SKYRIZI in Placebo-Controlled 12-Week Induction Studies

Adverse Drug Reactions	SKYRIZI 600 mg Intravenous Infusion[a] N = 620 n (%)	Placebo N = 432 n (%)
Upper respiratory infections[b]	66 (10.6)	40 (9.3)
Headache[c]	41 (6.6)	24 (5.6)
Arthralgia	31 (5.0)	19 (4.4)

[a] SKYRIZI 600 mg as an intravenous infusion at Week 0, Week 4, and Week 8.
[b] Includes: influenza like illness, nasopharyngitis, influenza, pharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, COVID-19, nasal congestion, respiratory tract infection viral, viral pharyngitis, tonsillitis, upper respiratory tract inflammation
[c] Includes: headache, tension headache

Adverse reactions reported in >3% of subjects in the maintenance study and at a higher rate than placebo are shown in Table 3.

Table 3. Adverse Reactions Reported in >3% of Subjects with Crohn's Disease Treated with SKYRIZI[a] in Placebo-Controlled 52-Week Maintenance Study (CD-3)

Adverse Drug Reactions	SKYRIZI 180 mg Subcutaneous Injection N = 155 n (%)	SKYRIZI 360 mg Subcutaneous Injection N = 142 n (%)	Placebo N = 143 n (%)
Arthralgia	13 (8.4)	13 (9.2)	12 (8.4)
Abdominal pain[b]	9 (5.8)	12 (8.5)	6 (4.2)
Injection site reactions[c,d]	7 (4.5)	8 (5.6)	4 (2.8)
Anemia	7 (4.5)	7 (4.9)	6 (4.2)
Pyrexia	4 (2.6)	7 (4.9)	4 (2.8)
Back pain	3 (1.9)	6 (4.2)	3 (2.1)
Arthropathy	1 (0.6)	5 (3.5)	2 (1.4)
Urinary tract infection	1 (0.6)	5 (3.5)	4 (2.8)

[a] SKYRIZI 180 mg or 360 mg at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks
[b] Includes: abdominal pain, abdominal pain upper, abdominal pain lower
[c] Includes: injection site rash, injection site erythema, injection site swelling, injection site urticaria, injection site warmth, injection site pain, injection site hypersensitivity, injection site reaction
[d] Some subjects had multiple occurrences of injection site reactions. In this table, injection site reactions are counted only once per subject for the rate calculations.

Specific Adverse Drug Reactions

Infections

In the maintenance study (CD-3) through Week 52, the rate of infections was 32.3% (50.2 events per 100 subject-years) in subjects who received SKYRIZI 180 mg and 36.6% (60.8 events per 100 subject-years) in subjects who received SKYRIZI 360 mg compared to 36.4% (60.3 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction. The rate of serious infections was 2.6% (2.7 events per 100 subject-years) in subjects who received SKYRIZI 180 mg and 5.6% (7.4 events per 100 subject-years) in subjects who received SKYRIZI 360 mg compared to 2.1% (2.4 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction.

Lipid Elevations

Elevations in lipid parameters (total cholesterol and low-density lipoprotein cholesterol [LDL-C]) were first assessed at 4 weeks following initiation of SKYRIZI in the induction trials (CD-1, CD-2). Increases from baseline and increases relative to placebo were observed at Week 4 and remained stable to Week 12. Following SKYRIZI induction, mean total cholesterol increased by 9.4 mg/dL from baseline to a mean absolute value of 175.1 mg/dL at Week 12. Similarly, mean LDL-C increased by 6.6 mg/dL from baseline to a mean absolute value of 92.6 mg/dL at Week 12. Mean LDL-C increased by 3.1 mg/dL from baseline to a mean absolute value of 99.0 mg/dL at Week 52 with SKYRIZI 180 mg maintenance treatment and by 2.3 mg/dL from baseline to a mean absolute value of 102.2 mg/dL at Week 52 with SKYRIZI 360 mg maintenance treatment.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

Plaque Psoriasis

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

Psoriatic Arthritis

By Week 28, approximately 12.1% (79/652) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had

antibodies that were classified as neutralizing. Antibodies to risankizumab-rzaa were not associated with changes in clinical response for psoriatic arthritis. A higher proportion of subjects with anti-drug antibodies experienced hypersensitivity reactions (6.3% (5/79)) and injection site reactions (2.5% (2/79)) compared to subjects without anti-drug antibodies (3.8% (22/574) with hypersensitivity reactions and 0.7% (4/574) with injection site reactions). None of these hypersensitivity and injection site reactions led to discontinuation of risankizumab-rzaa.

Crohn's Disease

By Week 64, antibodies to risankizumab-rzaa developed in approximately 3.4% (2/58) of subjects treated with SKYRIZI induction followed by 360 mg maintenance regimen. No subjects (0/57) treated with SKYRIZI induction followed by 180 mg maintenance regimen developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing.

Postmarketing Experience

The following adverse reactions have been reported during post-approval of SKYRIZI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to SKYRIZI exposure:

- *Skin and subcutaneous tissue disorders*: eczema and rash

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161 or visiting http://glowpregnancyregistry.com.

Risk Summary

Available pharmacovigilance and clinical trial data with risankizumab use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on risankizumab-rzaa, monoclonal antibodies can be actively transported across the placenta, and SKYRIZI may cause immunosuppression in the in utero-exposed infant. There are adverse pregnancy outcomes in women with inflammatory bowel disease *(see Clinical Considerations)*.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 or 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. Increased fetal/infant loss was noted in pregnant monkeys at the 50 mg/kg dose *(see Data)*. The 50 mg/kg dose in pregnant monkeys resulted in approximately 10 times the exposure (AUC) in humans administered the 600 mg induction regimen and 39 times the exposure (AUC) to the 360 mg maintenance doses, respectively. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

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

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal adverse reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because risankizumab may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to SKYRIZI in utero. There are insufficient data regarding infant serum levels of risankizumab at birth and the duration of persistence of risankizumab in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 5 months after birth should be considered because of the half-life of the product.

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition, and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg and the NOAEL for developmental toxicity was identified as 5 mg/kg. On an exposure (AUC) basis, the 5 mg/kg dose in pregnant monkeys resulted in approximately 1.24 times the exposure in humans administered the 600 mg induction regimen and 5 times the exposure in humans administered the 360 mg maintenance doses, respectively. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17%-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

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

Pediatric Use

The safety and effectiveness of SKYRIZI have not been established in pediatric patients.

Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in SKYRIZI exposure, safety, or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

Clinical studies of SKYRIZI for the treatment of Crohn's disease did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

No clinically meaningful differences in the pharmacokinetics of risankizumab-rzaa were observed in geriatric subjects compared to younger adult subjects with Crohn's disease.

PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions

Advise patients to discontinue SKYRIZI and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions]*.

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*.

Hepatotoxicity in Treatment of Crohn's Disease

Inform patients that SKYRIZI may cause liver injury, especially during the initial 12 weeks of treatment. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of liver dysfunction. (e.g., unexplained rash, nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) *[see Warnings and Precautions]*.

Administration of Vaccines

Advise patients that vaccination with live vaccines is not recommended during SKYRIZI treatment and immediately prior to or after SKYRIZI treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SKYRIZI prior to a potential vaccination *[see Warnings and Precautions]*.

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique.

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI.

Instruct patients or caregivers in the technique of pen or syringe disposal.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to SKYRIZI during pregnancy *[see Use in Specific Populations]*.

Manufactured by:
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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Assessing Implicit Bias in Dermatology

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ABSTRACT

Background: Patients with skin of color (SOC), defined as Fitzpatrick skin types IV to VI, and of varying ethnicities are under-represented in dermatology. This includes practitioners, trainees, dermatologic teaching materials, and clinical studies.

Methods: Online survey study to assess dermatologists' perceptions that could impact patient care. Participants were screened for providers that spent ≥80% of their time in direct patient care; managed ≥100 unique patients per month; and had ≥20% aesthetic patients.

Results: A total of 220 dermatologists participated; 50 with SOC, 152 non-SOC, and 18 other. SOC dermatologists had a more diverse patient population by racial/ethnic background, but there was no difference in proportion of patients by Fitzpatrick skin phototype categories. While race/ethnicity is not considered a primary factor in clinical decision making, Fitzpatrick skin type is for many dermatologists. Most dermatologists agree that more diversity in medical training for dermatologic conditions would be beneficial. Dermatologists report that adding before and after photos of different skin types in educational materials and increasing training on cultural competency are likely to be the most effective strategies for improvement.

Conclusions: Although racial/ethnic diversity shows differences based on location of practice and the race of dermatologists, diversity of skin type based on Fitzpatrick scale is virtually identical across practices, illustrating the challenge of categorizing patients by this scale alone.

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INTRODUCTION

The population of the United States continues to diversify and the number of individuals with skin of color (SOC) seeking dermatologic care is increasing.[1] Yet there are accumulating data that patients with SOC (defined for working purposes here as Fitzpatrick skin phototypes IV-VI) tend to have less favorable outcomes in dermatologic diseases compared with patients with lighter skin.[2-7]

A number of factors contribute to disparities in dermatologic care. Dermatology is the second least diverse medical specialty, with only 9% of US dermatologists being Black, Indigenous, or Latino.[8,9] In addition, skin conditions often manifest differently on dark skin.[10] Medical literature and textbooks have historically under-represented images of diseases in patients with skin of color. This drastically hinders dermatologists' diagnostic accuracy, given how critical pattern recognition is in the field.[1,11-13] Further, there is a lack of research in diseases in darker skin and clinical features of skin disease are often influenced by skin tone.[11] In addition, the management approach that providers select may vary between ethnic groups, in many cases despite a lack of evidence-base to support such a variance.[3,14]

There is little research on the adequacy of current dermatologic training to produce dermatologists with cross-cultural competence, confidence, and skill in treating patients from diverse backgrounds.[3] It is unclear as to whether dermatologists have implicit biases (beliefs that may subconsciously influence thinking and reactions to information), whether these biases affect medical or aesthetic dermatology patients to a greater or lesser degree, and whether bias may affect patient care and outcomes. The purpose of this survey-based study was to assess biases and perceptions that could impact patient care based on a representative sample of dermatologists, and to determine which patient factors affect providers' clinical decisions in medical dermatology compared with aesthetic dermatology. We also sought to understand providers' perceptions toward the adequacy of cultural and implicit bias training received during and after residency. This was done in order to identify possible gaps in training and education as well as which factors may decrease bias and improve care.

MATERIALS AND METHODS

Study Design

This study utilized a quantitative online survey of dermatologists in the United States and was conducted from March 21 to April 26, 2022. An extensive review of literature was performed, and the questionnaire was developed in consultation with dermatology experts. The questionnaire addressed unmet needs in treating minority patients, including need for improved or enhanced training; need for improved patient support resources; perceptions of which conditions in dermatology offer most potential for improvement; and need for improved medical tools for assessing dermatologic conditions in SOC patients. In addition, participants were asked to rate the relative importance of race, ethnicity, and the Fitzpatrick skin phototypes scale as well as other demographic information. Participants were asked to rank their top three most important factors that guide either medical or aesthetic treatments.

A pre-survey screening tool was developed to identify and recruit dermatologists who met the following criteria: 1 to 40 years in practice with at least 80% of time spent in direct patient care; Board-certified dermatologists practicing in the US (except VT and MN); practice currently managing at least 100 unique patients in a typical month (with ≤60% surgical patients); and active management of aesthetic patients (at least 20% of total practice volume or >50 patients/month). Participants completed the survey in an anonymous fashion.

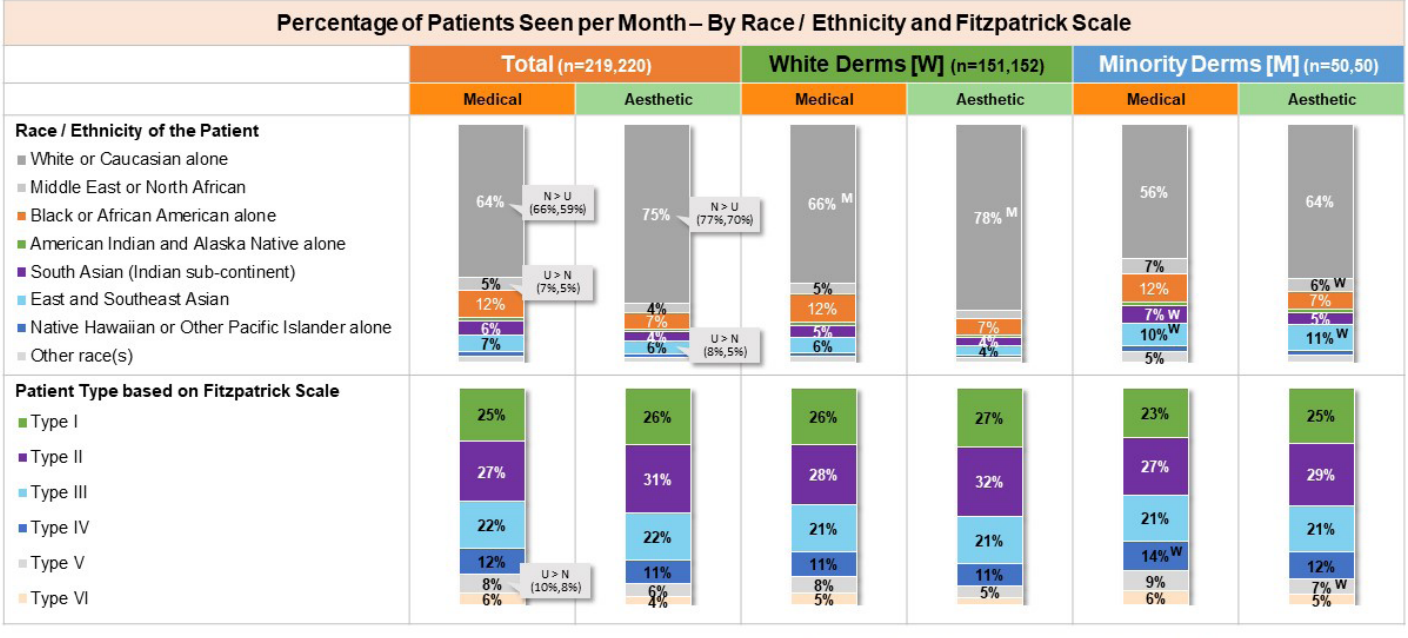
Statistical analyses included numeric race/ethnic background (SOC or non-SOC), practice location (urban or non-urban), and practice setting (academic hospital, non-academic hospital, or private practice clinic/office).

TABLE 1.

Characteristics of Participating Dermatologists			
Characteristic	**Total (n=220)***	**Skin of Color (n=50)**	**Non-SOC (n=152)**
Years in practice (mean)	17 years	15	17
Practice Setting			
Urban	30%	35%	28%
Non-urban	70%	64%	72%
Gender			
Male	50%	46%	53%
Female	46%	54%	47%
Prefer not to answer/other	4%	0%	0%
Race/Ethnicity			
White/Caucasian alone	69%	--	100%
Middle East or North Africa	2%	8%	--
Black/African American alone	3%	8%	--
South Asian (Indian sub-continent)	5%	20%	--
East/Southeast Asian	10%	46%	--
American Indian/Alaska Native	1%	4%	--
Hawaiian/Pacific Islander	1%	4%	--
Prefer not to answer/other	9%	6%	--
Patient Mix by Treatment Type			
Medical (treating disease)	61%	60%	61%
Aesthetic (enhancing appearance)	23%	24%	22%
Surgical	16%	16%	16%
Patient Insurance Type			
Private (HMO/PPO/POS)	51%	51%	51%
Medicare (with or without secondary)	35%	34%	36%
Medicaid	4%	4%	4%
Cash/other	10%	10%	9%

*18 participants did not provide information on race/ethnicity so are included in the total group but were excluded from the SOC and the non-SOC groups.

FIGURE 1. Analysis of patient race/ethnicity and Fitzpatrick skin phototype in respondents' practices.



S100. What percentage of the patients your practice sees per month fall into the following racial/ethnic categories?
S105. What percentage of the patients your practice sees per month fall into the following types based on the Fitzpatrick Scale?

[U/N] denote significant differences between Urban and Non-Urban at 95% C.L.
[W/M] denote significant differences between White and Minority at 95% C.L.

*18 participants did not provide information on race/ethnicity so are included in the total group but were excluded from the SOC and the non-SOC groups.

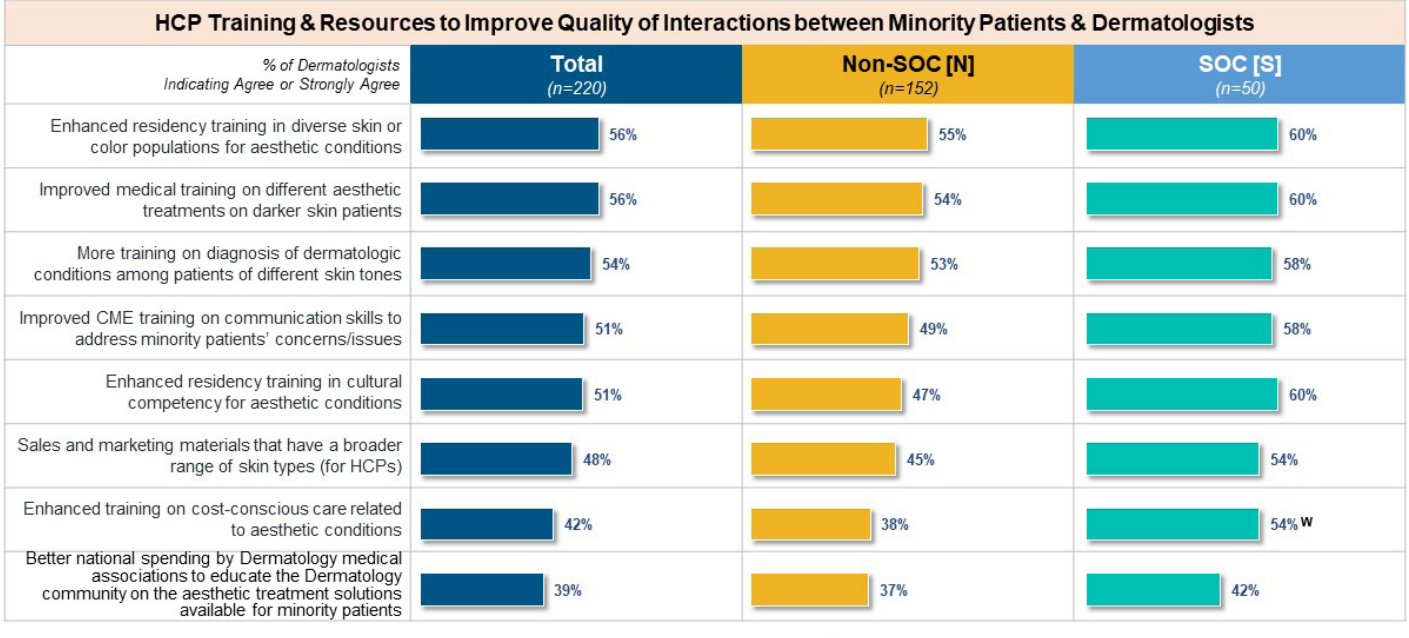
TABLE 2.

Medical/Aesthetic Decision-Making Factors. Importance of factors while assessing patients for either medical and aesthetic treatments: percent of participants who rated each factor as top importance (scores of 1-3 out of 10) in decision-making.

Medical Treatment Decision-Making	All Dermatologists (n=220)	SOC Derms (n=50)	Non-SOC (n=152)
Severity of Condition	75%	76%	72%
Negative Impact on QoL	62%	64%	60%
Comorbidities	42%	43%	44%
Out of Pocket Cost/Cost to Pt	24%	26%	14%
Fitzpatrick Skin Type	23%	23%	28%
Advanced Age	19%	16%	22%
Race/Ethnicity	11%	12%	10%
Aesthetic Treatment Decision-Making	**All Dermatologists (n=220)**	**Non-SOC Derms (n=152)**	**Non-SOC (n=152)**
Severity of Condition	63%	63%	62%
Negative Impact on QoL	52%	54%	52%
Out of Pocket Cost/Cost to Pt	48%	48%	40%
Advanced Age	30%	31%	24%
Fitzpatrick Skin Type	28%	27%	34%
Comorbidities	22%	23%	22%
Race/Ethnicity	15%	16%	10%

*18 participants did not provide information on race/ethnicity so are included in the total group but were excluded from the SOC and the non-SOC groups.

FIGURE 2. Areas where dermatology training could be improved, % of participants reporting "agree" or "strongly agree."

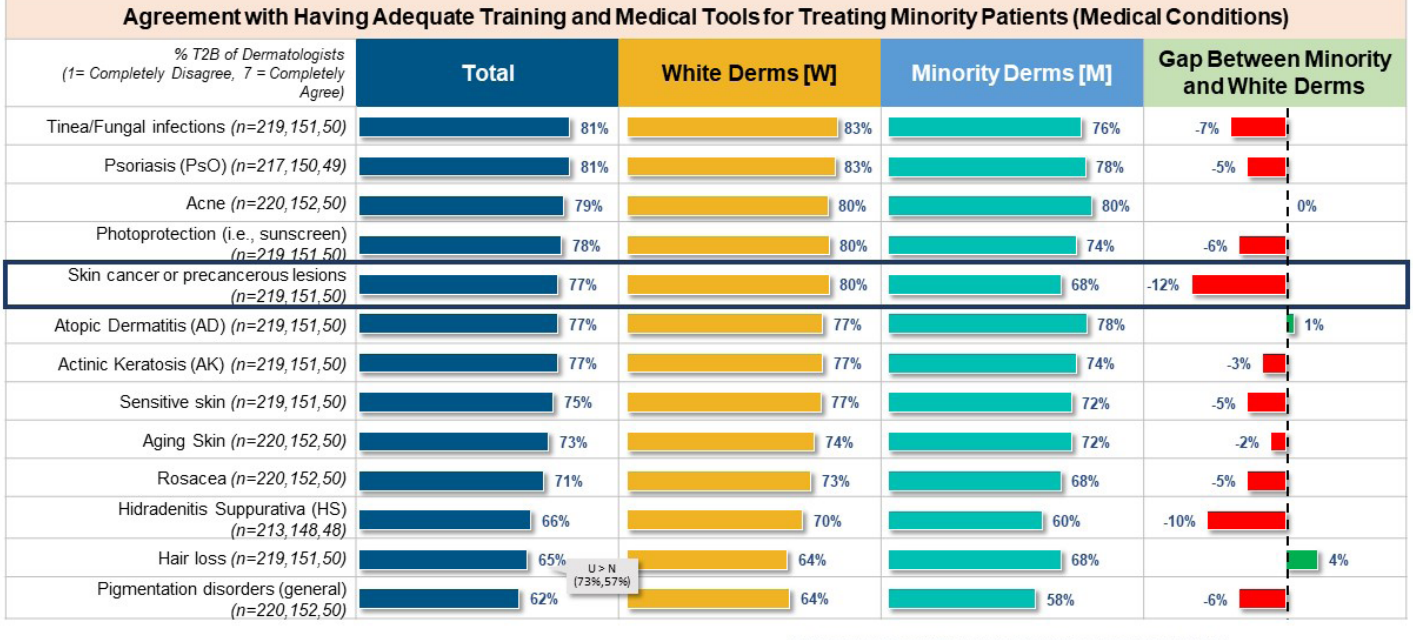


Q200. To what extent, if any, do you agree that the following HCP training and resources could improve quality of clinical interactions between minority race patients and dermatologists for aesthetic treatments / procedures?

No significant differences between Urban and Non-Urban at 95% C.L.
[W/M] denote significant differences between White and Minority at 95% C.L.

* 18 participants did not provide information on race/ethnicity so are included in the total group but were excluded from the SOC and the non-SOC groups

FIGURE 3. Perceptions of current training and resources for treating Skin of Color patients with specific medical conditions.



Q140. To what extent do you agree that you have adequate training and medical tools for treating minority patients (patients higher on the Fitzpatrick scale) for the following medical conditions?

[U/N] denote significant differences between Urban and Non-Urban at 95% C.L.
No significant differences between White and Minority at 95% C.L.

RESULTS

Participant Characteristics

A total of 220 dermatologists participated, including 50 with SOC, 152 non-SOC and 18 other (note: these 18 dermatologists were not included in the analyses comparing SOC and non-SOC); 50% were male, 46% were female, and 4% responded "other" or "prefer not to answer" (Table 1). They spent the majority (96%) of professional time seeing patients and 95% were in private practice. On average, these dermatologists reported a patient volume of 522/month, with 61% of visits for medical dermatology, 23% for aesthetic dermatology, and 16% surgical. Table 1 presents additional characteristics of the participants.

Practice Diversity

While SOC dermatologists reported a significantly more diverse population according to racial/ethnic background of their patients, there was no discernable difference in proportion of patients by Fitzpatrick skin phototype categories between SOC and non-SOC dermatology practices (Figure 1). As shown, there was a higher proportion of White/Caucasian patients reported to be seeking aesthetic treatment, which was consistent in both SOC and non-SOC dermatology practices, although the difference was more prominent in non-SOC practices. In the overall group of dermatologists, stratification of urban (U) vs non-urban (N) showed non-urban practices had a higher proportion of White/Caucasian patients compared with other races/ethnicities.

Importance of Diversity as a Decision-Making Factor for Dermatologists

As shown in Table 2, the top 2 factors rated as important in both medical and aesthetic treatment decisions were severity of condition and negative impact on quality of life. The other factors varied between medical and aesthetic treatments, with comorbidities assuming greater importance with medical decisions and out-of-pocket costs with aesthetic decisions. Race/ethnicity was the lowest ranked factor for both types of decision-making, identified as one of the top 3 most important factors in medical decision-making with only 12% of non-SOC dermatologists and by 10% of SOC dermatologists (none of whom rated race/ethnicity as the first most important factor). In contrast, 23% of non-SOC dermatologists rated Fitzpatrick skin type as a top 3 most important factor in medical decision making, as did 28% of SOC dermatologists. For aesthetic treatments, 27% of non-SOC and 34% of SOC dermatologists ranked Fitzpatrick skin type as an important factor (Table 2).

Need for Improved or Enhanced Training

Most dermatologists agree that medical training for diagnosis and treatment of dermatological conditions could be improved by including more diversity in training across patient skin types (Figure 2), with a higher percentage of SOC dermatologists reporting this compared with non-SOC dermatologists. When evaluating whether there is a need for sales and marketing materials with a broader range of representation of skin types, there was a more distinct gap between non-SOC and SOC dermatologists, with 68% of non-SOC dermatologists rating this as a factor that could improve clinical interactions compared with just 49% of SOC dermatologists. Of note, approximately half of all dermatologists agree that clinical trials should include a broader coverage of SOC patients, with 52% indicating additional resources should be allocated to ensure clinical trials have broader coverage of SOC patients and 50% agreeing there is a need for more inclusive clinical trial designs.

The most common medical conditions that dermatologists treat daily included skin cancer, acne, and actinic keratoses. Botulinum toxin, fillers, and different laser treatments were the most common aesthetic procedures used by dermatologists daily. Participants were asked to rate the adequacy of training and medical tools for treating non-SOC patients (Fitzpatrick IV-VI) for 13 medical conditions. As shown in Figure 3, there was a gap in perceptions of SOC dermatologists and non-SOC dermatologists for 10 of the conditions, with the greatest difference being skin cancer; in this condition, 68% of SOC dermatologists felt they had adequate training to manage their patients with SOC compared with 80% of non-SOC dermatologists. The respondents in this survey also indicated a need for better patient education tools. All participants specified they could also benefit from more training on aesthetic procedures for patients with SOC, citing peels and laser treatments as being top needs for training.

Increased Patient Support Resources

A majority of dermatologists (55%) were not certain of the types of resources that may improve interactions between SOC patients and dermatologists. However, there were write-in suggestions that before/after photos including different skin types, resources tailored to treatment options for SOC, and training on specific aspects of care (eg, hair pathologies) could be useful. Dermatologists also agree they would benefit from improved cultural training (60% SOC, 47% non-SOC) including: continuing medical education (CME) training to improve communication with SOC patients and residency training on cultural competency.

DISCUSSION

The United States is seeing a significant rise in racial and ethnic diversity, resulting in an increased demand and focus on health outcomes in diverse patient populations.[15] Further, race and ethnicity reporting in dermatology clinical trials is lacking compared with other areas of medical research.[16] One notable finding of this study is that only half of the dermatologists surveyed perceived that increased diversity in clinical trials is needed. This could suggest implicit bias among practicing dermatologists, a lack of understanding of the importance

of this diversity, or both. Potential solutions for dermatology offices could include implementing implicit bias screening for providers, staff, and management; implicit bias trainings; as well as regular reassessments to monitor progress. An interesting finding was that SOC dermatologists relied more on Fitzpatrick skin phototype than out of pocket cost for decision-making. Further, SOC dermatologists think there should be more training on how to provide cost-conscious care for aesthetic treatments.

In 2022, Abduelmula et al reported that across 26 dermatology textbooks, there were just 11.2% images of skin of color, showing that under-representation of SOC is a clear problem in dermatology.[12] Further, Slaught et al reported that use of online Perceptual and Adaptive Learning Modules composed of dark skin images significantly ($P \leq 0.0001$) improved the diagnostic accuracy of common skin conditions by medical students.[11] Many dermatologists in this study agree that increasing the diversity of skin types in medical and aesthetic training materials and in residency training are needed. This group also agreed that adding before and after photos of different skin types in sales and marketing materials, and increasing training on cultural competency may be effective approaches for improving management of SOC. The Fitzpatrick skin phototype scale is a useful clinical tool and was ranked more highly than race/ethnicity in medical and aesthetic decision-making by this group. However, moving beyond Fitzpatrick skin types toward a more inclusive method of identifying and defining race and ethnicity variables that may impact clinical decision-making should be a future goal. The Fitzpatrick skin phototype scale has limited utility and using it as a clinical decision making factor without also considering race and ethnicity can mask cultural differences and perceptions of treatment. Alternative systems have been proposed, but none to date have become widely accepted.

A study limitation is potential study participation bias inherent in anonymous surveys, which may reduce the ability to generalize results to all dermatologists. Additional study limitations include the duration of study.

The first step in mitigating bias is awareness. One step toward remedying biases in dermatology and among providers in general is implementing the use of the Harvard Implicit Bias test at various milestones during medical training. These can be conducted at several timepoints throughout medical school and residency programs to monitor for progress. Further, healthcare professionals could incorporate bias testing and plans throughout their careers to monitor any areas of shortcomings. This should be done for providers as well as for nurses and staff. Each patient has their unique history which is more than race and ethnicity — and the patient as a whole must be taken into consideration during clinical decision making. Both individual and institutional efforts must be made to achieve a better future in dermatology for all patients.

DISCLOSURES

Dr Beer and Dr Downie have no conflicts of interest to declare. Dr Noguiera and Dr Meckfessel are employees of Galderma Laboratories, LP.

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ORIGINAL ARTICLE

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Modified Fitzpatrick Scale-Skin Color and Reactivity

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ABSTRACT

Background: There is growing interest in the development of a skin classification system that captures the world's diverse population. The Fitzpatrick skin classification scale is used both clinically and in research settings to determine an individual's skin color. With the high global burden of skin sensitivity (atopic dermatitis, keloid formation, etc), there is a need for a skin classification system that takes into consideration an individual's reaction to environmental insults and injuries. Our proposal builds on the existing Fitzpatrick skin classification scale by asking two additional questions of patients: do patients have sensitive skin; do patients have a history of hypertrophic scarring or keloids. By separating patients into 2 categories (sensitive vs non-sensitive skin), we create a system that can help dermatologists decide on which treatments to offer patients based on their skin classification. Dermatologists can better predict patient outcomes for dermatologic or cosmetic procedures by knowing how they react to environmental insults/injury.

J Drugs Dermatol. 2023;22(7):641-646. doi:10.36849/JDD.6859

INTRODUCTION

Efforts to reduce the burden of skin cancer globally have focused on prevention and early diagnosis. Knowing an individual's skin color and their sensitivity to sun exposure helps with predicting their skin cancer risk.[1] The former ways of classifying individuals by broad descriptive categories include skin color (ie, white, brown, and black); race and ethnicity (eg, Japanese or Indian); and response to injury. These classifications are limited and do not adequately categorize the diverse population of the world. Multiple scales have been developed over the years in attempts to better capture the variety of skin colors. Skin color has also been used to predict skin reactivity to insult or injury. Some skin types are more sensitive to allergens and irritants compared with others. Some skin types are more likely to develop hyperpigmentation, hypopigmentation, scarring, and keloids from insult/injury.[2] Analyzing skin reactivity is especially important as it enables clinicians to predict an individual's response to treatments including phototherapy or surgical/cosmetic procedures. While skin color may correlate with certain patterns of skin reactivity, skin color alone is not the sole predictor of adverse effects from dermatologic or cosmetic treatments such as chemical peels or laser treatments. A few newer scales have tried to predict cosmetic outcomes in different skin types. In this article, we propose a modification to the Fitzpatrick skin classification scale that includes skin sensitivity response, based on the common immune signaling pathways between atopic dermatitis (skin sensitivity reaction) and risk factor for keloid formation (response to injury). In addition, we review definitions of skin color, the commonly used Fitzpatrick skin classification scale and other new or modified skin classification systems.

Our Proposal:
Modified Fitzpatrick Scale-Skin Color and Reactivity

Human skin color can be defined on the basis of genetics in the absence of environmental exposures (constitutive) or defined on the basis of exposures to environmental stimuli such as sunlight (facultative).[3] Constitutive skin color is determined by a number of chromophores including melanin, hemoglobin, bilirubin, and carotene.[4,5] Tools for measuring skin color can be subjective or objective. Subjective tools rely on an individual's self-reported skin color and their response to environmental stimuli such as sun exposure. Objective tools rely on colorimeters and spectrophotometers that measure skin color.

In dermatology, the Fitzpatrick skin classification scale is one of the most common systems used to classify an individual's skin color. Developed in 1975, the purpose of the Fitzpatrick skin classification scale was to determine the initial ultraviolet A (UVA) dose for people with fair-skin undergoing photo chemotherapy for psoriasis treatment. Later, the scale was expanded to include people with brown and black-skin.[6] The Fitzpatrick skin types are classified as I through VI. By constitutive skin color typing, type I through III are considered white, type IV is considered light brown, type V is considered brown, and type VI is considered black. By facultative skin typing, the classification is based on what patients report as their 24-hour reaction to 3 minimal erythema doses (MED) of sun exposure and how much tan developed in 7 days. Skin types I through IV will have responses ranging from "always burn, never tan" to "never burn, always tan."[4,6] Skin types V and VI never burn and always tan.

The Fitzpatrick skin classification scale has several limitations, the first being the subjective nature of determining reactivity to sun exposure. Secondly, there are many people with darker skin tones who are photosensitive and so their constitutive skin type by Fitzpatrick phototype may not accurately depict their reaction to sun exposure. The Fitzpatrick skin classification scale has also been criticized for not accurately accounting for a variety of races and ethnicities. In practice, this scale also does not consider reactivity to environmental insult/injury, and thus cannot be used practically to predict one's response to certain dermatologic or cosmetic procedures such as laser therapy or chemical peels. Multiple classification systems have been proposed in order to address some of the flaws of the Fitzpatrick skin classification scale.

The burden of atopic dermatitis in individuals with skin of color is significant worldwide. In the United States, atopic dermatitis is one of the top 5 diagnoses for African American patients in dermatology clinics.[7] Keloid formation is very common in individuals with skin of color, with studies reporting a range of 6% to 16% incidence in African populations.[8,9] There are studies showing a strong association between atopic dermatitis and keloid formation in individuals with skin of color particularly of Asian descent.[10,11] A study from Taiwan showed a more than 3-fold greater risk of keloid development in patients with atopic dermatitis compared with patients without atopic dermatitis.[10] A study from Korea showed increased odds of keloids in patients with atopic dermatitis compared with patients without atopic dermatitis.[11] There remains a research gap in exploring the pathophysiologic mechanisms behind the atopic dermatitis and keloid associations seen in individuals with skin of color.

A recent retrospective study suggests that atopic dermatitis may be an independent risk factor for keloid formation.[10] Studies suggest several common immune signaling pathways between atopic dermatitis and keloid formation.[8-10,12-19] A specific pathway highlighted by Maeda et al showed an extracellular matrix protein, periostin, increases Th2-type cytokines, interleukin (IL)-4 and IL-13, that stimulate human dermal fibroblasts to secrete transforming growth factor beta.[16] This has led to several studies demonstrating resolution of keloid symptoms and reduction in keloid size in patients who were treated with the IL-4 receptor antagonist, dupilumab.[8-9,16-19]

With increasing global burdens of atopic dermatitis and keloid formation, there is a need for a skin classification system that includes these hyperreactive skin conditions. Atopic dermatitis and keloid formation are more common in individuals with skin of color (Asians, Hispanics, and Africans). However, it is important to keep in mind that keloids can occur in all skin types. Therefore, we propose the following additions to the current Fitzpatrick skin classification scale:

I. Divide the current Fitzpatrick skin classification scale into A and B by asking two questions:

1. *Do you have sensitive skin (ie, atopic dermatitis, multiple skin allergies, etc)?*
2. *Do you have a history of hypertrophic scarring or keloids?*

II. If both answers are "no", patient is categorized as A (see Figure 1 and Table 1).

III. If "yes" to either or both of these questions, patient is categorized as B (see Figure 1 and Table 1).

Our proposal expands on the Fitzpatrick skin classification scale by incorporating hyperreactive skin types (ie, atopic dermatitis, multiple skin allergies, etc) and the tendency for keloid formation with an emphasis on improving dermatologic or cosmetic treatment outcomes for individuals with high skin reactivity. Our skin classification scale can be referenced during clinical practice prior to selecting dermatologic or cosmetic treatment options for individuals with the goal of avoiding undesired cosmetic results in patients with sensitive skin or patients who are prone to keloid formation. We define skin sensitivity based on reactivity to environmental insults or injury with examples in atopic dermatitis and keloid formation.

NEW/MODIFIED SCALES

Skin Phototyping Scales

The following skin classification scales are mostly objective and some subjective with the aim of predicting skin cancer risk. These scales do not take into consideration skin hyperreactivity or tendency for keloid formation. Despite the development of these new scales, the Fitzpatrick skin classification scale is still the most commonly used scale in clinical practice. Therefore, we have chosen to modify the Fitzpatrick skin classification scale to connect skin phototype with skin hyperreactivity and keloid formation, making it more relevant to the diverse skin types that exist today.

Pigment Protection Factor

Pigment protection factor (PPF) is an objective measure of skin phototype using diffuse remittance spectroscopy with a dedicated instrument, the Optimizer Scientific B555.[20] PPF is equal to the number of standard erythema doses (SED, 100 J per meter squared) required to provoke just perceptible erythema after a single exposure. It can range from PPF of 1 (erythema is elicited by 1 SED) in fair-skinned persons to PPF of 25 in darker-skinned persons.[20] In 2010, Wulf et al compared PPF with Fitzpatrick skin type and found PPF correlates better to MED and minimal melanogenesis dose (MMD) and therefore is better at predicting photosensitivity than Fitzpatrick skin type.[21]

Calorimetry and Spectrophotometry

Colorimetry involves the quantification of the appearance of color. Spectrophotometry involves the measure of the spectral

FIGURE 1. Diagram showing skin classification by color and skin sensitivity (hyperreactivity) or hypertrophic scarring/keloid history.

TABLE 1.

Skin Type Classification by Color and Hyperreactivity or Hypertrophic Scarring/Keloid History	
Skin Classification Type	**Description**
Skin type 1a	pale white; non-sensitive skin **without** hypertrophic scarring/keloid history
Skin type 1b	pale white; **with** sensitive skin or hypertrophic scarring/keloid history
Skin type 2a	white; non-sensitive skin **without** hypertrophic scarring/keloid history
Skin type 2b	white; **with** sensitive skin or hypertrophic scarring/keloid history
Skin type 3a	beige; non-sensitive skin **without** hypertrophic scarring/keloid history
Skin type 3b	beige, **with** sensitive skin or hypertrophic scarring/keloid history
Skin type 4a	light brown; non-sensitive skin **without** hypertrophic scarring/keloid history
Skin type 4b	light brown; **with** sensitive skin or hypertrophic scarring/keloid history
Skin type 5a	brown; non-sensitive skin **without** hypertrophic scarring/keloid history
Skin type 5b	brown; **with** sensitive skin or hypertrophic scarring/keloid history
Skin type 6a	dark brown; non-sensitive skin **without** hypertrophic scarring/keloid history
Skin type 6b	dark brown, **with** sensitive skin or hypertrophic scarring/keloid history

characteristics of color.[4] The Commission Internationale de l'Eclairage (CIE), is an international scientific organization that specializes in standardization of light and color. The individual typology angle (ITA) skin color classification is an objective skin classification system that is based on the CIE L* a* b* color space system. The CIE L*a*b color system is a 3-dimensional color system consisting of 3 axes. L* signifies the level of pigmentation of an individual, a* represents values on the red and green axis, which correlate with erythema, and b* represents values on the yellow and blue axis, which correlate with pigmentation and tanning. The ITA skin color classification uses calorimetric measurements of the L* and b* axes to classify skin color into 6 groups: very light, light, intermediate, tan, brown and dark.[22] One study showed that the ITA classification correlates with constitutive skin color.[22] The use of spectrophotometers is largely limited to research given their high cost and cumbersome use. Narrow-band reflectance spectrophotometers such as the Mexameter can be used objectively to determine skin color based on erythema and melanin indices.[23]

Color Bar Tool With Visual Analog Scale

The Color BarTool is a subjective tool for skin color categorization based on color bars. Individuals can determine their skin color by selecting the color bar that closely matches the skin tone on their upper inner arm.[24] One study showed a strong linear relationship between self-selected color bars and melanin indices measured by spectrophotometry.[24] This easily-used tool was developed to help identify individuals with increased skin cancer risk.[24]

Skin Tone Color Scale

The Skin Tone Color Scale is an objective tool for describing skin color using Munsell's color space system.[25] Munsell's color space uses Hue, value (V) and chroma. Determination of a specific skin color depends on the hue (absorbance or reflection of specific wavelengths of light), value (the intrinsic luminosity, ie, brightness), and chroma (the saturation).[4] There are five different hue plastic bars in the Skin Tone Color Scale, named – 1YR, 3YR, 5YR, 7YR, and 9YR.[25] Attached to the 5 plastic bars are 19 kinds of value color charts. Skin color is determined through a series of steps starting with 1 of the 5 plastic bars, next a chroma is determined and then finally a precise value is determined. The skin tone color scale was developed to assist in evaluating the effectiveness of therapies for diseases of pigmentation.[25]

Felix von Luschan Skin Color Chart

The Felix von Luschan skin color chart ranges from 1 to 36, with 1 representing the lightest color and 36 the darkest.[26] The numeric determination is subjectively based on skin color alone. One study showed a significant correlation between skin color determination by the Felix von Luschan skin color chart and a narrow-band reflectance spectrophotometer (Mexameter MX18).[26]

Skin Cancer Phototype (SCP)

Skin classification based on skin cancer risk has been proposed by Holm-Schou et al. The goal of their study was to establish a skin cancer (cutaneous malignant melanoma, basal cell carcinoma and squamous cell carcinoma) phototype classification system using questions from the Fitzpatrick skin classification scale.[20] The researchers asked 2 questions of study participants: tendency to burn (always burn, usually burn, sometimes burn, rarely/never burn), and ability to tan (never tan, tan less than average, tan as average, tan more than average).*20* They created a matrix of 16 classes based on responses. They classified individuals into skin cancer phototypes I through IV. Their results showed a linear relationship between the skin cancer phototypes and odds ratio for skin cancer.[20] Individuals with more sun sensitive skin showed an increased risk for skin cancer.[20]

Scales By Race/Ethnicity

The following skin classification scales have been developed based on the critique that the Fitzpatrick skin classification scale does not account for unique variations in skin types among different races and ethnicities. These scales take into consideration variations in individuals with skin of color however, there is no component of skin hyperreactivity or the tendency for keloid formation.

Kawada Skin Classification System for Japanese Individuals

The Kawada Skin Classification System for Japanese Individuals is similar to the Fitzpatrick skin classification scale as it is also based on UV radiation. Instead, patients are classified based on Japanese skin types and personal history of sun reactivity.[27] Investigators also studied the mechanism of UVA-induced delayed tanning to further determine the seasonal variations of these characteristics and their relation to skin color.[28]

Willis and Earles Scale

Willis and Earles reasoned that the Fitzpatrick skin classification scale does not accurately encompass the variability in skin phototypes amongst African Americans. The proposed scale accounts for the mixture of races (Africans, European Caucasians, and Native Americans) that represent contemporary African Americans. With this in mind, they deduce most African Americans could be classified as Fitzpatrick skin types II to IV instead of IV to VI.[29] The scale further classifies skin color based on reaction to UV light and association of pigmentary disorders in people of African descent.[29]

Modified Fitzpatrick Scale of Skin Phototyping for Indian Population

Sharma et al suggested modifications to the Fitzpatrick skin classification scale based upon Indian cultural behaviors and correlated this to skin color by using narrowband diffuse reflectance spectrophotometry. The author explains that individuals are less likely to tan as fair skin is highly valued

amongst the Indian population.[30] Two items related to purposeful sun exposure, use of tanning booths and/or creams, were removed as they were deemed irrelevant. Response options on genetic disposition were modified to account for the lack of differences in eye color, hair color, and color of unexposed skin amongst the Indian population.[30]

Scales for Cosmetic Procedures

Most of the aforementioned scales are primarily used to predict skin cancer risk. In some cases, one's risk of skin cancer may parallel their risk of adverse reactions such as dyspigmentation and poor scar formation from surgical or cosmetic procedures, but this is not universally true. Some scales have therefore been developed with the purpose of better predicting dermatologic or cosmetic treatment outcomes. These scales, especially the Roberts Skin Type Classification System, closely align with our proposal however they do not take into consideration skin hyperreactivity (atopic dermatitis, etc).

Lancer Ethnicity Scale

The Lancer Ethnicity Scale (LES) is a skin classification system developed for the purpose of determining outcomes for cosmetic laser surgery.[31] Individuals are typed based on their Fitzpatrick skin type and the ancestry of their parents and grandparents.[31] The LES skin type ranges from type I to type V.[31]

Fanous Skin Classification

The skin classification system created by Nabil Fanous utilizes individuals' skin color as well as the coarseness of their features to predict treatment outcomes for chemical peels and laser resurfacing.[32] The 6 racial categories include Nordics (light skin, fine features), Europeans (average color and coarseness), Mediterranean (darker and more coarse than Europeans), Indo-Pakistanis (coarser and darker than Mediterranean), Africans (black to deep black and coarse to very coarse), and Asians (light to medium dark and coarse to very coarse).[32] Based on the study for racial classification by Fanous, Europeans are the best candidates with least potential for complications from chemical peels or laser resurfacing.[32] Indo-Pakistanis and Africans were more susceptible to complications including scarring and hypopigmentation, when exposed to chemical peels or laser resurfacing.[32]

Goldman World Classification of Skin Type

The Goldman World Classification Scale considers the patients ancestry and Fitzpatrick phototype. The scale categorizes 5 races on their tendency to burn, tan, and develop post-inflammatory hyperpigmentation when exposed to UV radiation, laser, or surgical or chemical injury.[33]

Taylor Hyperpigmentation Scale

In 2006, the Taylor Hyperpigmentation Scale was proposed as a simple method of monitoring improvement in hyperpigmentation after cosmetic treatment.[34] It is a visual hyperpigmentation scale consisting of 15 color plastic cards that have 10 to 15 skin hues and up to 100 gradations of different colors of pigmentation. Each card has 10 bands of increasingly darker gradations of skin hues representing progressively increasing severities of pigmentation. Areas of hyperpigmentation are matched to the card color.[34]

The Roberts Skin Type Classification System

This 4-part skin classification system was developed in 2008 as a tool for predicting how an individual's skin would react to dermatologic and cosmetic procedures.[2] The Roberts Skin Type Classification System evaluates 4 elements including Fitzpatrick skin phototype, Glogau photoaging scale, Roberts Hyperpigmentation Scale, and Roberts Scarring Scale.[2,35-37] Each of the elements are assigned a score, which can then be used to develop a treatment plan that provides optimal outcomes for individuals.[2,35] While comprehensive, the Roberts Skin Type Classification System does not include skin sensitivity to environmental insults such as allergens.

CONCLUSION

Given the world's growing diverse population, a skin classification scale that represents the diversity of the population is important. Predicting skin cancer risk has long been a factor in skin classification. With increasing global burdens of atopic dermatitis and keloid formation, there is a need for a skin classification system that includes these hyperreactive skin conditions. Recent evidence has linked atopic dermatitis as an independent risk factor for keloid formation. Given this link, we have developed a modified Fitzpatrick skin classification scale that takes into consideration skin sensitivity/hyperreactivity and keloid formation. Interestingly, several studies have demonstrated resolution of keloid symptoms and reduction in keloid size in patients who were given the IL-4 receptor antagonist dupilumab.[8-9,16-19] Dupilumab is the first biologic medication approved by the US Food and Drug Administration for use in moderate-to-severe atopic dermatitis. Despite these studies, there have been contradictory findings and many questions remain prompting need for further research in this aspect of treatment.[38,39]

To our knowledge, there is no skin classification tool or classification system that accounts for an individual's response to environmental insults, particularly focusing on the link between atopic dermatitis and keloid formation. In clinical practice, our modified Fitzpatrick skin classification scale proposal can be used during decision making for dermatologic or cosmetic procedures to avoid unfavorable complications or poor treatment outcomes. Our scale is easy to implement as it is based on the widely recognized Fitzpatrick skin classification scale and can be used for all skin types.

DISCLOSURES

The authors involved with this journal-based activity report no relevant financial relationships with commercial interest(s).

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Diagnosis of Skin Disease in Moderately to Highly Pigmented Skin by Artificial Intelligence

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ABSTRACT

Background: Triage of patients with skin diseases often includes an initial assessment by a nurse or general practitioner, followed by a dermatologist. Artificial intelligence (AI) systems have been reported to improve clinician ability to diagnose and triage skin conditions. Previous studies have also shown that diagnosis in patients with skin of color can be more challenging.

Purpose: This study seeks to determine the performance of AI in the screening and triage of benign-neoplastic, malignant-neoplastic, and non-neoplastic skin conditions for Fitzpatrick skin types IV-VI.

Methods: A set of 163 non-standardized clinical photographs of skin disease manifestations from patients with Fitzpatrick skin types IV-VI were obtained through a publicly available dataset (Scale AI and MIT Research Lab, "Fitzpatrick 17 Dataset"). All photos were diagnosed by a specialist and categorized into three disease classes: benign-neoplastic, malignant-neoplastic, or non-neoplastic. There were 23, 14, and 122 cases of each disease class, respectively.

Results: Overall, the AI was able to classify the disease classes with a high degree of accuracy for the Top 1 diagnosis (86.50%). Based on its first prediction, the AI demonstrated the greatest accuracy when classifying non-neoplastic conditions (90.98%), high accuracy in detecting malignant-neoplastic conditions (77.78%), and moderate accuracy of classifying benign-neoplastic conditions (69.57%).

Conclusion: The AI had an overall accuracy of 86.50% in diagnosing skin disease in Fitzpatrick skin types IV to VI. This is an improvement over reported clinician diagnostic accuracy of 44.3% in darker skin types. Incorporating AI into front-line screening of skin conditions could thereby assist in patient triage and shorten the time to accurate diagnosis.

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INTRODUCTION

Early diagnosis of skin disease, especially malignant neoplasms, can significantly reduce patient morbidity and mortality. Assessment of most skin conditions is often first performed by a nurse and/or general practitioner before a subsequent referral to a dermatologist is made. Previous publications by numerous groups report the ability of custom-built Artificial Intelligence (AI) systems to help assess skin conditions.[1-6]

In 2021, Jain et al examined the use of Google's AI-based algorithm by primary care physicians and claimed it could improve the triage of skin conditions.[7] The study however severely underrepresented patients with more highly pigmented skin. Specifically, the AI was validated on only 15 out of 152 (9.9% of total) histologically verified cases of skin conditions in Fitzpatrick skin types IV and V and no histologically verified cases of the darkest Fitzpatrick skin type (VI). Due to the class imbalance present, the test set was heavily skewed towards the 3 lightest skin types with 90.1% of the data representing 50% of the Fitzpatrick classes (I-III), while only 9.9% of the data represented the other 50% of the Fitzpatrick classes (IV-VI). These investigators did not generate sufficient evidence to support the study's conclusion.

Recent studies have also highlighted the decreased diagnostic accuracy among clinicians and clinician-trainees on photos of patients with skin of color (SOC).[8-10] Specifically, Diao et al reported that the diagnostic accuracy of identifying cutaneous/subcutaneous pathology in darker skin types was significantly lower at 44.3% compared with 50.5% in intermediate skin and 50.4% in light skin.[8] This is likely due to poor representation of SOC in textbooks and instructional guides, comprising as low as 4% to 18% of the total number of photos in these teaching materials.[11] Furthermore, previous studies have reported that people with SOC have worse prognoses and lower survival rates compared to individuals with light skin. These poorer patient outcomes are due to delayed or incorrect diagnoses.[12-16]

The correct diagnosis of skin disease by general practitioners may be affected by skin type. The use of AI, especially that equipped to accurately diagnose conditions in patients with SOC, may be a means of improving the diagnostic performance of providers assessing and managing dermatologic conditions. The purpose of this study is to evaluate the effectiveness of AI in identifying and classifying cutaneous disease in patients with Fitzpatrick skin types IV-VI.

MATERIALS AND METHODS

A set of 163 de-identified clinical photos of skin disease manifestations from SOC patients with Fitzpatrick skin types IV-VI were obtained through a publicly available dataset published by Scale AI and MIT Research Lab, also known as the Fitzpatrick 17 Dataset. The Fitzpatrick 17 database can be accessed online.[17,18] It contains 16, 577 photos of skin lesions from 3 top-level disease categories: benign-neoplastic, malignant-neoplastic, and non-neoplastic. The photos were obtained from 2 online open-source dermatology atlases: 76% of photos from DermaAmin and 24% of photos from Atlas Dermatologico.[19,20]

The Fitzpatrick 17 Dataset is comprised of the most common dermatology conditions. It excludes 22 categories of skin conditions (Table 1). These categories were excluded because they were either too broad, too rare, or the photos were of poor quality. The final dataset includes 114 diseases with a range of 53 to 653 photos per skin condition.[18]

TABLE 1.

Categories of Skin Conditions That Were Excluded From Fitzpatrick 17 Database
Viral diseases, HPV, herpes, molluscum, exanthems, and others
Fungal infections
Bacterial infections
Acquired autoimmune bullous disease
Mycobacterial infection
Benign vascular lesions
Scarring alopecia
Non-scarring alopecia
Keratoderma
Ichthyosis
Vasculitis
Pellagra-like eruption
Reiters disease
Epidermolysis bullosa pruriginosa
Amyloidosis
Pernio and mimics
Skin metastases of tumors of internal organs
Erythrokeratodermia progressive symmetric
Epidermolytic hyperkeratosis
Infections
Generalized eruptive histiocytoma
Dry skin eczema

The Fitzpatrick skin type of each photo was described by a team of human annotators from Scale AI. Labels were determined by consensus opinion of the annotators, resulting in 72, 277 annotations for the entire Fitzpatrick 17 Dataset.[18]

Each photo in the Fitzpatrick 17 Dataset is further labeled with a specialist-provided diagnosis, which was confirmed through biopsy or response to treatment. These labeled photos serve as a reference and have been used and cited in dermatology and visual recognition software literature numerous times.[21-25] A total of 349 photos have a peer-reviewed, specialist-provided diagnosis and 163 of the photos with a peer-reviewed diagnosis are for skin types IV-VI. These 163 photos were selected as test data for our study.

The 163 photos in our test dataset were categorized at the highest level of the skin lesion ontology system into 3 classes (non-neoplastic, benign-neoplastic, or malignant-neoplastic) based on the photo diagnosis label provided in the dataset (Table 2).[21] This was denoted as the "Dataset classification." The classes defined in this published Dataset classification were used as the ground truth to maintain the ability to accurately compare predictions.

Next, the photos were uploaded to the custom-built AI software (Triage Inc.), and the top 2 diagnoses were recorded (first prediction = Top 1, second prediction = Top 2). A US and Canadian board-certified dermatologist (A.J.M.) categorized each diagnosis into 1 of the 3 classes: benign-neoplastic, malignant-neoplastic, or non-neoplastic. This was denoted the "Triage classification."

The Triage classification was compared with the Dataset classification for accuracy. Accuracy of the AI software was determined by the ratio of correct diagnoses to total diagnoses for each ontological class. Top 2 diagnosis was recorded as correct if the AI was able to correctly classify the photo with either its first or second attempt.

This study was monitored by Advarra Institutional Review Board. Statistical analysis was performed by GraphPad Prism 9. The Shapiro-Wilk test was performed to test for normality of distribution. Subsequently, Kruskal-Wallis test and Dunn's multiple comparison test were used to test for statistical differences in accuracy between the 3 classes. Results were considered statistically significant at a P-value <0.05.

TABLE 2.

Example List of Conditions and Corresponding Classification	
Dataset Label	**Classification**
Acanthosis nigricans	non-neoplastic
Acne	non-neoplastic
Acne vulgaris	non-neoplastic
Actinic keratosis	malignant
Basal cell carcinoma	malignant
Cheilitis	non-neoplastic
Darier disease	non-neoplastic
Dermatomyositis	non-neoplastic
Disseminated actinic porokeratosis	benign
Drug eruption	non-neoplastic
Dyshidrotic eczema	non-neoplastic
Eczema	non-neoplastic
Ehlers-Danlos syndrome	non-neoplastic
Erythema elevatum diutinum	non-neoplastic
Erythema multiforme	non-neoplastic
Erythema nodosum	non-neoplastic
Factitial dermatitis	non-neoplastic
Fixed eruptions	non-neoplastic
Folliculitis	non-neoplastic
Granuloma annulare	non-neoplastic
Hailey-Hailey disease	non-neoplastic
Halo nevus	benign
Ichthyosis vulgaris	non-neoplastic
Incontinentia pigmenti	non-neoplastic
Kaposi sarcoma	malignant
Keloid	non-neoplastic
Lichen amyloidosis	non-neoplastic
Lichen planus	non-neoplastic
Lichen simplex	non-neoplastic
Lupus erythematosus	non-neoplastic
Lymphangioma	benign
Melanoma	malignant
Mycosis fungoides	malignant
Naevus comedonicus	benign
Necrobiosis lipoidica	non-neoplastic
Nematode infection	non-neoplastic
Neurofibromatosis	non-neoplastic
Neurotic excoriations	non-neoplastic
Neutrophilic dermatoses	non-neoplastic
Nevocytic nevus	benign
Nevus sebaceous of Jadassohn	benign
Papilomatosis confluentes and reticulate	non-neoplastic

TABLE 2. CONTINUED

Example List of Conditions and Corresponding Classification	
Dataset Label	**Classification**
Pediculosis lids	non-neoplastic
Pityriasis rosea	non-neoplastic
Pityriasis rubra pilaris	non-neoplastic
Porokeratosis actinic	benign
Port wine stain	benign
Prurigo nodularis	benign
Psoriasis	non-neoplastic
Pyogenic granuloma	benign
Sarcoidosis	non-neoplastic
Scabies	non-neoplastic
Scleroderma	non-neoplastic
Scleromyxedema	non-neoplastic
Seborrheic keratosis	benign
Solid cystic basal cell carcinoma	malignant
Squamous cell carcinoma	malignant
Stasis edema	non-neoplastic
Sun damaged skin	non-neoplastic
Superficial spreading melanoma	malignant
Syringoma	benign
Tuberous sclerosis	non-neoplastic
Tungiasis	non-neoplastic
Urticaria pigmentosa	non-neoplastic
Vitiligo	non-neoplastic
Xanthomas	non-neoplastic
Xeroderma pigmentosum	non-neoplastic

RESULTS

Of the 163 photos collected and used in the "Dataset classification," 122 (75%) were non-neoplastic, 23 (14%) were neoplastic-benign, and 18 (11%) were neoplastic-malignant. Additionally, 81 (50%) of the photos were Fitzpatrick skin type IV, 43 (26%) Fitzpatrick V, and 39 (24%) Fitzpatrick VI.

The AI software was able to classify the photos into 1 of 3 disease classes (non-neoplastic, benign-neoplastic, malignant-neoplastic) with a high degree of overall accuracy. Top 1 diagnosis had an overall accuracy of 86.50%, and Top 2 diagnosis had an overall accuracy of 93.25% (Table 3). The AI had the greatest accuracy when classifying non-neoplastic conditions, with a Top 1 diagnostic accuracy of 90.98% and Top 2 accuracy of 94.26%. The AI was also able to detect malignant-neoplastic conditions at a high degree of accuracy (Top 1, 77.78%; Top 2, 83.33%). The AI was moderately accurate at classifying benign-neoplastic conditions (Top 1, 69.57%; Top 2, 82.61%). Notably, there was a statistically significant difference in the Top 1 accuracy between the benign and non-neoplastic class (P=0.018; Table 4).

TABLE 3.

Top 1 and Top 2 Accuracy of Artificial Intelligence Diagnosis of Non-Neoplastic, Benign, and Malignant Skin Conditions		
	Top 1 Diagnosis	Top 2 Diagnosis
Total Correct	141	152
Total Incorrect	22	11
Total Cases	163	163
Overall Accuracy	86.50%	93.25%
Non-Neoplastic Correct	111	115
Non-Neoplastic Incorrect	11	5
Total Non-Neoplastic Cases	122	122
Non-Neoplastic Accuracy	90.98%	94.26%
Benign Correct	16	19
Benign Incorrect	14	15
Total Benign Cases	23	23
Benign Accuracy	69.57%	82.61%
Malignant Correct	14	15
Malignant Incorrect	4	3
Total Malignant Cases	18	18
Malignant Accuracy	77.78%	83.33%

TABLE 4.

Differences in Top 1 Accuracy Among the Three Classes (Non-Neoplastic, Benign, and Malignant)		
Dunn's multiple comparison test	Accuracy	*P*-value
Benign vs. non-neoplastic	69.57% vs. 90.98%	0.018*
Benign vs. malignant	69.57% vs. 77.78%	>0.999
Malignant vs. non-neoplastic	77.78% vs. 90.98%	0.381

*Significant at *P*-value <0.05

DISCUSSION

In the present study, we demonstrated that AI performed with a high overall accuracy in diagnosing various skin conditions among Fitzpatrick skin types IV-VI, with the first diagnosis being correct 86.50% of the time. The AI was most accurate in diagnosing non-neoplastic, followed by malignant and then benign conditions. The lower accuracy for the benign class and the significant difference in accuracy between benign and non-neoplastic classes can be explained by class weights in the AI algorithm. Class weights in machine learning adjust the importance of different classes during training to ensure that the model learns equally well from all classes. This is important when dealing with imbalanced datasets where some classes may be more common than others. For example, in a skin disease detection model, assigning higher weights to less common skin diseases ensures that the model learns to detect all types of skin diseases equally well, even if some are less common than others. By using class weights, the model can be trained to avoid becoming biased towards the more common classes and perform better overall.

Class weight imbalance is a common problem in machine learning. Class weight imbalance occurs when the data used to train or develop AI software is not evenly distributed between classes, thus resulting in one class being overrepresented compared with another. A class weighting technique can address these imbalances by modifying the cost function of the model. Here, incorrectly classifying an observation from the smaller class is penalized more than incorrectly classifying an observation from the larger class thereby rebalancing the class distribution and increasing the accuracy of the model.[26]

The cost function of the AI used in our study has been adjusted so that misclassifying a photo from the malignant class is more heavily penalized than misclassifying an observation from the benign class. This serves 2 important functions. The algorithm is intentionally biased towards overclassifying lesions as malignant to ensure equivocal cases are further examined by dermatologists, dermoscopy, and/or biopsy to reduce the likelihood of a missed malignant skin lesion. Second, the AI has a high sensitivity and a low specificity for diagnosing malignant lesions to decrease the chances of a false negative result and missing a malignancy. While decreasing false negatives is important, we recognize an abundance of false positives is also an issue. Overdiagnosis can lead to unnecessary procedures for the patient and increased healthcare costs. Therefore, it is critical that clinicians consider AI as an aid, and do not solely rely on the AI when rendering a diagnosis.

The accuracy of Top 2 diagnosis was consistently higher than the accuracy of Top 1 diagnosis in our study. Top 2 diagnosis was recorded as correct if the AI was able to correctly classify the photo with either its first or second attempt. Therefore, the number of correct diagnoses after the second attempt will be equal to or greater than the number of correct diagnoses after the first attempt. It follows that Top 2 accuracy will be equal to or greater than the Top 1 accuracy. The quality and accuracy of the input data are also important to consider when testing the efficacy of any AI system. Groh et al performed a data quality check on a random 3% sample of the Fitzpatrick 17 Dataset (504 photos) and reported that 2 "board-certified dermatologists identified 69.0% of photos as diagnostic of the labeled condition, 19.2% of photos as potentially diagnostic (not clearly diagnostic but not necessarily mislabeled, further testing would be required), 6.3% as characteristic (resembling the appearance of such a condition but not clearly diagnostic), 3.4% are considered wrongly labeled, and 2.0% are labeled as

other."[18] This is consistent with the 3.4% average inaccuracy rate in the most used test datasets for visual, language, and audio processing software.[18]

As mentioned, 349 of the 504 photos in the Fitzpatrick 17 dataset were peer reviewed by a specialist to confirm the diagnosis label, and the 163 photos of cases manifesting in patients of Fitzpatrick skin types IV-VI were selected from this subset and used in our study. This subset of data included photos that were labeled as "diagnostic" of the labeled condition by 2 peer reviewers who conducted the quality check. This subset of data excluded data that was peer reviewed as "potentially diagnostic," "characteristic," "wrongly labeled," or "other." Therefore, this study only evaluated cases where the "diagnostic" label was confirmed by multiple peer reviewers.

Previous studies have shown the utility of this specific AI system (Triage Inc.) in assessing skin conditions prior to referral to a dermatologist. In a 2022 study, our group evaluated the accuracy of diagnosing 100 non-standardized, variable-quality telemedicine photos using AI compared with a panel of dermatologists. The results demonstrated no significant difference in diagnostic accuracy with AI correctly diagnosing 63% of photos compared with the 64.3% correctly diagnosed by the dermatologist panel.[1] The study demonstrated AI as a beneficial resource for triaging patients with potential skin cancer.

Another 2022 study evaluated the efficacy of 3 well-established algorithms in differentiating benign versus malignant lesions in a dataset of diverse skin tones. Daneshjou et al reported that all 3 algorithms performed worse on Fitzpatrick skin types V-VI compared to skin types I-II.[27] Additional studies report the poor performance of certain algorithms in diagnosing disease in patients with darker skin, with diagnostic accuracy as low as 17%.[28] These findings are likely a result of low representation of SOC in the algorithm training and development and demonstrate that fine tuning AI algorithms on more diverse image data could close this performance gap.[27] In our current study, our AI maintained a high diagnostic accuracy in Fitzpatrick skin types IV-VI.

One limitation of our current study is the uneven distribution of disease classes (75% non-neoplastic, 14% neoplastic-benign, 11% neoplastic-malignant) within the dataset. Furthermore, it is important to consider the classification system itself. In specific cases, classifying skin conditions into non-neoplastic, neoplastic-benign, and neoplastic-malignant may be ambiguous. For example, certain syndromes (eg, genodermatoses) are comprised of a constellation of dermatologic manifestations. Each manifestation might be considered a unique dermatologic condition by itself—but when considered as a whole, the syndrome is the most likely diagnosis. Diagnostic criteria for these syndromes require a certain number of these individual manifestations to be present to accurately diagnose the condition. These nuances result in difficulty categorizing conditions as exclusively one disease class. In a real-world setting where rare cases occur, one could therefore imagine how powerful the joint opinion of the specialist and AI might be, rather than relying on AI or the specialist alone. Lastly, our study does not compare the AI algorithm's performance in darker vs lighter skin types, however, it demonstrates a high overall diagnostic accuracy and the clinical utility of AI for patients with moderately to highly pigmented SOC.

CONCLUSION

The AI algorithm in this study demonstrates high diagnostic accuracy in classifying skin disease in Fitzpatrick skin types IV-VI. While the development of AI in identifying skin conditions has advanced significantly over the past several years, opportunity for further refinement remains, especially for SOC. Future development of SOC case photo repositories and algorithms trained on photos with equal representation of all Fitzpatrick skin types will be essential to optimize diagnostic accuracy and clinical utility for all patients.

DISCLOSURES

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ORIGINAL ARTICLE

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Racial and Ethnic Disparities Among US Academic Dermatology Leadership and Its Influence on Resident Diversity

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ABSTRACT

Background: Diversity in medicine improves mentorship and patient care. However, dermatology is one of the least diverse specialties. We analyzed the racial distributions across leadership positions at academic dermatology programs and explored potential influences on resident racial/ethnic composition.

Methods: A list of ACGME-accredited dermatology programs was obtained. Residency program websites, hospital websites, and publicly available data were used to ascertain race and ethnicity of academic dermatology leadership and residents. SAS version 9.4 was used to calculate descriptive statistics and associations between racial/ethnic composition of dermatologists in leadership positions and residents.

Results: Underrepresented in medicine (URM) individuals were significantly underrepresented across both leadership (6.9%) and resident (12.0%) positions. No statistically significant correlation was found between the percent of URM leadership and URM residents.

Conclusion: Diversity among the US population, medical students, dermatology trainees, and faculty are not reflected in departmental leadership in academic dermatology. This may influence URM recruitment into the field, retention of URM faculty and residents, and mentorship opportunities for URM dermatologists interested in leadership positions. Efforts are needed to improve disparities in representation across leadership roles in academic dermatology.

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INTRODUCTION

It is known that dermatology is one of the least diverse fields in medicine. It continues to fall behind most other specialties in attracting and matching underrepresented in medicine (URM) applicants, which is defined by the AAMC as American Indian/Alaska Native, Black, Latino/Latina, or Native Hawaiian/Pacific Islander.[1-4] URM applicants report racial and ethnic diversity as being very important in regard to residency program selection,[5] and race-concordant recruitment and mentorship are highly effective.[6] In addition, the absence of URM dermatologists in mentorship and leadership positions has been cited as a barrier for URM students interested in dermatology.[7,8] Unfortunately, URM dermatologists make up less than 10% of all academic dermatology faculty.[9] Therefore, URM recruitment may be limited by the small proportion of URM faculty members, and potentially even fewer URM leaders, available to provide support and mentorship.

To our knowledge, there are no prior studies of URM composition among academic dermatology leadership and the relationship to the racial and ethnic composition of residents. Therefore, we sought to (1) determine the current racial and ethnic composition of US dermatology residency leadership and (2) investigate the relationship between leadership diversity and the composition of URM residents. Developing a better understanding of racial gaps will allow us to create actionable goals to close gaps and ensure academic dermatology leadership is reflective of the faculty, trainees, and patients we serve.

MATERIALS AND METHODS

This study was deemed exempt by the Penn State Health Human Research Protection Program. A cross-sectional study of the racial and ethnic makeup of US dermatology residency programs was performed in March 2022. A list of US accredited dermatology programs was obtained from the Accreditation Council for Graduate Medical Education (ACGME) website. Program and hospital websites were used to identify program leadership and residents. Leadership positions included Chair, Vice Chair, Chief, Program Director, Associate Program Director, and Assistant Program Director. If an individual held multiple positions, only their highest position was recorded to avoid redundancy. Two

independent reviewers (MF and PS) determined the races and ethnicities of dermatologists holding leadership positions and the URM status of residents. Biographical information and photographs provided on department websites in conjunction with public information from the Association of American Medical Colleges (AAMC) were utilized to assist in ascertaining the outcomes.

Race and ethnicity were considered mutually independent within the context of this study: Hispanic or Latino/Latina individuals were referred to as Hispanic; non-Hispanic White individuals were referred to as White; non-Hispanic Black or African American individuals were referred to as Black; non-Hispanic Asians or Asian Americans were considered Asian; non-Hispanic American Indians, Alaska Natives, Native Hawaiians, or Pacific Islanders were categorized as Native American; non-Hispanic people of another race or multiple races were grouped as "other." URM was defined, based on the AAMC definition, as Latino/Latina, Black, American Indian/Alaska Native, or Native Hawaiian/Pacific Islander.[4] If there was no information available to aid in delineating race, it was recorded as missing data. Advanced practice providers, non-physician administration, and affiliate faculty were excluded.

R version 4.0.4 was used for statistical analysis. Descriptive statistics were calculated, and Spearman's rank correlation was used to determine potential associations between URM faculty and URM resident composition.

RESULTS

Racial and Ethnic Composition of Dermatology Leadership

Of the 305 faculty members identified as holding one of the included leadership positions, 21 (6.9%) were considered URM, while 242 (79.3%) were White, and 42 (13.8%) were Asian. URM dermatologists were the minority across every leadership position (Table 1).

Compared to dermatology residents, medical students, and the US population, URMs in leadership were underrepresented, while only Whites in leadership were overrepresented. Hispanics, Native Americans, and Asians in leadership were also underrepresented compared to their respective percentages of faculty (Table 2).

Associations Between Leadership and Resident Racial and Ethnic Composition

Based on our data, 12.0% of residents were considered URM. There was not a statistically significant correlation between the

TABLE 1.

Racial and Ethnic Distribution Among US Academic Dermatology Program Leadership

	White (%)	Asian (%)	Black (%)	Hispanic (%)	Native American (%)
Chairs	81.9	10.6	5.3	2.1	0.0
Vice Chairs	81.8	18.2	0.0	0.0	0.0
Chiefs	62.5	18.8	0.0	18.8	0.0
Program Directors	79.8	14.0	1.8	3.5	0.9
Associate Program Directors	79.3	13.2	3.8	3.8	0.0
Assistant Program Directors	76.5	23.5	0.0	0.0	0.0
All Leadership Positions	79.3	13.8	3.0	3.6	0.3

TABLE 2.

Racial and Ethnic Distribution Among Dermatology Program Leadership Compared to Academic Dermatology Faculty, Dermatology Residents, Medical Students, and the US Population

	Dermatology Leadership	Academic Dermatology Faculty (Leadership and Non-leadership)[9]	Dermatology Residents[3]	Medical Students Applying to All Residencies (2017-2021)[2]	US Population[10]
Black	3.0%	2.9%	5.0%	8.1%	13.4%
Hispanic	3.6%	4.5%	6.6%	9.1%	18.5%
Native American	0.3%	0.12%	0.9%	0.8%	1.5%
Total URM	6.9%	7.5%	12.5%	18.0%	33.4%
Asian	13.8%	20.9%	23.5%	25.5%	5.9%
White	79.3%	66.9%	61.5%	47.5%	76.3%

*The races/ethnicities of academic dermatology faculty, dermatology residents and medical students are as reported by the AAMC. These numbers differed slightly from ours as some individuals (as published by the AAMC) reported multiple races/ ethnicities, while others did not report any. However, we were unable to make such distinctions, and categorized these individuals based on a singular race/ethnicity.

percent of URM leadership and URM residents at each program (Spearman's rank correlation coefficient P=0.06, P=0.505).

DISCUSSION

These results highlight the issue of lack of ethnic and racial diversity in academic dermatology leadership. URM individuals were significantly underrepresented across both leadership and residents. Among leadership positions, URM faculty were underrepresented at every position included in the study. However, no correlation between the percent of URM faculty and URM residents was established.

The lack of URMs in leadership roles in academic dermatology may be secondary to several potential reasons: overlooked and undervalued unique capabilities, unconscious biases of those who decide on who leaders, personal and family obligations, overt prejudice, and lack of mentorship, among others.[11,12] Future studies are needed to discern the specific reasons. Regardless, underrepresentation of minoritized dermatologists in leadership roles suggests that people of color are not proportionately influencing the profession, contributing new perspectives to improve patient care, or modeling leadership for those that could come after them.

Minoritized populations are the most rapidly growing in the US, with a majority-minority population projected for the first time in 2043.[13] However, representation across dermatology, especially in academic leadership, to this point, has not kept up. Only 6.9% of dermatology leadership were considered URM, in stark contrast to the URM population of 33.4% in the US[10] Beyond direct impacts on patient care,[14] the lack of URM influence at leadership levels may have repercussions on the cultural climate of programs as well as recruitment efforts of URM medical students and faculty. The authors believe this will propagate a feed-forward loop of inadequate intercultural competence that may negatively affect the standard of care in the growing URM community.

The small number of URM leaders was irreflective of the diversity of residents and medical students. Only 6.9% of leadership were considered URM, compared to 12.0% of dermatology residents, 16.2% of medical students applying to dermatology, and 18.1% applying to all specialties.[1,2] Consistent with prior data,[15] this means that URM medical students are neither applying nor being accepted to dermatology residency programs at representative rates. This may be due to lack of group identity, mentorship, and role models available to support URM medical students.[7,8] Lack of diversity among faculty has specifically been cited by URM students as a barrier to applying to dermatology.[7,8] Further, hospitals with greater representation of URMs in leadership positions demonstrate greater commitments to diversity initiatives.[16] Having leadership that is more reflective of the students who most need their support would improve recruitment into the field and convey that a career in dermatology is an achievable path to future professional success.

The results of our study should be taken within the context of its limitations. In addition to AAMC data, the authors of this study utilized department websites to assess biographies and photos for racial determinations. This data was difficult to validate and may not be congruent with how subjects self-identify. However, each subject was assessed by two independent evaluators with the same resources utilized by residency applicants to gauge their perception of diversity at each program. Secondly, our data differed slightly when compared to numbers published by the AAMC. This was likely due to our inability to make distinctions between subjects who may have identified as having multiple races/ethnicities or subjects who did not report their race/ethnicity to the AAMC. Finally, as departmental leadership frequently changes, some of these positions may have changed since data collection, especially given that some identified dermatologists held interim positions.

CONCLUSION

In conclusion, the current composition of academic dermatology leadership is not reflective of the students and patients who would benefit most from their support. Delineating concrete steps in working toward more diverse leadership will improve several facets of the field, including, but not limited to support for URM medical students and residents and retention of URM faculty and trainees into academic dermatology. It will ensure URMs have the space and voice to proportionately influence the practice of dermatology and, ultimately, strengthen the care available to vulnerable patients.

DISCLOSURES

The authors have no conflicts of interest or funding sources to declare.

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Racial and Ethnic Variations in Skin Barrier Properties and Cultural Practices in Skin of Color Newborns, Infants, and Children

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ABSTRACT

Background: The skin of newborns and infants of all races/ethnicity is more susceptible to skin barrier disruption than adult skin. This consensus paper offers insights into potential skincare implications for using gentle cleansers and moisturizers for skin of color (SOC) newborns, infants, and children.

Methods: Six pediatric dermatologists and dermatologists used a Delphi communication technique to adopt 5 statements for SOC newborns, infants, and children on skin barrier integrity and the importance of skin care to promote a healthy skin barrier.

Results: Regardless of ethnicity, newborn and infant skin is still developing and more susceptible to infections and chemical and thermal damage. A growing body of evidence supports skincare starting early in life, recognizing that the ongoing daily use of gentle cleansers and moisturizers containing barrier lipids, such as ceramides, promotes a healthy skin barrier. Understanding cultural differences in everyday skincare practices for SOC newborns, infants, and children is critical for developing an evidence base to substantiate skincare practices.

Conclusions: Closing knowledge gaps in the clinical presentation, cultural differences, and approach to treating skin conditions using skincare for SOC newborns, infants, and children may improve patient outcomes.

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INTRODUCTION

Newborn and infant skin is still developing, as indicated by elevated trans-epidermal water loss (TEWL), skin surface pH, and desquamation.[1-8] The skin of newborns and infants, with its distinct anatomical and functional properties, is susceptible to skin barrier disruption.[1-8]

Newborn and infant skin has elevated thermal conductance and is more susceptible to infections and chemical and thermal damage because of immature barrier function.[1-9] The neonatal and infant skin requires particular caution with topical skincare regimens.[8-14] Advice on how best to care for newborns' and infants' skin has long been debated, with opinions repeatedly changing over time in response to new concerns.[14] Further, skincare guidelines should also consider racial/ethnic variations in skin properties and cultural practices to allow healthcare professionals to tailor recommendations to individual patients.

Data on racial and ethnic variations, effects on barrier function, and the potential role of adjunctive skin care for newborns, infants, and children are relatively limited. Newborns and infants with a skin of color (SOC) include people of African,

Asian, Latinx, and First Nations descent. Knowledge gaps in the clinical presentation, cultural differences, and approach to treating skin conditions using skincare for SOC newborns, infants, and children contribute to disparities in care.[1]

This manuscript offers insights into these knowledge gaps and their potential skincare implications for using gentle cleansers and moisturizers for SOC newborns, infants, and children.

MATERIALS AND METHODS

A panel of 6 pediatric dermatologists and dermatologists (advisors) who treat newborns, infants, and children of SOC developed a consensus paper for this population on skin barrier integrity and the importance of ceramides (CERs)-containing skincare to help maintain their developing skin barrier. The paper used the Delphi communication technique for interactive decision-making for medical projects.[16,17] The selected information from the literature searches, coupled with the advisors' opinions and experience, was used to adopt statements that aim to provide clinical information for pediatric dermatologists, dermatologists, and pediatric healthcare providers treating SOC newborns, infants, and children.

Structured Literature Review

On February 12, 2022, the advisors convened in Miami Beach, Florida. In preparation for the meeting, a structured search of the English-language literature was performed on December 23, 2021, using PubMed, with Google Scholar as a secondary source. The search included literature on skin barrier function, the current best practices for using nonprescription skincare, and clinical research studies for SOC newborns and infants published in English from 2010 to 2021. Excluded were publications with no original data (unless a review article was deemed relevant), not dealing with nonprescription skincare, and written in a language other than English.

Search Terms: *SOC newborns, infants AND skin barrier physiology, function, dysfunction, barrier maturation, vernix, OR erythema, OR skin breakdown, OR diaper care, umbilical cord care, OR skin barrier protection, AND depletion of stratum corneum lipids, AND atopic dermatitis prevention, AND treatment, OR mitigation of atopic dermatitis, AND skincare, cleansers, moisturizers, emollients, ceramides, ce¬ramide containing skincare, AOR SOC newborns, infants AND skin maturation and moisturization, efficacy, safety, tolerability, OR SOC newborns, infants, AND skin irritation using skincare.*

Selected publications were manually reviewed for additional resources.

The searches yielded 128 papers and, after the exclusion of 21 articles, 107 papers clinically relevant to current best practices in SOC newborns and infants to promote skin barrier integrity and to help mitigate atopic dermatitis (AD) remained. Of the 107 papers, 60 addressed newborns, infants, and skincare generally, and 19 discussed specifically SOC newborns, infants, and skincare. Although the number of clinical studies on skincare for this group is growing, there were no robust comparative studies on skincare for SOC newborns, infants, and children to justify a systematic review.[17]

To estimate the state of the art in skin care for SOC newborns, infants, and children, the 23 clinical studies were graded independently by 2 reviewers (AA and HA). The reviewers assigned a level of evidence for each treatment (Type of study: A [high quality clinical double-blind, randomized controlled trial (RCT)], B [lesser quality RCT], C [comparative study with severe methodological limitations], and 1 [further research is unlikely to change confidence in the estimate of treatment effect] to level 4 [any estimate of effect is very uncertain]) using the pre-established criteria.[17]

Development of the Statements

The reviewers drafted 17 evidence-based statements on the role of skin care in promoting a healthy barrier in SOC newborns and infants and the potential mitigation of AD in SOC children. During the meeting, the advisors were divided into 3 groups, and drawing from the draft statements, they each selected their top 5 statements. After discussion, the advisors reached a consensus on 5 statements focusing on the science of racial/ethnic skin barrier differences and the importance of cultural practices, underscoring the need for clinicians to understand that there are physiological and cultural differences to consider when treating newborns and infants with SOC.

RESULTS

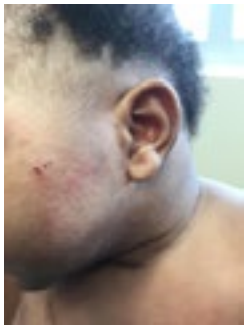
Statement 1: *Excluding culture and ethnicity restricts our overall understanding of health research evidence.*

Studies evaluating racial/ethnic differences in skin properties have been small-scale and mainly include adults rather than children.[10,18] These studies have shown inter-individual differences and inconsistencies in anatomical study sites measured, which are greater than racial/ethnic differences measured by the investigators.[10,18] Xerosis occurs in all races; however, the severity and impact of xerosis between racial/ethnic groups can vary.[18]

Misdiagnosis of dermatologic conditions is common in newborns/infants with SOC, as many clinicians expect these conditions to look and behave as they do in White infants.[19,20]

An algorithm for practitioners to address skin conditions in newborns and infants was published previously; however, the racial/ethnic variations in the skin of neonates as well as cultural differences, require additional considerations for clinicians and

FIGURE 1. Infant with a violaceous atopic dermatitis lesion on the cheek. *Photo courtesy of Jaggi Rao MD*



offer even more opportunity to tailor their approach to skincare for these patients.[15] A study on SOC newborns in the United Kingdom (UK) evaluated TEWL, pH, stratum corneum (SC) hydration, melanin, dryness, and erythema at birth and week 4; while parents/caretakers completed a qualitative diary on skin care practices and skin observations.[67] SC hydration and melanin increased in the first 4 weeks of life, and SC pH and erythema decreased significantly. Parents reported being frequently insecure, and noted all minor skin changes in the infants' skin prompted product use. The study observed that skin integrity and skin care practices of infants from SOC groups in the UK differed significantly from White infants. The SOC study group used more skincare products than their White counterparts, particularly oils (used on 62.4% of SOC infants, n=83). This study, and more deliberative studies with SOC newborns, infants, and children that investigate racial/ethnic and cultural differences, may be useful for infant skin care guidelines to provide culturally sensitive advice relevant to the real-world context of newborns and infant care.

Statement 2: *Genetic and environmental factors influence the stratum corneum barrier properties and function. Biophysical studies are needed to help patients make informed skincare choices.*

Increasingly studies on SOC groups show variability in the skin's physiological properties, which influences the SC condition and sensitivity to exogenous agents.[18] Investigations using biophysical measurements to report racial/ethnic differences in skin properties may include TEWL, water content, SC pH, ceramide level, and skin reactivity.[18] Studies reporting TEWL differences between adult SOC groups have yielded conflicting results. Studies on adults showed differences in SC characteristics among SOC groups. These included a higher TEWL and ceramide content in Asian skin and lower water and ceramide content in Black skin.[18] Additionally, the study showed a higher skin reactivity in Asian compared with Black and White skin.[18] Additional biophysical assessments to better determine racial/ethnic variations in skin properties would assist in more tailored skincare product selection.[10,18]

Statement 3: *Literature suggests racial/ethnic variations in ceramide content, stratum corneum structure, and filaggrin mutations.*

Although the role of race and ethnicity in the pathophysiology of AD remains unclear, variations in the epidemiology, clinical presentation, disease course, and impact on quality of life have been reported in different racial/ethnic populations.[36-42] An extensive population-based survey of 102,353 families representing all 50 US states (National Survey of Children's Health [NSCH]) showed that African American children are 1.7 times more likely to have AD than their White counterparts even when adjusting for household income, parental education level, metropolitan vs rural environment, and health insurance coverage status.[36]

Although several studies have consistently found filaggrin (FLG) loss-of-function mutations in up to 50% of European and 27% of Asian patients with AD, FLG mutations were 6 times less common in African Americans than in European American patients, even in patients with severe AD.[41] Korean, Japanese,

FIGURE 2. Child with a dark brown atopic dermatitis lesion. *Photo courtesy of Jaggi Rao MD.*

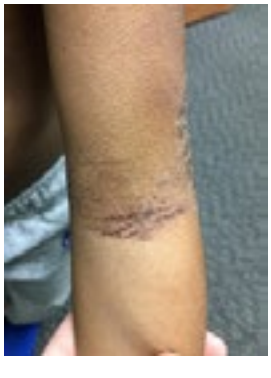
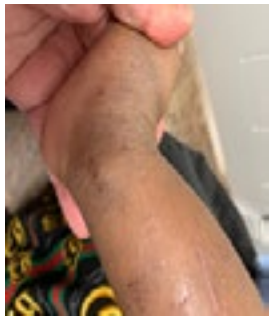


FIGURE 3. Infant with a reddish brown atopic dermatitis lesion. P*hoto courtesy of Jaggi Rao MD.*



Chinese, Singaporean, and Taiwanese populations all have specific FLG null mutations unique to their ethnic group, and they rarely exhibit the mutations commonly observed in White patients with AD.[43] FLG mutations seem to play less a pathogenic role in patients of African origin than in individuals of European or Asian ancestry.[41,43]

Loss of function in FLG has been associated with skin barrier abnormalities, the abnormal architecture of the lamellar bilayer, and increased TEWL in White patients with AD.[44] The prevalence of loss of function in FLG varies by population, with lower frequencies reported in AD patients of East Asian and African descent.[44]

Some data do suggest that an increase in TEWL and a decrease in CER in Black skin may contribute to pruritus and its related conditions.[45,46] Studies from AD patients of Asian and African descent living in Europe and the US indicate that pruritus may be more frequent and severe.[46] Further variations in mast cell composition have been shown in Black skin, which may be of functional relevance.[47]

Studies mostly on White newborns have indicated an impaired SC barrier function at birth in AD-predisposed newborns.[11] An impaired skin barrier function assessed at birth and 2 months of age may precede clinical AD.[12] Following this assumption, therefore, a genetically predisposed child may present with xerosis; however, the exposure to environmental triggers may lead to actual AD flares.[31,32]

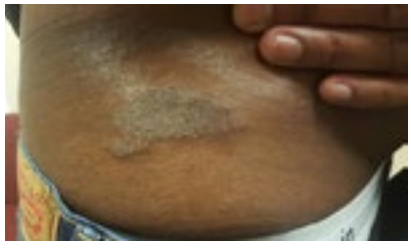
Two small prospective, randomized controlled trials demonstrated that daily moisturizer use prevented AD in 32% of Japanese and 50% of Anglo-American high-risk newborns.[50,51] The Japanese study further suggested that allergic sensitization during this period was associated with AD but not with moisturizer use.[50] More recent and ongoing studies are still evaluating whether neonatal moisturization in AD-prone newborns is significantly beneficial.[52]

Although there are few studies including SOC infants and children, skincare such as cleansers and moisturizers should be integral to AD prevention, treatment, and maintenance for all newborns, infants, and children.[14,15]

Statement 4*: In all ethnic categories, newborn/infant skin has elevated transepidermal water loss, altered skin surface pH values, and increased desquamation, making it more susceptible to sensitization, infections, and chemical and thermal damage.*

Skin surface pH at birth is typically more alkaline than adult skin, ranging from 6.34 to 7.5, depending on the anatomical site.[14,15] A mature SC has a pH usually between 4.0 to 6.0, while the body's internal pH is about 7.4.[24] Skin acidification plays an important role in barrier maturation and the activation of enzymes involved in the extracellular processing of SC lipids.[6,8-11,14]

FIGURE 4. Gray atopic dermatitis lesion in a deeply pigmented child. *Photo courtesy of Jaggi Rao MD.*



Studies comparing newborn and infant with adult skin properties in various SOC populations found similar differences in SC thickness, water handling properties, and SC pH between infants and adults, as studies that did not distinguish between ethnicities.[1,35,55-57] Infant SC was thinner than adult SC and exhibited higher SC pH, water content, and TEWL levels (Table 1).[1,35,55-57]

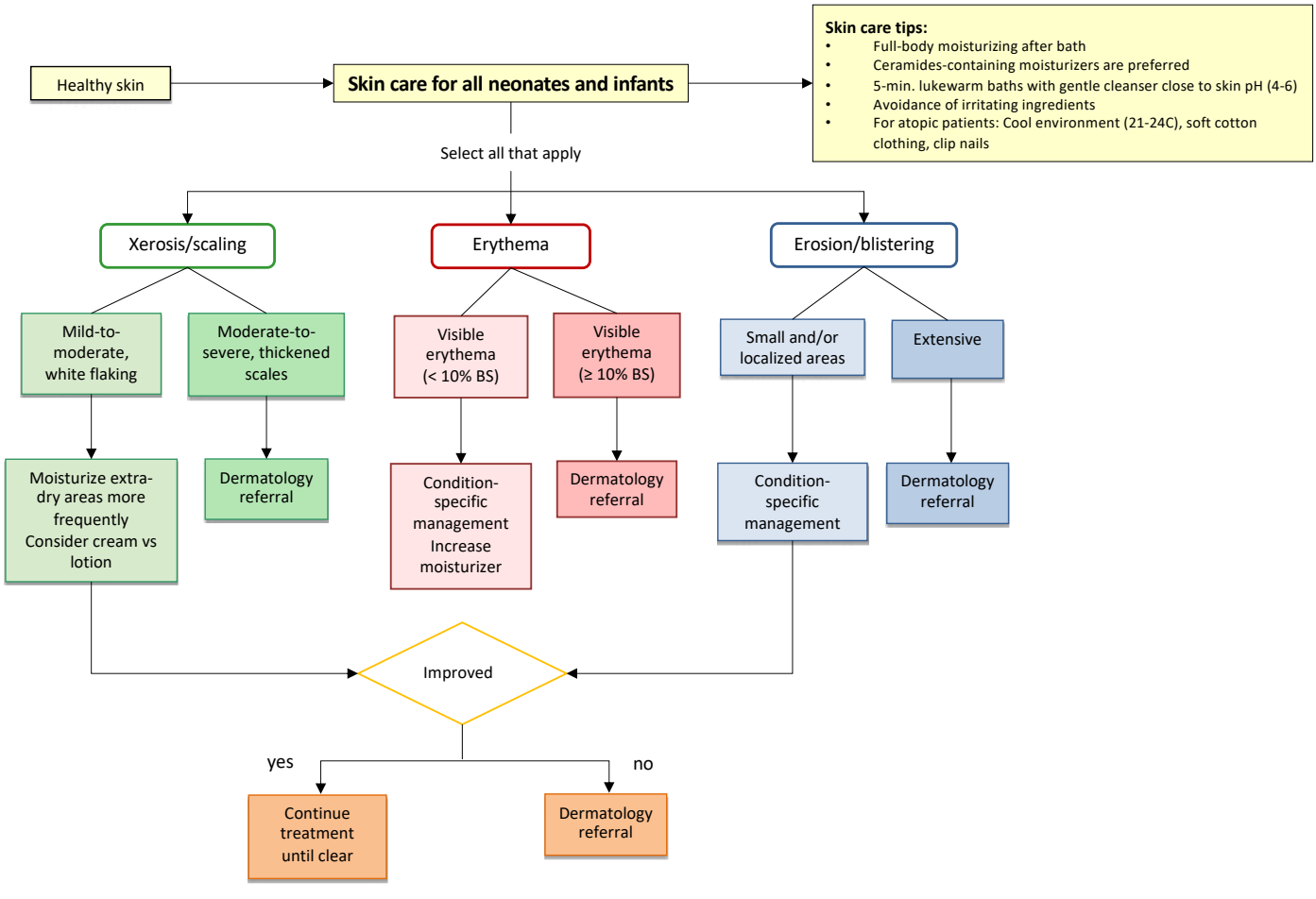
The skin of newborns and infants is more fragile and at risk of heat loss, has elevated thermal conductance, and is more susceptible to infections and chemical and thermal damage than adult skin.[1-9] Exposure to common irritants, including saliva, nasal secretions, urine, feces, fecal enzymes, dirt, and microbial pathogens for long periods can lead to discomfort, irritation, infection, and skin barrier disruption in the vulnerable newborn and infant skin.[14,15] Particular caution with topical skincare regimens is needed for newborns and infants, requiring products with a physiological pH-(4.0 to 6.5).[8-14] The use of cleansers and moisturizers containing SC lipids may help maintain and promote the protective skin barrier and soothe with long-term moisturizing benefits.[14]

Newborns and infants are particularly vulnerable to transcutaneous toxin exposure as they have a high surface-to-weight ratio, immature epidermis, and a compromised skin barrier.[58] Topical agents, which are harmless for adults, may cause respiratory distress, neurological toxicity, and even death in the pediatric and neonatal age groups depending upon systemic absorption.[14,15,58] Topical agents that may cause toxic reactions include isopropanol, benzocaine, pyrethrin, hexachlorophene, salicylic acid, and many others.[14,15,58]

Statement 5: *Skincare for neonates and infants should be:*

- *Safe*
- *Promoting a healthy skin barrier*
- *Fragrance and sensitizing agent-free*
- *Pleasant to use*
- *Containing ingredients that benefit the lipid and water content of the stratum corneum, such as those products containing ceramides.*

FIGURE 5. Algorithm for skincare in newborn and infant skin. Reproduced with permission from Schachner LA et al, *J Drugs Dermatol.*[15]



Given the vulnerability of their skin, safety is the primary consideration for the selection of skincare for newborns and infants. Additionally, SC surface pH, water content, and lipid composition must be considered when maintaining a healthy skin barrier.[14,24] Soaps, surfactants, and detergents, especially those with a pH >6, may excessively remove skin lipids, elevating SC pH and damaging the newborn and infant skin.[14,15] Gentle cleansers (pH 4.0-6.0) containing CERs and no soap are less irritating than alkaline soaps.[14,15,24,59-66]

A study in children comparing a synthetic cleanser of non-ionic and amphoteric surfactants (pH around 5.5) with water showed that neither the cleanser nor water compromised SC integrity.[65] Other reports recommend that a gentle liquid cleanser (pH 4–6.5) is preferred for infants; however, studies are frequently small or have other methodological flaws.[14,15,24,59-66]

The advisors agreed that understanding cultural differences in everyday skincare practices is critical for developing an evidence base to substantiate SOC newborn, infant, and children's skincare practices. The advisors discussed how the potentially sensitizing ingredients, including the use of fragrance or essential oils, is often associated with cultural tradition. These culture practices are important to consider when recommending skincare products or practices to the parents of SOC newborns, infants, and children.

The choice of cleanser and moisturizer is dependent on individual preference.[14,15] However, the advice that may be given to parents includes the use of gentle cleansers and moisturizers containing a mixture of fatty acids, cholesterol, and CERs (Figure 5).[14,15,60,61]

TABLE 1.

Functional Differences Between Newborn, Infant, and Adult Skin				
Functional Differences Between Infant and Adult Skin		**Infant**	**Adult**	**References**
Structural Differences	Epidermal thickness	Thinner	Thicker	8
	Cell attachments and epidermal cellularity	Less	More	8
	Dermo-epidermal junction	Flat	Undulating	8
	Lipids	Less	More	8
Functional Differences	Melanin	Less	More	2
	Sweat	Less	More	2
	Water content	Higher	Lower	8
	Natural moisturizing factor concentration	Lower	Higher	5,6,11
	Stratum corneum pH	Higher	Lower	5,6
	Skin immune system	Lower	Higher	10,11
	Skin surface levels of host defense proteins Low levels of IL-1α were found to increase during the neonatal period	Lower	Higher	10,11

LIMITATIONS

Although the number of clinical studies on skincare for infants and children is growing, there were no robust comparative studies on skincare for SOC newborns, infants, and children. After discussion, the advisors reached a consensus on 5 statements focusing on the science of racial/ethnic skin barrier differences and the importance of cultural practices, underscoring the need for clinicians to understand that there are physical and cultural differences to consider when treating newborns and infants with SOC.

CONCLUSION

Regardless of ethnicity, newborn and infant skin is still developing and more fragile and susceptible to infections and chemical and thermal damage. Understanding cultural differences in everyday skincare practices for SOC newborns, infants, and children is critical for developing an evidence base to substantiate skincare practices.

Data on skincare for SOC infants and children are scarce. However, for all ethnicities, a growing body of evidence supports skincare starting early in life, recognizing the benefits of ongoing daily use of gentle cleansers and moisturizers containing barrier lipids to help maintain the protective SC barrier. Skincare for newborns and infants should be safe, effective, inexpensive, and fragrance- and sensitizing agent-free. Additionally, the skincare should be pleasant to use, containing ingredients that benefit the SC's lipid and water content, such as those products containing CERs.

DISCLOSURES

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Review on the Use of Topical Ruxolitinib for the Treatment of Vitiligo

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ABSTRACT

Background: This article describes the clinical trial, safety, and efficacy of ruxolitinib 1.5% cream or repigmentation in patients with vitiligo.

Data Sources: A systematic review was done using ruxolitinib or Opzelura in MEDLINE (PubMed) and EMBASE. ClinicalTrials.gov was used to identify ongoing or unpublished studies.

Study Selection and Data Extraction: Studies included were written in English and relevant to pharmacology, clinical trials, safety, and efficacy.

Data Synthesis: In two 52-week phase 3 trials, 52.0% of subjects had at least 75% improvement in their Facial Vitiligo Area Scoring Index (F-VASI).

Relevance to Patient Care and Clinical Practice: Ruxolitinib is a topical Janus kinase (JAK) inhibitor newly approved by the US Food and Drug Administration for repigmentation in patients with vitiligo.

Conclusion: Topical ruxolitinib is the first medication approved for repigmentation in patients with vitiligo. It is a safe and effective treatment; however, cost may be a barrier to some patients when prescribing this medication. Trials to compare the efficacy and side effect profile of topical ruxolitinib with other topical treatments are still needed.

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INTRODUCTION

Vitiligo is a multifactorial depigmentation disorder characterized by the destruction of melanocytes, resulting in loss of pigmentation of the skin.[1] An autoimmune process plays an important role in the disease pathogenesis, with CD8+ T cells in vitiligo lesions, producing a variety of cytokines, such as interferon-gamma (IFN-γ).[2] Treatment up until now has been with the use of topical corticosteroids, immunomodulators, and narrow band-ultraviolet (UV) B, none of which is approved by the US Food and Drug Administration (FDA) for the treatment of vitiligo.[1] Monobenzone is an FDA-approved treatment for the depigmentation of vitiligo, offering patients with more extensive disease an option for treatment by inducing melanocyte necrosis giving patients a more uniform skin tone.[3]

Ruxolitinib 1.5% cream, a topical Janus kinase (JAK) inhibitor, was approved by the FDA in July 2022 for treatment of nonsegmental vitiligo in patients ages 12 and up.[4] Topical ruxolitinib is the first drug FDA-approved for repigmentation in patients with vitiligo.[4] Ruxolitinib can be used topically up to 60 grams in one week, or 100 grams over 2 weeks on ≤10% body surface area (BSA).[5] The purpose of this review is to describe the pharmacology, clinical trials, safety, and efficacy of ruxolitinib in the treatment of vitiligo.

MATERIALS AND METHODS

A systematic review was performed using the terms ruxolitinib OR opzelura in MEDLINE (PubMed) and EMBASE databases. Available studies were considered for inclusion if they were written in English and related to pharmacology, clinical trials, adverse events (AEs), and safety prior to July 2022. References of the included sources were also searched to identify additional studies for inclusion. ClinicalTrials.gov was searched to identify ongoing or unpublished studies.

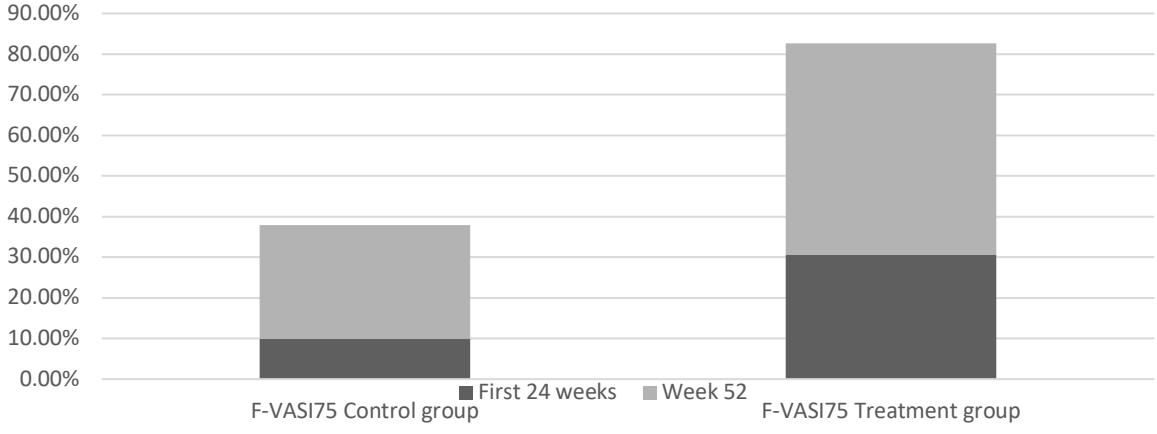
RESULTS

Drug Pharmacology

Mechanism of Action

There is an ongoing clinical trial (TRuE-MOA NCT04896385) to assess the mechanism of action of topical ruxolitinib.[6] Ruxolitinib is a selective JAK1 and JAK2 inhibitor that works on multiple cytokines and growth factors. The therapeutic relevance of JAK enzyme inhibition is not currently known.[7]

FIGURE 1. Results from the phase 3 TRuE trials compared week 24 with the last 28 weeks where both the control and treatment group received ruxolitinib.[8,9]



Pharmacokinetics

The pharmacokinetics of topical ruxolitinib were studied in 41 patients over the age of 13, using 1.5 mg/cm^2 of the topical twice daily for 28 days.[7] 97% of topical ruxolitinib was protein bound in the plasma and primarily metabolized by the enzyme cytochrome P450 3A4 in the liver.[7] The mean elimination half-life of ruxolitinib is 116 hours.[7] It is excreted in the urine or feces, with less than 1% unchanged.[7] After 28 days there was no evidence of metabolites in human plasma.[7]

Summary of Clinical Trials for Vitiligo Treatment

Two phase 3, crossover, randomized, double blind, trials TRuE-V1(NCT04052425) and TRuE-V2 (NCT04057573), evaluated the safety and efficacy of ruxolitinib 1.5% cream compared with a vehicle control.[8,9] In TRuE-V1(NCT04052425) 330 subjects were enrolled, and in TRuE-V2 (NCT04057573) 344 subjects were enrolled.[8,9] Patients 12 years or older with non-segmental vitiligo, not exceeding 10% BSA, with less than or equal to 0.5% facial BSA, and 3% or more non-facial BSA were randomly assigned 2:1 to one of 2 groups.[10] Pooling data from the 2 studies, subjects in the treatment group (n=450) applied ruxolitinib cream 1.5% twice daily (BID) for 24 weeks, and the control group (n=224) applied the vehicle cream for 24 weeks.[10] After the initial 24 weeks, both groups applied ruxolitinib cream 1.5% for a 28 week extension period.[8,9]

The Face Vitiligo Area Scoring Index (F-VASI) score and the Total Vitiligo Area Scoring Index (T-VASI) were used to assess the outcomes, with greater than or equal to 75% improvement from baseline in the F-VASI score being the primary outcome measurement.[8,9] After 24 weeks, a greater proportion of patients in the treatment group (30.7%), applying ruxolitinib BID, achieved the F-VASI75, compared with the 9.9% in the control group (P<0.0001).[8,9] Over the next 28 weeks, both groups used ruxolitinib BID. In the original treatment group, F-VASI75 was achieved in 52% of patients and 28% in the control group (Figure 1).[7] In a phase 2, randomized, double-blind, 52 week trial (NCT03099304), 10.% of patients achieved a T-VASI75 using ruxolitinib once daily, and 15% achieved it while using ruxolitinib twice daily.[11] Common side effects include application site acne, erythema, or pruritus, nasopharyngitis, headache, urinary tract infection, and pyrexia (Table 1).[7] Clinical trials are currently in process to further examine safety and efficacy of ruxolitinib, A current trial, NCT04530344, is currently being completed to assess the long-term efficacy and safety.[12]

TABLE 1.

Adverse Reactions of Topical Ruxolitinib From TruE Trials
Adverse reactions that occurred in greater than or equal to 1% of patients in the first 24 weeks.[7]

Adverse Reaction	Treatment Group (Ruxolitinib)	Control Group (Vehicle Only)
Overall, any reaction	48%	35%
Application site acne	6%	1%
Application site pruritus	5%	3%
Application site erythema	2%	<1%
Nasopharyngitis	4%	2%
Urinary tract infection	2%	<1%
Pyrexia	!%	0%

TABLE 2.

Classes of Topical Medications Prescribed for the Treatment of Vitiligo
Safety and efficacy measures are independent of each other when comparing each topical treatment.[17,21,22]

	Topical JAK Inhibitor (Ruxolitinib)	Topical Corticosteroids	Calcineurin Inhibitors
Mechanism	Downregulation of the JAK_STAT pathway	Inhibition of inflammation	Inhibit calcinruin, a proinflammatory protein decreasing cytokine formation allowing for melanocyte proliferation
FDA approval status	Approved	Not approved for use in vitiligo	Not approved for use in vitiligo
Cost	$2,063 retail for 60 grams	$187 retail for 60 grams of clobetasol	$279 retail for 30 grams of 0.1% tacrolimus
Safety	Side effects include application cite acne, erythema, and pruritus, nasopharyngitis, headache, urinary tract infection, and pyrexia	Side effects include telangiectasias, skin atrophy, striae	Side effects include burning sensation, increased infections with herpes simplex and molluscum contagiousm, and pruritus
Efficacy	In phase 3 trials 52% of patients achieved greater than 75% repigmentation	55% achieved greater than 75% repigmentation in a meta-analysis study using very potent topical corticosteroids	Comparable with topical corticosteroid use in the meta-analysis

FDA, Food and Drug Administration; JAK, Janus kinase.

Relevance to Patient Care and Clinical Practice

Topical ruxolitinib is the first FDA-approved medication for repigmentation for patients with non-segmental vitiligo.[1] Ruxolitinib acts by inhibiting JAK1 and JAK2, blocking the effects of T-cell activation through the JAK-STAT pathway.[1] CD8+ T cells produce IFN-γ along with other cytokines.[1] IFN-γ helps promote the recruitment of autoreactive CD8+T cells to the skin that targets melanocytes.[1] IFN-γ binds to receptors recruiting JAK1 and JAK2, leading to the transcriptional activation of IFN-γ inducible genes.[1] Vitiligo lesions express JAK1 more diffusely compared with non-affected lesions.[1]

The most common side effects seen with the use of ruxolitinib topically are acne, pruritus, redness at the application site, nasopharyngitis, headaches, urinary tract infections, and fever.[7] In a phase 2 study (NCT03099304) comparing the use of ruxolitinib with the application of the vehicle control, the most common AEs were pruritus and acne at the application site, both being mild to moderate in severity.[13] In the TRuE trials, there were no clinically significant adverse reactions among the participants.[10]

Oral JAK inhibitors have been linked to increased risk of infection with fungal or bacterial opportunistic pathogens, thrombotic events, blood disorders such as lymphoma, neutropenia, anemia, and thrombocytopenia, major cardiovascular events, and malignancies.[7,14] However, compared with oral JAK inhibitors, topical application has minimal systemic accumulation.[7]

Ruxolitinib is limited to use in up to 10% BSA.[15] This is a limitation for those with extensive disease in terms of qualifying for the medication; however, use of a topical in greater BSA may result in poor adherence. Until the FDA approval for ruxolitinib, topical corticosteroids, and topical calcineurin inhibitors were commonly used for the treatment of vitiligo (Table 1).[16,17] Repigmentation rates, defined as greater than 50% repigmentation, are over 60% and over 40% with the use of topical corticosteroids and a calcineurin inhibitor, respectively (P=0.154).[16]

Cost is a drawback of ruxolitinib. The 1.5% cream costs over $2,000.00 for a 60-gram tube.[18] Eligible participants have options. For patients with commercial prescription insurance, the company offers a copay savings program where patients can pay as little as $10 for the medication. For patients whose commercial prescription insurance denies coverage, IncyteCARES program could approve patients to receive the medication at no cost for up to 12 months. Patients who are uninsured or underinsured with Medicare coverage and cannot afford their copay may receive assistance from IncyteCARES if they meet certain income eligibility criteria.[19] Topical corticosteroids can offer a more affordable treatment option for patients, with strong topical corticosteroids ranging from as low as $6 to a few hundred dollars.[20,21] Topical calcineurin inhibitors costing less than $200 retail make them a cheaper option as well.[22] Corticosteroids can be offered in generic forms, helping lower their cost. For insurance companies to approve coverage of ruxolitinib a prior authorization requiring patients have failed previous treatments may be required. A common reason for failing topical medications is poor adherence.[23] If insurance companies require prior authorization for topical ruxolitinib and if the prior authorization

requires failure of other topical treatment, that could select for patients who are nonadherent to topicals, potentially leading to poor results for those using topical ruxolitinib.[23]

CONCLUSION

Vitiligo affects 0.1% to 2% of people worldwide, commonly associated with other autoimmune conditions.[24] Not unlike other dermatologic conditions, vitiligo can impact patients' social wellbeing and psychological health. Ruxolitinib offers the first FDA-approved repigmentation treatment for those affected. Until now, topical corticosteroids and immunomodulators have been the mainstay of treatment. With minimal reported adverse reactions and side effects, ruxolitinib is considered safe and effective in the repigmentation of vitiligo patients. It may be a good treatment option if it is accessible.

DISCLOSURES

Dr. Steven Feldman has received research, speaking, and/or consulting support from Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Helsinn, PHD Biosciences, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate, and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Meghan Grossmann and Dr. Haidari have no conflicts to disclose.

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ORIGINAL ARTICLE

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Efficacy, Convenience, and Safety of Calcipotriene-Betamethasone Dipropionate Cream in Skin of Color Patients With Plaque Psoriasis

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ABSTRACT

Background: Psoriasis affects diverse racial and ethnic groups. In July 2021, the US Food and Drug Administration approved calcipotriene/betamethasone dipropionate (CAL/BDP) 0.005%/0.065% cream to treat plaque psoriasis in adults. The efficacy and safety of CAL/BDP in patients with skin of color (SOC) who have psoriasis is not well characterized.

Method: A post hoc analysis of phase 3 clinical trial data (NCT03308799) was conducted to assess the efficacy, convenience, and safety of CAL/BDP cream versus CAL/BDP topical solution and vehicle cream in people with Fitzpatrick skin types IV to VI.

Results: This study included 784 participants, 280 (35.7%) of whom had Fitzpatrick skin types IV to VI. Patients treated with CAL/BDP cream had greater disease improvement, treatment convenience scores, and overall satisfaction than those treated with CAL/BDP topical solution in the subgroup with skin types IV to VI and the total study population. Adverse event rates were similar between the subgroup with skin types IV to VI and the total study population for all treatment arms.

Conclusion: Psoriasis is associated with a greater physical and psychosocial impact in patients with SOC. While many effective topical therapies exist, it may be helpful to conduct separate analyses of patients with SOC to assess the efficacy and safety of treatment in this population. This sub-analysis of phase 3 clinical trial data supports the efficacy and safety of CAL/BDP cream in the treatment of plaque psoriasis in patients with SOC. CAL/BDP cream also had greater convenience, formula acceptability, and overall satisfaction in both the subgroup with SOC and the total trial population, which may improve adherence to topical therapy and treatment outcomes for people with SOC who have psoriasis.

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INTRODUCTION

Psoriasis is a chronic inflammatory skin condition that affects diverse racial and ethnic groups. The US prevalence is 3.7% in White individuals, 2.0% in Black individuals, and 1.6% in Hispanic individuals/others.[1] However, the prevalence of psoriasis in the Black and Hispanic populations may be underestimated. Due to systemic and sociocultural barriers, psoriasis is less likely to be diagnosed in non-White individuals than in White individuals.[1]

Numerous treatments have been developed for psoriasis. First-line treatment for mild-to-moderate psoriasis is topical treatment, including corticosteroids, vitamin D analogs, keratinolytics, calcineurin inhibitors, salicylic acid, and tar.[2] Topical vitamin D analog/corticosteroid combination therapy is a common treatment and is superior to vitamin D analogs or corticosteroids alone.[3] Several topical formulations of calcipotriene and betamethasone dipropionate (CAL/BDP) have been approved for treating psoriasis, including a foam, topical suspension, and gel formulation. In July 2021, the US Food and Drug Administration approved a cream formulation of CAL/BDP 0.005%/0.065% for plaque psoriasis in adults.[4] In an 8-week, phase 3 clinical trial (NCT03308799), once daily CAL/BDP cream was more effective, had a faster onset of action, greater itch reduction, and a greater treatment convenience score than the CAL/BDP topical solution or placebo.[5]

However, the efficacy and safety of this medication for psoriasis in patients with skin of color (SOC) is not well characterized. Genetic differences in various ethnic and racial groups may

affect treatment responses and safety profiles in these groups, as seen with oral and biologic treatments for psoriasis. For example, genetic differences in transporter genes can affect the response to methotrexate treatment.[1] Pharmacogenetic differences may affect the efficacy and safety of topical CAL/BDP cream in diverse ethnic groups. This review analyzed the efficacy and safety of CAL/BDP cream in the treatment of people with SOC who have plaque psoriasis.

MATERIALS AND METHODS

In phase 3, randomized, multicenter, investigator-blind, parallel-group, 8-week trial (NCT03308799), participants aged 18 years and older with mild-to-moderate plaque psoriasis were randomized 2:1:2 to once daily CAL/BDP 0.005%/0.065% cream (Wynzora®), vehicle cream, and CAL/BDP 0.005%/0.065% topical solution.[6] The primary endpoint was treatment success, defined as the number of participants who achieved a minimum 2-grade improvement in Physician Global Assessment (PGA) score (on a scale of 0-4) from baseline to week 8 (where 0=clear, 1= almost clear, 2=mild plaque thickening, 3=moderate plaque thickening, 4=severe plaque thickening). Secondary endpoints included the percent change in modified Psoriasis Area Severity Index (mPASI) score from baseline to 8-weeks and treatment convenience scale score. The mPASI is a tool to assess the severity and extent of psoriasis on the arms, legs, and trunk. Scores can range from 0 to 64.8, with higher scores indicating worse disease. To be included in the study, patients must have had a baseline mPASI of at least 2. Treatment convenience was based on scores from the Psoriasis Treatment Convenience Scale (PTCS). This validated 5-question scale assesses application ease, treatment's disruptions to daily routines, product greasiness, residual skin greasiness, and the treatment's ability to moisturize the skin.[7] Each question was scored on a scale from 1 to 10, with a maximum score of 50, with higher scores indicating greater treatment convenience. An additional question assessed overall treatment satisfaction.

A post hoc analysis was conducted to assess the efficacy, convenience, and safety of CAL/BDP cream in patients with SOC compared to the total study population. The group with SOC included participants with Fitzpatrick skin types IV to VI (types IV-VI subgroup) and those who self-identified as "Black or African American." A modified intention-to-treat (mITT) was employed, which included all participants randomly assigned to a treatment arm with at least one PGA assessment following treatment initiation.

RESULTS

Demographics

This study included 784 participants, of whom 64 (8.2%) self-

TABLE 1.

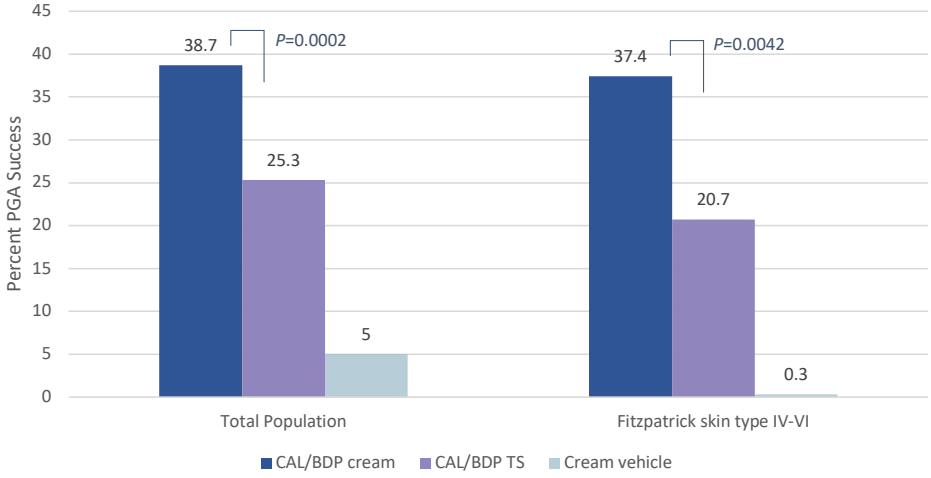
Subjects Included in Primary and Secondary Analyses[11]

	Total Population		Fitzpatrick Skin Types IV-VI	
	Subjects in mITT	Subjects in safety set	Subjects in mITT	Subjects in safety set
CAL/BDP Cream	338 (43.1%)	342 (43.1%)	129 (16.5%)	131 (16.5%)
CAL/BDP TS	334 (42.6%)	337 (42.4%)	114 (14.5%)	116 (14.6%)
Cream Vehicle	112 (14.3%)	115 (14.5%)	37 (4.7%)	39 (4.9%)
Total	**784**	**794**	**280**	**286**

Key: calcipotriene/betamethasone dipropionate (CAL/BDP); modified intention-to-treat (mITT); topical solution (TS)

TABLE 2.

Percent of Subjects Achieving PGA Success in Primary and Secondary Analyses[11]



Key: calcipotriene/betamethasone dipropionate (CAL/BDP); physician global assessment (PGA); topical solution (TS)

identified as "Black or African American" and 280 (35.7%) were categorized as Fitzpatrick skin types IV to VI (Table 1). Results from the subgroup self-identifying as "Black or African American" are not presented in the graphs as relatively few patients identified as such, and these participants were not evenly distributed among the treatment arms.

PGA Success

After 8 weeks of treatment, the CAL/BDP cream had greater PGA success than the CAL/BDP topical solution in the types IV-VI subgroup and the total study population (P=0.0042 and P=0.0002, respectively). The rates of PGA success with the CAL/BDP cream in the types IV-VI subgroup were similar to the success rates in the total study population, 37.4% and 38.7%, respectively (Table 2).

mPASI

After 8 weeks of treatment, the CAL/BDP cream had greater change from baseline mPASI than the CAL/BDP topical solution in the types IV-VI subgroup and the total study population (P=0.003 and P<0.0001, respectively, Table 3).

Psoriasis Treatment Convenience Scale

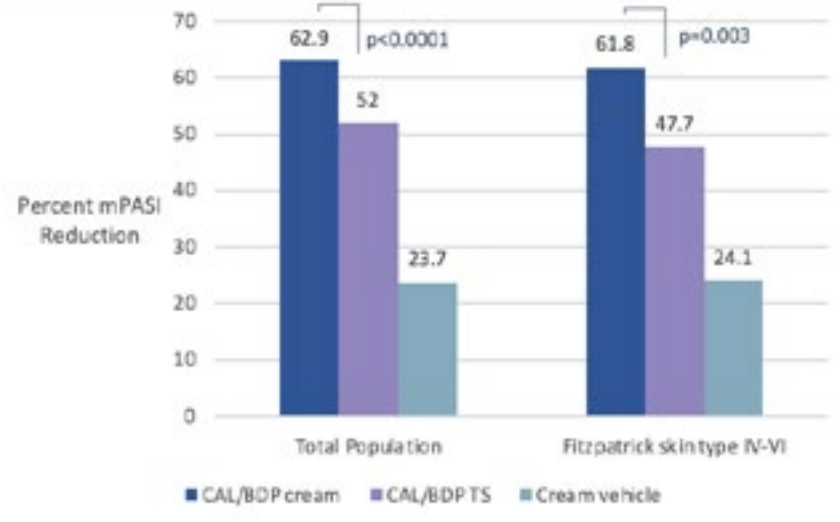
In the types IV-VI subgroup and the total study population, the CAL/BDP cream had higher scores on the PTCS compared to the CAL/BDP topical solution (P<0.0001 for both comparisons). Additionally, in the types IV-VI subgroup and total study population, the CAL/BDP cream consistently scored higher in each individual PTCS question compared to the CAL/BDP topical solution. Overall treatment satisfaction was highest in the CAL/BDP cream group (Table 4).

Adverse Events

Adverse event (AE) rates were similar between the types IV-VI subgroup and the total study population for CAL/BDP cream, topical solution, and vehicle (Table 5). The most common AEs in the CAL/BDP cream group were upper respiratory tract infection (7%), headache (2%), and application site pain (1%) vs 5%, 0%, and 0%, respectively, in the vehicle cream group.[8]

TABLE 3.

Percent mPASI Improvement from Baseline[11]



Key: calcipotriene/betamethasone dipropionate (CAL/BDP); modified Psoriasis Area Severity Index (mPASI); topical solution (TS)

TABLE 4.

Psoriasis Treatment Convenience Scale Results[11]

Questions	Total Population		Fitzpatrick Skin Types IV-VI	
	CAL/BDP Cream	CAL/BDP TS	CAL/BDP Cream	CAL/BDP TS
Ease of application	9.4	9.1	9.5	9.2
Treatment's disruptions to daily routine	9	8.7	8.9	8.7
Product greasiness during application	7.5	6	7.9	5.9
Residual skin greasiness	7.5	6.1	7.6	5.8
Treatment's ability to moisturize skin	8.1	7.7	8.2	7.6
Total PTCS Score	**41.5**	**37.5**	**41.8**	**36.9**
Overall treatment satisfaction	8.9	8	9	7.7

Key: calcipotriene/betamethasone dipropionate (CAL/BDP); Psoriasis Treatment Convenience Scale (PTCS); topical solution (TS)

TABLE 5.

Subjects With Treatment-Emergent and Treatment-Related Adverse Events[11]

	Total Study Population		Fitzpatrick Skin Types IV-VI	
	Subjects with TEAE	Subjects with trAEs	Subjects with TEAE	Subjects with trAEs
CAL/BDP Cream	90 (26.3%)	12 (3.5%)	36 (27.5%)	4 (3.1%)
CAL/BDP TS	76 (22.6%)	11 (3.3%)	28 (24.1%)	4 (3.4%)
Vehicle Cream	32 (27.8%)	5 (4.3%)	6 (15.4%)	0 (0.0%)

Key: treatment-emergent adverse events (TEAE); treatment-related adverse events (trAEs), calcipotriene/betamethasone dipropionate (CAL/BDP); topical solution (TS)

DISCUSSION

Psoriasis is associated with a greater physical and psychosocial impact in SOC patients. Black patients tend to have worse disease outcomes, including more extensive disease involvement than White patients.[1] More than half (55%) of psoriasis experts reported thicker plaques, increased scale, and greater body surface area involvement in Black patients compared to White patients.[1] Even after correcting for body surface area and disease severity, patients with SOC report poorer quality of life on the Dermatology Life Quality Index, a questionnaire that measures the impact of dermatologic conditions on quality of life.[1] While many effective topical therapies exist for mild-to-moderate psoriasis, given the potential for pharmacogenetic differences in diverse populations, it may be helpful to conduct separate analyses of patients with SOC to assess the efficacy and safety of treatment in this population.

In a subgroup analysis of patients with SOC, CAL/BDP cream was more effective than the topical solution, mirroring the results in the total study population. The cream and TS also had similar adverse event rates in the patients with SOC compared to the total study population.

While CAL/BDP cream was effective in the tightly controlled setting of the clinical trial, patients must adhere to daily medication application for successful treatment outcomes. Real-world adherence to topical psoriasis treatments is poor and is impacted by inconvenience, complex treatment plans, and vehicle and formula preferences.[7,9-10] CAL/BDP cream had greater convenience scores, formula acceptability, and overall satisfaction in the subgroup with SOC and the total study population, which may improve adherence to therapy and treatment outcomes.

This phase 3 study was not powered for analysis of patients with SOC, although this limitation exists for all post hoc analyses. In addition, too few participants self-identified as Black or African American to conduct separate statistical or descriptive comparisons. As a result, this secondary analysis relied on Fitzpatrick skin types to identify patients with SOC. In conclusion, this sub-analysis of phase 3 clinical trial data supports the efficacy, convenience, and safety of CAL/BDP cream in the treatment of people with SOC who have plaque psoriasis.

DISCLOSURES

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ORIGINAL ARTICLE

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Skin of Color Sun Protection: Reddit Analysis Reveals Perceptions, Preferences, Unmet Needs, and Knowledge Gaps

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ABSTRACT

Background: Patients are increasingly seeking medical advice, recommendations, and general information through online forums and social media. In June 2021 Reddit reported 430 million active monthly users globally and is the most popular mobile social app in the United States. Skincare is a popular forum topic and a space for patients to source information regarding photoprotection. Skin of color patients have specific needs regarding sun protection that remain underserved.

Objective: To uncover perceptions, preferences, unmet needs, and knowledge gaps regarding sun protection for skin of color patients.

Methods: The authors analyzed posts from August 1, 2019, through August 1, 2022, related to sun protection in skin of color. Search terms were based on National Institutes of Health (NIH) racial and ethnic categories. A total of 208 posts were analyzed and sorted into categories and subcategories to elucidate common themes.

Results: The three most common categories of posts included seeking recommendations (57.7%), seeking/providing general information (25.5%), and product reviews (13.5%). The remaining 3.3% of posts were categorized as miscellaneous.

Limitations: Reddit users may not adequately reflect the general population and their perceptions, preferences, and knowledge.

Conclusions: Analysis of Reddit posts regarding photoprotection in skin of color yields valuable insights into the perceptions, preferences, unmet needs, and knowledge gaps regarding sun protection for this group of patients. Physicians can use this information to better educate patients and improve photoprotection adherence. This information is also valuable for pharmaceutical and sun protection industries that can use these insights to fill unmet sunscreen needs for patients of color.

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INTRODUCTION

The Impact of Photodamage

Photodamage and photoaging are complex, ongoing processes resulting from cumulative exposure to ultraviolet (UV), visible (VL), and infrared (IR) radiation emitted by the sun. Repeated solar radiation leads to accumulated skin damage.[1] This process can lead to skin cancers including melanoma, basal cell carcinoma, and squamous cell carcinoma. Photoaging clinically manifests as cutaneous rhytids, atrophy, laxity, dyspigmentation, telangiectasias, roughness, and mottled appearance of the skin.[2]

UV light causes direct DNA damage. It can be separated into UVA, UVB, and UVC radiation. Recent research has further elucidated the role of UV, VL, and IR in photodamage. These forms of radiation increase reactive oxygen species, collagen degrading enzymes, and other inflammatory cytokines causing skin damage.[3] Increased melanin content found in skin of color has photoprotective effects against UV radiation. However, radiation from across the spectrum still results in damage to darker skin. Persons of color may be more sensitive to certain wavelengths, such as those in the visible light range, contributing to dyspigmentation, melasma, and post inflammatory hyperpigmentation.[4,5] Sun protection is important for skin of color patients to prevent these clinical manifestations in addition to preventing malignancy and photoaging.

The Role of Sunscreens

The market for global sunscreen creams was 8.5 billion USD in 2019 and is forecasted to grow to over 10.7 billion USD by 2024.[6] Despite the importance of photoprotection, persons of color are less likely to use sunscreen than Caucasians.[7] This may be due to knowledge gaps about the need for sun protection, lack of cosmetically elegant products, or experience of milder symptoms such as sunburn.

Sunscreens are categorized as organic or inorganic. Organic sunscreens contain carbon-based chemicals that filter or absorb UV radiation and prevent it from reaching the skin.[8] Inorganic sunscreens, also known as mineral or physical sunscreens, contain minerals and metal oxides such as ZnO and TiO_2 that absorb, reflect, or scatter UV radiation to create a barrier that blocks it from the skin.[8,9] Sun protection factor (SPF), a measure of the amount of UV radiation needed to induce erythema/

burn on protected skin relative to unprotected skin, does not distinguish between protection against UVB and other forms of radiation.[10,11] Inorganic sunscreens are broad spectrum, offering superior protection against UVA radiation which contributes to over 80% of facial premature aging.[2] However, they have historically been limited by cosmetic consumer preference, especially in skin of color users, due to the chalky white appearance these products may produce on the skin.

Patients Are Seeking Sunscreen Advice Online

Skincare, including sun protection, is a prevalent topic in online forums. Reddit is the most popular social app in the United States and has over 430 million active monthly users globally as of 2022.[12,13] In the first five months of 2022 there have been over 1.5 billion visits to Reddit per month.[12] Users can create, join, participate in, and browse subcommunities or "subreddits" based on their interests. Skincare is a popular topic on Reddit as demonstrated by the participation in these subreddits including "r/SkincareAddition" (1.4 million members), "r/Skincare_Addition" (960K members), and "r/SkincareAddicts"(707k members).

Given the ease of accessibility and anonymity, Reddit provides a space for patients to source information regarding photoprotection. We aimed to analyze the discussions regarding sun protection for skin of color to better understand the unique experiences, challenges, and perspectives of this population. This analysis can help elucidate popular misconceptions and common themes for barriers to sun protection use.

MATERIALS AND METHODS

The authors reviewed posts related to sun protection in skin of color over a three-year period of August 1, 2019, through August 1, 2022. Search terms were determined based on NIH racial and ethnic categories. Search terms included a racial/ethnic category followed by a sun protection related term. Racial and ethnic categories included American Indian, Alaskan Native, Black, African American, Native Hawaiian, Pacific Islander, Hispanic, Latino, Skin of Color, Brown Skin, and Dark Skin. Sun protection related terms included sunscreen, sunblock, sun care, and sun protection. In total 44 search terms were used as each of the 11 racial/ethnic categories were searched with each of the four sun protection terms. To be included in the analysis, the post had to mention race/ethnicity/skin color/skin tone, or other descriptors indicating skin of color. Replies to the post that sought new information/recommendations were also included. Posts mentioning only White/pale/Caucasian or posts with no reference to skin of color were excluded from the analysis. Also excluded from analysis were posts that were direct repeats of an already included post; posts that only included links to outside articles or videos with no other information or context; and posts that were purely advertising or coupon offers with no other information or context elaborating on the product. A total of 208 posts were analyzed and sorted into categories and subcategories to elucidate common themes.

The username, title/text, number of comments, and subreddits were recorded for each post. The number of upvotes, or votes of approval/support from users for specific posts, was also recorded. Each post was placed into one of four broad categories: seeking recommendations, providing product reviews, general information, and miscellaneous. For each category, a more granular analysis was performed. The SUNY Downstate Institutional Review Board deemed this analysis exempt from review.

RESULTS

A total of 208 posts from users regarding photoprotection for skin of color were analyzed. The average number of comments was 18.7 and the average number of upvotes was 60.4 for each original post. Most users (98.8%) only submitted one original post. The majority of posts were classified as seeking recommendations (57.7%, Table 1). The second most common

TABLE 1.

Proportion of Questions by Category	
Category	**No. (%), n=171**
Seeking Recommendations	120 (57.7)
General Information	53 (25.5)
Product Reviews	28 (13.5)
Miscellaneous	7 (3.3)

TABLE 2.

Example Posts by Category	
Category	**Example Post Titles**
Seeking Recommendations	Sunscreen recommendations for rosacea prone skin of color? Something that's not oily and doesn't leave a white cast.
General Information	Do darker skin tones need to wear sunscreen?
Product Reviews	[Sun Care] Ultralight SPF that causes no breakouts or leaves white marks, absorbs into the skin instantly, and dries invisibly. It does not contain octinoxate like a majority of other chemical sunscreens – no damage to corals! Perfect for those with dark skin tones and oily skin. Criticism – cost.
Miscellaneous	[Misc] I just listened to this and feel so much better about how to use sunscreen/products going forward! If you have skin of color, check out this podcast episode where a dermatology NP goes over hyperpigmentation, laser hair removal, sunscreen, medical misinformation.

category of posts was classified as general information (25.5%). The third most popular category was users providing product reviews (13.5%). The remaining small portion of posts did not fit into either of these three broad categories and was classified as miscellaneous (3.3%). Titles of example posts are provided (Table 2). Each category was further analyzed by most referenced subtopics. The most popular subreddit from the original analyzed posts was r/SkinCareAddiction (52.0%).

Seeking Recommendations

Users most commonly sought sunscreen recommendations for skin of color (57.7%). Of the posts in this category, 52.5% mentioned white-cast, some of which included descriptions such as pale, grey, or purple appearances of skin from sunscreen use. 28.6% of posts were looking for sunscreens that were suitable for acne-prone skin. 14.2% of posts mentioned other cosmetic factors such as mattifying or greasy appearances of the skin after sunscreen application. 16.7% of posts in this category described sunscreen textures, such as creamy, lightweight, or greasy.

35.8% of users sought recommendations for specific skin types including oil, dry, and combination skin. 19.2% of posts sought recommendations for products compatible with sensitive skin/eyes. 8.3% of posts sought sunscreens suitable for specific skin conditions including rosacea and hyperpigmentation.

26.7% of posts mentioned sunscreen types such as mineral or chemical. 11.7% of posts cited specific ingredients including zinc oxide, octocrylene, oxybenzone, and nicotinamide. 10.0% of posts discussed SPF specifications or UVA/UVB coverage.

16.7% of posts mentioned affordability/price as a concern. 20.0% of posts mentioned product accessibility, including product availability in certain countries/territories or stores.

General Information

The second most common broad category of posts was general information, comprising 25.5% of the total analyzed posts. Most of these posts (43.4%) inquired whether sunscreen is needed, why it is needed, and how important it is for skin of color. 22.6% of information posts asked or provided information regarding the level of sun protection needed, including types of UV protection, SPF levels, and how often protection is needed. 15.1% of posts discussed sunscreen application.

17.0% of posts inquired about whether persons of color use sunscreen or not. 7.5% of posts inquired about whether persons of color burn from sun exposure. 13.2% of posts in this category mentioned skin cancer and associated risks. 7.5% of general information posts mentioned hyperpigmentation. 9.4% of posts mentioned aging/anti-aging.

Product Reviews

Product Reviews made up 13.5% of total analyzed posts. The most mentioned product characteristic was white-cast or the color appearance of the product on the skin after application (85.7% of review posts). 7.1% of reviews discussed acne/breakouts. 67.9% of review posts mentioned other cosmetic factors such as mattifying or greasy appearance on the skin after sunscreen application. 39.9% of posts in this category described sunscreen textures, such as creamy, lightweight, or greasy.

Skin type was mentioned in 28.6% of posts regarding product reviews. 35.7% of posts mentioned skin/eye sensitivity in their review. 10.7% of review posts discussed specific skin conditions including eczema and hyperpigmentation.

32.1% of posts mentioned sunscreen type. 32.1% of posts cited specific ingredients. 32.1% of posts discussed level of protection including SPF specifications or UVA/UVB coverage. Ease of application/removal/absorption was discussed in 35.7% of reviews.

35.7% of posts mentioned affordability/price in their review. 21.4% of posts discussed product accessibility. 25.0% of posts discussed if the product was waterproof or compatible with sports/sweating. 35.7% of posts mentioned fragrance/sent in their review.

Some posts reviewed multiple sunscreens resulting in a total of 76 product reviews, 70 of which were unique. Black Girl Sunscreen Kids and Black Girl Sunscreen were reviewed a total of six times. Notably all six reviews were positive. Of the 76 reviews, the most commonly reviewed brands included La Roche-Posay (14.5%) and Black Girl Sunscreen (7.9%).

Miscellaneous

The remaining 3.3% of posts did not fit into one of the above categories and were subsequently categorized as miscellaneous. Examples of these posts included a podcast recommendation for sun protection/skincare for skin of color and posts with links to surveys/market research regarding sun care for skin of color.

DISCUSSION

Our analysis of Reddit posts regarding photoprotection for skin of color yielded valuable insights into perceptions, preferences, unmet needs, and knowledge gaps. Most users sought recommendations for sunscreens, suggesting patients may struggle to find products that meet their needs. The most common concern in both the recommendation and review categories was white-cast. There is a significant unmet need for sunscreens that do not leave discolored appearances on persons of color.

Mineral sunscreens that are nanosized have the benefit of reducing white-cast.[14] However, minerals in these sizes do not offer protection against VL.[5,15] Combining nanosized and non-nanosized inorganic filters may offer superior VL protection while minimizing cast. Dermatologists may also suggest tinted sunscreens for their skin of color patients. These products also offer VL protection and may produce less white-cast and be more cosmetically appealing.[15]

Our data suggests that educating patients about proper application, which was frequently mentioned in posts across categories, may also be of value to patients. The level of protection provided by SPF values is based on ideal values of sunscreen application, which is 2 mg/cm^2.[16] Patients generally apply much smaller amounts, around 0.5-1 mg/cm^2, in practice.[4] Counseling patients on how to adequately rub sunscreen into the skin can improve both utility and reduce white-cast.

Most general information posts inquired about the level of sun protection, if any, needed for skin of color. This aligns with the misconceptions found by Taylor, et al that sunscreens do not benefit persons of color.[17] This demonstrates a knowledge gap that can be addressed by physicians. These questions indicate that skin of color patients lack counseling regarding the need for sun protection. Providers have an opportunity to communicate the importance of photoprotection to promote skin health, prevent dyspigmentation, and decrease cancer risk to their skin of color patients.

Dermatologists can educate their patients on the types of solar radiation and the protection offered by different sunscreen types. Given the frequency of posts inquiring about the type and level of protection needed for various forms of radiation, it is clear that patients need more guidance regarding the specifics of sun protection. In a study specifically evaluating the use of sunscreen in patients with hyperpigmentation disorders, researchers found that almost half of the respondents who reported using sunscreen did not know if the product was broad-spectrum.[18] Persons of color are more prone to dyspigmentation disorders in general, including melasma and hyperpigmentation.[18]

In a clinical study investigating the effects of LED-RL on skin, skin of color participants had a lower maximum tolerated dose.[5] This suggests that persons of color may be particularly photosensitive to VL resulting in dyspigmentation, blistering, melasma, and post inflammatory hyperpigmentation.[5] UVA radiation has also been shown to cause dyspigmentation in darker skin.[19] Dermatologists should educate their patients on the value of broad-spectrum and combination sunscreens that offer UVA and VL protection, respectively. Furthermore, combination sunscreens have been clinically shown to improve melasma compared to products that were solely UV protective.[4,20]

Sunscreens that offer protection against specific forms of light, including UV, VL, and IR, may be especially valuable for skin of color patients. Through a modified Delphi method, a panel of dermatologists and photobiologists recommended a standard rating for UVA and VL protection as many sunscreens lack coverage for these radiation types. The panel also agreed that physicians should recommend photoprotection that is personalized and tailored to patients' specific skin types, preferences, and exposure.[21]

The significant number of posts, both in recommendations and reviews, that discussed specific ingredients, indicates that at least some patients are aware of the importance of these ingredients. Dermatologists have an opportunity to better educate patients on the particular ingredients to seek and avoid. For example, patients seeking VL protection should be instructed to look for inorganic ingredients like zinc oxide and titanium dioxide. Patients who suffer from melasma may want to target sunscreens that contain certain mineral ingredients. A study evaluating sunscreens with zinc oxide and titanium dioxide showed a clinical improvement of melasma lesions compared to sunscreens with iron oxide alone.[23,24]

There may also be an opportunity for dermatologists to educate patients about the aesthetic benefits of sun protection in addition to its role in reducing skin cancer risk. In a study comparing patient satisfaction with sunscreen after appearance-based education versus health-based education, researchers found that appearance-based education resulted in greater participant rated usefulness and appeal.[22] Proper sun protection can help prevent the effects of photoaging, including rhytids, uneven skin tone, and increased skin laxity. There may be opportunities to improve sunscreen adherence with education on the aesthetic benefits of sun protection and through products that minimize white-cast improving the cosmetic aspect of sunscreen.

Despite skincare popularity among users, Reddit remains a relatively untapped resource in the dermatology community. To our knowledge, no other research has analyzed Reddit discussions for sun protection in skin of color. A study analyzing prominent themes of 300 dermatology related posts found that most discussions centered on advice and wellbeing, although recommendations were often not evidence-based, even for those accepted as factual.[23] By understanding patients' common perceptions, physicians may be able to better connect with patients and provide relevant, meaningful information and treatment.

The strength of this study is that the authors analyzed the perceptions, preferences, and knowledge of patients in a forum that yielded valuable insights regarding sunscreen in skin of color. While Reddit has a vast number of users globally, this

study is limited by the fact that those who self-select to post may not adequately reflect the broader population. This study is also limited by the fact skin of color is based on self-identification and could not be verified by the researchers.

Our study elucidated common concerns and issues that persons of color face regarding sun protection. As patients continue to use Reddit and other social media platforms to source health information, there may also be opportunities for dermatologists to become active members of these online communities to provide evidence-based information.

DISCLOSURES

The authors have no conflicts of interest or funding sources to declare.

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Exploration of Skin of Color Dermatology Content on YouTube

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ABSTRACT

Background: There is a lack of diversity in dermatology regarding skin of color-related content. This has negative implications for patients of color and continues to be a hurdle to providing proper care to these patient populations. As patients increasingly look to the internet as a resource to gain insight on dermatologic conditions and potential treatment options, the information presented must be accurate and informational. The goals of this study included identifying and analyzing skin of color-related dermatology content found on YouTube, characterizing the content creators, and comparing board-certified dermatologists' content to that created by other YouTubers.
Methods: A total of 23 dermatology terms associated with skin of color were searched on YouTube. The top 9 relevant videos for each search term were analyzed for views, comments, likes, and content creator classification. Each video was also labeled as being promotional or educational. The content creator and the content subject were also analyzed. Content created by board-certified dermatologists as well as physicians was then compared to content created by non-physicians. Statistical comparison was done using Mann-Whitney U tests and Pearson's Chi-squared test where appropriate.
Results: The most popular search term was *dandruff* while the least popular search terms were *dermatosis papulose nigra, eczema,* and *central centrifugal cicatricial alopecia*. Of the total 207 videos analyzed (Figure 1), the majority of video profiles consisted of medical interest groups (77, 37.2%), whereas the majority of video subjects consisted of board-certified dermatologists (50, 24.2%). In contrast, the least common video profiles belonged to patients (2, 1%), and the least common video subjects were news media (2, 1%). When comparing board-certified dermatologists to all other classifications of content creators, there was a significant difference in views, comments, and likes (views P=0.0477, comments P=0.0324, likes P=0.0203). When comparing all physicians to all other content creators, there was a similar trend (views P=0.0009, comments P<0.0001, likes P<0.0001). Physicians were significantly less likely to include promotional content in their videos when compared to other content creators (P=0.0170).
Conclusion: Although skin of color-related dermatology content on YouTube is primarily educational, board-certified dermatologists are underrepresented as content creators on YouTube. It is pertinent that physicians continue to make content on YouTube and other social media platforms so that patients can have access to accurate yet salient information about their conditions.

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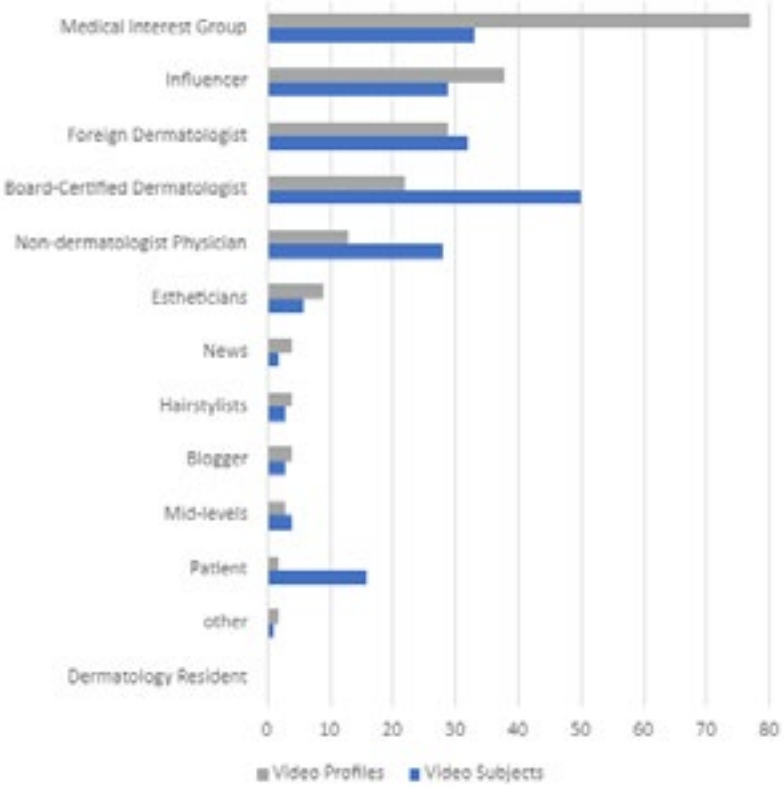
INTRODUCTION

The field of dermatology is one of the least ethnically and racially diverse medical specialties. Only 3% of dermatologists in the United States are Black and 4.2% are Hispanic, compared with 12.8% and 16.3%, respectively, of the total population.[1] Along with the lack of diversity among dermatology providers, textbook representation of dermatological conditions in patients with skin of color has also been found to be lacking.[2] Diversity in the current literature even appears to be an issue as the average percentage of overall publications relevant to skin of color among the top dermatology journals is quite low, with the higher-impact journals ranking the lowest in skin of color content.[3] The lack of diversity in dermatology has negative implications for patients of color and continues to be a hurdle to providing proper care to these patient populations. Organizations within the field of dermatology, such as the Skin of Color Society (SOCS), the Society for Investigative Dermatology (SID), and the American Academy of Dermatology (AAD), have begun prioritizing diversity in the specialty through the development of task forces and committees. While beneficial, these initiatives are somewhat slow to take effect, and racial disparities in dermatology continue to be an issue.[4]

Patients are increasingly looking to internet resources to gain insight into dermatologic conditions and potential treatment options. Previous studies have outlined the lack of board-certified dermatologists among people generating top skin of color dermatology-related content on social media platforms[5]; however, no studies regarding the skin of color dermatology

FIGURE 1. Number of videos per creator and subject matter. Out of a total of 207 videos, medical interest groups make up the most post profiles, whereas board-certified dermatologists make up the most post subjects. Residents were never involved in any of the videos.



content present on YouTube have been done. The goals of this study were similar to those outlined by Wells et al and included identifying and analyzing skin of color-related dermatology content found on YouTube, characterizing the content creators, and comparing board-certified dermatologists' content to that created by other YouTubers.

MATERIALS AND METHODS

Videos were queried on YouTube (https://www.youtube.com) on February 10, 2022. Search terms (Table 1) were generated from a list of common skin pathologies from the Skin of Color website (https://skinofcolorsociety.org) and individually searched on an incognito browser on YouTube followed by the words *skin of color*.[5] For example, the term *acne* was searched on YouTube with the search criteria *acne skin of color*. The top 9 videos that were relevant to each search term were recorded. Relevancy included any video that discussed the search term in the context of dermatology, videos that failed to do so were excluded. The total number of views, likes, and comments were recorded for each video along with the intention of the video (educational vs promotional). Each video was then analyzed to classify both the profile that posted the video and the subject of the video, if available. Classification categories (Figure 1) included board-certified dermatologists, US dermatology residents, foreign dermatologists, non-dermatologist physicians, medical interest groups, social media influencers, estheticians, news media, hairstylists, bloggers, mid-level providers, or patients. Classification was defined and discussed prior to data collection. Board-certified dermatologists were confirmed using the Find a Dermatologist tool on the American Academy of Dermatology (AAD) website (https://find-a-derm.aad.org/). The country of each foreign dermatologist was recorded. Non-dermatology physicians were verified on https://www.certificationmatters.org/. Mid-level providers included registered nurses, physician assistants, and nurse practitioners. Nurses were verified on the Nursys License Verification (https://www.nursys.com). Medical interest groups included any organization that functioned to promote educational or informative medical content on their website and/or YouTube channel. Other categories for classification were verified using their respective website information or their self-description in the video. If a video profile or subject did not fall into any of the established classifications, it was labeled as *other*.

Four binary comparisons of collected video profiles were performed based on the established classifications (Table 2): 1) all board-certified dermatologists vs all other classifications; 2) foreign dermatologists vs all other classifications; 3) non-

dermatologist physicians vs all other classifications; and 4) all physicians including board-certified dermatologists, foreign dermatologists, and non-dermatologist physicians vs all other classifications. For each comparison, the number of views, comments, and likes were quantitatively assessed using a Mann-Whitney U test. The proportion of subjects vs profiles and educational videos vs promotional videos were assessed using a Pearson's Chi-squared test. For all tests, statistical significance was defined as 2-sided *P*-value <0.05.[5]

RESULTS

The 23 skin of color search criteria yielded a total of 207 videos that were analyzed (Table 1). The most popular search term was *dandruff*, which resulted in 2 top videos: one with the highest comments (9,043) and a second with the highest likes (273,000) and views (10,447,011). The less popular search terms defined by number of views included *dermatosis papulosa nigra* (16,546), *eczema* (41,957), and *central centrifugal cicatricial alopecia* (97,092). Of the top 23 liked videos for each search term, 4

TABLE 1.

Common Skin of Color Search Terms and the Top Video Profiles in Terms of Likes, Comments, and Views
The classification of each top video profile is shown.

Skin of Color Term	Profile of Most Liked Post	Likes	Profile of Most Commented Post	Comments	Profile of Most Viewed Post	Views
dandruff	Medical Interest Group	273,000	Influencer	9,043	Medical Interest Group	10,447,011
pseudofolliculitis barbae	Non-dermatologist Physician	174,000	Non-dermatologist Physician	6,201	Non-dermatologist Physician	6,081,603
melasma	Foreign Dermatologist (UK)	6,500	Foreign Dermatologist (UK)	6,108	Foreign Dermatologist (UK)	1,420,978
seborrheic dermatitis	Esthetician	13,000	Board-Certified Dermatologist	1,458	Esthetician	1,411,602
hair breakage	Influencer	36,000	Hiarstylist	2,535	Influencer	1,090,871
traction alopecia	Influencer	36,000	Influencer	1,536	Influencer	1,079,512
razor bumps	Board-Certified Dermatologist	9,800	Influencer	902	Influencer	1,023,643
post inflammatory hyperpigmentation	Board-Certified Dermatologist	24,000	Foreign Dermatologist (UK)	3,191	Board-Certified Dermatologist	973,214
sarcoidosis	Medical Interest Group	9,900	Medical Interest Group	619	Medical Interest Group	765,428
tinea capitis	Medical Interest Group	3,700	Medical Interest Group	439	Medical Interest Group	659,659
keloid	Influencer	8,000	Influencer	536	Board-Certified Dermatologist	463,201
trichorrhexis nodosa	Blogger	18,000	Blogger	1,112	Blogger	457,290
dissecting cellulitis	Board-Certified Dermatologist	2,400	Board-Certified Dermatologist	195	Board-Certified Dermatologist	418,063
non melanoma skin cancer	Medical Interest Group	2,300	Medical Interest Group	158	Medical Interest Group	406,879
folliculitis papillaris	Influencer	10,000	Influencer	3,461	Influencer	392,205
melanoma	Medical Interest Group	1,600	Medical Interest Group	234	Medical Interest Group	317,503
acne	Foreign Dermatologist (UK)	7,900	Foreign Dermatologist (UK)	1,207	Foreign Dermatologist (UK)	206,000
vitiligo	Medical Interest Group	2,000	Medical Interest Group	367	Medical Interest Group	133,738
psoriasis	Board-Certified Dermatologist	2,800	Board-Certified Dermatologist	370	Medical Interest Group	131,639
acne keloidalis	Foreign Dermatologist (UK)	4,500	Foreign Dermatologist (UK)	1,149	Foreign Dermatologist (UK)	108,089
central centrifugal cicatricial alopecia	Influencer	2,100	Influencer	3,040	Esthetician	97,092
eczema	Foreign Dermatologist (UK)	3,100	Foreign Dermatologist (UK)	582	Foreign Dermatologist (UK)	41,957
dermatosis papulosa nigra	Foreign Dermatologist (UK)	1,800	Foreign Dermatologist (UK)	239	Foreign Dermatologist (ASTL)	16,546

were profiles of a board-certified dermatologist (17.4%), and 10 belonged to profiles of any physician (43.5%). Of the top 23 commented videos for each search term, 3 were profiles of board-certified dermatologists (13%), and 10 belonged to profiles of any physician (43.5%). Of the top 23 viewed videos for each search term, 3 were profiles of board-certified dermatologists (13%), and 9 belonged to profiles of any physician (39.1%).

Of the total 207 videos analyzed (Figure 1), the majority of video profiles consisted of medical interest groups (77, 37.2%), whereas the majority of video subjects consisted of board-certified dermatologists (50, 24.2%). In contrast, the least common video profiles belonged to patients (2, 1%), and the least common video subjects were news media (2, 1%). None of the videos had profiles or subjects of dermatology residents.

TABLE 2.

Characteristics of Top Videos Created by Board-Certified Dermatologists, Foreign Dermatologists, Non-Dermatologists Physicians, and All Physicians Compared to All Other Classifications of Content Creators. The classification of all physicians includes board-certified dermatologists, foreign dermatologists, and non-dermatologist physicians.

	Board-Certified Dermatologists	Other	*P*-value
Number of Profiles (%)	22 (11)	185 (89)	0.0003 (χ^2)
Number of Subjects (%)	50 (24)	157 (75)	
Total Views (%)	4,038,445 (8)	45,266,701 (92)	0.0477 (Mann-Whitney)
Total Comments (%)	10,416 (11)	87,233 (89)	0.0324 (Mann-Whitney)
Total Likes (%)	86,043 (7)	1,127,341 (93)	0.0203 (Mann-Whitney)
Educational (%)	22 (100)	173 (94)	0.2184 (χ^2)
Promotional (%)	0 (0)	12 (6)	
	Foreign Dermatologists	**Other**	***P*-value**
Number of Profiles (%)	29 (14)	178 (86)	0.6774 (χ^2)
Number of Subjects (%)	32 (15)	175 (85)	
Total Views (%)	5,415,379 (11)	43,889,767 (89)	0.0031 (Mann-Whitney)
Total Comments (%)	32,683 (33)	64,966 (67)	<0.0001 (Mann-Whitney)
Total Likes (%)	208,836 (17)	1,004,548 (83)	<0.0001 (Mann-Whitney)
Educational (%)	29 (100)	166 (93)	0.1497 (χ^2)
Promotional (%)	0 (0)	12 (7)	
Country of Origin UK (%)	23 (79)	6 (21)	--
	Non-Dermatologist Physicians	**Other**	***P*-value**
Number of Profiles (%)	13 (6)	194 (94)	0.0136 (χ^2)
Number of Subjects (%)	28 (13)	179 (86)	
Total Views (%)	6,597,823 (13)	42,707,323 (87)	0.6599 (Mann-Whitney)
Total Comments (%)	8,499 (9)	89,150 (91)	0.7188 (Mann-Whitney)
Total Likes (%)	185,738 (15)	1,027,646 (85)	0.7114 (Mann-Whitney)
Educational (%)	13 (100)	182 (94)	0.3555 (χ^2)
Promotional (%)	0 (0)	12 (6)	
	Physicians	**Other**	***P*-value**
Number of Profiles (%)	64 (31)	143 (69)	<0.0001 (χ^2)
Number of Subjects (%)	110 (53)	97 (47)	
Total Views (%)	16,051,647 (33)	33,253,499 (67)	0.0009 (Mann-Whitney)
Total Comments (%)	51,598 (53)	46,051 (47)	<0.0001 (Mann-Whitney)
Total Likes (%)	480,617 (40)	732,767 (60)	<0.0001 (Mann-Whitney)
Educational (%)	64 (100)	131 (92)	0.0170 (χ^2)
Promotional (%)	0 (0)	12 (8)	

A large portion of video profiles and subjects belonged to social media influencers (38, 18.4% and 29, 14%, respectively). Of the 29 foreign dermatologist profiles, the majority (23, 70%) were from the United Kingdom.

Mann-Whitney U tests were used to make comparisons between each category (Table 2) due to a non-parametric distribution caused by a small number of very popular outlier videos and/or very unpopular outlier videos. In the comparison between board-certified dermatologists and all other classifications, there were significant differences in views, comments, and likes (views P=0.0477, comments P=0.0324, likes P=0.0203). Similar findings were observed when comparing foreign dermatologists vs all other classifications (views P=0.0031, comments P<0.0001, likes P<0.0001) and physicians vs all other classifications (views P=0.0009, comments P<0.0001 likes P<0.0001). There was no significant difference between the views, comments, and likes between non-dermatologist physicians and other classifications. Board-certified dermatologists, non-dermatologist physicians, and physicians, in general, were more likely to be subjects in videos rather than video creators (P=0.003, P=0.0136, P<0.0001, respectively). When comparing physicians and all other classifications, physicians were significantly less likely to include promotional content (P=0.0170).

DISCUSSION

Modern-day internet accessibility has placed an abundance of health information at the fingertips of the general population. Consequently, many patients utilize the internet, rather than their physician, as their first source of health-related information.[6] Considering this, within the field of dermatology, it is becoming increasingly pertinent that reliable content presented by board-certified dermatologists for all skin types is available and easily accessible online. Regarding YouTube engagement between board-certified dermatologists' content and that created by all other classifications, there were significantly fewer views, comments, and likes on the board-certified dermatologists' content (views P=0.0477, comments P=0.0324, likes P=0.0203). This lack of engagement may be explained by most board-certified dermatologists lacking the amount of YouTube subscribers needed to generate the degree of attention that other classifications seem to produce for their videos. Lack of subscribers could be due to a deficiency of consistent content from board-certified dermatologists or, if present, less visually appealing content due to time constraints surrounding video editing. Similar results are seen when comparing content made by foreign dermatologists to all other classifications and when comparing non-dermatologist physicians to all other classifications. In contrast, it is difficult to explain why non-dermatologist physician content is insignificantly different from all other classifications.

Of the top 7 profiles creating the most-viewed posts, 3/7 in this category were influencers. Social media influencers can be bloggers, experts, or celebrities who generate an audience to follow their content.[7,8] Influencers utilize the power of personal connection to share experiences and give recommendations in a personable and friendly manner. This human element of influencer marketing is believed to be a large source of the recent success seen in the use of influencers across many industries.[8] Researchers have, likewise, begun to utilize influencers to help further research with public health interventions, such as promotion of flu vaccinations and healthy diets, as well as deep searching of a specific population of interest that may use certain social media platforms.[8,9,10,11] In 2020, YouTube was found to be the most popular social media platform, used by 81% of social media users. Of the 74% of internet users who use social media, 80% have searched media for health-related issues.[12-14] A recent study also found that over 20% of dermatology patients knew their provider through a social media platform.[15]

In another study, when searching the hashtag *#dermatology* on Instagram, only 7/146 (5%) accounts belonged to dermatologists, while 136/146 (93%) belonged to influencers. Furthermore, only 7% of the accounts were defined as being educational, and 68% of accounts had no type of medical credentialing.[16] Our data suggests that YouTube is more educational in nature, with 94% of top videos being defined as educational. These findings illustrate vastly different priorities of content creators on different social media platforms and demonstrate a need for influencers with expertise in the health-related content they create.[16,17] This expert presence is vital, as social media allows rapid dissemination of information, providing access to both educational content and misinformation. There is an increasing body of evidence that fabrications and misrepresentations on social media spread more rapidly than correct information does, while also reaching a broader range of people.[12,18] An observational cross-sectional study found that 44.7% of the dermatology content shared on social media was designated as imprecise, 20% as confusing, and only 35.5% as precise.[12,19] This further elucidates the need for accurate educational information from accredited resources such as board-certified dermatologists and related health professionals. Additionally, disparities already exist relating to the amount of educational dermatological resources relating to skin of color.[20] Increasing the presence of professionals in dermatology on social media platforms and skin of color-related content will be increasingly necessary for the future with the rise in social media usage and the growing percentage of skin of color populations in the United States.[20]

Despite an increase in traffic on YouTube in recent years, there has been a decrease in content available for education and outreach on skin of color, particularly in countries with a predominately

Caucasian population, such as the United States (76.3%).[21,22] Our data suggests that 9% of foreign dermatologists were from the United Kingdom, where only 13% of the population belong to Black, Asian, mixed, or other ethnic groups.[23] This constitutes a need for education initiatives focused on skin of color abroad as well as in the US.

The value of patient experiences should be further explored on YouTube, as our study found that patients were rarely involved as video subjects. Patient leader networks have found that patients are more likely to respond to content that comes from other patients similar to them and that online communities and social media platforms play a significant role in making health decisions.[24,25]

When comparing our results to those published by Wells et al[5] regarding skin of color-related dermatology content on Instagram, we see some similarities. They found that board-certified dermatologists were underrepresented among Instagram accounts that produce popular skin of color-related dermatology content with board-certified dermatologists generating only 12% of top posts. Our study had strikingly similar results with only 11% of top YouTube skin of color dermatology content coming from profiles of board-certified dermatologists. These similar findings raise concern for a significant scarcity of dermatologist-created content readily available across various forms of social media. However, as established previously, we found the skin of color dermatology-related content on YouTube to be more educational than promotional, whereas, on Instagram, it was more promotional. We also found that YouTube had substantially more skin of color-related dermatology content created by medical interest groups than Instagram.[5] These findings suggest that while there is a lack of dermatologist-created content available across both platforms, the content available on YouTube may be more informative than that found on other social media platforms.

Alongside the charge to increase skin of color-related dermatology content on social media, it is important to call attention to the ethical implications that surround healthcare providers using social media. The American Medical Association (AMA) has addressed the educational benefit that an online presence can provide to patients and fellow physicians and outlines clear guidelines as to what constitutes appropriate social media behavior.[26] While the AMA has created guidelines, there are still concerns regarding possible breaches of patient confidentiality, violations of patient-provider boundaries, licensing issues, and damage to a provider's professional image that are important to consider.[27] Due to the visual nature of dermatology, it is even more important that providers be vigilant in keeping patient information confidential when creating social media content. The protection of the right to self-image and protection of personal information are two principles of legal protection for patients with regard to medical photography that should be considered when dermatologists consent patients for collecting images, especially ones that can make a patient identifiable.[12,28] There have been instances of dermatologists convicted for publishing photographs of patients who consented to their usage for healthcare purposes, but not for scientific publication or media.[12,28] These implications further enhance the notion that, while social media is beneficial in education and reaching large groups of patient populations, legalities need to be strictly followed to protect patient privacy. Reliable information is also a necessity when using social media due to scant regulation policies among platforms. Medical guidance and facts need to come from qualified sources in order to prevent misguided management of patients and unnecessary treatments.[16]

YouTube content is constantly changing, and this study was limited to only being able to provide a brief snapshot of YouTube's current skin of color dermatology content. A follow-up study with a similar methodology could help assess the expansion of skin of color dermatology content on YouTube in the future. Another limitation involves the algorithm of the YouTube search engine. Several skin pathologies have multiple names and/or abbreviations that make accounting for all available content for each pathology difficult. Analyzing videos based on popularity can also pose an issue as viral content is often a product of chance and may not have any intrinsic merit. Accurate and informative dermatology presentations were often buried beneath more popular videos. A follow-up study analyzing a larger breadth of videos and perhaps the content of the videos themselves may help better explain our results. There were possibly also limitations with our use of the phrase *skin of color* when searching for content as opposed to using more specific terminology, such as deducing content related to specific races or ethnicities and specific skin pathologies.

CONCLUSION

Ultimately, these findings further support the lack of social media content related to skin of color that has previously been found on other web-based platforms. While finding that most of the content published on YouTube was educational rather than promotional is promising, further steps need to be taken to provide skin of color populations with increased ease of access to health-related information that is specific to their skin type. With the rise in social media popularity, healthcare providers and board-certified dermatologists should understand that social media is at the forefront of establishing accurate skin of color-related content. The collaboration between medical professionals and influencers who attract high traffic on their respective platforms could be a mutually beneficial partnership between fields of expertise to increase access to care for skin of color populations. The underrepresentation of education across social media regarding skin of color needs to be addressed by

providers in order to provide inexpensive access to accurate and specific information regarding the presentation of dermatologic conditions, diagnosis, and treatment.

DISCLOSURES

The authors have no conflicts of interest or funding sources to disclose.

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CASE REPORT

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Erythrodermic Bullous Pemphigoid in Skin of Color Treated With Dupilumab

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ABSTRACT

Bullous pemphigoid (BP) is an autoimmune blistering disease that typically presents with pruritic, tense bullae in elderly patients.[1] Several recognized presentations deviate from the classic bullous eruption, and erythrodermic BP, in particular, is thought to be a rare phenomenon. Herein, we present a case of erythrodermic BP in an African American male who initially presented with erythroderma in the absence of tense bullae. There have been no reports on erythrodermic BP in skin of color to our knowledge. The patient rapidly improved after treatment was started with dupilumab. He developed classic tense bullae seen in BP once dupilumab was discontinued.

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CASE REPORT

An African American male in his 80s with a past medical history of atrial fibrillation, congestive heart failure, type 2 diabetes mellitus, hypertension, prostate cancer, chronic kidney disease, and a previous cerebrovascular accident presented with complaints of a pruritic rash on his neck, chest, abdomen, arms, and groin for two weeks. He was given topical clotrimazole-betamethasone ointment by his primary care provider which was ineffective. Skin examination was significant for erythematous to brown scaly plaques arranged in a vertical linear and reticulated distribution throughout his entire chest, back, abdomen, flanks, groin, and proximal thighs (Figures 1–3).

Additionally, there were a few pink oval plaques scattered on his forearms and a hyperpigmented patch on the right neck. An initial punch biopsy of the right shoulder yielded findings of subacute spongiotic and psoriasiform dermatitis with areas of confluent parakeratosis and eosinophils. The exam and biopsy were consistent with contact dermatitis or a drug-induced psoriasiform eruption. The patient was started on topical triamcinolone ointment and an oral prednisone taper. The patient's pruritus improved on the oral steroids; however, taper had to be stopped after 2 days due to a severe increase in his blood glucose levels. He was re-evaluated in dermatology clinic and a second punch biopsy was sent for direct immunofluorescence (DIF). At that time, he was started on dupilumab injections given recurrent pruritus, as well as clobetasol ointment. Immunofluorescence studies demonstrated IgG and IgA deposition on the epidermal side and C3 deposition on the dermal side, consistent with BP. The patient experienced significant improvement in pruritus and skin appearance and agreed to continue the dupilumab

FIGURE 1. An 80-year-old African American male with erythematous to brown scaly plaques arranged in a vertical linear and reticulated pattern.

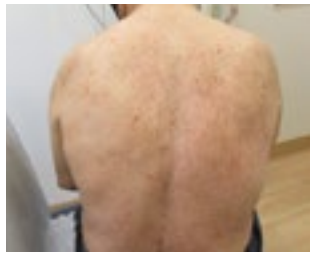


FIGURE 2. View of chest, abdomen, and upper extremities.

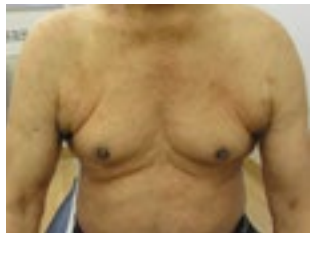
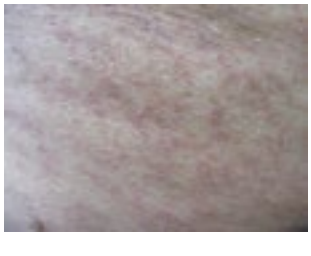


FIGURE 3. Close up view demonstrating slightly scaly erythematous and urticarial papules.



injections. Due to a lapse in insurance coverage for dupilumab, the patient experienced a flare of pruritus and rash but instead presented with tense bullae scattered throughout the neck, chest, abdomen, back, upper extremities, and thighs, as well as small, whitish subcutaneous nodules scattered throughout his bilateral palms and volar wrists. The patient re-initiated dupilumab treatment and again his skin appearance and pruritus improved.

DISCUSSION

There have been only a handful of case presentations on erythrodermic BP, none of which include clinical photos of people of color to our knowledge. Bal et al presented a patient in 2021 with erythrodermic non-bullous pemphigoid.[2] The patient appears to be Caucasian in the images; however, no race or ethnicity was specified. Huet et al presented an image in 2016 of a Caucasian male with exfoliative, erythrodermic non-bullous pemphigoid.[3] Alonso-Llamazares et al reported on a case of exfoliative erythrodermic BP in 1998, and the image provided appeared to be of a Caucasian male, though his race and ethnicity were not specified in the article.[4] These three reports share an absence of bullae at the time of diagnosis and throughout follow-up. Our patient presented without any bullae like the three aforementioned cases; however, he did go on to develop bullae during his follow-up. In contrast, Amato et al presented two cases of erythrodermic BP in 2001 presented with tense bullae.[5] Their ethnicities and races were not specified, and skin type cannot be ascertained.

Our patient was started on dupilumab injections before BP was confirmed by DIF. Within 2 weeks of his loading dose of dupilumab, he reported marked symptomatic improvement in his itching, and his erythematous, urticarial plaques were also noted to be significantly improved on physical examination. The improvement of his symptoms due to dupilumab is promising and consistent with other reports of BP responding to dupilumab.[6] Bal et al describe in their report a resolution of pruritus within 1–2 weeks of starting dupilumab injections and near-complete resolution of rash within 4 weeks.[2] These two cases share strikingly similar response timelines. Exceptionally, bullae did not appear in our patient until after the dupilumab was stopped for one month, which is the first report of this phenomenon to our current knowledge.

With this case report of erythrodermic BP in an African American male, we hope to add images of this presentation in skin of color to enrich the limited literature on erythrodermic BP. Furthermore, this presentation on skin of color serves to assist providers in making an already challenging diagnosis.

DISCLOSURES

The authors have no conflicts to disclose.

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CASE REPORT

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Leukemia Cutis in Skin of Color

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ABSTRACT

The various presentations of many dermatologic conditions among various skin types are slowly being elucidated throughout the recent years. These differences present as an issue as it leads to delayed diagnosis, treatment, and poorer quality of life. Herein, we present the characteristics of leukemia cutis in a skin of color patient with diagnosed chronic myelomonocytic leukemia.

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INTRODUCTION

The malignant transformation of hematopoietic cells leads to the manifestation of leukemia.[1] Depending on the cell lineage and maturity, the main overarching subtypes of leukemia are acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphoblastic leukemia (CLL).[1]

In addition to bone marrow and peripheral blood involvement, extramedullary forms of leukemia such as granulocytic sarcoma and leukemia cutis also exist.[2] Leukemia cutis (LC) is the infiltration of leukemia cells in the skin, leading to clinically apparent lesions, and occurs in about 3% of leukemia patients.[3] While the pathophysiology of LC remains unknown, there is speculation that the migration of leukemia cells to the skin is a result of an attraction between various expressed chemokines and adhesion molecules.[4] Genetic variations have also been associated with this extramedullary involvement of AML such as the inversion of chromosome 16, rearrangement of chromosome 11q23, and *NPM1* mutation.[5] LC typically occurs concomitantly or after leukemia diagnosis, but can rarely precede it by months to years.[6] Approximately 55-77% of LC patients are diagnosed with leukemia prior to presentation.[6] Compared with the other leukemias, AML and CLL have a higher propensity to cause LC, specifically those with AML. Poorer prognosis of leukemia is suspected when there is cutaneous involvement.[5] Wang et al conducted a retrospective study of matched AML subjects with or without LC and revealed the 5-year survival to be 8.6% and 23.8%, respectively.[5]

CASE

A 78-year-old African American female was referred to the dermatology clinic by her primary care physician due to a two-month history of raised, pruritic, dry lesions. The patient had a past medical history of untreated chronic myelomonocytic leukemia (CMML), Type II Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, Hypertension, and Major Depressive Disorder. Her physical exam revealed multiple, indurated, pearly plaques and nodules on her eyelids and upper and lower extremities (Figure 1). There was no evidence of ulceration or scaling and the lesions were not tender to palpation. A right forearm biopsy was collected. She was prescribed a 14-day course of twice daily 0.1% triamcinolone cream to soothe her itch.

FIGURE 1. Leukemia cutis lesions on the extremities and eyelid.

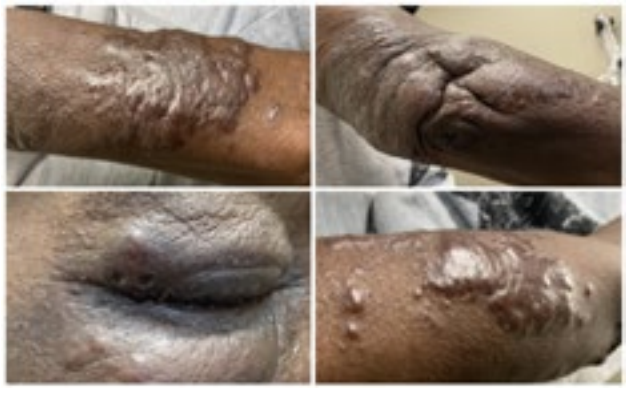
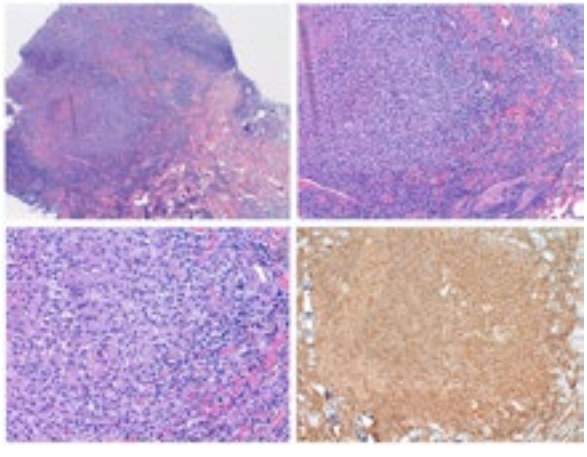


FIGURE 2. Nodular to diffuse infiltrate of monotonous large cells with a high nuclear to cytoplasmic ratio. H&E, 4x (top left); H&E, 10x (top right); H&E, 20x (bottom left); CD43 stain (bottom right).



Histopathology revealed nodular to diffuse infiltrate of monotonous large cells with a high nuclear to cytoplasmic ratio (Figure 2). There were round to slightly irregular nuclear contours with finely dispersed chromatin and prominent nucleoli. Immunohistochemistry (IHC) showed CD43+ cells that were concurrently negative for CD3 and CD20 antigens. A final diagnosis of leukemia cutis was made, and the patient was referred to the MD Anderson Cancer Center for further treatment.

DISCUSSION

There are a paucity of data available for LC, specifically in those of skin of color; however, the differences in how LC presents across various groups can provide insight. There are ethnic and racial disparities evident in the incidence of leukemia. Non-Hispanic Whites (NHW) typically have the highest incidence and yet a better survival rate than those that are not NHWs.[7]

TABLE 1.

Differential Diagnoses of Leukemia Cutis Based on Lesion Type

Lesion Type	Differential Diagnoses	Additional Comments
Maculopapular	Drug eruption	--
	Viral exanthems	--
	Morbilliform rash	--
	Syphilitic rash	--
Papulonodular/ Papulosquamous	Sweets syndrome	Can present as an associated disorder
	Lymphoma cutis	Can be difficult to differentiate histologically, if from lymphoid cell line
	Lymphomatoid papulosis	--
	Kaposi sarcoma	--
	Drug eruption	--
	Purpura/Petechiae nasculitides	Can present as an associated disorder
	Keloid	--
	Squamous cell carcinoma	--
	Basal cell carcinoma	--
	Metastatic neoplasms	--
	Erythema nodosum	Can present as an associated disorder
	Sarcoidosis	--
	Granuloma annulare	--
	Lichen planus	--
	Morphea	--
Ulcerative	Pyoderma gangrenosum	Can present as an associated disorder
	Squamous cell carcinoma	--
	Basal cell carcinoma	--
	Vasculopathies	Can present as an associated disorder

According to pooled data from 2010 to 2014, Whites had a higher incidence of AML than in Blacks, Pacific Islanders/Asians, and Hispanics.[8] However, additional data from 1999 to 2008 revealed a higher risk of death at 12% and 6% in Blacks and Hispanics, respectively, compared with Whites.[8]There were also apparent differences in treatment and treatment outcomes, where Hispanic and Black patients with AML and ALL were noted to have worse overall survival.[8] Being African American was discovered to be an independent predictor for a shortened overall survival in patients with CLL.[9]

Dermatologic conditions can present differently in SOC, leading to delayed diagnoses and worse outcomes. Given its rarity and variable morphology, LC mimics other pathologies; thus, differences due to SOC should be also considered. A known leukemia history increases suspicion for LC, but in the rare cases of aleukemic LC (occurring in 2-3% of cases), diagnosis can be more elusive.[6,10] Leukemia cutis lesions can present as erythematous/violaceous or skin-colored, solitary or multiple papules, nodules/tumors, plaques, ulcers, or even gingival hyperplasia.[6] The distribution can either be disseminated or localized, but lesions have no predilection for specific anatomical sites.[6] Differential diagnoses to be considered LC are included in Table 1.

Histology and immunohistochemistry are also crucial in the accurate diagnosis of LC. Histological findings typically reveal leukemia cells infiltrating superficial to deep layers of the skin.[11] There can also be evidence of a "Grenz zone" or dermal-epidermal junction, suggesting perivascular and periadnexal infiltrate, especially in the acute leukemias.[10]

Immunohistochemical stains can be positive for CD4, CD34, CD56, CD68, CD117, CD123, TdT, lysozyme, or myeloperoxidase (MPO).[12] Additional molecular testing is necessary for typing the leukemia in the setting of undiagnosed systemic leukemia.[11]

Treatment is aimed at addressing the underlying systemic leukemia.[13] The best route of treatment is based on the patient's health status and leukemia subtype, ranging from hematopoietic stem cell transplantation, chemotherapy, or observation.[13]

CONCLUSION

The awareness of delayed and inaccurate diagnoses in SOC has recently gained traction.These efforts can reduce the detrimental effects of this disparity. While the cutaneous extramedullary form of leukemia typically occurs after leukemia diagnosis, a suspicion of LC–although it presents similarly to other skin conditions–prior to known diagnosis can save lives.

DISCLOSURES

The authors have no conflicts of interest or funding sources to declare.

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CASE REPORT

Journal of Drugs in Dermatology

Poroma in a Patient With Fitzpatrick Type V Skin

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ABSTRACT

This case detailing a poroma in Fitzpatrick Type V skin presents gross, dermatoscopic, and histopathologic images that have not been adequately represented in the literature. Diagnosing poroma can be challenging and misdiagnoses can have tragic consequences. The scarcity of published poroma images in darker skin types can further complicate this problem.

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CASE

An 82-year-old African American male (Fitzpatrick Type V) presented with a tender, bleeding exophytic growth on the right lateral foot enlarging over the preceding three months. Examination showed a 0.9 x 0.7 cm exophytic erythematous papule with collarette and yellow, hemorrhagic crust (Figure 1A). Dermoscopy showed multiple colors with pale pink, red, yellow, and brown islands (Figure 1B). Vascular structures were not detected on dermoscopy.

FIGURE 1A. Clinical presentation of poroma in Fitzpatrick Skin Type V. Examination of the right lateral foot showed a 0.9 x 0.7 cm exophytic erythematous papule with collarette and slight yellow and hemorrhagic crust.

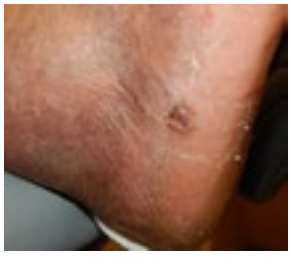
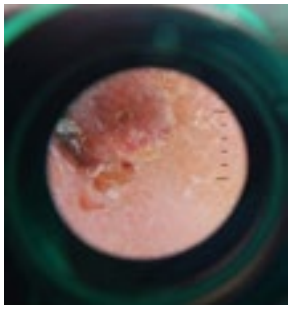


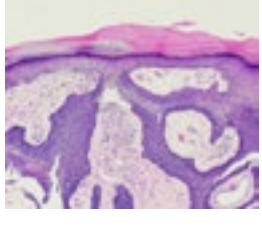
FIGURE 1B. Dermoscopic image of poroma in Fitzpatrick Skin Type V (DL4 Dermatoscope, 3Gen, Ca). Multiple colors were noted with pale pink, red, yellow-brown, and dark brown islands. Vascular structures were not detected on dermoscopy.



Two years prior, podiatry described the lesion as a 1 cm well-circumscribed, elevated, torn cyst-like lesion with mild bleeding and no signs of infection. An X-ray revealed "ovoid density measuring 7 mm along the lateral plantar aspect of the foot which may correspond to a foreign body." However, the patient had no recollection of trauma. Podiatrists performed four superficial debridements, curettage and silver nitrate treatments for multiple diagnoses including hemangioma and "skin tag-like lesion" resulting in temporary improvements, but the lesion kept recurring. Dermatologic history included a plantar wart on the right foot nine years prior, treated by podiatry with salicylic acid and urea cream, congenital dermal melanocytosis, seborrheic keratoses, and tinea pedis. Medical history was otherwise not relevant.

The differential diagnosis included both inflamed benign lesions (poroma, pyogenic granuloma, and verruca) and malignancies (amelanotic melanoma, squamous cell carcinoma, and porocarcinoma). A shave biopsy was performed and the base was electrodessicated with a hyfrecator. Dermatopathology showed proliferation of uniform basophilic staining cuboidal epithelial cells, emanating from the epidermis, forming anastomosing bands extending throughout the dermis, confirming the diagnosis of eccrine poroma (Figure 2). The site healed well without sequelae or recurrence at one-year follow-up.

FIGURE 2. Dermatopathology of poroma in Fitzpatrick Skin Type V, magnification 100x. There is a proliferation of uniform basophilic staining cuboidal epithelial cells, emanating from the epidermis, forming anastomosing bands extending throughout the dermis. This is characteristic of a poroma.



DISCUSSION

Poromas are benign ductal adnexal neoplasms that tend to exhibit eccrine differentiation. They often present on soles, sides of feet, or palms as solitary 2–12 mm sessile skin colored/red papules or plaques with possible scale.[1] They grow slowly and are generally asymptomatic but can rarely progress to malignant porocarcinomas.[2]

Poromas present equally across sex, race, and ethnicity and tend to appear in adulthood, but have been insufficiently studied in darker skin types.[3] As our case highlights, diagnosing lesions on skin of color feet can present diagnostic challenges that might not be fully realized by many clinicians, due in part to poor representation in the published literature. Our Pubmed search for poromas did not yield any gross or dermoscopic images from patients with skin types V or VI. One case report detailed a malignant eccrine poroma on the helix of an African American female that included gross and histopathology images but no dermoscopy.[4]

Dermoscopic features of poromas include white interlacing areas around vessels, yellow structureless areas, milky-red globules, and poorly visualized vessels which might be more difficult to appreciate in darker skin types.[5,6] Lesions with multiple colors can make differentiation from malignancies particularly difficult. Eccrine poromas evaluated by dermoscopy can mimic other skin neoplasms including skin cancer and other pigmented lesions.[5] Biopsy should be done to exclude melanoma or porocarcinoma.[6] Excision or electrosurgery are reported to be successful treatments and prognosis is excellent.[3]

DISCLOSURES

The authors have no conflicts of interest or funding sources to declare.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Racial Disparities in the Treatment of Hidradenitis Suppurativa: An Analysis of Data from the National Ambulatory Medical Care Survey

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ABSTRACT

Hidradenitis suppurativa (HS) is a painful, disfiguring, chronic inflammatory disease affecting the axillary, inframammary, and groin regions. Black Americans are disproportionately affected by HS. Structural barriers may be responsible for a lack of better prevention and management. This paper discusses possible reasons that may lead to a more severe presentation and barriers to treatment.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by recurrent nodules, abscesses, and sinus tracts with secondary scarring and fibrosis resulting from immune responses to follicular occlusion.[1,2,3] Black patients, in the United States, have a higher prevalence of HS than White patients.[3]

HS has previously been associated with obesity/high body mass index (BMI) and lower socioeconomic status (SES), suggesting that patients of low SES may have more severe cases due to a variety of variables, including nutritional options, medication coverage, research funding for the condition, health insurance coverage, and reimbursement for physician treatment.[3,4,5] Black Americans are more likely to be uninsured or underinsured than their White counterparts, which may cause barriers to accessing care or coverage for medication or treatment.[6] Here we investigate racial disparities in the management of HS using data from the National Ambulatory Medical Care Survey (NAMCS), and identify whether structural barriers may reduce equitable care to those with HS.

MATERIALS AND METHODS

The data set in this study was obtained for the years 2012–2018 from the publicly available National Ambulatory Medical Care Survey, Centers for Disease Control and Prevention. Disparities in demographics, practices, and care for HS between White and Black patients were examined for many variables (Table 1). Data

TABLE 1.

Summary Statistics				
Characteristic	**n, White patients (%)**	**n, Black patients (%)**	**χ-square *P*-value**	**Fisher's Exact Test Result**
Age				
< 18 years old	41 (13.3)	14 (26.4)	.0214	Probability Age > 18 years is greater for White patients (*P*=.0160)
> 18 years old	267 (86.7)	39 (73.6)		
Payment Type				
Medicaid or Medicare	111 (37.0)	31 (59.6)	.0097	n/a
Private Insurance	139 (46.3)	15 (28.9)		
Other	50 (16.7)	6 (11.5)		Copy
Was there a documented skin exam?				
Yes	192 (62.3)	25 (47.2)	.0392	Probability of a skin exam is greater for White patients (*P*=.0276)
No	116 (37.7)	28 (52.8)		

TABLE 2.

Medicare Reimbursement for Hidradenitis Suppurativa Treatment

CPT Code	Code Description	MPFS National Payment Amount ($)	Global Period (days)
10060; 10061	Incision and drainage of abscess; complicated or multiple abscesses.	$121.68; $218.71	10;10
11450; 11451	Excision of skin and subcutaneous tissue for hidradenitis, axillary; with simple or intermediate repair; with complex repair	$454.03; $550.24	90;90
11462; 11463	Excision of skin and subcutaneous tissue for hidradenitis; inguinal, with simple or intermediate repair; with complex repair	$440.54; $559.58	90;90
11470; 11471	Excision of skin and subcutaneous tissue for hidradenitis, perianal, perineal, or umbilical, with simple or intermediate repair; with complex repair	$475.49; $568.93	90;90
17110; 17111	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions (up to 14 lesions); 15 or more lesions	$116.62; $136.35	10;10

distributions were calculated between the two racial groups (Black and White). Chi-squared statistics and Fisher Exact Tests were computed to evaluate for significant differences between the above variables as a function of race. Chi-squared values were calculated based on Likelihood Ratio Theory. Fisher's exact tests were performed for 2 x 2 contingency tables.

RESULTS

Chi-square tests indicated an association between age and race, with the probability of age over 18 years greater for White patients (*P*=.0160). Additionally, an association between payment method and race (*P*=.0089) was found indicating that Black patients were more likely to pay with Medicare or Medicaid, while White patients were more likely to pay with private insurance. White patients were also more likely to receive a skin exam (*P*=0.0267) and to be scheduled for a long-term follow-up (>2 months from the initial visit, *P*=.0017) compared to Black patients. Variables that were observed to be significantly different between White patients and Black patients were then used in logistic regression analysis.

DISCUSSION

As in other diseases that predominantly affect minorities, HS research has been historically underfunded in the United States.[7] NIH funding for HS research did not occur until 2020, when the NIH created the Accelerated Basic and Translational Research in HS grant consisting of 2.5 million dollars to support HS research initiatives. However, even though Black patients have a 3-fold higher likelihood of developing HS than White patients, Black subjects remain underrepresented in clinical trials[8] and tend to go longer without a diagnosis or treatment.[9] Compared to White patients, Black patients have more severe episodes of HS and may have increased risk of developing comorbid skin diseases, such as squamous cell carcinoma, a rare but potential malignancy that may arise in such chronic inflammatory diseases.[10] Systemic issues related to nutrition, medication coverage, research funding, and reimbursement for surgical treatment may contribute to the increased morbidity among Black patients.

Medical management of HS is first line, but coverage may be difficult. Treatments for HS include antiandrogen therapy (spironolactone), metformin, antibiotics, immune modulator medications, incision and drainage of abscesses, excision of skin and subcutaneous tissue with/without repair, and laser surgery. Insurance coverage may impact treatment choices. For example, treatments, such as immune modulators are often more difficult to have covered with Medicare and Medicaid than with private insurance plans. Surgical treatments for HS may also have limited access as procedures are complex, such as marsupialization of sinus tracts, requiring extensive time to complete. These procedures have a 90-day global period, requiring a great deal of follow-up relative to reimbursement. Thus, possibly inhibiting physicians from taking on challenging cases due to inadequate reimbursement.[11,12] We found that Black patients were more likely than White patients to pay with Medicare/Medicaid, which poorly reimburses for these procedures.[11] Barriers to medical management and poor reimbursement/compensation for necessary procedural interventions may present a barrier to finding providers and access to treatment among Black patients who are disproportionately affected by HS.

As obesity is associated with worse HS symptoms, a reduction in weight is also important, but aspects like lack of access to healthful foods, gyms, and nutrition education may make this difficult. Greater distance to supermarkets (food deserts) and higher food prices have been correlated with obesity in majority Black American neighborhoods.[12]

CONCLUSIONS

In conclusion, there are multiple factors, including structural barriers, such as funding for medical and surgical management and assistance in prevention, which lead to a disparity in severity of HS, treatment, and social impact on Black Americans. Poorly

controlled HS and the chronic, debilitating nature of this disease may result in increased social services and a reduction in work productivity, and a negative effect on socioeconomic status.

DISCLOSURES

The authors have no conflicts of interest to declare.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Cutaneous Sarcoidosis in Skin of Color

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ABSTRACT

Cutaneous sarcoidosis presents in 25% of all sarcoidosis cases. African American populations, particularly African American women, are more likely to develop the dermatologic manifestations of the disease. There are several types of skin manifestations of sarcoidosis, which can make it more difficult to diagnose it clinically. Given the higher incidence of sarcoidosis and the poorer outcomes in these populations, it is essential to understand and recognize the variety of dermatologic symptoms associated with sarcoidosis. By doing so, patients can be diagnosed and treated earlier in their disease progression.

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INTRODUCTION

Sarcoidosis is a systemic disease that is identified by the key feature of non-caseating granulomatous inflammation in the affected organ.[11] The diagnostic criteria for sarcoidosis include a clinical and radiologic presentation of sarcoidosis, evidence of non-caseating granulomas, and exclusion of other causes of disease.[11] While the etiology of sarcoidosis is unknown, it is hypothesized that there may be a genetic predisposition or environmental factors that influence the disease progression.[1,10] The non-caseating granulomas develop due to the overstimulation of Th1 cells to secrete interferon gamma (IFN-γ), which activates macrophages. The activated macrophages then promote the secretion of cytokines such as tumor necrosis factor alpha (TNF-α) which leads to the production of the epithelioid histiocytes and the formation of the multinucleated giant cells that make up the composition of the non-caseating granuloma.

Sarcoidosis can affect patients of all ages and racial backgrounds, but it predominantly presents in African American females.[1,4] The pulmonary system is the most affected organ, and the skin is the second most common. Cutaneous sarcoidosis can be found on any skin surface including mucosal layers, and it has a higher propensity to develop in sites of previous skin disruption such as in scarring from injury or tattoos.[4] Clinical presentations of cutaneous sarcoidosis include lupus pernio, papular sarcoidosis, nodular sarcoidosis, plaque sarcoidosis, scar sarcoidosis, and erythema nodosum.[7] Given its high prevalence in African American women, it is essential to be familiar with the various cutaneous presentations of sarcoidosis for early detection and treatment, especially in skin of color.

Types of Cutaneous Sarcoidosis

Diagnosing sarcoidosis can be challenging because of the wide array of presentations associated with the disease. Comprehensive evaluations for sarcoidosis must be done early and include combined evaluations of a patient's clinical exam, blood work, radiologic imaging, and histologic features. The diagnosis of sarcoidosis is confirmed with biopsy indicating the presence of non-caseating granulomas. The absence of non-caseating granulomas in the skin does not rule out the diagnosis but is required in all of the specific skin findings described below.[6]

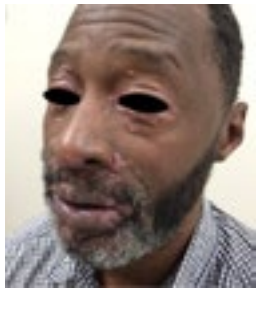
Specific Skin Findings

Papular Sarcoidosis

Papular sarcoidosis is the most common skin manifestation of sarcoidosis.[6] The papules are elevated skin lesions typically seen on the face, but they can be seen in any location on the body (Figure 1). Papular sarcoidosis is <1 mm in size and varies in color from reddish-brown to violaceous.[5] The papules are firm to palpation and have an "apple jelly" appearance when pressure is applied.[6]

Differential diagnoses: Rosacea, Sebaceous hyperplasia, Xanthoma.

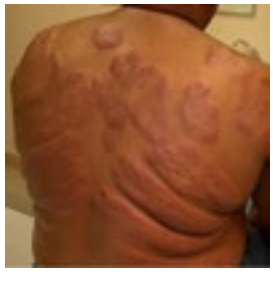
FIGURE 1. Papular sarcoidosis.



Plaque Sarcoidosis
Plaque sarcoidosis is characterized by elevated lesions >5 mm in size.[6] Plaques can be found on the face, extremities, or trunk, and may occur alone or in multiples. When plaques present in multiples, they are typically seen in a symmetric distribution (Figure 2).[5] Plaques are more likely to develop in deeper skin layers than papules.[6]

Differential diagnoses: Lichen planus, Psoriasis, Cutaneous T-cell lymphoma.

FIGURE 2. Plaque sarcoidosis.



Scar Sarcoidosis
Scar sarcoidosis involves patches that appear in areas of previous scarring. The patches may present as erythematous or violaceous in color and will affect areas such as the face, trunk, scalp, and extremities. The initial scarring can be caused by any mechanical trauma to the skin including venipunctures, previous infections, and tattoos (Figure 3). These lesions themselves are often asymptomatic and can be an indication of a sarcoidosis exacerbation.[6]

Differential diagnoses: Keloids, Hypertrophic scar.

FIGURE 3. Scar sarcoidosis.

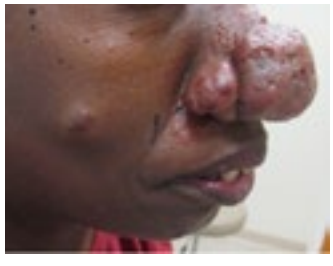
Lupus Pernio
Lupus pernio more commonly affects women with skin of color.[6,9] It presents as indurated papules or plaques that vary in color from red to purple.[9] Lupus pernio is seen predominantly on the skin over the cheeks, nose, lips, and ears.[6]

Differential diagnoses: Lupus erythematosus, Lupus vulgaris, Leprosy.

Nodular (Subcutaneous) Sarcoidosis
Nodular sarcoidosis, also known as Darier-Roussy sarcoidosis, involves non-tender firm subcutaneous nodules that are mobile and 0.5 - 2 cm in size (Figure 4).[6]

Differential diagnoses: Granuloma annulare, Lipomas.

FIGURE 4. Nodular sarcoidosis.



Ulcerative Sarcoidosis
Ulcerative sarcoidosis may arise with or without the presence of a pre-existing lesion on the lower extremities.[3] Ulcerative lesions are twice as likely to develop in women and individuals with darker skin tones.[6]

Differential diagnoses: Ulceration from stasis dermatitis, Cutaneous tuberculosis.

Hypopigmented Sarcoidosis
Hypopigmented sarcoidosis typically presents in patients with darker skin tones as well-demarcated hypopigmented macules and can also present as papules or nodules.[6] The papules are erythematous or skin-colored and may develop at the center of a hypopigmented lesion, giving the appearance of a fried egg.[8]

Differential diagnoses: Seborrheic dermatitis, Pityriasis alba, Vitiligo.

Ichthyosiform Sarcoidosis
Ichthyosiform sarcoidosis is rare and presents as scaly hyperpigmented plaques that are polygonal in shape and vary in color from gray to brown.[8] These plaques are commonly found on the lower extremities and are nontender and nonpruritic.[6] Approximately 95% of patients with ichthyosiform sarcoidosis will develop systemic sarcoidosis.[6]

Differential diagnoses: Eczema, Ichthyosis vulgaris.

Nonspecific Skin Findings
Erythema Nodosum
Erythema nodosum is caused by inflammation of subcutaneous fat (panniculitis) and is characterized as tender erythematous nodules that typically present on the shins anteriorly. It more commonly presents in patients of European, Puerto Rican, and Mexican descent, and often remits without treatment.[6] Erythema

nodosum is the most common nonspecific skin finding in patients. However, it can have other causes such as fungal and bacterial infections, leprosy, and inflammatory bowel disease.

Differential diagnoses: Erysipelas, Thrombophlebitis, Nodular Vasculitis.

Lofgren Syndrome

Lofgren syndrome includes erythema nodosum in addition to bilateral hilar lymphadenopathy, symmetric polyarthralgia, anterior uveitis, and fever. It predominantly affects patients of African, Puerto Rican, and Scandinavian descent and has a favorable prognosis with resolution of all symptoms within 2 years of the initial diagnosis.[6]

Differential diagnoses: Infectious (Coccidioidomycosis, Histoplasmosis, Tuberculosis), Inflammatory bowel disease.

Dermatologic Manifestations in Skin of Color

Sarcoidosis is a multisystemic disease and cutaneous manifestations occur in approximately 25% of cases, with some patients only manifesting cutaneous symptoms.[6] Sarcoidosis affects all races, but in the United States, African Americans have a higher prevalence of disease.[6] Additionally, due to the variety of skin manifestations, African American patients are more likely to be diagnosed when they are already in an advanced stage of the disease.[2] Factors influencing poorer prognosis in African Americans include access to healthcare, income, and level of education.[2] African American patients present earlier in life with more advanced disease, and have higher rates of hospitalization and higher rates of mortality.[1] These trends all lead to a poorer prognosis for African American patients with sarcoidosis.[6]

Treatment

The majority of cutaneous manifestations associated with sarcoidosis resolve without treatment. The prognosis of the disease is determined by the systemic symptoms and cannot be determined by the skin manifestations alone.[6] While the dermatologic changes are not an indication of disease severity, they can help clinicians diagnose and treat the disease earlier. Since sarcoidosis cannot be cured, treatment is based on providing symptomatic relief and preventing disease progression.

First-line agents used for cutaneous sarcoidosis are corticosteroids, which work by inhibiting the inflammatory response in the production of non-caseating granulomas.[6] If the cutaneous sarcoidosis is localized to a distinct area on the skin, then topical treatments such as clobetasol may be used. If the skin lesions include plaques and papules, then injections of triamcinolone every 4 weeks may be more effective.[6] If the cutaneous sarcoidosis does not respond to initial topical corticosteroid treatment, there is extensive skin involvement, or there is a potential for scarring, then systemic corticosteroids such as prednisone are employed.[6]

Antimalarials such as chloroquine and hydroxychloroquine may also be used for cutaneous sarcoidosis and work similarly to prevent granuloma formation.[6] Second-line treatments include immunosuppressive therapies such as methotrexate and cyclosporine. Additional options for refractory cutaneous sarcoidosis are monoclonal antibodies (infliximab), thalidomide, and isotretinoin.[6]

CONCLUSIONS

Cutaneous sarcoidosis can present in multiple forms and locations on the body. While the cutaneous manifestations may not be an indication of the severity of the disease, they can be an important clue for the prompt diagnosis of sarcoidosis. African American females are disproportionately affected by sarcoidosis. These populations are more likely to not only develop the disease but also have higher rates of hospitalization and worse outcomes. Given these higher incidence rates, it is critical to recognize the potential cutaneous manifestations that can be seen in African American patients.

DISCLOSURES

The authors have no conflicts of interest to declare.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

TikTok and Black Skin: Is This a Missed Opportunity for Dermatologists?

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ABSTRACT

Background: A study by Villa-Ruiz et al (2021) found that educational videos dominate the content of dermatologic videos on TikTok with 25.8% of the videos being posted by board-certified dermatologists. We sought to examine if these results would differ when the search is adjusted to hashtags specific to black skin.

Methods: On October 12th, 2021, an investigator input #BlackSkinCare, #BlackSkinTreatment, #BlackSkinAdvice, and #BlackSkinCareTips in TikTok. #SkinOfColor was not searched as this term is used almost exclusively by dermatologists and could skew the results. After the total of 200 videos was obtained, the videos were then classified into categories regarding their content, and the skin concern and creator were recorded.

Results: Most of the videos were of educational content (57.1%), followed by personal experiences (23.2%). Clinical demonstrations/live procedures, business/advertisement, and entertainment/humor followed with 9.6%, 5.6%, and 4.5%, respectively. 54.5% of posts were about general skin care. 22.7% of posts addressed dark spots followed by acne (12.1%). Ingrown hair/razor bumps and skin texture/open pores followed, both with 3.5% each. 54% of videos were posted by vloggers or personal accounts. Board-certified dermatologists followed with 18.7% of the videos posted. Estheticians accounted for 16.2% and, lastly, business/industry comprised 8.6% of the videos analyzed.

Conclusions: When searching black skin, TikTok posts are mostly educational and were less likely to have been created by a board-certified dermatologist. The top skin concern specified was dark spots. These findings suggest that there is an opportunity for dermatologists to increase educational content relating to black skin on TikTok.

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INTRODUCTION

The role of social media in patient education cannot be overlooked, 80% of internet users in the United States have searched online for health information.[1] A recent study by Villa-Ruiz et al found that educational videos dominate the content of top dermatologic videos on TikTok. This group also reported that the majority, 48%, of those videos were posted by patients, followed by board certified dermatologists at 25.8%.[2] We sought to examine if these results would differ when the search is adjusted to hashtags specific to black skin. Additionally, such results would provide board-certified dermatologists with insight into the specific skin concerns for which Black patients seek educational content on social media. Previous studies have analyzed the sources of skin of color content on other social media platforms. One study found that board-certified dermatologists only accounted for 22% of the top posts relating to skin of color on Instagram. In this study, most of the top skin of color posts were promotional (61.6%).[3] In regard to TikTok and skin of color, a recent study used hashtags generated from a list of common conditions from the skin of color website. Their search revealed that dermatologists were responsible for 20% of the content posted.[4] To our knowledge, there are no studies that analyze TikTok content when searching hashtags specific to black skin.

OBJECTIVES

1. To determine what type of content is seen in the top posts on TikTok when using hashtags specific to black skin.
2. To report the top skin concerns that are discussed in TikTok videos related to black skin.
3. To determine who is posting dermatology TikTok videos related to black skin and what percentage of the posters are board-certified dermatologists.

MATERIALS AND METHODS

On October 12th, 2021, an investigator input the following hashtags into the TikTok application's search bar: #BlackSkinCare, #BlackSkinTreatment, #BlackSkinAdvice, and #BlackSkinCareTips. We did not use the search term #SkinOfColor as this term is used almost exclusively by dermatologists and could have the potential to skew the results. TikTok's pre-set search filters of "all time" for date posted and "relevance" for sorting were kept to mimic the results that users would come across when searching organically. With each search, the top 50 videos were copied into an Excel spreadsheet via a URL link to be analyzed later.

After the total of 200 videos was obtained, the videos were then classified into the following categories: educational content, personal experience, clinical demonstration/procedure, business/advertisement, or entertainment/humor. Videos that were unrelated to dermatology were excluded. Next, the skin concern addressed in each video was recorded. If a specific dermatologic concern was not addressed, the video was categorized as "general skin concern/not specified." Finally, the creator of each video was recorded. The identities of content creators were confirmed through biographic information in the bio and/or other linked social media profiles.

RESULTS

Content Type

Of the 200 TikTok videos collected, 2 were excluded as they were unrelated to dermatology. A total of 198 were further analyzed. 57.1% of the videos posted were educational content, followed by 23.2% containing personal experiences. Clinical demonstrations/live procedures, business/advertisement, and entertainment/humor followed with 9.6%, 5.6%, and 4.5%, respectively.

Skin Disease/Concern

Most posts, 54.5%, were about general skincare and did not specify a skin disease/concern. 22.7% of the posts addressed dark spots which included hyperpigmentation, acne scars, and sunspots. Acne followed dark spots with 12.1% of posts addressing it as a concern. Ingrown hair/razor bumps and skin texture/open pores followed, both with 3.5% each. Finally, chemical burns, cysts/abscess, dark armpits, psoriasis, skin tag/moles, strawberry legs, and tinea versicolor all came in last with 0.5% each.

Sources of Content

54% of the videos were posted by vloggers or individuals based on their personal accounts. Board-certified dermatologists were the second leading posters, with 18.7% of the videos posted. Estheticians accounted for 16.2% of the videos posted and, lastly, content posted by a business/industry comprised 8.6% of the videos analyzed.

TABLE 1.

Analysis of TikTok Videos Resulting from Hashtags Related to Black Skin	
Content Type	**Number of Videos, n (%)**
Educational	113 (57.1)
Personal Experience	46 (23.2)
Clinical Demonstration/Live Procedure	19 (9.6)
Business/Advertisement	11 (5.6)
Entertainment/Humor	9 (4.5)
Skin Disease/Concern	**Number of Videos, n (%)**
General Skin Care/Not Specified	108 (54.5)
Dark Spots*	45 (22.7)
Acne	24 (12.1)
Ingrown Hair/Razer Bumps	7 (3.5)
Texture/Open Pores	7 (3.5)
Chemical Burn	1 (0.5)
Cyst/Abscess	1 (0.5)
Dark Armpits	1 (0.5)
Psoriasis	1 (0.5)
Skin Tag/Mole	1 (0.5)
Strawberry Legs	1 (0.5)
Tinea Versicolor	1 (0.5)
Source	**Number of Videos, n (%)**
Vlogger/Personal Account	107 (54.0)
Dermatologist	37 (18.7)
Esthetician	32 (16.2)
Business/Industry	17 (8.6)

*Dark spots include hyperpigmentation, acne scars, and sunspots.

CONCLUSIONS

This study aimed to determine the sources of content related to black skin on TikTok. Previous studies looking at dermatology content on TikTok found that 25.8% of the top dermatology posts were created by board-certified dermatologists.[2] Another study reported that dermatologists were responsible for 20% of the skin of color posts on TikTok.[4] Our study found that when looking specifically at black skin, posts were less likely to be created by a board-certified dermatologist (18.7%). This finding suggests that there is an opportunity for dermatologists to increase educational content relating to black skin on TikTok.

It is encouraging that most of the dermatologic content relating to black skin on TikTok is educational (57.1%). This contrasts with the Instagram study where most skin of color videos were promotional (61.6%).[3] This finding, combined with TikTok's growing popularity, makes TikTok an excellent opportunity for

board-certified dermatologists to provide users with accurate information regarding dermatologic conditions in black skin, especially to reach individuals with limited access and resources to visit a board-certified dermatologist. Additionally, these data reveal which skin concerns in black skin are most popular on TikTok, with dark spots and hyperpigmentation being the leading concern. Overall, our study suggests that there is a need for more dermatology content on black skin from board certified dermatologists. More studies are needed to increase our knowledge of the role of TikTok in patient education for black skin.

DISCLOSURES

The authors have no relevant financial disclosures.

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BRIEF COMMUNICATION

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Dermatologist Practical Guide to Encouraging Photoprotection in Skin of Color Patients

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INTRODUCTION

Patients with skin of color (SOC) are at risk for skin cancers and photoaging and have a unique predisposition to pigmentary disorders that are exacerbated by ultraviolet light exposure. Sun protection with a Sun Protection Factor (SPF) > 15 sunscreen has been shown to not only decrease the incidence of melanoma and non-melanoma skin cancers, but also improve and prevent the exacerbation of certain ultraviolet (UV)-sensitive conditions, such as post-inflammatory hyperpigmentation (PIH), melasma, and Lichen Planus Pigmentosus (LPP).[1] Despite this, the use of sunscreen among SOC patients have been shown to be inadequate, with barriers such as a poor blend with some skin complexions and lack of awareness being attributed as its drivers. Recent studies have also highlighted issues related to cultural and communication barriers that affect the way dermatologists relate to their skin of color patients.[2] The purpose of this article is to provide practical tips to dermatologists interested in improving sunscreen adherence in their SOC patient population.

Tip 1: Explore the reasons why your SOC patient does not currently wear sunscreen to better target your recommendations. Explicitly dispel the myth that SOC patients do not need sunscreen.

Malignant melanoma and keratinocyte carcinomas are the most common malignancy in the US, accounting for 40% of neoplasms in Whites.[1] The incidence of skin cancer is significantly lower in people of color when compared to Whites, contributing to the myth that SOC patients do not need SPF sunscreen. However, there is a considerably increased risk of morbidity and mortality in skin of color patients compared to Whites with skin cancer, which can be attributed to biologic and socioeconomic differences that are still being studied.[1] Additionally, in a study evaluating the correlations between melanin content and the degree of UVA- and UVB-induced DNA damage in normal appearing skin in various ethnic groups, it was found that although DNA damage is most severe in lighter skin, even low exposure to UV radiation induced appreciable DNA damage in all skin types.[3] This should be emphasized to patients to dispel the misconception that SOC is immune to UV-induced DNA damage.

Tip 2: Highlight how poor sunscreen adherence may be relevant to their current dermatology visit (eg, worsening pigmentary changes in PIH and melasma).

Despite increased photoprotection provided by darker skin, it should be mentioned to patients that individuals with skin of color are more susceptible to developing certain pigmentary disorders, such as PIH, melasma, and LPP. Acne and dyschromia were previously shown to be the top two reasons African-Americans visit dermatology offices.[4] Pigmentary disorders are worsened by ultraviolet exposure. These conditions can be cosmetically disfiguring, impacting one's quality of life and self-esteem; therefore, photoprotective methods such as daily sunscreen use, with SPF of at least 30, are essential to halt the worsening of these conditions.

Consider other common skin conditions and how they may impact sunscreen use and adherence. Patients with atopic dermatitis may experience photosensitivity or aggravation when exposed to sun, which can be improved with sunscreen use.[5] Given drier skin, these patients may benefit from more moisturizing sunscreens or moisturizers with SPF. These patients may also have more sensitive skin and should avoid oxybenzone containing products to avoid potential allergic contact dermatitis. In patients with oily or acne-prone skin, recommend the patient to cleanse the skin prior to the application of sunscreen and to use less greasy formulations, mineral sunscreens with low absorption, or oil-absorbing moisturizers with SPF. It is crucial that patients with rosacea apply sunscreen daily.

Skin of color patients may also present to clinic with concerns of premature aging and photoaging, which can be moderated by regular sunscreen use. It is a common misconception that sunscreen is less crucial in skin of color patients given that there is less apparent photoaging in darker skin. However, in skin of color, both intrinsic aging and photoaging significantly impact skin function and composition despite additional photoprotective properties of increased melanin.[1] Additional cutaneous manifestations of photoaging in ethnic skin include the development of solar lentigines and dermatosis papulose nigra, which may be considered unsightly to some patients.

Tip 3: Strongly consider tinted sunscreens.

Consumer studies have demonstrated that cosmetic elegance is of top importance when evaluating sunscreens.[6] In patients with darker skin tones specifically, the white residue or cast that is left on their skin after application of many sunscreens significantly impedes regular use.[6] These hesitancies can significantly deter patients from regular sunscreen use and should be specifically addressed with patients. Newer formulations of tinted sunscreens have been developed to accommodate a richer variety of skin tones, with different shades available. These options can help skin of color patients with challenges related to poor blending of sunscreens with their natural skin tones.

In addition to the photobiologic effects of UV radiation on the skin, visible light has now been shown to induce long-lasting pigmentation in people with darker skin types.[7] Although broad spectrum sunscreens protect against UV radiation, they do not adequately protect against visible light, which must be visible on the skin to be protective. Tinted sunscreens provide protection against visible light by including iron oxides and pigmentary titanium dioxides. These sunscreens combine UV filters with color-based coverage. These formulations are very beneficial and should be encouraged in patients with darker skin types, especially those with pigmentary disorders. Patients with melasma, LPP, or PIH frequently complain of worsening disease with sun exposure despite regular sunscreen use.[7] Additionally, cutaneous porphyrias, solar urticaria, and chronic actinic dermatitis are all photodermatoses with active spectrums in the visible light range.

Tip 4: Consider sunscreen options that extend beyond over the counter products. Bring a variety of sunscreens into your office that patients may test. We recommend having a test tube in a room where patients can easily apply to the skin. Additional samples can also be provided to patients in small plastic containers that may be taken home. Notably, many retailers provide small samples for patients to try if their product is carried in the office. If not, inform patients of where they can purchase whichever sunscreen they prefer. A pre-created handout may be helpful here to save time for busy offices.

In a recent study, it was shown that surveyed dermatologists from multiple tertiary care centers in Boston highly value cosmetic elegance of sunscreen for personal use but viewed cosmetic elegance as the least important factor when making recommendations for patient use.[6] This may indicate that perhaps dermatology providers underestimate the importance of cosmetic elegance to patients. Cosmetic elegance can certainly be found in many over the counter products but can also be found in products that extend beyond over the counter. Additionally, a more diverse selection of product options that are presented to SOC patients may present the chance to identify a product that fits their personal criteria for good sunscreen that will encourage daily use and at a cost that is acceptable to the patient. A discussion of challenges that come with different types of sunscreens in addition to a wide array of products that may address those challenges may be concordant with increased patient satisfaction.

Dermatologists should be diligent about trying samples of different types of sunscreens to gain exposure and knowledge as to the best products that may be more suitable for SOC patients. When providing samples for patients to try and/or creating a pre-created handout for patients, it is important that the physician incorporate products that address the diverse and specific needs of many SOC patients, including products that contain iron oxides and physical sunscreens with cosmetic elegance when applied to darker skin.

Tip 5: Follow up with the patient at the next visit. Devote time to follow up on sunscreen use. Provide/encourage trying a different sample if only one was tried previously.

It is prudent that dermatologists understand and empathize with the frustrations that patients with darker skin types may experience when trying to find the right sunscreen on the market for their skin types. This is especially given the fact that traditionally, sunscreens have not been produced to target this particular patient population. In addition to encouraging patients to continue trying new sunscreens until the right fit is found, we also recommend monitoring progression and improvement of sun-induced photodermatoses and PIH to encourage continued use.

DISCLOSURES

The authors have no relevant disclosures to declare.

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BRIEF COMMUNICATION

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Minimizing Bias in Alopecia Diagnosis in Skin of Color Patients

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ABSTRACT

Alopecia is one of the most common dermatologic conditions affecting Black patients, with a significantly negative impact on quality of life.[1,2] Timely and accurate diagnosis is therefore critical in order to reverse or halt progression of disease.[3] Unfortunately, lack of representation of skin of color (SOC) patients in the current literature may contribute to misdiagnosis as providers may be unfamiliar with the clinical spectrum of alopecia presenting in darker scalps.[4] Some scarring alopecia subtypes such as Central Centrifugal Cicatricial Alopecia (CCCA) are more prevalent in certain racial groups. However, focusing solely on patient demographics and gross clinical findings may obscure accurate diagnoses. To distinguish alopecia findings in Black patients, a dedicated approach using a combination of clinical exam findings and patient history, along with trichoscopy and biopsy, is essential to prevent misdiagnosis and improve clinical and diagnostic outcomes. We present three cases of alopecia in patients of color which the initial suspected clinical diagnosis did not correspond with trichoscopic and biopsy results. We challenge clinicians to reexamine their biases and fully evaluate patients of color with alopecia. An examination should include a thorough history, clinical examination, trichoscopy, and potentially a biopsy, particularly when findings do not correlate. Our cases highlight the challenges and disparities that exist in diagnosis of alopecia in Black patients. We emphasize the need for continued research regarding alopecia in skin of color and the importance of a complete workup for alopecia to improve diagnostic outcomes.

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INTRODUCTION

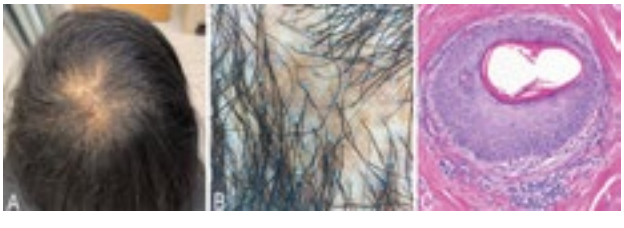
Alopecia is one of the most common dermatologic conditions affecting Black patients, with a significantly negative impact on quality of life.[1,2] Timely and accurate diagnosis is therefore critical in order to reverse or halt progression of disease.[3] Unfortunately, lack of representation of skin of color (SOC) patients in the current literature may contribute to misdiagnosis as providers may be unfamiliar with the clinical spectrum of alopecia presenting in darker scalps.[4] In particular, vertex alopecia in SOC patients can be subject to bias as certain scarring alopecias, such as central centrifugal cicatricial alopecia (CCCA), occur at a higher prevalence in patients of African descent[5] and classically presents as hair loss in the vertex of the scalp.[6] Other forms of alopecia may present with vertex involvement in patients of color, so clinicians should fight the urge to jump to a diagnosis of CCCA without performing a thorough examination. Trichoscopy, or scalp dermoscopy, allows dermatologists to evaluate alopecia based on visualization of morphologic patterns and can provide diagnostic clues to help clinicians avoid misdiagnosis of alopecia. Key studies have defined trichoscopic findings in SOC.[7,8] While trichoscopy does not replace the need for biopsy, it is a critical tool in the initial evaluation of hair loss.

We aim to highlight the importance of challenging bias in the clinical diagnosis of alopecia in SOC. The diagnosis of alopecia based on gross clinical morphology alone can lead to misdiagnosis of alopecia type in Black patients. Barriers to early diagnosis must be reduced to ensure quality care is given to patients of all racial backgrounds. Herein, we present three cases of vertex alopecia in which the initial suspected clinical diagnosis did not correspond with trichoscopic and biopsy results. To distinguish alopecia findings in Black patients, a dedicated approach using a combination of clinical exam findings and patient history, along with trichoscopy and biopsy, may be essential to prevent misdiagnosis and improve clinical and diagnostic outcomes.

CASE 1

A 52-year-old African American woman presented with concerns of hair loss and scalp pruritus. The patient reported a two-year history of progressive hair loss with an associated mild itch on her scalp. She denied scalp tenderness or hair breakage at her crown. She denied a family history of hair loss. Gross examination revealed hair thinning on her crown with decreased density and discrete areas of scarring (Figure 1A). Based on the patient's demographics and initial gross examination, CCCA rose to the top of the differential. Trichoscopy of the region, however, revealed significant perifollicular scale and subtle erythema. Honeycomb pattern was also present with uneven white dots (Figure 1B). Histopathological examination of a biopsy specimen demonstrated perifollicular fibrosis, polytrichia, and a subtle lichenoid folliculitis (Figure 1C) that was most suggestive of lichen planopilaris (LPP).

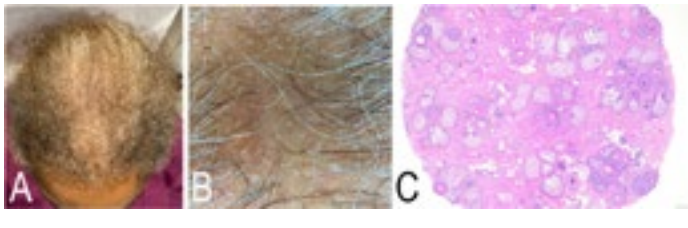
FIGURE 1. Case (1A) Thinning of scalp vertex. (1B) Trichoscopy of lesion showing perifollicular scale and erythema. (1C) Histopathology revealing perifollicular fibrosis, polytrichia, and a subtle lichenoid folliculitis. Hematoxylin and Eosin (H&E).



CASE 2

A 75-year-old African American woman presented with a 5-year history of progressive hair loss. The patient reported scalp pruritus for the past five to six months. She mentioned dyeing her hair 3 or 4 times per year for the past 10 years. Gross examination revealed significant thinning of hair on the frontal scalp with extension to the crown (Figure 2A). Prior to trichoscopic exam, clinical findings were more consistent with CCCA. Trichoscopy revealed miniaturized hair. Honeycombing was noted with presence of multiple pinpoint white dots with mild erythema (Figure 2B). A biopsy specimen from the mid-scalp revealed miniaturized hairs, retained sebaceous gland lobules, and no significant inflammatory infiltrate (Figure 2C) that was most consistent with androgenetic alopecia.

FIGURE 2. Case (2A) Superior scalp with thinning of frontal and vertex scalp. (2B) Trichoscopy of lesion showing miniaturized hair with honeycomb pattern and multiple pinpoint white dots with mild erythema. (2C) Histopathology revealing miniaturized hairs, retained sebaceous gland lobules, and no significant inflammatory infiltrate. H&E.

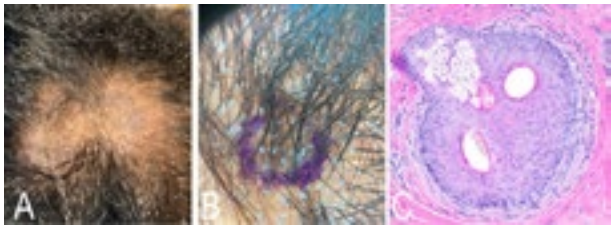


Superimposed features of chronic rubbing were also noted. Upon further inquiry, the patient noted a different hair dye may have been used prior to the onset of her pruritus. She was instructed to temporarily cease dyeing her hair and was started on fluocinonide 0.05% solution daily as needed and minoxidil 5% solution twice a day. After exactly 2 months of treatment, patient started to show signs of new hair growth.

CASE 3

An Afrolatino male presented with a 3-year history of progressive hair loss with associated mild itch. The patient denied any family history of hair loss. Gross examination revealed two round patches of alopecia on his right parietal scalp with decreased hair density and loss of follicular ostia with slight hyperpigmentation centrally. (Figure 3A). Based purely on the initial gross clinical exam, the clinician was concerned about possible discoid lupus erythematosus (DLE) or CCCA. Trichoscopy, however, revealed significant peripilar casts and scale; no follicular plugging was noted (Figure 3B). Histopathological examination demonstrated polytrichia, perifollicular fibrosis, and a perifollicular lichenoid folliculitis (Figure 3C) that was consistent with LPP. A deep inflammatory infiltrate or deposits of mucin that would point to DLE were not identified. The patient was not interested in intralesional triamcinalone acetonide injections and was started on TCM therapy (tacrolimus, clobetasol, and minoxidil) applied twice daily. He was later lost to follow up.

FIGURE 3. Case (3A) Right parietal scalp with two round alopecia patches with loss of follicular ostia and slight hyperpigmentation centrally. (3B) Trichoscopy of lesion showing significant peripilar casts and scale. (3C) Histology revealed polytrichia, perifollicular fibrosis, and a perifollicular lichenoid folliculitis. H&E.



DISCUSSION

We present three cases of alopecia initially suspected to represent CCCA based on a hair loss pattern predominantly involving the vertex or crown of the scalp in skin of color patients. CCCA is the most common form of primary scarring alopecia in African American females and presents with hair loss beginning on the crown and spreading centrifugally.[5,6] In each of these cases, however, trichoscopic findings were suggestive of alternate diagnosis and led to a clinical decision of performing a biopsy. Histopathological examination from the biopsy specimens in each of these cases led to diagnoses other than CCCA.

In Patients 1 and 3, trichoscopic findings of perifollicular scale, which can be seen in LPP, were corroborated with the histopathological features on biopsy. The distinction between CCCA and LPP is important as treatment can vary between the two conditions. While initial treatment approaches with intralesional triamcinolone and oral antibiotics may be similar, 3rd line agents such as naltrexone and/or pioglitazone for LPP or topical metformin for CCCA may necessitate a more definitive diagnosis.[9-11]

In Patient 2, the biopsy specimen demonstrated androgenetic alopecia with features of chronic rubbing. External breakage of hair from trauma or rubbing is likely an under-reported contributing factor to presentations of alopecia. Therefore, treatments that also target pruritus or concomitant allergic contact dermatitis or seborrheic dermatitis should be added for optimal results.

4-mm punch biopsies down to the subcutaneous tissue are optimal specimens for the evaluation of alopecia.The presence of premature desquamation of the inner root sheath, perifollicular fibrosis, and follicular compounding point to a scarring process. Lymphocytic-mediated scarring alopecias such as CCCA, LPP, and DLE can be further distinguished by the depth and density of the infiltrate, the presence of interface changes at the dermal-epidermal junction as well as the basal layer of follicular epithelia, and the presence or absence of mucin. In late-stage or end-stage disease, however, histopathological features can be non-specific and dermatopathology may present similarly.

All three cases presented were in patients of color and revealed pathologic changes in the scalp during trichoscopic evaluation and biopsy that differed from the initial suspected clinical diagnosis. Some scarring alopecia subtypes are more prevalent in certain racial groups. However, focusing solely on patient demographics and gross clinical findings may obscure accurate diagnoses. We challenge clinicians to reexamine their biases and fully evaluate patients of color with alopecia. An examination should include a thorough history, clinical examination, trichoscopy, and potentially a biopsy, particularly when findings do not correlate. Our cases highlight the challenges and disparities that exist in diagnosis of alopecia in Black patients. We emphasize the need for continued research regarding alopecia in skin of color and the importance of a complete workup for alopecia to improve diagnostic outcomes.

DISCLOSURES

Dr. Adotama serves on the Advisory Boards for Argenx and Janssen.The other authors have no conflict of interest to declare.

Dr. Lo Sicco has been an investigator for Regen Lab. She is a current investigator for Pfizer and a consultant for Pfizer and Aquis.

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Women of Childbearing Age With Hidradenitis Suppurativa Frequently Prescribed Medications With Pregnancy Risk

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ABSTRACT

Introduction: Hidradenitis suppurativa (HS) disproportionately affects women of childbearing age. As almost half of pregnancies in the United States are unplanned, dermatologists must give special consideration to medication safety when managing patients in this population.

Methods: We conducted a population-based cross-sectional analysis utilizing the National Ambulatory Medical Care Survey from 2007 to 2018 (most recent years available) in order to characterize the treatment modalities most commonly being used for treatment of hidradenitis suppurativa in women of childbearing age.

Results: There were 43.8 million estimated total visits for females ages 15 to 44 with HS. Women of childbearing age with HS were most commonly seen by general and family practice (28.6%), general surgery (26.9%), and dermatologists (24.6%). Obstetricians saw 1.84% of all visits. Oral clindamycin was the most commonly prescribed drug, followed by amoxicillin-clavulanate, minocycline, naproxen, and trimethoprim-sulfamethoxazole. Adalimumab was prescribed at an estimated 10.3 thousand visits (0.211%). At visits in which medication from the 30 most common therapies was prescribed, 31% of visits included a medication that was pregnancy category C or above.

Discussion: Nearly a third of women of childbearing age with HS are receiving medications considered teratogenic. As many female patients feel that their physicians are not counseling them regarding the impact of HS therapy on childbearing, the results of this study serve as a reminder to dermatologists and non-dermatologists managing skin disease to continue to facilitate conversations about potential pregnancy risk when prescribing medications with pregnancy risk.

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INTRODUCTION

Hidradenitis suppurativa (HS) disproportionately affects women of childbearing age.[1] In a survey of female HS patients of reproductive age, 83% reported not receiving counseling from their physician on how HS and their prescribed medications could impact childbearing.[2] As almost half of pregnancies in the United States are unplanned, with women ages 18 to 24 most at risk, dermatologists must give special consideration to medication safety when managing patients in this population.[2,3] To our knowledge, the treatment modalities most commonly being used for treating HS in women of childbearing age has yet to be quantified.

MATERIALS AND METHODS

We utilized the National Ambulatory Medical Care Survey (NAMCS) from 2007 to 2018, the most recent years available, for all visits where international classification of disease ninth-modification (ICD-9) code 705.83 and ICD-10 code L73.2 were a primary through quinary diagnosis. Two NAMCS pre-determined age categories, 15-24 and 25-44, defined women of childbearing potential as ages 15 to 44. The frequency of visits was determined utilizing survey procedures of SAS v9.4 (SAS Institute Inc., Cary, NC).

RESULTS

There were 43.8 million estimated total visits for females ages 15 to 44 with HS. Demographic data of the study population are included inTable 1.Women of childbearing age with HS were most commonly seen by general and family practice (28.6%), general surgery (26.9%), and dermatologists (24.6%). Obstetricians saw 1.84% of all visits. Oral clindamycin was the most commonly prescribed drug, followed by amoxicillin-clavulanate, minocycline, naproxen, and trimethoprim-sulfamethoxazole (TMP-SMX) (Table 2). Amongst patients ages 15 to 24, those at highest risk for unintended pregnancy, clindamycin, naproxen,

TABLE 1.

National Ambulatory Medical Care Survey Demographic Information
Demographic information for NAMCS visits for women aged 15-44 with hidradenitis suppurativa between 2007 and 2018.
Other includes American Indian, Alaska Native, or more than one race reported. Metropolitan Statistical Area (MSA).

	Weighted Frequency of Visits (millions)	Percentage of Visits
Race		
White	30.4	69.3%
Black or African American	13.1	29.8%
Other	0.352	0.803%
Ethnicity		
Hispanic	1.55	3.53%
Not Hispanic	42.3	96.5%
Region		
Northeast	3.89	18.9%
Midwest	4.37	21.2%
South	9.70	47.1%
West	2.63	12.7%
MSA		
MSA	41.9	95.6%
Not MSA	1.93	4.41%
Smoking Status		
Smoker	13.9	38.8%
Non-smoker	21.9	61.2%
Insurance		
Private	24.3	62.9%
Public	12.0	31.0%
Other	2.35	0.704%

and topical clobetasol were most commonly prescribed (Table 3). Adalimumab was prescribed at an estimated 10.3 thousand visits (0.211%). At visits in which medication from the 30 most common therapies was prescribed, 31% of visits included a medication that was pregnancy category C or above (Table 2). We were unable to accurately determine the number of visits for HS in pregnant patients and pregnancy tests ordered at visits due to the relatively small frequency of patient visits.

DISCUSSION

As almost half of pregnancies are unintended, it is important that dermatologists are considering a medication's pregnancy risk when prescribing to this population. Since only 1.84% of all visits for women of childbearing age with HS were with obstetricians, it is the responsibility of primary care physicians, surgeons, and dermatologists to facilitate conversations about potential pregnancy risk when prescribing HS therapy. Special attention should be given to safety data in the first trimester, as this is likely when the patient would be unknowingly pregnant yet still taking HS therapy.

Oral clindamycin, the most commonly prescribed medication in this study, is not recommended unless clearly needed in the first trimester of pregnancy due to lack of data.[4] The third most commonly prescribed drug, minocycline, and the seventh most commonly prescribed drug, doxycycline, are well known to cause teratogenicity, teeth discoloration after in utero exposure, and hepatotoxicity in pregnant females.[4] TMP-SMX, the fifth most commonly prescribed drug, should also be avoided during the first trimester due to its increased risk of neural tube defects.[5]

With the 2018 Food and Drug Administration approval of adalimumab for HS and the increasing evidence supporting the use of other biologics in HS treatment, prescribing patterns have likely changed since 2018.[6] With increased use of biologics, there is the potential to reduce the over 31% of

TABLE 2.

Most Common Prescription Medications for Hidradenitis Suppurativa
Thirty most common medications prescribed at visits for women aged 15 to 44 with hidradenitis suppurativa between 2007 and 2018. Trimethoprim/sulfamethoxazole (TMP-SMX).

Medication	Pregnancy Category During First Trimester	Weighted Frequency of Visits (thousands)	Percentage of Visits for HS
Clindamycin (oral)	B	490	10.0%
Amoxicillin-clavulanate	B	345	7.04%
Minocycline	D	333	6.80%
Naproxen	B	248	5.06%
TMP-SMX	C	163	3.32%
Acetaminophen-oxycodone	C	143	2.91%
Doxycycline	D	139	2.84%
Topical clobetasol	C	113	2.30%
Phentermine	C	81.0	1.65%
Triamcinolone (injection)	C	79.1	1.61%
Acetaminophen-hydrocodone	C	73.6	1.50%
Metformin	B	71.4	1.46%
Ibuprofen	B	67.0	1.37%
Triamcinolone	C	64.4	1.31%
Ciprofloxacin	C	59.7	1.22%
Tretinoin topical	C	57.8	1.18%
Rifampin	C	55.0	1.12%
Topical Benzoyl peroxide-clindamycin	C/B	51.3	1.05%
Ethinyl estradiol-etonogestrel	Not assigned	47.4	0.97%
Topical sodium bicarbonate	Not assigned	46.1	0.94%
Cephalexin	B	41.9	0.86%
Tramadol	C	41.0	0.84%
Prednisone	B	39.7	0.81%
Isotretinoin	X	36.0	0.74%
Drospirenone-ethinyl estradiol	Not assigned	36.0	0.74%
Meloxicam	C	31.6	0.65%
Medroxyprogesterone	X	31.3	0.64%
Oxycodone	B	29.5	0.60%
Topical silver sulfadiazine	B	29.0	0.59%
Clonazepam	D	26.7	0.54%

women of childbearing age with HS who are receiving therapy that is classified as pregnancy category C or above. However, since systemic antibiotics and hormonal therapy remain first line therapy for mild-to-moderate HS according to the North American Clinical Management Guidelines for HS, there is likely continued and significant use of these teratogenic medications.[6]

We are unable to determine if a teratogenic medication was clinically indicated or if appropriate counseling was provided. However, as many female patients feel that their physicians are not counseling them regarding the impact of HS therapy on childbearing, the results of this study serve as a reminder to dermatologists and non-dermatologists managing skin disease to continue to facilitate conversations about potential pregnancy risk when prescribing teratogenic medications in this population.[2]

TABLE 3.

Age-Stratified Prescription Medications for Hidradenitis Suppurativa. Ten most common medications prescribed at visits for women with hidradenitis suppurativa between 2007 and 2018 were stratified into 2 age groups: 15 to 24 and 25 to 44.

Medication	Pregnancy Category During First Trimester	Weighted Frequency of Visits (thousands)	Percentage of Visits for HS
Ages 15 to 24			
Clindamycin	B	358	22.4%
Naproxen	B	248	15.5%
Topical Clobetasol	C	111	6.94%
TMP-SMX	C	111	6.94%
Topical Lidocaine	B	92.2	5.77%
Rifampin	C	47.6	2.97%
Topical sodium bicarbonate	Not assigned	46.1	2.88%
Minocycline	D	43.7	2.73%
Topical silver sulfadiazine	B	29.0	1.82%
Isotretinoin	X	27.1	1.70%
Ages 25 to 44			
Minocycline	D	258	10.5%
Doxycycline	D	139	5.68%
Clindamycin	B	120	4.90%
Amoxicillin-clavulanate	B	94.8	3.87%
Phentermine	C	81.0	3.31%
Acetaminophen-hydrocodone	C	71.4	2.91%
Ibuprofen	B	67.0	2.74%
Triamcinolone (injection)	C	64.4	2.63%
Topical triamcinolone	C	63.8	2.60%
Ciprofloxacin	C	59.7	2.44%

DISCLOSURES

Gabrielle Marie Rivin BA MD has no conflicts of interest to disclose. Alan Fleischer MD is a consultant for Boerhringer-Ingelheim, Incyte, Qurient, SCM Lifescience, Syneos, and Trevi. He is an investigator for Galderma and Trevi.

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LETTERS TO THE EDITOR

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Barriers to Dermatologic Care and Use of Internet Sources in Hidradenitis Suppurativa

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INTRODUCTION

Although hidradenitis suppurativa (HS) often requires multidisciplinary care, dermatologists specialize in the diagnosis and management of this condition. As HS is associated with low socioeconomic status, individuals may face barriers accessing dermatologic care due to financial and insurance challenges.[1,2] A qualitative study of HS participants noted that frustrations with delays in care may drive patients to use the Internet to learn about HS.[3] This study further evaluates barriers to dermatologic care and the use of internet sources amongst those with HS.

MATERIALS AND METHODS

An anonymous, 40-item, multiple-choice survey was distributed in HS-related online groups. Participants 18 years and older in the United States with a diagnosis of HS were included. Data were collected between August and September 2022 and analyzed with Microsoft Excel version 16.65. Chi-square tests were performed. The Northwestern University Institutional Review Board approved this study.

RESULTS

Overall, 302 participants completed the survey. Table 1 shows the characteristics of the respondents. Regarding the primary medical providers for management of their HS, 69.9% (211/302) reported seeing a dermatologist, 20.5% (62/302) reported seeing a non-dermatology provider, and 9.6% (29/302) reported not seeing any medical provider for their HS. Of those with a non-dermatology provider for their HS, 64.5% (40/62) reported seeing a primary care provider, 21.0% (13/62) reported seeing a surgeon, and 14.5% (9/62) reported seeing a gynecologist. Thirty-nine percent (82/211) of those with a dermatologist visited them yearly or less often. Over half of all respondents (51.3%, 155/302) reported that seeing the dermatologist is difficult or very difficult. Black (odds ratio [OR], 2.09; 95% CI, 1.20–3.66; $P<0.01$) and Medicaid-insured individuals (OR, 2.64; 95% CI, 1.44–4.85; $P<0.01$) were more likely to report difficulty than those who were White or had private insurance, respectively. Commonly reported barriers to seeing the dermatologist include long wait times to schedule appointments (59.6%, 180/302), financial/insurance challenges (24.2%, 73/302), HS-related pain hindering appointment attendance (23.8%, 72/302), work-related challenges (18.9%, 57/302), commute/transportation challenges (13.9%, 42/302), and inability to obtain referrals (7.3%, 22/302).

TABLE 1.

Characteristics of Survey Participants	
Characteristic	No. (%)
Total	302
Gender	
Female	271 (89.7)
Male	31 (10.3)
Age, mean (SD)	37.5 (17.7)
Race/Ethnicity	
White	168 (55.6)
Black/African American	76 (25.2)
Hispanic/Latinx	33 (10.9)
Asian	7 (2.3)
Multiracial	12 (4.0)
Other	6 (2.0)
Education	
Less than high school	4 (1.3)
High school graduate	88 (29.1)
Occupational school	22 (7.3)
Bachelor's degree	133 (44.0)
Graduate degree	55 (18.2)
Household Income	
< $19,999	39 (12.9)
$20,000-$89,999	161 (53.1)
$90,000-$179,999	76 (25.2)
$180,000+	26 (8.6)
Frequency of Flares	
Once a month or more	169 (84.8)
Less than once a month	46 (15.2)
Insurance	
Private	186 (61.6)
Medicaid	64 (21.2)
Medicare	30 (9.9)
No insurance	22 (7.3)
Primary HS Provider	
Dermatologist	211 (69.9)
Non-dermatology Provider	62 (20.5)
No Provider	29 (9.6)

TABLE 2.

Use of Interest Sources Among Those With HS	
Characteristic	No. (%)
Total Internet Users	225
Website	
Facebook	144 (64.0)
Google	131 (58.2)
HS-specific Organizations	113 (50.2)
Reddit	75 (33.3)
TikTok	39 (17.3)
YouTube	32 (14.2)
Instagram	7 (3.1)
Source of Information	
Others with HS	175 (77.8)
Medical professionals	50 (22.2)
Reasons for Using Internet Sources	
To better understand HS	167 (74.2)
To find a community of others with HS	164 (72.9)
To find alternative treatments or specific products	146 (64.9)
Internet is free and more accessible than a doctor	93 (41.3)
Not getting enough time with doctor	68 (30.2)
Want a second opinion besides a doctor	40 (17.8)

Most participants (74.5%, 225/302) reported using the internet to access information about HS, namely Facebook (64.0%, 144/225), Google (58.2%, 131/225), HS-specific organizations (50.2%, 113/225), and Reddit (33.3%, 75/225). Reasons for using internet sources included desires to better understand HS (74.2%, 167/225), find a community of others with HS (72.9%, 164/225), and learn about alternative treatments (64.9%, 146/225; Table 2). Thirty percent (68/225) reported using the internet as they do not get enough time with their doctor.

DISCUSSION

Among this cohort, one-third reported not seeing a dermatologist for their HS, and one-tenth reported not seeing any provider for their HS. Providers of other specialties need to ensure referrals to dermatology for HS patients who do not see a dermatologist. Of those that see a dermatologist, over one-third reported having visits yearly or less often, despite most of them having active disease with monthly flares. Many participants noted difficulties accessing dermatological care, particularly long wait times and financial and insurance challenges. HS disproportionately affects Black individuals,[4] and in this survey, Black participants were also more likely to report challenges seeking dermatologic care than White individuals. Medicaid-insured individuals similarly reported more difficulty accessing a dermatologist, consistent with a recent study that noted that Medicaid-insured patients face lower success and longer wait times in obtaining dermatology appointments than those with private insurance.[5] Teledermatology and increased access to safety-net providers may help decrease the disparities.

Additionally, internet use amongst those with HS is prevalent with many citing the internet as free and more accessible than a physician. The online community provides support to those with HS, especially since many may struggle with embarrassment or mental health.[6] These online sources can allow medical professionals to increase visibility of evidence-based recommendations and information about access to HS specialists. Many individuals reported using the internet for information since they do not get enough time with their doctor, suggesting that those with HS may also benefit from longer appointment lengths.

Study limitations include the low proportion of certain racial/ethnic groups and males; respondents from online support groups may not represent the general HS population. Nevertheless, these findings highlight the need to increase timely access to dermatologic care for those with HS and improve evidence-based content on online HS sources.

DISCLOSURES

The authors have no conflict of interest to declare.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Rising Interest in Sunscreen for Skin of Color: An Analysis of Google Trends

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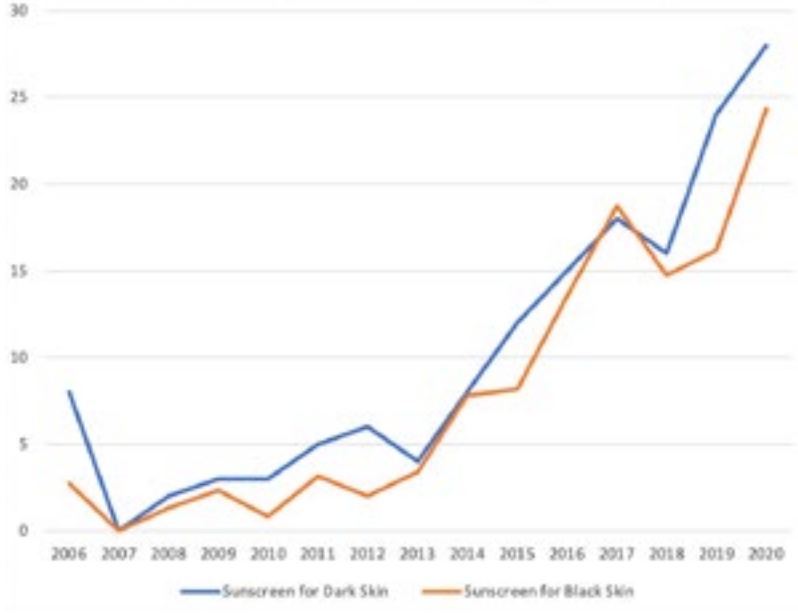
INTRODUCTION

Individuals with skin of color (SOC) are less likely to use sunscreen and other sun-protective measures due to misinformation and common misconceptions regarding the benefits of sunscreen.[1] In addition to skin cancer prevention, many SOC individuals are unaware that sunscreen can also be used to slow down signs of extrinsic aging and prevent worsening of dyspigmentation.[2,3,4] We hypothesized that new formulations of chemical and mineral sunscreens for darker skin colors in recent years, along with increased education about the benefits of sunscreen, have helped create a shift in interest regarding sunscreen use in darker skin. This study sought to formally and objectively analyze these trends online.

Google Trends, an engine used to analyze search trends temporally and geographically, was used to analyze the trends in searches of the phrases "sunscreen for dark skin" and "sunscreen for black skin" since 2004. Search trends are analyzed based on relative search volume (RSV); a value that quantifies the absolute number of searches compared to the total number of searches over a given time period on a scale of 0-100. Monthly RSVs were then averaged to determine the mean RSV for each year. A value of 100 represents the highest RSV within a set period, while 0 indicates few searches. Additional phrases such as "Sunscreen for ethnic skin" and "Sunscreen for brown skin" were also searched but did not produce data significant enough to establish a trend.

The estimated annual RSV for the phrase "sunscreen for dark skin" ranged from 0 to 28, with the peak being reached in 2020. Since 2006, the annual RSV has nearly quadrupled reflecting an almost 400% increase in Google searches on the topic of sunscreen for dark skin. Of note, the yearly times of peak interest were primarily seen in the months leading up to the summer and the summer months themselves. A sharp increase can be seen between the months of March and August/September of each year. In 2006, there was a sharp peak in interest to 50 RSV in January, after which RSV remained between 0 and 30 each month for many years. It was not until the summer of 2016 that there was a rise in searches on the topic of sunscreen for dark skin. The trend continued to rise each year following this resurgence. Geographically, the states of MD, GA, NJ, NY, and CA held the positions for the highest associated RSVs for the phrase "sunscreen for dark skin", with MD at an RSV of 100

FIGURE 1. Estimated annual RSV for "Sunscreen for Dark Skin" and "Sunscreen for Black Skin" from 2006-2020 depicting an overall upward trend in searches.



and CA at 58. Related queries associated with "sunscreen for dark skin" included "best sunscreen for dark skin", "mineral sunscreen for dark skin", and "best mineral sunscreen for dark skin" all 3 of which received the designation of "breakout" search terms signifying >5,000% increase in searches.

Annual RSV for "sunscreen for black skin" ranged from 0.83 to 24.33 with the peak also being reached in 2020. Since 2008, the first year with available trends, the annual RSV has increased 18-fold. The peak interest times can be seen from around May each year to roughly October. Annual RSV steadily began to rise in 2013, with the most significant jump being seen between the years 2019 and 2020 when estimated annual RSV jumped from 16.16 to 24.33. Geographically, the states with the highest associated RSVs were MD, GA, NC, NY, and NJ with Maryland at an RSV of 100 and NJ at 34. Top related queries included "best sunscreen for black skin", "sunscreen for Black people", and "black girl sunscreen" all of which also received the designation of "breakout" signifying >5,000% increase in searches.

The sharp increase in Google searches for sunscreen for darker skin reflects an important shift in sunscreen interest in communities of color. Continued formulations that are cosmetically appealing to darker skin and education on the benefits of sunscreen may help lead to a continued increase in sunscreen usage by people of color. Dermatologists, primary care physicians, and other health care providers can help in providing this important public health education to their patients of color which can hopefully help sustain continued increase in sunscreen usage in this population.

DISCLOSURES

Dr. Elbuluk is the director of the skin of color and pigmentary program at USC. She has served as a paid consultant, advisory board member, and/or speaker for Allergan, La Roche Posay, Scientis, Galderma Laboratories LP, Estee Lauder, Beiersdorf, and Unilever. Nicole Syder has no conflicts of interest.

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From the Community to Capitol Hill

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Dear Editor:

Telemedicine has increasingly gained more attention and use since the onset of the pandemic as quality healthcare can be delivered at a distance, reach underserved populations, decrease the burden of patients needing medical care,[1] and potentially reduce healthcare costs. Further, access to cellular and internet networks has outpaced access to healthcare.[2,3] Teledermatology has been proposed as a way to address dermatologic disparities in access as it overcomes barriers to time, transportation, distance, and mobility. Teledermatology is not only useful for clinical dermatology but also for dermatology clinical trials in regards to recruitment/retention, clinical trial patient representation (reaching historically underrepresented patients), and facilitating virtual clinical trial visits.

Many patients who are otherwise eligible for clinical trials may not be able to participate due to lack of transportation or financial means to pay for travel costs. While some clinical trials compensate for travel, others do not. Research on health-related outcomes demonstrates that patients who live in non-metropolitan counties have poorer outcomes due to reduced access to care, particularly if specialized, and longer travel times.[4] Though our nation's overall poverty rate has increased, Blacks/African Americans had the highest poverty rate as of 2020,[5] and non-metropolitan Blacks/African Americans had the highest incidence of poverty.[6] Virtual clinical trials have the unique benefit of enabling access to vulnerable populations and patients living in geographically remote and underserved areas, eg, rural and non-metropolitan, which may potentially lead to more representation and generalizability of rare diseases but also patients with skin of color (SOC), and SOC patients with rare diseases. Teledermatology may curtail issues with tardiness and no-shows for participants who have difficulty committing to frequent on-site appointments. Other advantages include efficiency for study coordinators as there is less time spent on recruitment/retention. It also supports centralizing data and decreases the number of sites to maintain, thereby cutting costs and accelerating trial completion.[1]

The evolution of clinical trial research has come a long way since 500 BC.[7] As a Dermatology Clinical Research Fellow and Sub-Investigator, I realize there is room for change in the realm of clinical trial research. However, change often requires collaboration and sometimes, unconventional and nontraditional ways of thinking and doing. Advocacy can take place at any (or every) level of our training, eg, during medical school or residency, as part of an organization, as an attending, or in clinical trials, and can occur locally in the community or nationally on Capitol Hill.

DISCLOSURES

The author has no conflicts of interest relevant to this article to disclose.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Racial Disparities in Primary Therapy for Newly Diagnosed Psoriasis Patients

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To the Editor:

Psoriasis treatments have been shown to vary by race, but racial differences in initial psoriasis treatment has not been adequately studied.[1,2] Our objectives were to compare the initial prescription treatments received by different racial groups and examine trends over time.

After Weill Cornell Medicine IRB approval, annual numbers of patients with psoriasis were collected between January 1, 2005 and December 31, 2019. The initially prescribed treatment (phototherapy, biologics, apremilast, immunosuppressants) and demographics were recorded. Race was determined by patient self-identification. Odds ratios (OR) were calculated using proportions of patients treated and linear regression modeling was performed. T-tests were used to compare slopes between groups of patients.

Overall, 4976 White, 478 Asian, and 400 Black newly diagnosed patients received psoriasis treatment over the study period. For initial treatments, patients were prescribed topicals (5166, 88.2%), immunosuppressants (269, 4.6%), phototherapy (174, 3.0%), biologics (159, 2.7%), or apremilast (59, 1.0%).

TABLE 1.

Linear Regression of Proportion of Patients Per Year Receiving Initial Treatment by Identified Race

	Overall % of Patients Receiving for Initial Therapy	Regression Slope	95% CI	R Square	*P*-Value	Regression Slope Comparison	*P*-Value
Phototherapy							
Asian	4.6%	-1.16%	[-1.80%, -0.52%]	0.540	**0.00**	Asian, Black	0.78
Black	6.0%	-1.33%	[-2.48%, -0.19%]	0.326	**0.03**	Black, White	0.16
White	2.6%	-0.54%	[-0.80%, -0.28%]	0.602	**0.00**	Asian, White	0.06
Biologics							
Asian	3.6%	0.02%	[-0.44%, +0.48%]	0.001	0.93	Asian, Black	0.07
Black	3.0%	0.64%	[+0.10%, +1.18%]	0.338	**0.02**	Black, White	0.13
White	2.6%	0.25%	[+0.17%, +0.34%]	0.755	**< 0.001**	Asian, White	0.29
Immunosuppressants							
Asian	3.6%	-0.03%	[-0.38%, +0.33%]	0.002	0.87	Asian, Black	**0.03**
Black	7.8%	0.77%	[+0.10%, +1.45%]	0.319	**0.03**	Black, White	0.20
White	4.4%	0.35%	[+0.18%, +0.52%]	0.595	**0.001**	Asian, White	0.05
Apremilast							
Asian	1.7%	0.56%	[-0.25%, +1.38%]	0.478	0.13	Asian, Black	0.44
Black	2.3%	1.28%	[-1.07%, +3.63%]	0.364	0.21	Black, White	0.31
White	0.8%	0.36%	[-0.11%, +0.83%]	0.528	0.10	Asian, White	0.56
Topicals							
Asian	86.4%	0.87%	[-0.01%, +1.74%]	0.262	0.05	Asian, Black	0.30
Black	80.3%	-0.20%	[-2.20%, +1.80%]	0.004	0.83	Black, White	0.99
White	89.1%	-0.19%	[-0.48%, +0.10%]	0.130	0.19	Asian, White	**0.02**

Linear regression of proportion of patients per year receiving phototherapy, biologics, immunosuppressants, and apremilast as initial treatment between 2005-2019, by identified race. Column 1 percentages are calculated by percent of racial group receiving specific treatment as initial therapy. Regression slope represents average change in percentage of patients per year. *P*-values in bold are significant at a level of $\alpha = 0.05$.

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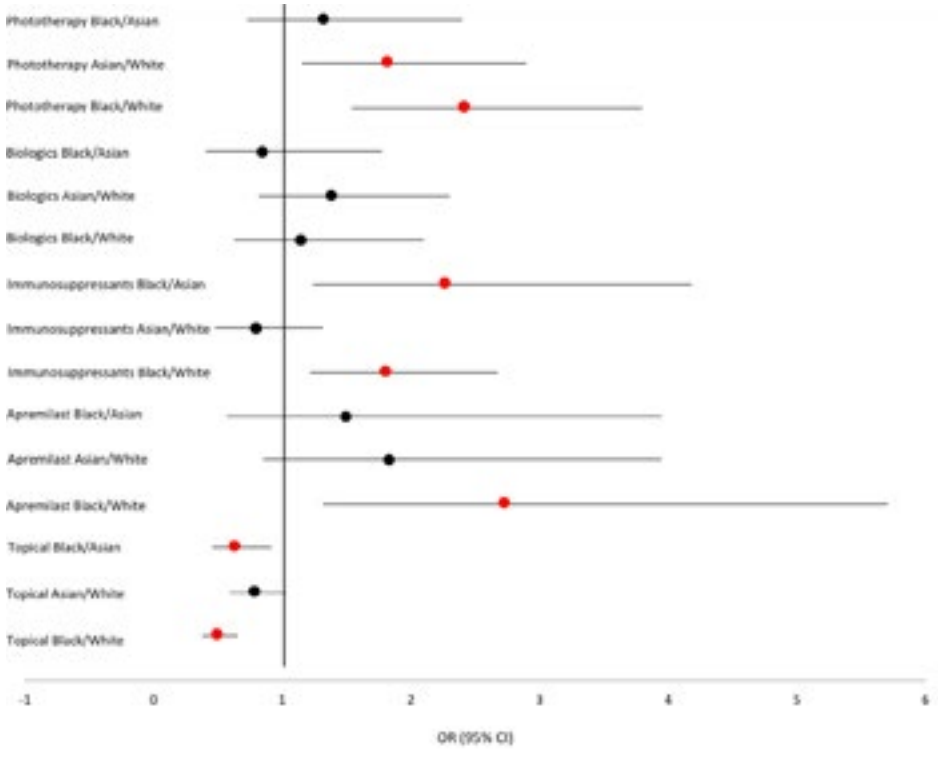
FIGURE 1. OR for likelihood of specified treatment as initial psoriasis therapy compared between racial groups.



With regard to logistic regression trends, phototherapy usage for initial treatment significantly decreased over the period of the study for all races (average decline of 0.5% to 1.3% of patients per year). Biologic and immunosuppressant use significantly increased for Blacks and Whites, with no significant trends for Asians (Table 1). Apremilast usage increased for all races but was non-significant in all groups. Topical therapies were by far the most common initial therapy in all groups (80-89%), and there was no clear trend in change over time. Mean yearly rate of change in utilization was not significantly different between races for any of the therapies except for a greater increase in immunosuppressants usage in Blacks vs. Asians (*P*-value = 0.03).

Asians and Blacks were significantly more likely to be prescribed phototherapy as initial non-topical treatment vs Whites (Asian/White OR: 1.83, 95% CI [1.15, 2.9]; Black/White OR: 2.42, 95% CI [1.54, 3.79]). Blacks were significantly more likely to receive immunosuppressants initially vs Whites and Asians (Black/White OR: 1.81, 95% CI [1.22, 2.67]; Black/Asian OR: 2.28, 95% CI [1.24, 4.18]). Blacks were statistically more likely to be prescribed apremilast than Whites (OR: 2.74, 95% CI [1.32, 5.71]). Blacks were significantly less likely to receive topicals as initial prescription treatment vs Whites and Asians (Black/White OR: 0.50, 95% CI [0.38, 0.65]; Black/Asian OR: 0.64, 95% CI [0.45, 0.92]). Prescribing of biologics for initial therapy did not differ between groups (Figure 1).

Our findings indicate that for initial treatments, Black patients were more likely than Asian/White patients to receive phototherapy and systemics for initial psoriasis treatment and less likely to receive topicals. One possible explanation for this trend is that Black patients have been shown to be more frequently diagnosed with psoriasis in later stages, attributed to unfamiliarity of presentation in skin of color, due to an underrepresentation of skin of color patients in textbooks, training materials, and research.[4] Therefore, Blacks in our study may have had more severe disease, which may warrant further research and possible intervention. While our study analyzed initial therapy, previous studies have demonstrated that Black patients are less likely to receive systemic treatments overall.[1-3] Additionally, similar to previous research, phototherapy usage showed a decreasing trend, which we found in this study to be persistent across races.[5] In contrast, biologics and immunosuppressants increased overall, but only for Blacks and Whites.

Limitations include single-center, retrospective design, patients excluded due to unknown/other race (n = 4881, 45.5%), a primarily White population, and small sample sizes for some subgroups in certain years. Only initial treatments were examined. The study was not powered to assess for disease severity, comorbidities, or concomitant psoriatic arthritis.

Overall, in regard to initial treatment, phototherapy usage for psoriasis has decreased across races, and compared to other races, phototherapy/systemics are prescribed more often to Black patients as initial treatment. Further research is needed to elucidate these differences to provide equitable and effective psoriasis treatments for all patients.

DISCLOSURES

Rhiannon Miller, Dr Mytrang Do, Sajjad Abedian declare that they have no conflicts of interest. Dr Lipner has served as a consultant for Ortho-Dermatologics, Verrica, Hoth Therapeutics, Hexima, and BelleTorus Corporation.
IRB: Approved, Protocol #1901019900

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FEATURED CONTENT

JOURNAL OF DRUGS IN DERMATOLOGY

NEWS, VIEWS, & REVIEWS

Nitric Oxide as a Promising Antiviral Agent: What Dermatologists Should kNOw

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INTRODUCTION

Nitric oxide (NO) is an endogenous molecule produced by nitric oxide synthase (NOS) in the 2-step oxidation reaction of L-arginine.[1] NO readily diffuses and is highly reactive, causing it to have a broad range of physiologic and pathophysiologic effects. NO plays a role in crucial physiologic processes throughout the body including regulating vascular tone, neurotransmission, and immune responses.[2,3] In skin, NO is involved with maintenance and regulation of the skin barrier, antimicrobial defense, maintaining circulation, and response to UV irradiation.[1,4] Dysregulation of NO is implicated in numerous pathologies; both excess and low levels of NO may be detrimental.

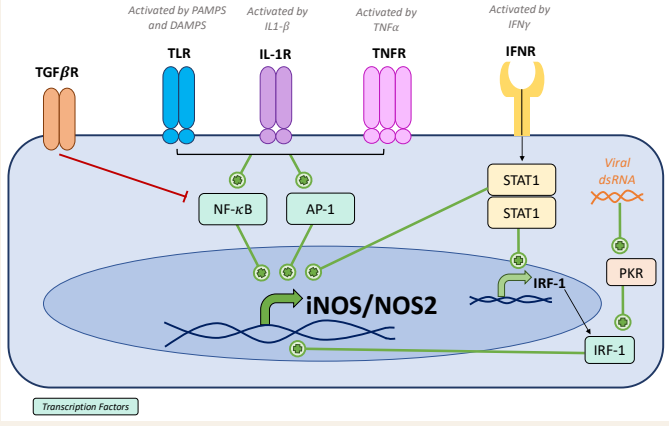
NO has immense therapeutic potential given the breadth of its interactions. Within dermatology, it has been studied most notably for its immunomodulatory properties and as a broad-spectrum antimicrobial agent with activity against bacteria, yeast, fungi, and viruses.[2,4] Herein, relevant evidence supporting the anti-viral properties of NO will be reviewed. This topic is clinically relevant for dermatologists; NO-based topical therapies are currently being explored as treatment options for viral infections, such as human papillomavirus (HPV) and molluscum contagiosum (MC).

Anti-Viral Properties of NO

NO exhibits concentration-dependent immunomodulatory properties and is considered an important part of the innate immune response.[5-7] NO is produced by many immune cells including activated macrophages, dendritic cells, mast cells, natural killer cells, monocytes, eosinophils, and neutrophils.[7] At low concentrations, NO is immunostimulatory, increasing cytokine signaling, cell migration and differentiation, and vascular dilation and permeability.[4,8,9]

When viral infection occurs, there is increased transcription and activity of iNOS, an inducible isoform of NOS. iNOS transcription is multimechanistic and can be stimulated by both viral and immune factors (Figure 1).[4,6,7,10] When activated, iNOS generates a large amount of NO. At high concentrations (>1 μM), NO becomes oxidized, generating reactive nitrogen oxide species (RNOS).

Figure 1. Overview of iNOS/NOS2 induction pathways.[6,10]



There are multiple mechanisms by which iNOS can be stimulated. For example, toll-like receptors (TLRs) on immune and non-immune cells (ex, macrophages, lymphocytes, epithelial cells) detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), activating NF-κB and AP-1 signaling to upregulate iNOS. Pro-inflammatory cytokines (ex, IL1-β, TNFα) upregulate iNOS through the same pathways. Interferon gamma (IFNγ) produced by lymphocytes upregulates iNOS via the signal transducer and activator of transcription 1 (STAT-1) signaling pathway. Viral double stranded RNAs (dsRNAs) induce IFNs and bind and activate protein kinase-R (PKR), leading to upregulation of iNOS. Of note, only key signaling molecules are shown, complete pathways are not included in this figure. IRF-1= Interferon Regulatory Factor.

RNOS are important for the anti-viral and anti-microbial response.[4] RNOS nitrosylate cysteine residues of viral proteins; this process disrupts viral DNA repair enzymes and inhibits the viral replication cycle when proteases, reductases, and reverse transcriptases become inactivated.[6] RNOS also causes damage to viral DNA/RNA structure by deaminating cytosine, adenine, and guanine, inducing strand breaks, generating genotoxic alkylating agents, and causing other alterations.[4,7] With viral replication halted, virions are unable to infect additional cells, allowing for more efficient host clearance. NO can also contribute to cytotoxicity and death of infected cells by reacting with iron-containing mitochondrial enzymes, reducing their activity.[11]

Importantly, NO's genotoxic activity affects both the viral and host genome; however, host genomes contain more robust repair nucleases and polymerases.[6] Nevertheless, NO production is tightly regulated by host cells to balance indiscriminate inflammatory activity with antiviral effects; excessive NO may lead to additional complications.[6,12]

Table 1. Summary of Evidence for Anti-viral Activity of NO in HPV Infection.[14-17]

Citation	Study Type	Study Purpose/Design	Results	Conclusions
Ormerod et al. 2015	Phase 2, dose-finding trial • Randomized • Multicenter • Double-blind • Placebo-controlled	*Purpose:* Assess treatment effect of acidified nitrite for external anogenital warts (EAW) *Study population:* 299 adults with 2-50 EAW *Treatment groups:* 1. Sodium nitrite 3%/citric acid 4.5% BID 2. Sodium nitrite 6%/citric acid 9% QD (placebo applied in AM) 3. Sodium nitrite 6%/citric acid 9% BID 4. Placebo BID *Treatment duration:* 12 weeks *Primary efficacy endpoint:* Complete clearance of target warts	Patients who achieved complete clearance: 1. SN 3%/CA 4.5% BID: 15% 2. SN 6%/CA 9% QD: 23% 3. SN 6%/CA 9% BID: 31% 4. Placebo: 14% Treatment site reactions in 66-92% of active treatment groups (most commonly itching)	Sodium nitrite 6%/citric acid 9% BID was more effective than placebo for treatment of anogenital warts
Tyring et al. 2018	Phase 2 dose-escalation trial • Randomized • Double-blind • Vehicle-controlled	*Purpose:* Assess treatment effect of SB206 for extragenital/perianal warts (EGW/PAW) *Study population:* 108 adults with 2-20 EGW/PAW *Treatment groups:* 1. SB206 4% QD or BID 2. SB206 8% QD 3. SB206 12% QD 4. Vehicle *Treatment duration:* 12 weeks *Primary efficacy endpoint:* Complete clearance of baseline EGW/PAW	Complete clearance was achieved in: 1. SB206 4% QD: 20.8% 2. SB206 8% QD: 14.3% 3. SB206 12% QD: 33.3% 4. Vehicle: 4.3%	Complete clearance was achieved in a higher proportion of patients in the SB206 group compared to vehicle, especially for SB206 12% QD
Yu et al. 2018	In vitro study	*Purpose:* Investigate role of NO in regulating HPV gene transcription *Methods:* Human cervical carcinoma cells (HPV16+) were treated with NO-donor (DETA-NO) at varying concentrations, E6 gene expression was measured by real-time PCR	DETA-NO inhibited cervical carcinoma cell proliferation and levels of HPV E6 mRNA in dose and time dependent manner	Expression of HPV E6 protein mRNA was inhibited by NO
Banerjee et al. 2019	In vitro study	*Purpose:* Investigate impact of exposing HPV-18 infected raft cultures to NO donor SB206 *Methods:* • Primary human keratinocytes infected with HPV-18 were exposed to SB206 at various concentrations • S-phase cells, E6 and E7 protein levels, HPV-18 DNA replication were assessed	SB206-treated cells compared to control had: • Reduced HPV-18 DNA by 95% • Decreased number of cells in S phase • Decreased E6 and E7 protein levels, increased p53 protein	SB206 inhibited HPV DNA replication by reduction of E6 and E7 oncoproteins, impairing S-phase progression

NO-based Anti-viral Therapies

NO has promising therapeutic applications, including as an anti-viral agent. NO has been studied in several viruses clinically relevant to dermatologists including herpes simplex virus (HSV), HPV, and MC. HSV was one of the first viruses where NO was demonstrated to have anti-viral activity; a 1993 in vitro study demonstrated that NO reduced HSV1 replication, protein, and DNA synthesis in macrophages in vitro, and addition of a NOS inhibitor reduced the anti-viral effect of macrophages.[13]

In HPV and MC, NO is actively being studied in vivo and in vitro as a potential treatment for infection. NO has been shown in vitro to inhibit HPV DNA replication through reduction of E6 and E7 oncoproteins and has demonstrated success in treating anogenital warts in clinical trials (Table 1).[14-17] Efficacy of NO for MC infection was first seen in a 1999 clinical trial: a nitric oxide donor coadministered with 5% salicylic acid under occlusion was more effective than salicylic acid alone in treating MC (cure rate 75% vs 21%), however, the tested formulation caused frequent

Table 2. Summary of Evidence from Clinical Trials of SB206 for MC Infection.[20-23]

Citation	Trial Type	Trial Purpose/Design	Results	Conclusions
Hebert et al. 2020	Phase 2, dose-finding trial • Randomized • Multicenter • Double-blind • Vehicle-controlled	*Purpose*: Assess treatment effect of SB206 for MC lesions *Study population:* 256 patients (age ≥2 YO) with MC lesions • Mean baseline lesions=18.3 (vehicle), 19.3 (SB206) *Treatment groups:* 1. SB206 4% BID 2. SB206 8% BID 3. SB206 12% QD or BID 4. Vehicle *Treatment duration:* 12 weeks *Primary efficacy endpoint:* Complete clearance of MC lesions	Patients who achieved complete clearance: 1. SB206 4% BID: 10.6% 2. SB206 8% BID: 33.3% 3. SB2016 12% BID: 27.7% 4. SB206 12% QD: 37.5% 5. Vehicle: 18.2% 40-50% reported mild-moderate AEs in treatment groups	SB206 12% QD dose had greatest MC lesion clearance
Maeda-Chubachi et al. 2021	Integrated analysis of 2 Phase 3 clinical trials (NCT03927703, NCT03927716) • Randomized • Multicenter • Double-blind • Vehicle-controlled	*Purpose*: Assess impact of SB206 on BOTE* status, and BOTE status on MC lesion reduction *Study population:* 707 patients (age ≥6 mo) with MC lesions • Mean baseline lesions=17.8 (vehicle), 18.4 (SB206) • Baseline BOTE Status: 34.8% BOTE+, 64.4% BOTE- *Treatment groups:* 1. SB206 12% QD 2. Vehicle *Treatment duration:* 12 weeks *Outcomes evaluated:* BOTE score over time, BOTE score and MC lesion reduction	• 80% incidence of BOTE sign, regardless of treatment assignment • At week 12, MC lesion count decreased from baseline by: 1. *SB206:* 63.3% for BOTE+, 51.7% for BOTE-; p=0.0194 2. *Vehicle:* 50.7% for BOTE+, 29.1% for BOTE-; p=0.0015 • Baseline BOTE+ patients treated with SB206 had overall greatest lesion reduction over time Most common AEs were application-site pain and erythema	Patients who were both BOTE+ and treated with SB206 had the greatest reduction in MC lesion count SB206 may trigger BOTE sign, promote faster lesion clearance
Cartwright et al. 2022	Phase 1 prospective, open-label study • Multicenter	*Purpose:* Evaluate safety, tolerability, pharmacokinetic parameters of SB206 10.3% *Study population:* 34 patients with (Age ≥2YO) with 20+ MC lesions • Mean baseline lesions=50 • Total treatment area= 484 cm^2 *Treatment:* SB206 10.3% QD *Treatment duration:* • 2 week pharmacokinetic period • 10 week treatment extension	• Minimal systemic exposure of SB206 • Progressive decrease in baseline MC lesions was seen • 4 patients achieved complete clearance at week 12 Mild-moderate AEs reported in 47% of treatment group, most commonly application site erythema or pain	SB206 10.3% gel applied QD was well-tolerated with minimal systemic absorption
Browning et al. 2022	Phase 3 clinical trial • Randomized • Multicenter • Double-blind • Vehicle-controlled	*Study population:* 891 patients (age ≥6 mo) with 3-70 MC lesions • Mean baseline lesions=20.5 (vehicle), 23.1 (SB206) *Treatment groups:* 1. SB206 10.3% gel QD 2. Vehicle *Treatment duration:* 12 weeks *Primary efficacy endpoint:* % difference of patients who achieve complete clearance of MC lesions	• Patients who achieved complete clearance of all MC lesions: 1. SB206: 32.4% 2. Vehicle: 19.7% *Absolute difference:* *12.7%, P<0.001* • Patients who achieved 90%+ reduction in baseline lesion count: 1. SB206: 43% 2. Vehicle: 23.9% Mild-moderate AEs reported in 43% of treatment group, most commonly application site erythema or pain	Treatment with SB206 10.3% gel for 12 weeks resulted in significantly greater complete MC lesion clearance than patients treated with vehicle

* Beginning of the end (BOTE) sign refers to clinical inflammatory signs that predict imminent resolution of MC. BOTE+ indicates presence of BOTE sign, while BOTE- indicates that it is not present.

side effects of skin staining and irritation.[18] More recently, SB206, a NO-releasing topical medication, has shown encouraging results for treatment of MC in clinical trials. SB206 is comprised of a gel containing berdazimer sodium, a macromolecule covalently bound to NO donors, and a hydrogel that acts as a proton donor.[19] Evidence from the clinical trials of SB206 in MC can be found in Table 2. In 2023, SB206 was submitted to the US Food and Drug Administration as a New Drug Application; if accepted, this would be the first approved therapy for MC.

Conclusion

NO has therapeutic potential as an anti-viral agent. The observations from in vitro and in vivo work to date suggest that NO-releasing therapies should be further developed, tested, and explored in viral infections, such as HPV and MC. Future comparative trials will be required to assess efficacy of SB206 and other NO-based therapies relative to currently available treatments.

Disclosure

EM and SD have no relevant conflicts to disclose. AF has developed several nitric-oxide releasing technologies, though none are referenced in this paper.

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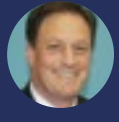

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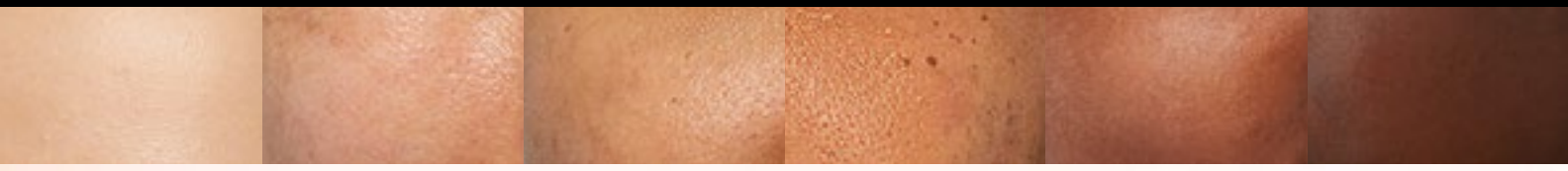

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