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JOURNAL OF DRUGS IN DERMATOLOGY

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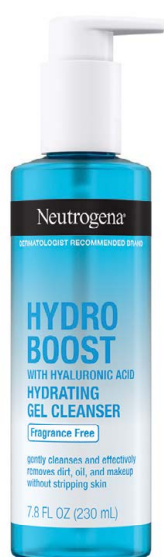
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JOURNAL OF DRUGS IN DERMATOLOGY

ORIGINAL ARTICLES

-
- 346 **The Utility of Oral *Polypodium Leucotomos* Extract for Dermatologic Diseases: A Systematic Review**
Melissa P. Zundell BS, Abigail Katz BA, Milaan Shah MD, Joshua Burshtein MD, Darrell Rigel MD MS, Danny Zakria MD MBA
-
- 352 **An Innovative Cream Improves Signs and Symptoms of Dermatoporosis in Patients Aged 65 and Over**
Alan Widgerow MBBCh MMed, Mathieu Grivet-Seyve PhD, Sarah Anjuwon MS, Christine Emesiani PharmD, Matthew Meckfessel PhD
-
- 360 **Racial and Ethnic Representation in Atopic Dermatitis Clinical Trials**
Margaret Kabakova BS, Jennifer Y. Wang BA, Paras Patel BA, Kayla Zafar BA, David Bitterman BA, Jared Jagdeo MD MS
-
- 366 **Clinical Utility of TRPV1 Modulation for Skincare Sensitivity**
Rohan Shah MD, Nalini Kaul PhD, Isabella Tan BS, Anthony Rossi MD
-
- 376 **An Algorithm Integrating Acneceuticals Into the Management of Acne Vulgaris**
Hilary Baldwin MD, Cheri Frey MD, Adelaide Hebert MD, Edward (Ted) Lain MD, Todd Schlesinger MD
-
- 381 **The State of the Clinical Management Union: A Cross-Sectional Survey of Persons With Hidradenitis Suppurativa**
Andeulazia Murdock BA, Cleo Whiting BA, Sara Abdel Azim MS, Savanna I. Vidal BS, Nikita Menta BA, Brindley Brooks, Adam Friedman MD FAAD

ORIGINAL ARTICLES

- 387 **Rituximab in the Treatment of Epidermolysis Bullosa Acquisita: A Systematic Review of the Literature**
Dimitra Xenopoulou MS, Justin W. Marson MD, Falguni Asrani MD
- 394 **Single-Center, Open-Label Study to Evaluate Improvement of Hair Appearance With Novel Hair Growth Serum**
Suleima Arruda MD, Alyssa Swearingen MD, Zahyaa Elmadany BS, Anna Nakagama BS, Emely Alvarado Lemoine BS, Sophia Clara Valmeus BS, Neil Sadick MD
- 397 **Improvement in Skin Moisturization and Lack of Barrier Damage Following Treatment With Clascoterone Cream 1%**
Zoe D. Draelos MD, Kizito Kyeremateng PharmD, Nicholas Squittieri MD
- 403 **Top Chief Complaints and Diagnoses for Outpatient Dermatology Patients of Color**
Arielle Carolina Mora Hurtado BS, Sarah Gonzalez BS, Nicole C. Syder MD, Melissa Gonzalez BA, Sanmeet Atwal BS, Kayla Blair BS, Ivan Rodriguez BS, Audrey Hao BS, Autumn L. Saizan MD, Simone N. Montgomery MD MPH, Jack Rodman MPH, Nada Elbuluk MD MSc
- e19 **Artificial Intelligence-Generated Educational Curriculum on Facial Neurotoxin Injections: Assessment of Educational Content, Curriculum Structure, and Course Logistics**
Jad Abi-Rafeh MD MSc, Leila Cattelan MD, Brian Bassiri-Tehrani MD FACS, Jacob Marks MD, Roy Kazan MD PhD FRCSC, Sachin Shridharani MD FACS, Mark Albert MD FACS, Andreas Nikolis MD PhD FRCSC, Mirko S. Gilardino MD MSc FRCSC FACS, Foad Nahai MD FACS

CASE REPORTS

- 410 **Improvement of Hailey-Hailey Disease Following Administration of Dupilumab**
Shravya Kichena MD, Jocelyn Carnicle MD, Mara Haseltine MD

BRIEF COMMUNICATIONS

413 **A Retrospective Comparative Analysis of Cutaneous Adverse Reactions in GLP-1 Agonist Therapies**

Sophia Daniel BS, Stephanie Waggett BS, Elliott Lyles BS, Pelin Sagut MD, Parisa Shamaei Zadeh MSPH, Anthony Marcelletti BHS, Carol Stegura ME, Lara Wine Lee MD PhD

416 **Effects of a Moisturizer Containing Colloidal Oatmeal and Filaggrin Technology on *Staphylococcus* Species In Vitro**

Cleo Whiting BA, Sara Abdel Azim MS, Nicolas Joly-Tonetti PhD, Nadège Lachmann MS, Adam Friedman MD FAAD

e31 **Acetyl Hexapeptide-8 as a Topical Alternative to Botulinum Toxin: A Review of the Literature**

Kalisa Lum BS, Milan M. Hirpara BA, Christine Pham MD, Megan Nguyen BS, Natasha Mesinkovska MD PhD

LETTERS TO THE EDITOR

419 **Readability and Content Characterization of Online Reading Materials for Individuals With Vitiligo**

Arielle Carolina Mora Hurtado BS, Nada Elbuluk MD MSc

422 **Exploring the Therapeutic Potential of GLP-1 Agonists in Hidradenitis Suppurativa**

Aarthi Parvathaneni BA BS, Emelie N. McQuitty MD, Bailey Slawin BA, Sanjana Likki BS, T. Austin Black BS, Nadeen Gonna MD, Rashid M. Rashid MD PhD

NEWS, VIEWS, AND REVIEWS

425 **Off-Label Management Strategies for Generalized Granuloma Annulare: What's New?**

Nikita Menta BA, Savanna I. Vidal BS, Adam Friedman MD FAAD

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The Utility of Oral *Polypodium Leucotomos* Extract for Dermatologic Diseases: A Systematic Review

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ABSTRACT

Background: *Polypodium leucotomos* extract (PLE), a fern plant product with strong anti-inflammatory and immunomodulatory properties, has been employed to reduce photoaging and skin cancer. PLE may also serve as an adjuvant treatment for psoriasis, vitiligo, atopic dermatitis, photodermatoses, and melasma. This systematic review synthesizes the current data on PLE usage to manage dermatological diseases.

Methods: This systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed/MEDLINE, Embase, and Cochrane Library were queried using keywords. Articles were screened for inclusion and subsequently grouped by dermatological condition.

Results: Twenty-one of the 152 identified articles met inclusion criteria, including 11 randomized controlled trials and 5 treatment trials. Implicated dermatological conditions were photoaging/skin cancer (9 studies), actinic keratosis (3), photodermatoses (3), melasma (2), vitiligo (3), and atopic dermatitis (1). A thorough article review revealed several potential applications of PLE.

Conclusion: PLE exhibits strong therapeutic potential with an encouraging safety profile. It has photoprotective and immunomodulatory properties, underscoring its potential as an adjuvant therapy for multiple dermatological conditions.

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INTRODUCTION

Polypodium leucotomos is a South American fern rich in antioxidants that produces *polypodium leucotomos* extract (PLE) from its leaves. PLE exhibits immunomodulatory and anti-inflammatory properties, making it beneficial for treating psoriasis, vitiligo, atopic dermatitis, and melasma.¹⁻³ PLE also inhibits ultraviolet (UV) induced generation of radical oxygen species, decreasing photoaging and skin cancer development.⁴ PLE formulations include topical gels, creams, powders, and oral capsules. The most prominent commercially available oral PLE supplement is Heliocare, (Heliocare®, Ferndale Healthcare®, Ferndale, Michigan).

Numerous applications of PLE have been studied. In 2014, Choudry et al completed a literature review of PLE summarizing its indications for dermatological conditions.¹ Multiple studies supporting its efficacy have since been published. This updated systematic literature review synthesizes the emerging data on PLE's role in managing dermatological diseases.

MATERIALS AND METHODS

This systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. On May 8, 2023, PubMed/MEDLINE, Embase, and Cochrane Library were queried using “*polypodium leucotomos*” as keywords. Results were limited to full text, English-language articles, with humans as the study subject.

RESULTS

The literature search yielded 152 unique articles, which were screened by 2 independent reviewers (MPZ and DZ). Fifty-two articles underwent full text review and 21 studies met inclusion criteria, 11 of which were randomized controlled trials (RCTs). Articles were grouped by dermatologic condition: photodermatoses, photoaging and skin cancer, vitiligo, melasma, psoriasis, and atopic dermatitis. The findings are summarized in Table 1.

TABLE 1.

Clinical Studies Summary					
Skin Condition	Study	Subjects	Dose	Type	Outcome
Photoaging and Skin Cancer	Aguilera P et al (2012)	61	720+360 mg (total 1080 mg) 1 day and 3 hr before UVB exposure	Treatment trial	PLE significantly decreased UVR sensitivity in high-risk melanoma.
	Emanuele E, et al (2017)	40	PLE/pomegranate combination 480 mg daily (n=20) or PLE 480 mg daily alone (n=20) for 3 months	RCT	PLE and PLE/pomegranate improved photoaging skin parameters. The combination yielded a greater improvement than PLE alone.
	Kohli I, et al (2017)	22	240mg 2 hours and 1 hour (480 mg total) before irradiation with UVA1, UVB, and visible light	Open Treatment trial	PLE exhibited significant chemoprotective and anti-inflammatory properties against UVB-induced damage.
	Middelkamp-Hup MA, et al (2004)	10	7.5 mg/kg oral PLE+PUVA at various intervals	Open Label study	PLE decreased clinical and histological indicators of phototoxic damage, indicating it is an effective chemophotoprotector against PUVA-induced phototoxicity.
	Middelkamp-Hup MA, et al (2004)	9	7.5 mg/kg oral PLE+UV Radiation at various intervals	Open Label study	PLE-treated skin had a significant decrease in erythema, sunburn-cell formation, DNA damage, epidermal hyperproliferation, and dermal mast cell infiltration. PLE has chemophotoprotective properties, against UV radiation.
	Mohammad TF, et al (2019)	22	480 mg daily x 28 days + visible light irradiation	Open Label study	PLE administration before visible light decreased pigmentation. There was a statistically significant reduction in persistent pigment darkening, delayed tanning, and decreased inflammation on immunohistochemistry.
	Nestor MS, et al (2015)	40	240 mg BID x 60 days	Randomized, double-blinded, placebo-controlled	PLE group showed a decreased likelihood of sunburn, an increased minimal erythema dose, and a greater likelihood of decreased ultraviolet-induced erythema intensity. PLE (240 mg BID for 60 days) was safe and effectively reduced damaging effects of ultraviolet radiation.
	Villa A, et al (2010)	10	240 mg 8 and 2 hours before UVA exposure	Randomized, investigator blinded, controlled trial	PLE pretreatment showed a strong, but not significant, trend towards preventing increased CD levels 24 hours after UVA irradiation and with increasing UVA doses.
	Gonzalez S, et al (1997)	21	1080 mg oral PLE vs topical PLE in psoralen-sensitized and nonsensitized patients	Open treatment trial	Oral and topical PLE were photoprotective. PLE significantly increased the UV dose required for immediate pigment darkening, the minimal erythema dose, and the minimal phototoxic dose.
Melasma	Ahmed A, et al (2013)	40	240 mg TID (720 mg total daily) x 12 weeks	Randomized, double blinded, placebo controlled	PLE was not significantly better than placebo as an adjunct to sunscreen for melasma treatment.
	Goh CL, et al (2018)	40	480 mg daily x 12 weeks	Randomized, double blinded, placebo controlled	PLE was an effective coadjutant treatment for melasma in combination with topical 4% hydroquinone and SPF 50.
Actinic Keratosis	Auriemma M, et al (2015)	34	960 mg QD x 1 month then 480 mg QD x 5 months after 2 PDT sessions (2 weeks apart)	RCT	PLE improved PDT clearance and decreased AK recurrence rates at month 6 in bald males with >2 scalp AKs.
	Miola AC, et al (2022)	50	500 mg oral PLE BID vs Placebo + either colchicine, ingenol mebutate, or sunscreen	RCT	Colchicine was effective and tolerable in treating AKs and cutaneous field cancerization. There was no difference when PLE was added.
	Pellacani G, et al (2023)	131	Topical PLE+SPF100 vs oral PLE 240 mg QD+SPF100 vs self-administered sunscreen	Open label RCT	Topical and oral PLE groups demonstrated decreased AKs and field cancerization parameters. Oral PLE+SPF100 showed the greatest improvements, suggesting a potential photoprotective advantage.

TABLE 1. (CONTINUED)

Clinical Studies Summary					
Skin Condition	Study	Subjects	Dose	Type	Outcome
Photo-dermatoses	Caccialanza M, et al (2007)	28 (26 PMLE; 2 solar urticaria)	480 mg daily x 15 days before UV exposure	Open treatment trial	PLE significantly reduced skin reactions and subjective symptoms in patients with treatment nonresponsive PMLE. Two patients with solar urticaria did not improve.
	Caccialanza M, et al (2011)	57 (53 PMLE; 4 solar urticaria)	480 mg daily x 15 days before UV exposure	Open treatment trial	PLE significantly reduced skin reactions and subjective symptoms in patients with treatment nonresponsive PMLE. Three of four patients with solar urticaria did not improve.
	Tanew A, et al (2012)	35	Weight dosing: <55 kg=720 mg QD; 56-70 kg=960 mg QD; >70 kg=1200 mg QD	Open, uncontrolled (no placebo)	After PLE, 30%and 28% of patients did not react after UVA or UVB exposure. The mean number of UVA and UVB irradiations required to elicit PMLE significantly increased (UVA: $P=0.005$, UVB: $P=0.047$)
Vitiligo	Middelkamp-Hup MA, et al (2007)	50	250 mg TID+NB-UVB twice weekly x 25-26 weeks	Randomized, double-blinded, placebo-controlled	PLE group trended towards increased re-pigmentation compared to placebo across all anatomical locations. PLE repigmentation was nearly statistically significant in the “head and neck” ($P=0.06$)
	Reyes E, et al (2006)	19	PUVA+ oral PLE 720 mg daily vs PUVA+placebo for 12 weeks	Randomized, double-blinded, placebo-controlled	PLE+PUVA significantly increased skin repigmentation, normalized T-cell activation, and , decreased peripheral blood mononuclear cells proliferation compared to PUVA+placebo.
	Pacifico A, et al (2006)	44	480 mg oral BID+NB-UVB vs NB-UVA+placebo	Randomized, prospective, controlled study	PLE+NB-UVA significantly increased repigmentation compared to placebo. PLE+NB-UVA may also enhance the speed and extent of repigmentation.
Atopic Dermatitis	Ramirez-Bosca A, et al (2012)	105	Daily PLE (240 mg, 360 mg, or 480 mg by age) vs placebo	Randomized, double-blind, placebo-controlled	PLE may control pruritus more effectively than antihistamines and decrease their consumption. There was no difference in topical corticosteroid usage between groups.

Abbreviations: PLE: Polypodium leucotomos extract, UVR: Ultraviolet radiation, UVB: Ultraviolet B radiation, UVA: Ultraviolet A radiation, NB-UVA: Narrow-band ultraviolet light A, RTC: Randomized clinical trial, QD: Once daily, BID: Twice daily, TID: Three times daily, PDT: Photodynamic therapy, AK: Actinic Keratosis, SPF: Sun protection factor, PMLE: Polymorphous light eruption

DISCUSSION

Photoaging/Skin Cancer

PLE protects against phototoxicity, making it beneficial in preventing photoaging and skin cancer. Middelkamp-Hup et al evaluated PLE in reducing psoralen-UVA (PUVA)-induced phototoxicity clinically and histologically.⁵ Ten participants were exposed to PUVA or PUVA+oral PLE 7.5 mg/kg. PLE subjects exhibited consistently reduced signs of phototoxic damage. In a comparable study, PLE-treated skin displayed reduced erythema, sunburn cell formation, DNA damage, epidermal hyperproliferation, and dermal mast cell infiltration.⁶ This suggests that PLE is an effective chemo-photoprotective agent against UV-radiation and PUVA-induced phototoxicity.

Nestor et al conducted a double-blinded RTC with 40 patients comparing oral PLE-240 mg (60 days BID) vs placebo.² The placebo group showed a greater likelihood of >1 sunburn episode ($P=0.04$). PLE subjects demonstrated greater likelihood of increased minimal erythema dose ($P=0.01$) and decreased UV-induced erythema intensity ($P<0.01$).

Kohli et al used a split-back design to examine PLE’s protective effects against UV-irradiation-induced skin damage grossly and histologically.⁷ Twenty-two patients were irradiated with UVA and UVB on their left back on day 1. On days 3 and 4, patients consumed PLE-240 mg 2 hours and 1 hour before UV treatment on their right back. Skin erythema and pigmentation were assessed via Investigator’s Global Assessment (IGA) 24 hours after each session, along with colorimetry and biopsies for immunohistochemistry analysis. The average IGA score was 19% lower in the PLE group ($P<0.05$). On colorimetry, the relative erythema intensity was 8% lower in the PLE group ($P<0.05$). Histological assessment of biomarkers associated with UV damage found that all deleterious effects were significantly reduced ($P<0.05$), with a 32% improvement in pyrimidine dimers and decreased UVA-induced phototoxicity.

Villa et al assessed PLE on the mitochondrial DNA ‘common-deletion’ (CD), a marker of chronic UVA radiation.⁸ Ten participants received UVA at minimal erythema dose (MED) with pretreatment of oral PLE-240 mg 8 and 2 hours prior. Though

not statistically significant, PLE showed a clear trend toward preventing increased CD levels 24 hours after UVA irradiation and with increasing UVA doses.

Aguilera et al explored PLE's photoprotection in high-risk skin cancer patients.⁹ Sixty-one melanoma-prone patients received PLE-720 mg one day and PLE-360 mg 3 hours before UVB exposure. Subjects served as their own controls. Results showed a significant increase in mean MED across all groups, indicating reduced UV-radiation sensitivity. In subgroup analysis, darker eye color and lower baseline MED predicted a better response to PLE.

Mohammad et al investigated PLE's protection against visible light.¹⁰ Twenty-two participants were given oral PLE-480 mg for 28 days and exposed to visible light. Statistically significant reductions in persistent pigment darkening, delayed tanning, and inflammation were noted. A nonsignificant decrease in pigmentation was observed ($P=0.07$).

Emanuele et al compared daily oral PLE vs a PLE/pomegranate combination for 3 months on 40 participants.¹¹ Both groups demonstrated improvements in photoaging-related biophysical parameters. PLE/pomegranate showed superior reductions in erythema index, melanin index, and sebum content. Gonzalez et al explored the photoprotective properties of oral and topical PLE.¹² Twenty-one patients were divided into psoralen-sensitized and nonsensitized groups and given either oral PLE-1080 mg or topical-PLE. Both preparations protected skin from acute sunburn reaction and PUVA-induced phototoxicity. These studies underscore PLE's systemic photoprotective properties, offering benefits against photoaging and skin cancer development.

Actinic Keratosis

The first RTC investigating PLE and precancerous actinic keratosis (AK) found that supplementation after photodynamic light therapy (PDT) improved PDT clearance and decreased AK recurrence 6 months post-treatment.¹³ Thirty-four bald men with 2+ scalp AKs underwent 2 PDT sessions one week apart, followed by either oral PLE daily (960 mg for 1 month, then 480 mg for 5 months) or nothing. All patients demonstrated reductions in AK numbers, which was statistically significant for both PLE and control groups at month 2, but only PLE at month 6. The PLE cohort also had superior clearance rates compared to controls ($P=0.04$). PLE may act synergistically with PDT for AK treatment via increased clearance rate and recurrence prevention.

Pellacani et al demonstrated that oral PLE with topical sunscreen offered significant protective benefits in patients with high-risk AK recurrence.¹⁴ This RCT randomized 131 subjects with photoaging and ≥ 3 AKs to [Cnt] general nonspecific photoprotection, [T] topical photoprotection (SPF-100)+PLE gel twice daily, or [TO] topical (SPF-100) + oral PLE 240 mg once

daily. Outcomes, including AK area score index (AKASI), AK field assessment (AK-FAS), new lesions, and additional AK treatment (were assessed at trial initiation (t0), month 6 (t6), and month 12 (t12). In AKASI analysis, [Cnt] had a 3% increase ($P=0.001$) at t6, [T] had no differences, and [TO] had a 3% decrease at t6 and t12 ($P=0.001$). AK-FAS found significant changes in hyperkeratinization across time (t0, t6, t12): hyperkeratinization increased in [Cnt] (9.3% to 20.5% to 30%) but significantly decreased in [T] (13.6% to 10.3% to 5.9%) and [TO] (13.6% to 8.6% to 3%). At month 6, 25% of [Cnt] developed ≥ 1 new AK compared to 2.6% of [T] and 0% [TO] ($P=0.008$). At month 12, 14% of [Cnt] but 0% of [T] and [TO] developed new AKs ($P<0.001$). Researchers observed a significant difference in the percent of subjects necessitating additional treatment: 23% [Cnt], 10% [T], and 3% [TO] ($P=0.027$). Oral PLE with sunscreen may protect against AK development, decrease keratinization, lesion size, and additional treatments. Though less pronounced, [T] had significant benefits compared to [Cnt], underscoring PLE's different immunomodulatory effects when administered orally vs topically.

Miola et al compared oral PLE vs placebo and either topical colchicine, ingenol mebutate (IM), or sunscreen for AK treatment.¹⁵ Fifty patients were randomized to oral PLE-500 mg BID or placebo for 1 month. Groups were then subdivided into 3 topical regimens: colchicine 0.5% cream BID (1 week), IM 0.05% gel once daily (2 days), or SPF-30 sunscreen. Researchers assessed total and partial AK clearance, cutaneous field cancerization (CFC) activity, forearm photoaging scale (FPS), and keratinocyte intraepithelial neoplasia (KIN) score. Both PLE and placebo had similar reductions in total (14.7% vs 16.1% $P=0.26$) and partial clearance (44% vs 44% $P=0.26$). KIN analysis showed no differences between groups.

PLE may be an effective adjuvant to PDT for AK treatment but further studies are warranted.

Photodermatoses

PLE may help prevent and treat photodermatoses, a group of immunologically mediated skin reactions provoked by UV sunlight, including polymorphic light eruption (PMLE), chronic actinic dermatitis, and solar urticaria.

Caccialanza et al investigated PLE's photoprotective properties in patients with treatment-resistant photodermatoses.¹⁷ Twenty-six patients with PMLE, and 2 with solar-urticaria) took oral PLE-240 mg BID with typical sun exposure. Clinical response was categorized as "normalization" if no rash appeared, "clear-improvement" (50-90%), "slight-improvement" (10-50%), or "no-improvement." The majority (80%) of patients reported improvement; 31% had complete normalization and 49% had slight or clear-improvement. Neither solar urticaria patients demonstrated improvement.

Caccialanza et al performed an identical study on a larger population, yielding similar results.¹⁸ Fifty-three patients with PMLE and 4 with solar urticaria received PLE-480 mg daily with typical sun exposure. Over 70% ($P<0.05$) of patients reported a clinical benefit of PLE: 29.3% had complete normalization, and 43.9% reported some degree of improvement. Only one solar urticaria patient reported improvement. No adverse effects were observed.

Tanew et al assessed whether PLE can prevent photoinduction of PMLE.¹⁹ Thirty patients with UVA-inducible PMLE (18 UVB sensitive) were given weight-based oral PLE (≤ 55 kg=720 mg/day, 56-70 kg=960 mg/day, >70 kg=1200 g/day). After 2 weeks, there was a statistically significant increase in the UV-light threshold needed to induce PMLE, with 9 (30%) patients having no PMLE-induction ($P=0.005$). Fifteen patients continued taking PLE for the summer, of which 47% remained without PMLE and 27% experienced significant symptomatic improvement. PLE can diminish or prevent UV induction of PMLE. However, it may not be as effective for solar urticaria.

Melasma

PLE's photoprotective properties have led to its exploration as an adjunct to melasma treatment. Ahmed et al conducted an RTC to evaluate oral PLE with sunscreen for melasma.²⁰ Forty patients received oral PLE-240 mg or placebo TID with SPF-55 sunscreen for 12 weeks. Melasma, measured by melanin index and Melasma Area and Severity Index (MASI), improved in both groups without statistically significant differences.

A double-blind, placebo-controlled study by Goh et al found more encouraging results.²¹ Forty patients received oral PLE-480 mg or placebo with 4% hydroquinone and SPF-50+ sunscreen. Both groups exhibited a significant improvement in the modified-MASI (mMASI)—44.4% reduction in the placebo group ($P\leq 0.01$) and 54.9% for PLE ($P\leq 0.01$). PLE saw a larger comparative decrease in mMASI with statistical significance at day 56 ($P\leq 0.05$). Melasma Quality of Life (MelasQoL) scores significantly improved with PLE. Oral PLE may accelerate outcomes of hydroquinone and sunscreen for melasma, but additional studies are required.

Vitiligo

PLE may enhance skin repigmentation in vitiligo treatment when used as an adjuvant to Narrow band (UVB) light therapy. A double-blind clinical trial by Reyes et al evaluated skin repigmentation and blood immunomodulatory effects of PLE plus PUVA light-therapy for vitiligo.²³ Nineteen patients were randomized to PUVA+PLE 720 mg daily or PUVA+placebo for 12 weeks. There was a significantly higher percentage of $>50\%$ skin repigmentation in PLE+PUVA than PUVA+placebo. Blood samples from baseline and after 12 weeks found that PLE+PUVA significantly decreased the expression of activating signals on CD8+ T-lymphocytes and the proliferative response of immune cells comparatively. This study elucidates the anti-inflammatory

and immunological properties of PLE at a molecular level and correlates them to enhanced repigmentation in vitiligo.

Middlekamp et al compared repigmentation in vitiligo patients treated with NB-UVB or NB-UVB+PLE in a double-blind, placebo-controlled study.²⁴ All 50 patients received twice-weekly NB-UVB for 25-26 weeks, and either oral PLE 250 mg TID or placebo. Results demonstrated a strong but not statistically significant trend towards increased repigmentation with PLE compared to placebo, especially in the head/neck ($P=0.06$). The increased repigmentation with PLE was statistically significant among patients attending 80% of NB-UVB sessions ($P<0.002$). PLE patients with Fitzpatrick skin-types II and III had significantly increased repigmentation compared to placebo ($P=0.01$). No conclusions were drawn about Fitzpatrick types IV and V due to small sample size. There were no differences in quality of life (Skindex-29). PLE can enhance repigmentation in vitiligo patients, especially in lighter skin tones and most prominently in the head/neck.

Pacifico et al investigated PLE in vitiligo patients with medium to darker skin types and found PLE with NB-UVB significantly improved repigmentation compared to NB-UVB alone.²² This double-blind RCT included 44 vitiligo patients with Fitzpatrick skin types III or IV. All patients underwent twice-weekly NB-UVB for 6 months with either PLE-480 mg BID or placebo. The NB-UVB+PLE group had greater repigmentation than NB-UVB alone in the head/neck ($P<0.001$), trunk ($P=0.080$), and extremities ($P<0.001$). At 3-month follow-up, the PLE group had maintained significantly more repigmentation than placebo, especially in the head/neck ($P<0.001$). The rate of NB-UVB induced erythema, pruritus, and burning was significantly lower in the PLE group ($P=0.023$). The addition of PLE to NB-UVB significantly enhanced repigmentation in vitiligo patients with darker skin tone, underscoring the promising potential of PLE as an adjuvant to phototherapy.

Atopic Dermatitis

Ramírez et al investigated whether PLE could reduce topical corticosteroid and antihistamine use in children with atopic dermatitis (AD).²⁵ One-hundred and five patients (2-17 years old) with moderate AD were randomized to oral PLE (age-dosing <6 : 240 mg/day, 6-12: 360 mg/day, >12 : 480 mg/day) or placebo for 6 months. Participants were given topical methylprednisolone-aceponate 0.1% for flares and desloratadine for pruritus. The percent of days subjects required topical corticosteroids did not differ between groups (11% PLE vs 12% placebo $P=0.20$); but PLE demonstrated a trend toward lower corticosteroid usage and number of flares comparatively. PLE, but not placebo, had significant decreases in corticosteroid usage between months 1 to 2 ($P=0.012$) and 4 to 5 ($P=0.012$). PLE patients required desloratadine on significantly fewer days than placebo ($P=0.038$). This trend became more significant over time, indicating a potential advantage of antihistamine intake reduction.

CONCLUSION

PLE exhibits therapeutic potential for an array of dermatological conditions with an encouraging safety profile. PLE's photoprotective properties and efficacy in mitigating phototoxicity underscore its importance in skin health. The compelling outcomes in AK and photodermatoses management reinforce PLE's therapeutic versatility. Experiments testing PLE in vitiligo, atopic dermatitis, and melasma suggest its potential role as an adjuvant therapy, but the data are mixed. Further research investigating optimal dosing and routes of administration is needed. Advancing our understanding of PLE's therapeutic effects could uncover additional applications and clinical utility.

DISCLOSURES

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REFERENCES

1. Choudhry SZ, Bhatia N, Ceilley RI, et al. Role of oral Polypodium leucotomos extract in dermatologic diseases: a review of the literature. *J Drugs Dermatol*. 2014;13(2):148-153.
2. Nestor MS, Berman B, Swenson N. Safety and efficacy of oral Polypodium leucotomos extract in healthy adult subjects. *J Clin Aesthet Dermatol*. 2015;8(2):19-23.
3. Solivellas BM, Martín TC. Polypodium leucotomos extract use to prevent and reduce the risk of infectious diseases in high-performance athletes. *Infect Drug Resist*. 2012;5:149-153.
4. Parrado C, Phillips N, Gilaberte Y, et al. Fernblock (Polypodium leucotomos extract): molecular mechanisms and pleiotropic effects in light-related skin conditions, photoaging, and skin cancers—a review. *Int J Mol Sci*. 2016;17(7):1026.
5. Middelkamp-Hup MA, Pathak MA, Parrado C, et al. Orally administered Polypodium leucotomos extract decreases psoralen-UVA-induced phototoxicity, pigmentation, and damage of human skin. *J Am Acad Dermatol*. 2004;50(1):41-49.
6. Middelkamp-Hup MA, Pathak MA, Parrado C, et al. Oral Polypodium leucotomos extract decreases ultraviolet-induced damage of human skin. *J Am Acad Dermatol*. 2004;51(6):910-918.
7. Kohli I, Nestor MS, Pally RB, et al. The impact of oral Polypodium leucotomos extract on ultraviolet B response: a human clinical study. *J Am Acad Dermatol*. 2017;77(1):33-41.e1.
8. Villa A, Viera MH, Amini S, et al. Decrease of ultraviolet A light-induced "common deletion" in healthy volunteers after oral Polypodium leucotomos extract supplement in a randomized clinical trial. *J Am Acad Dermatol*. 2010;62(3):511-513.
9. Aguilera P, Carrera C, Puig-Butlle JA, et al. Benefits of oral Polypodium leucotomos extract in MM high-risk patients. *J Eur Acad Dermatol Venereol*. 2013;27(9):1095-1100.
10. Mohammad TF, Mattox AR, Hamzavi IH, et al. Oral Polypodium leucotomos extract and its impact on visible light-induced pigmentation in human subjects. *J Drugs Dermatol*. 2019;18(12):1198-1203.
11. Emanuele E, Bertona M, Biagi M. Comparative effects of a fixed Polypodium leucotomos/pomegranate combination versus Polypodium leucotomos alone on skin biophysical parameters. *Neuro Endocrinol Lett*. 2017;38(1):38-42.
12. González S, Pathak MA, Cuevas J, et al. Topical or oral administration with an extract of Polypodium leucotomos prevents acute sunburn and psoralen-induced phototoxic reactions as well as depletion of Langerhans cells in human skin. *Photodermatol Photoimmunol Photomed*. 1997;13(1-2):50-60.
13. Auriemma M, Di Carlo A, Capasso R, et al. Polypodium leucotomos supplementation in the treatment of scalp actinic keratosis: could it improve the efficacy of photodynamic therapy? *Dermatol Surg*. 2015;41(8):898-902.
14. Pellacani G, Casari A, Vincenzi C, et al. The combination of oral and topical photoprotection with a standardized Polypodium leucotomos extract is beneficial against actinic keratosis. *Photodermatol Photoimmunol Photomed*. 2023;39:384-391.
15. Miola AC, Miot HA. Efficacy of oral Polypodium leucotomos, colchicine cream, and ingenol mebutate in the treatment of actinic keratoses and cutaneous field cancerization: a randomized clinical trial. *An Bras Dermatol*. 2023;98(2):232-236.
16. Lehmann P, Schwarz T. Photodermatoses: diagnosis and treatment. *Dtsch Arztebl Int*. 2011;108(9):135-141.
17. Caccialanza M, Percivalle S, Piccinno R. Photoprotective activity of oral Polypodium leucotomos extract in 25 patients with idiopathic photodermatoses. *Photodermatol Photoimmunol Photomed*. 2007;23(1):46-47.
18. Caccialanza M, Recalcati S, Piccinno R. Oral Polypodium leucotomos extract photoprotective activity in 57 patients with idiopathic photodermatoses. *G Ital Dermatol Venereol*. 2011;146(2):85-87.
19. Tanew A, Radakovic-Fijan S, Gonzalez S, et al. Oral administration of a hydrophilic extract of Polypodium leucotomos for the prevention of polymorphic light eruption. *J Am Acad Dermatol*. 2012;66(1):58-62.
20. Ahmed AM, Lopez I, Perese F, et al. A randomized, double-blinded, placebo-controlled trial of oral Polypodium leucotomos extract as an adjunct to sunscreen in the treatment of melasma. *JAMA Dermatol*. 2013;149(8):981-983.
21. Goh CL, Chuah JL, Tey HL. Double-blind, placebo-controlled trial to evaluate the effectiveness of Polypodium leucotomos extract in the treatment of melasma in Asian skin: a pilot study. *J Clin Aesthet Dermatol*. 2018;11(3):14-19.
22. Pacifico A, Gulli F, Cristaudo A, et al. NB-UVB plus oral Polypodium leucotomos extract display higher efficacy than NB-UVB alone in patients with vitiligo. *Dermatol Ther*. 2021;34:e14853.
23. Reyes E, Jaen P, Guerrero A, et al. Systemic immunomodulatory effects of Polypodium leucotomos as an adjuvant to PUVA therapy in generalized vitiligo: a pilot study. *J Dermatol Sci*. 2006;41(3):213-216.
24. Middelkamp-Hup MA, Pathak MA, Parrado C, et al. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: a randomized double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2007;21(7):942-950.
25. Ramírez-Bosca A, Martínez-Rodríguez A, Aranegui-Aranegui R, et al. Polypodium leucotomos extract in atopic dermatitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Actas Dermosifiliogr*. 2012;103(7):599-607.

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An Innovative Cream Improves Signs and Symptoms of Dermatoporosis in Patients Aged 65 and Over

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ABSTRACT

Background: There is increasing recognition of dermatoporosis — a condition of chronic cutaneous fragility of aging skin seen primarily in older adults. Dermatoporosis can be characterized by white pseudo scars, purpura/bruising, skin thinning, and loss of volume. This study evaluated a novel cream with microdoses of mandelic acid and *Centella asiatica* that was formulated to target physiologic processes involved in dermatoporosis.

Methods: A 12-week, proof-of-concept study of participants aged 65 years and older (n=54) with sensitive skin and dermatoporosis managed with twice-daily application of the cream on both forearms and 1 leg (randomly selected, with the other leg serving as control). Key assessments included transepidermal water loss (TEWL), skin thickness measurement by ultrasound, clinical scoring for dryness and roughness, a participant questionnaire, and standard safety assessments.

Results: Twice-daily use of the novel cream resulted in an ongoing consistent positive increase in skin thickness of 5% ($P<0.05$), with improvements primarily in the dermis and epidermis but also notable in the subdermal layer. Significant improvements in hydration were observed starting from day 7 and observed through day 84 (or end of study) ($P<0.05$). Changes in TEWL showed a 20% improvement in barrier function that also was apparent early (day 7) and sustained through the study (40% improvement at day 84, $P<0.05$). The cream demonstrated excellent safety with no adverse reactions and no worsening in tolerability parameters.

Conclusions: This cream, containing microdoses of mandelic acid and *Centella asiatica*, safely and effectively improved skin thickness, firmness, and resiliency, and had high acceptability with study participants.

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INTRODUCTION

Dermatoporosis describes thin, aged, and excessively fragile skin resulting from loss of the skin's protective mechanical function.¹ Other signs and symptoms include skin atrophy, purpura, pseudoscars, skin lacerations, and dissecting hematomas.² Progressive weakening of the skin barrier can lead to severe morbidity with clinical manifestations that may require hospitalization.³ Dermatoporosis is often seen on forearms, hands, presternal area, the pretibial area, and scalp.⁴ It accompanies skin aging and can be accelerated by factors such as photodamage, use of medications such as corticosteroids, and genetic susceptibility.⁵ These factors can trigger fibroblast senescence, which in turn leads to decreased production of elastin and collagen (with resultant negative effects on the extracellular matrix) and a reduction in hyaluronic acid in the skin.^{3,4} The reduction in these extracellular matrix components results in a lack of support for cutaneous

vessels rendering them susceptible to damage.^{4,5} Symptoms of dermatoporosis can occur as early as 40 years old, but manifests fully between the ages of 70 and 90 years.⁴

Interventions for dermatoporosis should work holistically to repair and rebuild skin with a goal of preventing progression and improving skin integrity.² Optimally, they should provide support to fibroblasts and components of the extracellular matrix (collagen, elastin).^{4,6} Consistent skincare regimens can help reduce the impact of aging by maintaining skin hydration, supporting a healthy skin barrier, preserving skin quality, and enhancing elasticity and smoothness.⁷

Recently, a new over-the-counter cream has been formulated with microdoses of mandelic acid and *Centella asiatica*.⁴ Mandelic acid is a gentle alpha hydroxy acid exfoliant that normalizes skin pH, supports the skin's lipid bilayer and

cornedosomesome integrity, while promoting desquamation and enhancing keratinocyte turnover. *Centella asiatica* is a soothing agent that enhances skin delivery, slows degradation of hyaluronic acid in the skin, and reduces inflammation. Unexpectedly, a synergistic effect has been reported between microdoses of mandelic acid and *Centella asiatica*, increasing the anticipated anti-inflammatory and anti-senescence effects and optimizing the targeting of dermatoporosis.⁴ We report here a study designed to test the cream under normal conditions in adults with sensitive skin and dermatoporosis after daily use for 12 weeks.

MATERIALS AND METHODS

In a 12-week proof of concept clinical study, the investigational cream was used under normal conditions of use by participants aged 65 years or older with self-reported sensitive skin and dermatoporosis. The investigational product was applied twice daily for 84 days on both arms and one leg, with one calf randomly excluded as a control. The clinical study was conducted in agreement with the most recent Helsinki Declaration and general principle of Good Clinical Practice, and all patients provided written informed consent and a HIPAA form. Study protocol was submitted to an Institutional Review Board before participant inclusion.

Participants were aged 65 years and older, and gender, race/ethnicity, and Fitzpatrick skin phototype were unrestricted. They had visibly aged skin on their extremities and evidence of dermatoporosis (skin atrophy and pigmentary changes) as well as sensitive skin per a screening questionnaire. Furthermore, their baseline health status was generally good, and participants agreed to discontinue their current body personal care products (cleansers, serums, sunscreens) for the duration of the study. They also agreed to not sunbathe/tan and avoid sun/ultraviolet exposure as much as possible during the study. Participants were excluded if they were taking any medications that could mask or interfere with test results at the time of the study start (corticosteroids, nonsteroidal anti-inflammatory drugs, antihistamines, and immunosuppressive medications). Those with an active (flaring) disease that would interfere with study evaluations or recently treated skin cancer were also excluded, as were those with damaged skin at or in proximity to test sites (dermal irritation, active lesions, excessive hyperpigmentation or moles, tattoos, or other abnormalities).

Assessments included skin hydration (Corneometer CM 825, Courage and Khazaka), skin barrier transepidermal water loss (TEWL, Dermalab Evaporimeter, Cortex Technology), skin thickness measured by ultrasound (Dermalab USB ultrasound 20 MHz, Cortex Technology), cutaneous tolerability evaluated by a dermatologist (0=none to 3=severe), clinical scoring of roughness (0=very soft skin to 9=not soft skin, very rough texture) and dryness (10-point visual analog scale), and a self-evaluation questionnaire to be answered by the participants.

Descriptive statistics were collected and reported. Changes from baseline in tolerability, clinical scoring, ultrasound, corneometer, and TEWL results were analyzed by paired *t*-test. If normality failed, Wilcoxon signed-rank test was used to assess differences. Binomial law test was used on percentages of participants with favorable responses from the questionnaire. For *n*=50, the minimum percentage of favorable responses for statistical significance was calculated at 69.3%. Statistical significance for all evaluations was declared if the 2-tailed *P* value was 0.05.

RESULTS

A total of 54 participants with self-perceived sensitive skin and dermatoporosis aged 65 years to 82 years participated, with demographics as shown in Table 1.

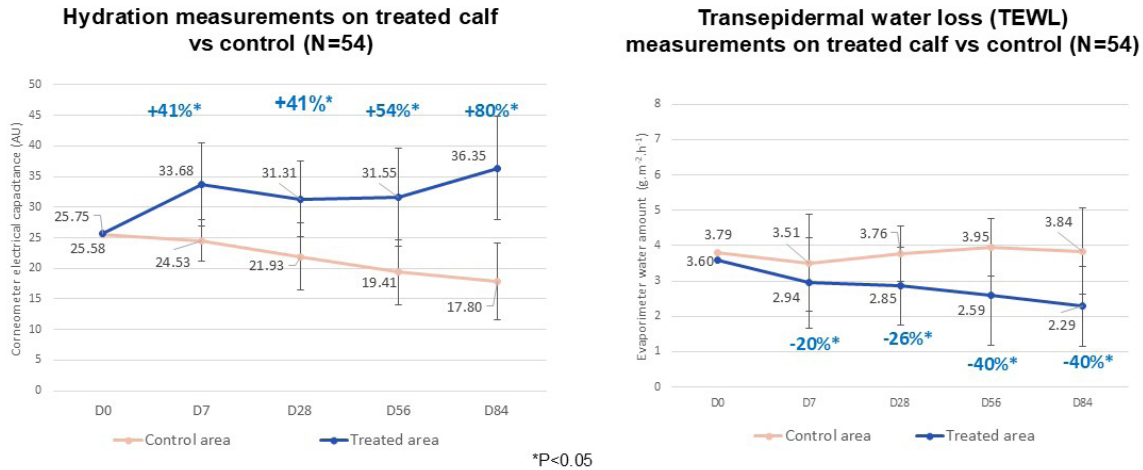
As expected, hydration and TEWL values were improved from baseline with the cream vs control (*P*<0.05 from day 7 to week 12, Figure 1). In a separate study, hydration occurred rapidly, with observable increases as early as 1 hour after a single application. In addition, the cream reduced water loss compared to the untreated control area.

There was a gradual increase in skin thickness (Figure 2), with inner forearm thickness increasing from a mean of 907.06µm at day 0 to 950.08 µm on day 84 (*P*<0.05). The visualization shows increased lighter colors, indicating improvements primarily in the epidermis and dermis tissues but also observable in the subdermal layer (Figure 2).

TABLE 1.

Participant Demographics; All Had Sensitive Skin	
Gender	
Male	9 (17%)
Female	45 (83%)
Age, mean (range)	68 years (65-82 years)
Ethnicity	
Caucasian/White	29 (54%)
Black/African American	12 (22%)
Hispanic/Latin American	10 (18.5%)
Asian/Indian	1 (2%)
Other	2 (4%)
Phototype	
I	4 (7%)
II	24 (44%)
III	15 (28%)
IV	4 (7%)
V	3 (6%)
VI	4 (7%)

FIGURE 1. Twice-daily cream application significantly improves skin hydration and barrier function vs control at all timepoints.



AU=arbitrary unit; TEWL=transepidermal water loss. *P<0.05.

FIGURE 2. Significant increase in skin thickness on ultrasound (A) graph of mean dermal thickness and (B) ultrasound showing increase in dermal thickness from day 0 to day 84 in a representative participant. The epidermis emits white/yellowish color (high intensity), the dermis emits a mix of colors, and the subcutaneous fat and muscle fibers emit dark green/black (low intensity).

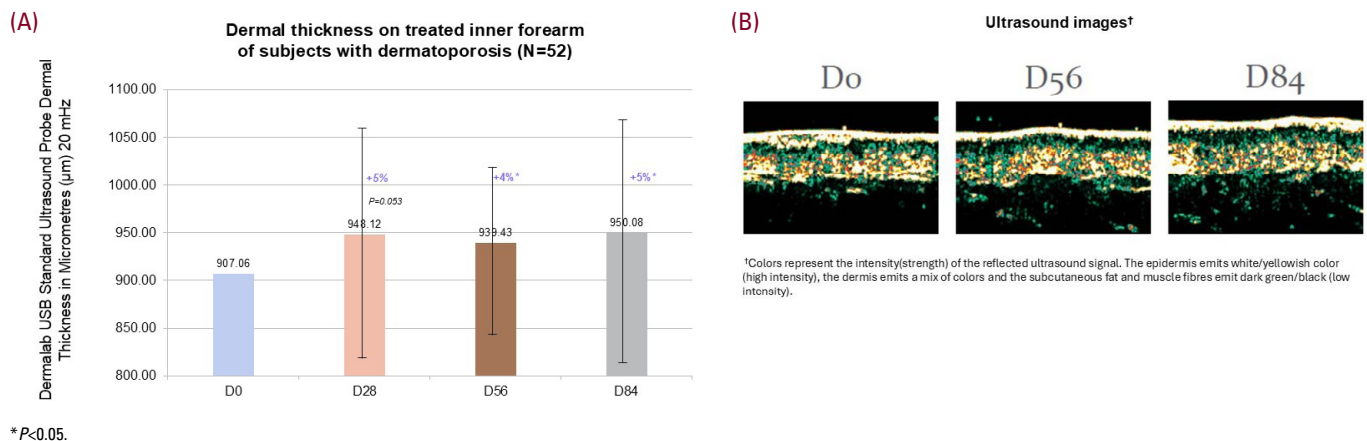
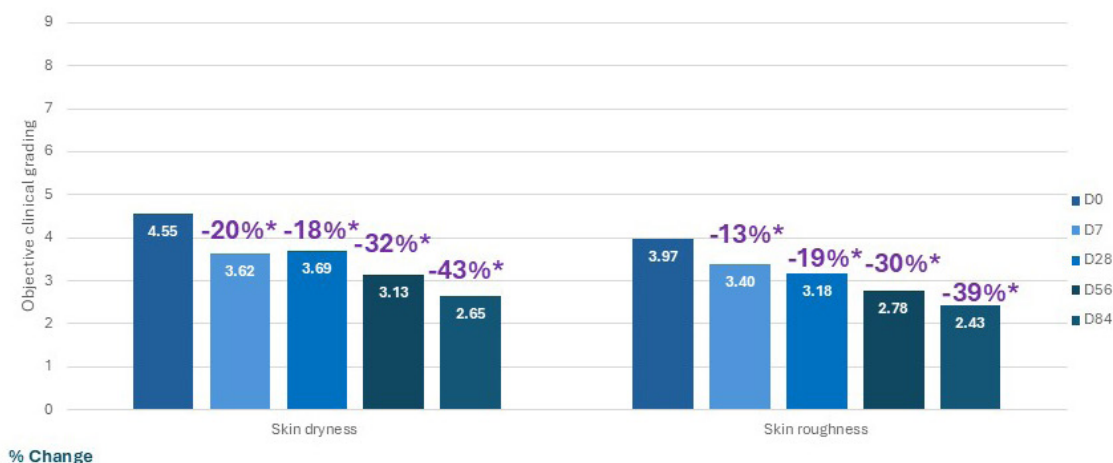
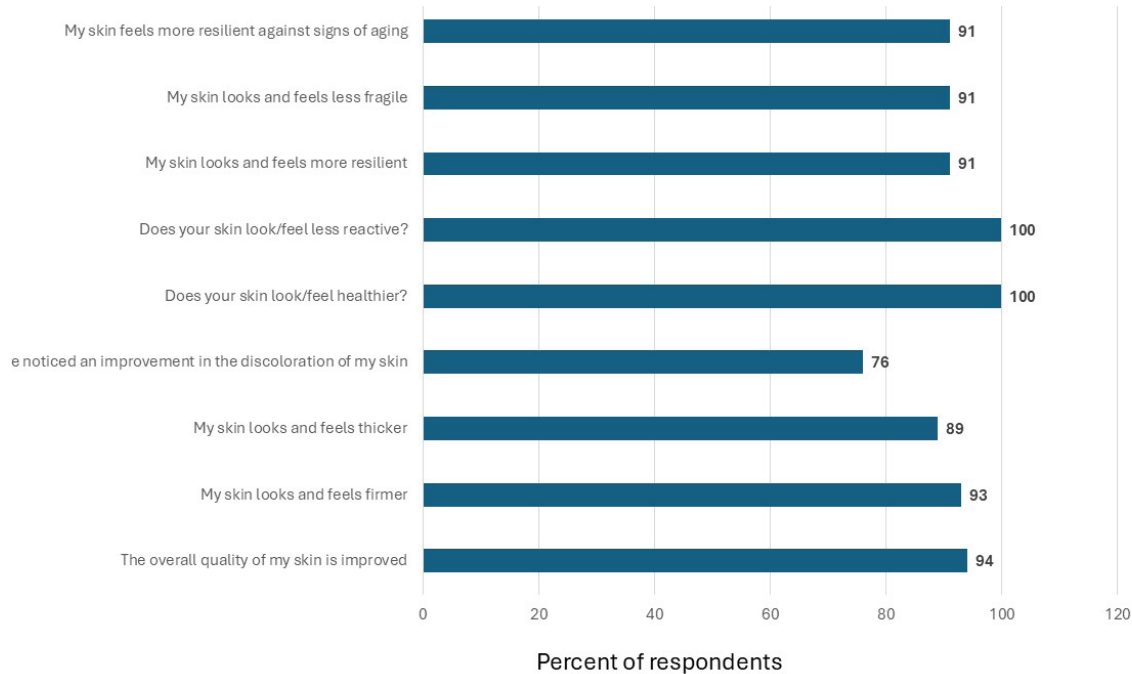


FIGURE 3. Investigator evaluation of improvements in skin dryness and roughness throughout the study period.



*P<0.05.

FIGURE 4. Results from participant questionnaire at week 12.

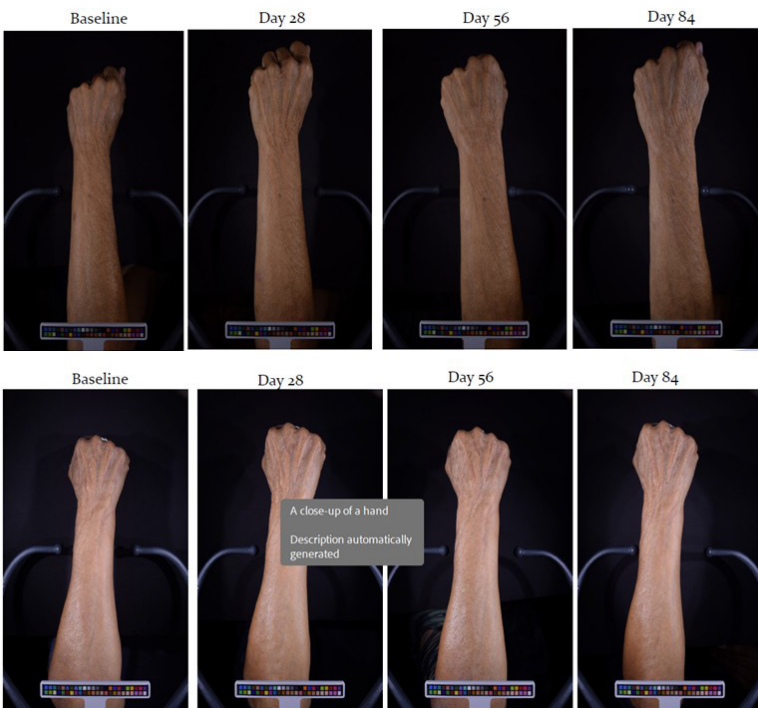


Four-point scale, answers given from “likely agree” to “strongly agree.”

The cream visibly improved skin dryness and tactile roughness on treated areas of skin in participants with dermatoporosis (Figure 3). Further, participants reported that their skin felt soothed from dryness as early as 1 week of twice-daily use. As shown in Figure 3, clinical grading showed a mean decrease of 1.9 points compared to baseline and a decrease of 1.5 in skin roughness at day 84.

Questionnaire results and correlation with improvements in clinical grading. At week 1, participants reported skin smoothness was improved (94%), skin quality was better (93%), their skin felt more hydrated (93%), and they noticed an overall improvement in skin (89%). Further, they reported the cream had good cosmetic qualities and they perceived their skin to look/feel healthier (96%) and less reactive (93%). At 4 weeks, >90%

FIGURE 5. Clinical photos of participants treated with the cream.



of participants reported improvements in overall appearance, skin quality, hydration and smoothness, firmness of skin, youthful appearance, and better skin tautness. Results on the questionnaire consistently improved, and Figure 4 shows the excellent participant satisfaction reported in the questionnaire at week 12.

Safety

The cream was found to have good tolerability with no related adverse events and no significant changes in cutaneous tolerability (erythema, edema, dryness, scaling, and peeling). Additionally, no potential for dermal irritation or allergic contact sensitization was observed.

DISCUSSION

Dermatoporosis is an increasingly recognized condition of chronic fragility of aging skin due to impairment of the skin's protective mechanical function.^{3,5} Consistent skin care can help to address dermatoporosis by supporting a healthy epidermal barrier and preserving skin integrity. This support may be particularly important for individuals with sensitive skin (an estimated 26% to 54% of studied populations in various countries), who often have stinging, burning, and itching that can be triggered by a number of environmental factors.⁸ Understanding key signs of aging/dermatoporosis skin can be used to tailor skincare solutions for patients; for skin atrophy, clinicians can target non-functioning senescent cells resulting in increased collagen production and promoting cellular turnover and proliferation, and for skin dryness, increasing skin surface hydration and decreasing TEWL.⁹⁻¹¹ Improvements in skin barrier function and exfoliation to allow product penetration can also ameliorate skin dryness, and increased collagen and elastin production translates to better skin elasticity.⁹⁻¹¹

In this proof-of-concept study with individuals presenting a variety of skin types and sensitive dermatoporotic skin, this novel cream improved and maintained skin thickness after 8 and 12 weeks of twice-daily use and was associated with an excellent level of participant satisfaction and overall local tolerability. This shows that an intervention with a consistent supportive skincare regimen can help prevent progression of dermatoporosis and sustain skin integrity.

Improvements in understanding the physiologic processes involved in dermatoporosis have been translated to new technology in moisturizing formulations. This study shows that novel ingredients such as microdosed mandelic acid and *Centella asiatica* formulated in a cream adapted to sensitive skin, can provide a gentle yet clinically effective solution for dermatoporosis-prone skin. It demonstrates the importance of skin care in protecting aging skin and supporting healthy skin function and the likelihood of better outcomes with increased awareness and early recognition.

CONCLUSION

A novel formulation adapted to sensitive skin and including 2 dedicated ingredients to address early "dermatoporotic" skin signs has shown to have a rapid onset and to be very efficient and well-tolerated. This product will bring a new cosmetic solution specifically adapted for aging patients with early "dermatoporotic" skin.

DISCLOSURES

All authors are employees of Galderma.

REFERENCES

1. Romano F, Serpico D, Cantelli M, et al. Osteoporosis and dermatoporosis: A review on the role of vitamin D. *Front Endocrinol (Lausanne)*. 2023;14:1231580.
2. Wollina U, Lotti T, Vojvotić A, et al. Dermatoporosis - the chronic cutaneous fragility syndrome. *Open Access Maced J Med Sci*. 2019;7:3046-3049.
3. Kaya G, Saurat JH. Dermatoporosis: A chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology*. 2007;215:284-294.
4. Widgerow AD, Ziegler M, Garruto JA, et al. Novel strategy for strengthening dermatoporotic skin by managing cellular senescence. *J Drugs Dermatol*. 2024;23:748-756.
5. Dyer JM, Miller RA. Chronic skin fragility of aging: Current concepts in the pathogenesis, recognition, and management of dermatoporosis. *J Clin Aesthet Dermatol*. 2018;11:13-18.
6. Chin T, Lee XE, Ng PY, et al. The role of cellular senescence in skin aging and age-related skin pathologies. *Front Physiol*. 2023;14:1297637.
7. Griffiths TW, Watson REB, Langton AK. Skin ageing and topical rejuvenation strategies. *Br J Dermatol*. 2023;189:i17-i23.
8. Duarte I, Silveira J, Hafner MFS, et al. Sensitive skin: Review of an ascending concept. *An Bras Dermatol*. 2017;92:521-525.
9. Ratz-Lyko A, Arct J, Pytkowska K. Moisturizing and antiinflammatory properties of cosmetic formulations containing centella asiatica extract. *Indian J Pharm Sci*. 2016;78:27-33.
10. Healthline. Mandelic acid. Accessed October, 2024. <https://www.healthline.com/health/mandelic-acid>
11. Diniz LRL, Calado LL, Duarte ABS, de Sousa DP. Centella asiatica and its metabolite asiatic acid: Wound healing effects and therapeutic potential. *Metabolites*. 2023;13(2):276.

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ONE SCRIPT
ONE 50G PUMP
ONE CO-PAY

Not an actual patient.



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



The first & only 3-in-1 topical acne treatment with 3 mechanisms of action for patients 12 years of age and older^{1,2 *}

*The clinical significance concerning the mechanism of action for clindamycin, adapalene, and benzoyl peroxide in acne treatment remains unknown.

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INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

CABTREO is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS

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

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

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

Skin Irritation and Allergic Contact Dermatitis: Stinging/burning/pain, erythema, dryness, irritation, exfoliation, and dermatitis may occur with use of CABTREO and may necessitate discontinuation.

Weather extremes, such as wind or cold, may be irritating to patients under treatment with CABTREO. Depending upon severity, patients can use a moisturizer, reduce frequency of application, or discontinue use. Avoid applying CABTREO to areas of broken, eczematous, or sunburned skin, and concomitant use with other potentially irritating topical products. Avoid use of "waxing" as a depilatory method on skin treated with CABTREO.

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

Use CABTREO with caution in patients receiving neuromuscular blocking agents.

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

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

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

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

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

CABTREO is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS

Hypersensitivity

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

Colitis

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

Photosensitivity

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

Skin Irritation and Allergic Contact Dermatitis

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

ADVERSE REACTIONS

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

Clinical Trials Experience

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

In two multicenter, randomized, double-blind, vehicle-controlled clinical trials (Trial 1 and Trial 2), 363 adult and pediatric subjects 10 years of age and older with facial acne vulgaris were treated with CABTREO or vehicle topically once daily for 12 weeks. Adverse reactions reported by >1% of subjects treated with CABTREO and more frequently than subjects treated with vehicle are summarized in Table 1. These adverse reactions were mild (59%), moderate (36.4%), and severe (4.5%). Overall, 2.5% (6/242) of subjects discontinued CABTREO because of local skin reactions.

Table 1: Adverse Reactions Reported by >1% of Subjects with Facial Acne Vulgaris Treated with CABTREO (and More Frequently than Vehicle) in Trials 1 and 2		
Adverse Reactions N (%)		
	CABTREO N=242	Vehicle N=121
Application site pain ¹	33 (13.6)	1 (0.8)
Application site erythema ²	11 (4.5)	0
Application site dryness ³	10 (4.1)	1 (0.8)
Application site irritation	5 (2.1)	0

Table 1: Adverse Reactions Reported by >1% of Subjects with Facial Acne Vulgaris Treated with CABTREO (and More Frequently than Vehicle) in Trials 1 and 2		
Adverse Reactions N (%)		
	CABTREO N=242	Vehicle N=121
Application site exfoliation	4 (1.7)	0
Application site dermatitis	3 (1.2)	0

¹Application site pain also includes application site stinging and burning

²Application site erythema also includes erythema

³Application site dryness also includes xerosis

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

Neuromuscular Blocking Agents

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Clindamycin

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

Adapalene

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

Benzoyl peroxide

The systemic exposure of topical benzoyl peroxide is unknown. Based on published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure of the drug.

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

Data

Animal Data

Animal reproductive/developmental toxicity studies have not been conducted with CABTREO or benzoyl peroxide. Clindamycin phosphate administration during the period of organogenesis in pregnant rats and mice at oral doses of up to 600 mg/kg/day (192 and 96 times the MRHD), respectively, based on a mg/m² comparison) or subcutaneous doses of up to 200 mg/kg/day 64 and 32 times the MRHD, respectively, based on a mg/m² comparison) did not cause fetal malformations or fetotoxicity.

No malformations were observed in rats treated with oral adapalene doses of 0.15 to 5.0 mg/kg/day adapalene (up to 13 times the MRHD based on a mg/m² comparison). However, malformations were observed in rats and rabbits when treated with oral doses of ≥ 25 mg/kg/day adapalene (64 and 128 times the MRHD, respectively, based on a mg/m² comparison). Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits. Dermal adapalene embryofetal development studies in rats and rabbits at doses up to 6.0 mg/kg/day adapalene (up to 15 and 30 times the MRHD, respectively, based on a mg/m² comparison) exhibited no fetotoxicity and only minimal increases in skeletal variations (supernumerary ribs in both species and delayed ossification in rabbits).

Lactation

Risk Summary

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

Clindamycin

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

Adapalene

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

Benzoyl peroxide

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

Clinical Considerations

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

Pediatric Use

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

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

Geriatric Use

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

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Racial and Ethnic Representation in Atopic Dermatitis Clinical Trials

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disorder afflicting approximately 31.6 million people in the United States, with a disproportionate impact on racial and ethnic minorities who often experience greater disease severity. This study aims to analyze racial and ethnic representation in recent atopic dermatitis clinical trials. A search on clinicaltrials.gov identified 73 completed AD trials with results available from January 1, 2019, to May 13, 2024, and out of these, 68 trials involving 20,679 patients provided race and ethnicity data. Out of all clinical trial participants, 65.4% identified as White, 17.3% identified as Asian, 13.4% identified as Black or African American, 0.5% identified as American Indian or Alaskan Native, 0.4% identified as Native Hawaiian or Pacific Islander, and 1.3% identified as more than one race. Hispanic or Latino participants comprised 10.8% of the clinical trial population. This study highlights an increasing trend in the inclusion of African American/Black and Asian populations in AD clinical trials; however, Hispanic participants remain notably underrepresented despite increased ethnicity reporting. These disparities emphasize the necessity of diverse representation in AD clinical trials to ensure equitable treatment outcomes, especially given the higher disease prevalence in skin of color groups. Achieving equitable representation will improve the generalizability of trial results, enhance treatment access, and reduce health inequities. Greater inclusivity in AD clinical trials is crucial for understanding the safety, efficacy, and side effects of treatments across diverse populations and should be a cornerstone of dermatologic clinical research.

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INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder globally, with an estimated prevalence of 31.6 million people in the United States (US) alone.^{1,2} AD characteristically presents with dry and itchy skin prone to infection.³ Although the pathophysiology of AD is not fully understood, it is well established that genetic predisposition, skin barrier dysfunction, immune dysregulation, and environmental factors contribute to AD pathogenesis.⁴ With acute disease flares often featuring intensely pruritic papules, exudation, and peeling of the skin, AD is the primary contributor to skin-related disability.^{5,6} Prevalent in both children and adults, 80% of AD sufferers experience disease onset before the age of 6, with African American/Black and Hispanic children typically experiencing more severe disease than White children.^{7,8} Furthermore, there is a known higher disease prevalence among Black or African Americans compared to Whites, reported in 2019 as 19.3% vs 16.1% in children and 4.4% vs 2.1% in adults.⁹ AD can lead to considerable psychological

and emotional distress, significantly affecting self-esteem, quality of life, and career choices, especially in patients of color due to higher disease prevalence and severity.^{7,9,10}

The growing diversity in the US underscores the crucial need for inclusivity in dermatologic research, with the US Census Bureau projecting that approximately half of the US population will be comprised of Hispanic, African American/Black, or Asian individuals by 2050.¹¹ Racial minorities are frequently underrepresented in dermatology clinical trials, including those focused on conditions such as acne, alopecia, hidradenitis suppurativa, nail psoriasis, psoriatic arthritis, and the majority of laser therapy applications.¹²⁻¹⁷ A gap exists in the understanding of patient representation in atopic dermatitis clinical trials. Due to the well-documented underrepresentation of participants with skin of color in dermatologic studies and the higher incidence of atopic dermatitis among these groups, our goal is to assess racial and ethnic representation in clinical trials for AD.

MATERIALS AND METHODS

A search was conducted on May 14, 2024, of the clinical trials database (clinicaltrials.gov), an international registry maintained by the US National Library of Medicine, to locate clinical trials focused on AD. The search utilized the terms “atopic dermatitis” and “eczema” and was filtered to include only those with a “completed” status as of January 1, 2019, through May 13, 2024, and “with results” available. Studies were selected if they included participants from the US. Studies lacking data on both race and ethnicity were excluded. This methodology aligns with approaches used in previous research examining racial and ethnic representation in dermatologic clinical trials overall as well as clinical trials specifically investigating hidradenitis suppurativa.^{12,14} The extracted data included the study title, National Clinical Trials (NCT) number, total participant count, and details on race and ethnicity. Percentages for race and ethnicity were calculated based on the trials that provided this specific information.

RESULTS

A total of 73 trials were identified on clinicaltrials.gov. After excluding studies lacking race or ethnicity data, 68 trials with a total of 20,679 patients were retained. Of these, 68 trials included race data, and 46 included ethnicity data. The racial distribution among trial participants was as follows: White (65.4%), Asian (17.3%), Black or African American (13.4%), American Indian or Alaskan Native (0.5%), Native Hawaiian or Pacific Islander (0.4%), and more than 1 race (1.3%; Table 1). In comparison, the 2020 US census data reports a population distribution of 61.2% White, 12.4% Black or African American, 5.9% Asian, 1.1% American Indian or Alaska Native, 0.2% Native Hawaiian or Pacific Islander, and 10.6% 2 or more races (Figure 1).¹⁸ Regarding ethnicity, 10.8% of trial participants were Hispanic or Latino, compared to 19.5% of the US population per the 2020 census (Figure 2).¹⁸ Although these comparisons are limited by the inclusion of clinical trials not exclusively conducted in the US, it provides a useful reference point for assessing current

TABLE 1.
Representation of Race and Ethnicity in Atopic Dermatitis Clinical Trials Compared to United States Census Demographic Data

Demographic or Parameter	Number of Study Participants, <i>n</i>	Representation in Clinical Trials, <i>n</i> (%)	2020 US Census, (%)
Race	20,679		
White	--	13,515 (65.4%)	61.2%
Black/African American	--	2,778 (13.4%)	12.3%
Asian	--	3,574 (17.3%)	5.9%
American Indian or Alaska Native	--	96 (0.5%)	1.1%
Native Hawaiian or Pacific Islander	--	79 (0.4%)	0.2%
Two or More	--	272 (1.3%)	10.6%
Ethnicity	15,912		
Hispanic/ Latino	--	1,716 (10.8%)	19.5%
Non-Hispanic	--	14,042 (88.3%)	80.5%
Unknown	--	154 (0.1%)	--

FIGURE 1. Racial representation in Atopic Dermatitis Clinical Trials compared to United States Racial Distribution.

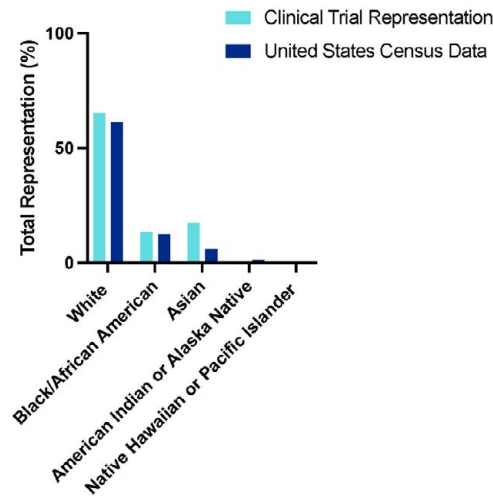
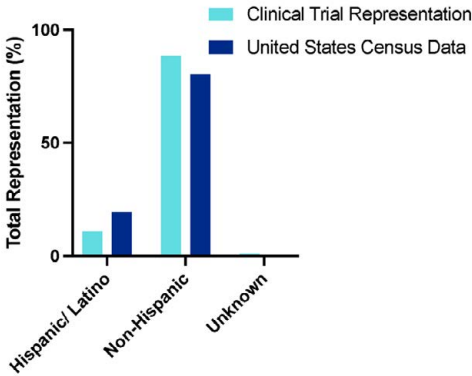


FIGURE 2. Ethnicity representation in Atopic Dermatitis Clinical Trials compared to National Ethnicity Distribution.



representation levels and for understanding the participant group from which current medical insights pertaining to AD are being derived.

DISCUSSION

This study provides a crucial, updated, and comprehensive analysis of racial and ethnic representation in recent AD clinical trials. Over the past 30 years, promoting the inclusion of women and underrepresented racial and ethnic minorities in clinical trials has been a major priority following the enactment of the National Institute of Health Revitalization Act in 1993.¹⁹ Given the genetic heterogeneity of AD among different racial and ethnic groups, achieving equitable representation in AD clinical trials is particularly important.⁹

Our data reveal an improving trend in representation among skin of color patients in recent years, especially among Black/African Americans. Reported AD prevalence among Black or African Americans ranges between 15.1% to 19.3%, with consistently higher prevalence than White Americans.^{9,20,21} Moreover, Black or African Americans are experiencing the greatest increase in eczema prevalence, rising from 10.1% to 18.4% between 1997 and 2018.²¹ In a prior study analyzing global phase II/III AD clinical trials published from January 2009 to July 2019, participants of African descent comprised only 8.9% of study participants.²² Another analysis of trials completed between January 2017 and December 2021 found Black/African Americans were underrepresented, comprising only 11.6% of the AD clinical trial patient population.¹⁴ Comparing these results to the current study, which found that Black or African American participants comprise 13.4% of clinical trial participants, highlights the continued progress made in recent years. While this is a notable improvement, representation exceeding the US population demographics is warranted for skin of color groups given the higher disease prevalence.

We found a surprisingly low representation of Hispanic or Latino patients in AD clinical trials despite a notable increase in the number of trials reporting ethnicity data.¹⁸ Research has shown AD is a major concern for Hispanic and Latino populations, especially children, with a prevalence as high as 25% in Latin American children.²³ Among a community that already encounters many barriers to healthcare, the impact on these children can be far-reaching, with a 3.4-fold increase in the likelihood of missing school due to AD in Hispanic children compared to their White counterparts.^{23,24} An analysis of US-only AD clinical trials from 2013 to 2021 found that 21.4% of participants were Hispanic or Latino, yet 72% of the trials analyzed failed to report ethnicity data, greatly undermining the statistical power of any reported numbers.^{19,25} Similarly, in another study looking at global AD clinical trials from 2009 to 2019, only 3.7% of participants identified as Hispanic, with a mere 15% of trials reporting ethnicity data.²² Our analysis found

more robust ethnicity reporting, with 63% of trials capturing ethnicity data, yet significant underrepresentation was evident, with only 10.8% of trial participants identifying as Hispanic.

Our analysis captured a considerable inclusion of Asian participants in AD clinical trials (17.3% vs the US Census reported 5.9%), well above and beyond demographic representation.¹⁸ The prevalence of AD is on the rise globally and is a growing concern, particularly in developing industrialized nations in Asia, with prevalence in children as of 2009 reported at 10 to 20%.²⁶ Asians and Pacific Islanders are 7 times more likely than Whites to receive an AD diagnosis during a dermatology office visit.⁹ The average prevalence of AD in specific Asian nations includes Korea (14.4%), China (12.9%), and Japan (9.9%).²⁶⁻²⁹ Prior studies have reported 10.3% and 16.2% of participants identifying as Asian or of Asian descent in US-based and global AD clinical trials, respectively.^{19,22} Our analysis incorporated global enrollment sites, with 47% of trials that enrolled participants outside the US and Canada featuring at least 1 clinical site in Asia. Despite being overrepresented based on US population demographics, the relatively high representation of Asians in AD clinical trials may reflect a prioritization by these nations to study a disease that features a unique phenotypic profile in Asian populations and afflicts many within the community.³⁰ Additionally, improved cost-effectiveness and the high availability of treatment-naïve patients have triggered a boom in clinical trials conducted in Asia.³¹ Sri Lanka and China have seen the largest increases, at 27.1% and 23.3% respectively, between 2008 and 2017, likely influencing our findings.³¹ Regardless, this increased focus on studying diseases among disproportionately impacted populations is a good benchmark to strive for with other populations similarly more prone to AD and featuring distinctive disease profiles.

Despite the higher disease prevalence in individuals with darker skin tones, a 2021 analysis of Google image results for dermatologic conditions found that only 4% of all AD Google image results featured darker skin tones.³² In skin of color, AD can appear as violaceous, ashen gray, or dark brown with perifollicular accentuation and annular lesions, differing from its presentation in lighter skin.³³ In Asian populations, the disease tends to present with more evident demarcation, lichenification, and more pronounced scale, appearing psoriasiform.³³ On a genetic mechanistic level there are differences seen among AD patients as well. The loss of function mutation in filaggrin, which is known to play an important role in AD pathogenesis, differs in Asian, European, and African populations.³⁴ The 3321delA mutation is seen in Asian populations but has not been identified in European populations.³⁴ The predominant mutations in Europe, R501X and E2422X, are rarely observed in African and Asian populations.³⁴ These differing phenotypic presentations and genetic variations highlight the importance of clinical trial representation for a comprehensive understanding

of the disease. Representation in clinical trials is also of paramount importance to furthering our understanding of the safety, efficacy, and side effects of treatments. By drawing such comparisons among patient populations, it is now known narrowband ultraviolet-B light treatment for AD requires larger doses in darker skin tones for comparable efficacy.³⁴ Furthermore, while considered effective for all skin types by many, research has shown that topical steroids are associated with an increased risk of hypopigmentation in skin of color patients.³⁵ Conversely, studies have demonstrated that pimecrolimus cream 1% is equally effective regardless of ethnicity.³⁵ In our analysis, nearly two-thirds of AD clinical trial participants were White despite higher disease prevalence rates in skin of color groups. While these findings align with US Census population demographics, they do not account for higher disease prevalence within Black/African American, Hispanic, and Asian populations or the expected increased diversity of the future US population. To account for the distinct responses to new treatments among patients from different racial and ethnic backgrounds, it is essential to conduct randomized controlled trials (RCTs) that include a diverse patient population.²²

Strengths of this study include our comprehensive analysis of all recent clinical trials related to AD involving US participants listed on clinicaltrials.gov. Additionally, the high level of reporting of race and ethnicity data among AD trials allowed for a robust and reliable analysis. However, there are a few limitations to this study. Many comparisons to existing analyses of clinical trial representation differ slightly in their inclusion and exclusion criteria, making direct comparisons challenging. Additionally, clinical trial enrollment in 2020 and 2021 was likely impacted by the COVID-19 pandemic. Finally, due to variability in reported AD prevalence among different races and regions, accurately comparing clinical trial representation to actual prevalence rates is difficult and as such we compared clinical trial representation to US Census data.

CONCLUSION

Our analysis highlights the important progress that has been made toward increased representation among African American/Black and Asian populations in AD clinical trials. Conversely, despite increased ethnicity reporting, our assessment uncovered significant underrepresentation of Hispanic participants within AD clinical trials, an area requiring greater focus for improvement. These findings are particularly relevant due to the increased disease prevalence among African American/Black, Asian, and Hispanic populations and the unique pathophysiological mechanisms among different racial and ethnic groups.^{4,9,30,35} Given the ongoing disparities in representation in AD clinical trials, the importance of greater inclusion must continue to be emphasized and strived for, especially in conditions like AD where there is increased disease prevalence in skin of color populations. Greater inclusion is

crucial for enhancing treatment access for the increasingly diverse population, improving the generalizability of clinical trial results, increasing access to cutting-edge treatments and technologies, and reducing health inequity.¹⁴ It is our recommendation that equitable representation be a cornerstone of clinical trial research for all dermatologic conditions.

DISCLOSURES

The authors have no conflicts of interest to declare.

REFERENCES

1. Eczema Stats. National Eczema Association. Updated 2024. <https://nationaleczema.org/research/eczema-facts/#:~:text=An%20estimated%2016.5%20million%20US,with%20moderate%20to%20severe%20disease.&text=80%25%20of%20individuals%20affected%20by,to%206%20years%20of%20age.&text=AD%20is%20not%20solely%20a,report%20adult%20onset%20of%20symptoms>. Accessed June 4, 2024.
2. Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: Clinical implications. *Allergy Asthma Proc*. 2019;40(2):84-92. doi:10.2500/aap.2019.40.4202
3. Evans VNHASJ. *Eczema*. StatPearls Publishing; 2021. Accessed June 4, 2024.
4. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-Variations in epidemiology, genetics, clinical presentation, and treatment. *Exp Dermatol*. 2018;27(4):340-357. doi:10.1111/exd.13514
5. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. *Br J Dermatol*. 2021;184(2):304-309. doi:10.1111/bjd.19580
6. Hadi HA, Tarnizi AI, Khalid KA, et al. The epidemiology and global burden of atopic dermatitis: a narrative review. *Life (Basel)*. 2021;11(9):doi:10.3390/life11090936
7. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis*. 2014;25(3):107-14. doi:10.1097/der.0000000000000034
8. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic dermatitis in america study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *J Invest Dermatol*. 2019;139(3):583-590. doi:10.1016/j.jid.2018.08.028
9. Brunner PM, Guttman-Yassky E. Racial differences in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2019;122(5):449-455. doi:10.1016/j.anai.2018.11.015
10. Sibbald C, Drucker AM. Patient burden of atopic dermatitis. *Dermatol Clin*. 2017;35(3):303-316. doi:10.1016/j.det.2017.02.004
11. US Census Bureau PD. Projected population by sex, race, and Hispanic origin for the United States, main series: 2022-2060. In: np2023-t4, editor. Census.gov2023.
12. Elhage KG, Davis MS, Hakimi M, et al. Ethnoracial representation in hidradenitis suppurativa clinical trials. *Arch Dermatol Res*. 2023;315(6):1793-1796. doi:10.1007/s00403-022-02510-4
13. Lebhar J, Jacobs J, Rundle C, Suggs A. Skin of color representation in laser therapy-based clinical trials. *Dermatol Surg*. 2023;49(8):812-813. doi:10.1097/dss.0000000000003834
14. Mineroff J, Nguyen JK, Jagdeo J. Racial and ethnic underrepresentation in dermatology clinical trials. *J Am Acad Dermatol*. 2023;89(2):293-300. doi:10.1016/j.jaad.2023.04.011
15. Price KN, Hsiao JL, Shi VY. Race and ethnicity gaps in global hidradenitis suppurativa clinical trials. *Dermatology*. 2021;237(1):97-102. doi:10.1159/000504911
16. Ricardo JW, Qiu Y, Lipner SR. Racial, ethnic, and sex disparities in nail psoriasis clinical trials: a systematic review. *Skin Appendage Disord*. May 2022;8(3):171-178. doi:10.1159/000520469
17. Shwe S, Nguyen C, Bhutani T. Racial disparities in clinical trials of biologic treatments for psoriatic arthritis. *J Am Acad Dermatol*. Oct 2022;87(4):910-912. doi:10.1016/j.jaad.2021.08.038
18. Data from: 2020 Census Demographic and Housing Characteristics File. 2020. <https://data.census.gov/all?d=DEC+Demographic+and+Housing+Characteristics>
19. Arbuiso S, Gorgy M, Shah S, et al. Review of ethnoracial representation in clinical trials (phases 1 through 4) of atopic dermatitis therapies. *Cutis*. 2022;109(4):233-234. doi:10.12788/cutis.0496
20. Williams HC, Pembroke AC, Forsdyke H, et al. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol*.

- 1995;32(2 Pt 1):212-7. doi:10.1016/0190-9622(95)90128-0
21. Choragudi S, Yosipovitch G. Trends in the prevalence of eczema among US children by age, sex, race, and ethnicity from 1997 to 2018. *JAMA Dermatol.* 2023;159(4):454-456. doi:10.1001/jamadermatol.2022.6647
22. Price KN, Krase JM, Loh TY, et al. Racial and ethnic disparities in global atopic dermatitis clinical trials. *Br J Dermatol.* 2020;183(2):378-380. doi:10.1111/bjd.18938
23. Andrus E. Dermatologic Concerns and Disparities Among Members of the Hispanic Community. <https://www.dermatologytimes.com/view/dermatologic-concerns-and-disparities-among-members-of-the-hispanic-community>. Accessed June 12, 2024.
24. Wan J, Margolis DJ, Mitra N, et al. Racial and ethnic differences in atopic dermatitis-related school absences among US children. *JAMA Dermatol.* 2019;155(8):973-975. doi:10.1001/jamadermatol.2019.0597
25. Suresh K, Chandrashekar S. Sample size estimation and power analysis for clinical research studies. *J Hum Reprod Sci.* 2012;5(1):7-13. doi:10.4103/0974-1208.97779
26. Cheng J, Wu JJ, Han G. Epidemiology and characterization of atopic dermatitis in east asian populations: a systematic review. *Dermatol Ther (Heidelb).* 2021;11(3):707-717. doi:10.1007/s13555-021-00516-w
27. Baek JO, Hong S, Son DK, et al. Analysis of the prevalence of and risk factors for atopic dermatitis using an ISAAC questionnaire in 8,750 Korean children. *Int Arch Allergy Immunol.* 2013;162(1):79-85. doi:10.1159/000351403
28. Furue M, Yamazaki S, Jimbow K, et al. Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study. *J Dermatol.* 2011;38(4):310-20. doi:10.1111/j.1346-8138.2011.01209.x
29. Guo Y, Li P, Tang J, et al. Prevalence of atopic dermatitis in Chinese children aged 1-7 ys. *Sci Rep.* 2016;6:29751. doi:10.1038/srep29751
30. Noda S, Suárez-Fariñas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol.* 2015;136(5):1254-64. doi:10.1016/j.jaci.2015.08.015
31. Ali S, Egunisola O, Babar ZUD, et al. Clinical trials in Asia: A World Health Organization database study. *Perspect Clin Res.* 2019;10(3):121-124. doi:10.4103/picr.PICR_109_18
32. Kurtti A, Austin E, Jagdeo J. Representation of skin color in dermatology-related Google image searches. *J Am Acad Dermatol.* 2022;86(3):705-708. doi:10.1016/j.jaad.2021.03.036
33. Gan C, Mahil S, Pink A, Rodrigues M. Atopic dermatitis in skin of colour. Part 2: considerations in clinical presentation and treatment options. *Clin Exp Dermatol.* 2023;48(10):1091-1101. doi:10.1093/ced/llad162
34. Sachdeva M, Joseph M. Dermatology: how to manage atopic dermatitis in patients with skin of colour. *Drugs Context.* 2022;11doi:10.7573/dic.2021-12-1
35. Chiricozzi A, Maurelli M, Calabrese L, et al. Overview of atopic dermatitis in different ethnic groups. *J Clin Med.* 2023;12(7)doi:10.3390/jcm12072701

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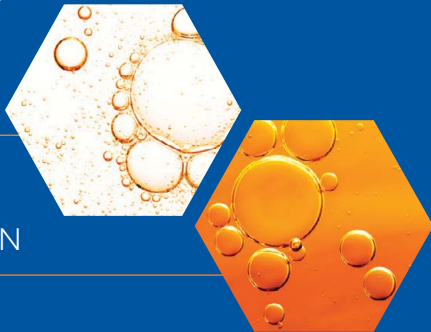
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Clinical Utility of TRPV1 Modulation for Skincare Sensitivity

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ABSTRACT

The Transient Receptor Potential Vanilloid 1 (TRPV1) protein, originally recognized for its role in modulating peripheral sensory neurons and transmitting pain and itch signals, has been increasingly implicated in various dermatological processes. TRPV1 is widely expressed in skin cells, including keratinocytes, fibroblasts, and mast cells, making it a promising target for treating inflammatory skin diseases, skin sensitivity, wound healing, and aging. Activation of TRPV1 by environmental stressors, such as heat and ultraviolet (UV) exposure, induces pro-inflammatory responses and contributes to the degradation of collagen, exacerbating conditions like chronic itch, atopic dermatitis, and dermatoheliosis. This study evaluates the effectiveness of topical formulations containing a sea anemone biomimetic peptide (SABMP), a TRPV1 antagonist, in improving skin texture, elasticity, hydration, and rejuvenation. Clinical trials involved participants with self-perceived sensitive skin, who applied the test formulations for 4 weeks. Results demonstrated significant improvements in skin texture, elasticity, and reductions in erythema and fine lines, highlighting the potential of TRPV1-targeting peptides as an alternative to conventional treatments like retinoids and Vitamin C, particularly for individuals with sensitive skin. The study underscores the clinical utility of TRPV1 antagonism in skin care, offering a novel approach to managing skin sensitivity and aging. These findings suggest that TRPV1-targeting peptides can provide a safe and effective treatment modality for enhancing skin quality and addressing conditions such as atopic dermatitis, rosacea, and acne.

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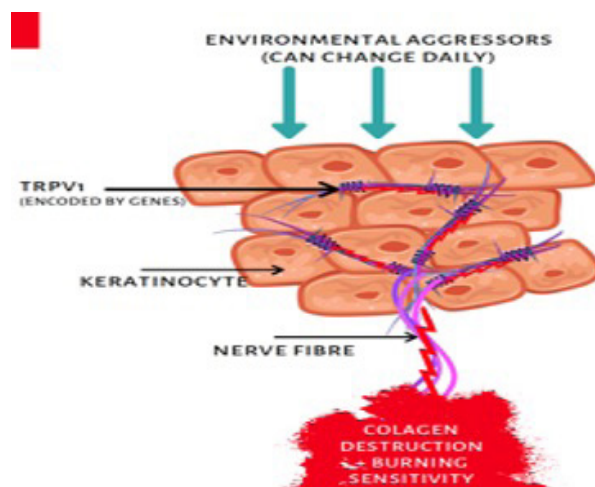
INTRODUCTION

Transient receptor potential vanilloid 1 protein (TRPV1) first became significant because of its ability to modulate peripheral sensory neurons and transmit pain and itch signals. This novel discovery was the recipient of the Nobel Prize for Physiology or Medicine in 2021. Studies before, and since then, have shown that TRPV1 is widely expressed in keratinocytes, skin fibroblasts, dermal vascular endothelial cells, dendritic cells, sweat gland duct cells, and mast cells warranting a curiosity about its utility for inflammatory skin diseases, skin sensitivity, wound healing, and cutaneous aging.^{1,2} Stimulated by heat, capsaicin, and acidic environments, TRPV1 creates a proinflammatory environment marked by interleukin (IL)-31 known to cause pruritus. TRPV1 also releases substance P (SP) and calcitonin gene-related peptide (CGRP) which are vasodilators that lead to local edema, erythema, and inflammatory mediators.

Because of TRPV1's widespread presence in the skin, antagonists or down regulators of this receptor can be used for common dermatological concerns and conditions (Figure 1). Chronic itch, for instance, can develop from a combination of neuropathic,

psychogenic, and dermatological diseases as seen in atopic dermatitis (AD), prurigo nodularis, and psoriasis.³ Rhytids

FIGURE 1. TRPV1 activation in the skin and its impact on sensitization and aging.



and dermatoheliosis, aging markers from the degeneration of collagen and elastin, are partially regulated by TRPV1 via the ultraviolet (UV) and heat-induced pathways of aging. Vanilloid receptors of the nociceptive C - fibers are activated by noxious stimuli and provoke the release of neuropeptides as substance P and CGRP. Constant activation of TRPV1 caused by environmental stressors leads to the upregulation of enzymes that destroy collagen.⁴

The clinical signs of sensitive skin are provoked by reactivity factors from the environment which include wind, sun, cold weather, abrupt changes in temperature, pollution, hydrocarbons, and UV exposure. Around 15 to 20% of women have sensitive skin to these environmental factors. Topical factors like hard water and cosmetics along with internal factors like life stressors, menstruation, and consumption of spicy foods also contribute to skin sensitivity exacerbation.

Oral TRPV1 antagonists were studied in phase 1 clinical trials but discontinued due to marked hyperthermia driving the need for topical formulations that target the channel. The sea anemone bio-mimetic peptide (SABMP) introduced in these topical formulations described here within, has been found to block and downregulate the TRPV1 receptor to provide analgesic effects by inhibiting capsaicin-induced currents,³ exemplifying how biomimicry can foster sustainable innovation by mimicking efficient biological systems. Our goal was to evaluate the safety and effectiveness of using four topical formularies (Dr Rossi DERM MD™ Seoul, Korea) containing SABMP, an antagonist of the TRPV1 receptor, to improve skin texture, elasticity, hydration, and rejuvenation in facial and undereye skin. Unique to these formulations was also the absence of common contact sensitizers and irritants such as fragrance mix I/II, parabens, formaldehyde-releasing- preservatives, sodium lauryl sulfate, retinol, or ascorbic acid.

MATERIALS AND METHODS

Study inclusion criteria consisted of healthy male and female volunteers aged 30 to 65 years with all skin phototypes, recruited based on self-perceived sensitive skin. Exclusion criteria included pregnancy; allergies; active skin diseases; inflammatory conditions; diabetes; use of anti-inflammatory medications, antihistamines, steroids, acne medications, hydrocortisone, or retinoids; recent chemical peels; cosmetic medical procedures; ocular disorders (for eye cream study); epilepsy (for eye cream study); sleep disorders (for eye cream study); or any condition deemed by the investigator to compromise subject safety or confound study results. Each participant reported self-perceived sensitive skin and facial redness, with specific baseline scores for fine lines and wrinkles (grade 3-8) and redness (grade 1-3). Participants were required to comply with study protocols and attend clinical study visits.

Participants with self-assessed sensitive skin and facial redness were included, determined through a Lactic Acid “Sting” test (participants who reacted to the test with a score minimum of 3), and testers with facial redness who scored at least 2 (mild erythema, definite redness) by expert grader assessments.

All participants provided written informed and photo consent along with a commitment to abstain from facial treatments such as neurotoxins, dermal fillers, microdermabrasion, peels, laser treatments, intense pulsed light (IPL) therapy, and tightening procedures during the study period. Topical retinol or retinoids as well as other active skincare compounds were discontinued before commencement depending on the specific product being tested. Compliance was ensured through verbal instructions, phone reminders, and confirmation at the first visit. Participants were allowed to use their usual cleanser without restriction, including sulfate-based cleansers. Outcome measures, assessed at baseline and week 4, included evaluations of fine lines, rhytids/wrinkles, redness, skin tone, texture, elasticity using a Cutometer^{®4,5} (Courage & Khazaka Electronic GmbH), trans-epidermal water loss (TEWL) using a Tewameter^{®6} (Courage & Khazaka Electronic GmbH) and erythema or dark circles (for eye cream study) using a Colorimeter^{®7} (Courage & Khazaka Electronic GmbH). Participants arrived with a clean face, acclimated for 20 minutes in an environment room with maintained temperature and humidity, and applied the test product after evaluations. Digital images with VISIA[®] (Canfield Scientific, New Jersey) photography were taken on clean skin post-evaluation and analyzed using VECTRA[®]. $P < 0.05$ was defined as statistically significant. Four clinical trials were conducted with each topical formulation studied independently to assess for individual effectiveness.

Safety Assessment of Test Articles

All 4 test articles used in the clinical trials first underwent Repeated-Insult Patch Testing (RIPT) on sensitive skin participants, affirming their safety and non-irritating properties. All 4 products achieved dermatologist approval and received affirmation for hypoallergenic, non-comedogenic, and safe for sensitive skin properties.

Efficacy and In-Use Safety Assessment

Topical Serum

The proprietary test article, supplied by the sponsor, was applied twice daily (AM and PM) for 4 weeks by study participants. Participants were instructed to gently massage 4 to 6 drops onto the face and neck after cleansing. At the baseline visit, each subject was shown how to apply the serum to standardize the application process. Skin attributes including fine lines/wrinkles, redness, skin tone, and texture were evaluated by an expert grader and by digital photos via Canfield’s VISIA imaging tool at baseline and week 4. Erythema was measured with a Colorimeter[®].

Topical Eye Emulsion

Participants were directed to abstain from using any eye cream products other than those supplied for the study. They were permitted to use their usual moisturizer on their face, except in the areas where the eye cream was administered. The test article was applied twice daily (AM and PM) for 4 weeks using the pad of the ring finger, dabbing lightly around both eyes. An expert grader assessed fine lines/wrinkles, under-eye dark circles, and puffiness using the infraorbital scale. Dark circles were assessed using a Colorimeter®.

Topical Night Concentrate

Participants were instructed to discontinue any previous night cream usage. They applied their regular morning moisturizer and continued with their eye makeup and cosmetics as desired. The test article was applied daily for four weeks by gently massaging the face and neck before bedtime. An expert grader assessed skin tone, skin brightness, and erythema using the VISIA Skin Analysis.

Topical Lactic Acid Essence

The test article was applied daily in the morning and night after cleansing but before any other topicals like sunscreen, moisturizer, or makeup use. The formulation was applied by gently massaging onto the face and neck. Graders assessed facial redness at baseline and week 4. TEWL was measured using a Tewameter®, and redness using a Colorimeter®.

RESULTS

Serum

In the face serum trial, significant improvements were observed after 4 weeks compared to baseline. Grader-assessed parameters including facial fine lines/wrinkles, erythema, skin tone, and skin texture showed statistically significant improvements ($P<0.05$) in the 4-week clinical trial involving 31 participants, demonstrating improvements in skin texture (63%), elasticity (18%), reduction in erythema (21%), and fine lines/wrinkles (12%) from baseline.

TABLE 1.

Compiled Visual Grading Comparison of Various Attributes of Facial Serum Treatment										
Attribute	Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment P-value	Percent Change Mean	Percent Change Subject	Number Approved	Percent Improved
Fine Lines/Wrinkles	Facial Serum	Baseline	32	4.61	--	--	--	--	--	--
--	--	Week 4	31	4.13	-0.53	<.0001	-11.5%	-12.7%	21	67.7%
Redness	Facial Serum	Baseline	32	1.55	--	--	--	--	--	--
--	--	Week 4	31	1.21	-0.32	.0012	-20.9%	-27.3%	16	51.6%
Skin Tone	Facial Serum	Baseline	32	4.50	--	--	--	--	--	--
--	--	Week 4	31	4.08	-0.40	.001	-9.0%	-8.1%	14	45.2%
Skin Texture	Facial Serum	Baseline	32	1.81	--	--	--	--	--	--
--	--	Week 4	31	0.69	-1.15	.0001	-63.2%	-67.2%	30	96.8%

FIGURE 2A. VISIA® digital imaging of lines and wrinkles at baseline and after 4 weeks of use of face serum.



Elasticity, measured with the Cutometer®, demonstrated a notable improvement at week 4 compared to baseline ($P<0.05$). However, erythema measured with the Colorimeter® and trans-epidermal water loss measured with the Tewameter® showed moderate improvements that did not reach statistical significance.

VISIA image analysis showed an overall reduction in wrinkles and decreased skin texture roughness without statistical significance. Although no significant changes were observed in the number and area of visible spots, reductions in pore count and area were noted, alongside increased background intensity behind pores, indicating improved skin lightening and brightening effects (Figure 2A).

Clinical Trial Summary

In the 4-week clinical trial involving 31 participants aged 32-66 of various ethnicities, the serum demonstrated improvements in skin texture (63%), elasticity (18%), reduction in erythema (21%), and fine lines/wrinkles (12%) from baseline. Participant feedback indicated high satisfaction with perceived improvements in skin rejuvenation, smoothness, and overall skin quality (Table 1).

FIGURE 2B. VISIA® digital imaging of facial redness at baseline and after 4 weeks of use of face serum.

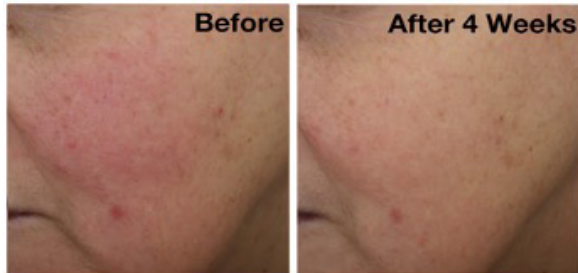
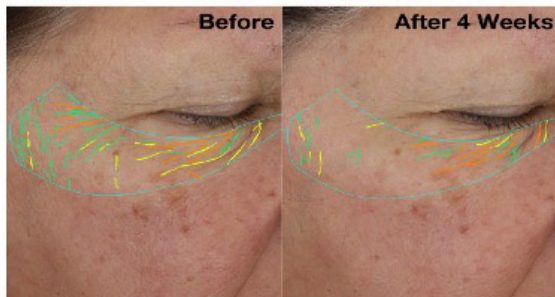


FIGURE 3. VISIA® digital imaging of lines and wrinkles in the eye area at baseline and after 4 weeks use of eye emulsion.



VISIA Skin Analysis of 16 participants showed 31% experienced a lightening or brightening effect on their skin, with a 0.6% improvement in skin brightness noted (Figure 2B).

Eye Emulsion

In the topical eye emulsion clinical trial, significant improvements were observed at week 4 compared to baseline, including statistically significant reductions in fine lines/wrinkles, under-eye dark circles, and puffiness as assessed by graders ($P<0.05$). While trends toward improved skin surface hydration and brightness in the under-eye area were noted, statistical significance was not achieved. Measurements of skin redness

with the Colorimeter® and elasticity with the Cutometer® showed no significant changes.

Analysis of VISIA images revealed reductions in various types of wrinkles, with statistically significant decreases observed in overall wrinkle count and area, under-eye dark circles, and improvements in skin texture roughness ($P<0.05$). Although increases in brightness in the under-eye area were clinically observed, they did not reach statistical significance (Figure 3).

Clinical Trial Summary

Thirty-one participants aged 36 to 71 from diverse ethnic backgrounds completed the 4-week clinical trial. Results indicated reductions in under-eye dark circles (31%), under-eye puffiness (13%), and improvement in skin hydration (16%), along with a reduction in fine lines and wrinkles (12%).

Participant feedback demonstrated overall satisfaction with the eye cream. Ninety percent of participants found it lightweight, 83% reported softer skin in the eye area, and 80% noticed smoother skin in the eye area. VISIA Skin Analysis of 13 participants supported these findings, showing 92% of participants experienced fewer fine lines and wrinkles, with an average of 12% reduction in each patient. Eighty-five percent exhibited a decrease in the overall area of fine lines and wrinkles. Additionally, skin roughness improved in 85% of participants evaluated using VISIA, with 70% reporting smoother skin (Table 2).

Night Concentrate

Thirty-one participants, aged 33 to 73 from diverse ethnic backgrounds completed the 4-week clinical trial. Thirty-six percent of the cohort saw an improvement in skin texture, 25% experienced a reduction in erythema, and 8% noticed a decrease in both fine lines and wrinkles as well as an improvement in skin tone evenness.

Participant feedback indicated high satisfaction: 87% noted their skin felt more supple and elastic, looked and felt smoother, felt

TABLE 2.

Compiled Visual Grading Comparison of Various Attributes of Eye Cream Treatment										
Attribute	Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment P-value	Percent Change Mean	Percent Change Subject	Number Approved	Percent Improved
Fine Lines/Wrinkles	Eye Cream	Baseline	31	5.95	--	--	--	--	--	--
--	--	Week 4	29	5.24	-0.72	<.0001	-12.2%	-14.7%	22	75.9%
Under Eye Dark Circles	Eye Cream	Baseline	31	3.08	--	--	--	--	--	--
--	--	Week 4	29	2.12	-0.97	<.0001	-31.3%	-32.5%	23	79.3%
Puffiness	Eye Cream	Baseline	31	3.55	--	--	--	--	--	--
--	--	Week 4	29	3.10	-0.45	.0003	-12.6%	-11.7%	15	51.7%
Hydration	Eye Cream	Baseline	31	65.295	--	--	--	--	--	--
--	--	Week 4	29	76.074	10.629	.0001	16.3%	19.7%	23	79.3%

healthier and energized, and noticed an overall improvement in skin quality. Ninety-four percent of participants found the product gentle for entire face use.

VISIA Skin Analysis of 14 participants corroborated these results, indicating that 79% experienced brightened or lightened skin tone, with a 1.5% increase in skin brightness, and 71% showed a reduction in erythema, with a 9% mean decrease in erythema.

Encapsulated Lactic Acid Essence

Thirty-one participants, aged 30 to 63 from diverse ethnic backgrounds, completed the 4-week clinical trial. Clinical results at the immediate timepoint showed a 10% reduction in visible pores, 36% smoother skin, and a 5% reduction in redness. Over the 4-week period, 54% of the cohort saw an improvement in skin texture, 20% experienced a reduction in visible pores, 10% noticed an improvement in skin tone evenness, 7% observed a decrease in fine lines and wrinkles, and 5% reported a reduction in redness.

Participant feedback indicated high satisfaction: 84% noted their skin felt soft and refreshed immediately after use, 90% agreed their skin felt clean and comfortable immediately after use, and 87% found the product lightweight and quick absorbing. After 4 weeks of use, 90% felt their skin was smoother, 84% stated their skin looked and felt revitalized, 97% agreed their skin felt clean and comfortable, and 87% noticed an overall improvement in skin quality.

VISIA Skin Analysis of 13 participants corroborated these results, indicating that 92% experienced brightened or lightened skin tone, and 92% showed a reduction in erythema.

DISCUSSION

Skin sensitivity is clinically characterized by subjective sensorial signs such as facial discomfort, stinging, burning, and itching which can be exacerbated by various environmental triggers including temperature, stress, and cosmetic products. Sensitive skin to topical factors in cosmetic products is seen in almost 25% of women and can be further compounded by environmental factors. We often see sensitivities in patients with inflammatory conditions such as rosacea and acne vulgaris.

TRPV1 expression by keratinocytes was first characterized in 2001. Since then, heat, photoaging, and natural aging have all been associated with increased TRPV1 expression on human keratinocytes *ex vivo* and *in vivo*.¹⁰ UV irradiation has been shown to enhance Src kinase-mediated trafficking of TRPV1 to the cell membrane surface from intracellular vesicles within 15 minutes of irradiation.¹¹ Inhibition of TRPV1 on keratinocytes may also dampen UV-induced inflammation. In mouse models, 5-iodoresiniferatoxin, a TRPV1 blocker, reduces UV-induced mRNA and protein expression of various MMP

subtypes and pro-inflammatory cytokines.¹² TRPV1 also impacts keratinocyte-mediated inflammation which was determined through an increased intracellular calcium and elevated release of cyclooxygenase-2 (COX-2), IL-8, and prostaglandin E2 in response to TRPV1 activators, capsaicin, and protons.^{13,14}

Vanilloid receptors of the nociceptive C-fibers are activated by such noxious topical and environmental stimuli and provoke the release of neuropeptides such as substance P and calcitonin gene-related peptide. The constant activation of TRPV1 caused by these stimuli leads to an upregulation of enzymes that destroy collagen. TRPV1, known for its role in modulating sensory neurons and transmitting pain signals, has emerged as a significant therapeutic target beyond pain management. Multiple studies underscore its involvement in skin conditions including inflammation, sensitivity, wound healing, and aging.¹⁵ The efficacy of TRPV1 targeting through the use of biomimetic peptides has been demonstrated across multiple studies,¹⁶ highlighting its potential in dermatological applications. The proprietary peptide complex employed in this clinical trial showed promising results comparable to those achieved with traditional treatments such as retinoids and ascorbic acid but with added benefits for individuals with sensitive skin intolerant to these therapies.

These topical formulations containing SABMP complexed with hyaluronic acid and niacinamide, aim to harness the receptor's modulation properties for enhancing skin texture, elasticity, hydration, and improvement. Furthermore, no formulations contained parabens, fragrance mix, sodium lauryl sulfate, or formaldehyde releasers, which are also known to be common irritants or allergic contact sensitizers.

In the clinical trials, our serum formulation demonstrated notable improvements in skin texture and elasticity, with significant reductions in fine lines, wrinkles, and erythema. These findings suggest that the proprietary biomimetic peptide formulation effectively mimics the effects of more traditional treatments, offering a viable alternative for individuals unable to tolerate retinoids or ascorbic acid and is suitable for those with sensitive or sensitized skin. Moreover, results from VISIA Skin Analysis supported these outcomes, highlighting substantial improvements in skin tone brightness and redness reduction among participants.

Similarly, the eye emulsion formulation showed clinically observed reductions in fine lines, dark circles, and puffiness around the eyes, though improvements in hydration and brightness were not statistically significant. The night synthesis formulation also demonstrated promising results, improving skin texture, reducing redness, and enhancing overall skin quality and elasticity.

Our night concentrate demonstrated notable improvements in skin texture and a decrease in fine lines and wrinkles. There was also a significant reduction in erythema and overall improvement in skin tone evenness. Given its high satisfaction rates for both skin and product quality, along with VISIA demonstrating an increase in skin brightness and lightened skin tone, the night concentrate is a viable and reliable option for those with sensitive skin.

Additionally, the Lactic Acid Essence resulted in a marked reduction in visible pores, smoother skin, and reduced erythema at both the immediate time point and over a 4-week period underscoring the formulation's continued efficacy. Patient satisfaction corroborated with these findings as nearly 90% of participants claimed their skin felt clean and refreshed, smoother, and revitalized.

While some trends show improvement in the tested parameters, some parameters failed to reach significance possibly because of the 4-week duration of the trials. Therefore, longer trials confirming the positive indications seen in our trials might be needed to attain significance.

Our findings indicate that TRPV1-targeting peptides offer a promising avenue for skincare innovation, presenting a safe and effective alternative for individuals with sensitive skin who may not tolerate conventional treatments. Future research should continue to explore the mechanisms underlying peptide-based therapies to optimize their efficacy and broaden their therapeutic applications in dermatology.

CONCLUSION

Targeting the TRPV1 skin receptor with our novel peptide offers a new and improved modality to address skin sensitivity while achieving a precise therapy for improving cutaneous signs of aging. Our clinical trials show that the use of topical skin care formulations with TRPV1 antagonism for face and eye areas has clinical utility. Additionally, our formulation can help modulate sensitivity in response to environmental stimuli which can be the foundation for treating highly prevalent medical conditions like atopic dermatitis, rosacea, and acne.

DISCLOSURES

Anthony Rossi has served as a consultant for Evolve CME, Almirall, Merz, Dynamed, Canfield Scientific, Evolus, Biofrontera, Quantia MD, Lam Therapeutics, Regeneron, and Cutera. He has received travel support from Mavig and L'Oréal and is an advisor for Skinfix. Additionally, he has served on the advisory board for Allergan Inc. and is the founder of DAR companies. He has received research grants from the ASLMS A Ward Memorial Research Grant, the Skin Cancer Foundation, LeoPharma, and Biofrontera, as well as research and study funding from Regen. Dr Rossi is a member of the editorial boards of *Lasers in Surgery*

and *Medicine*, *CUTIS*, *Journal of the American Academy of Dermatology (JAAD)*, and *Dermatologic Surgery*. He is also a board member of the American Society for Dermatologic Surgery (ASDS) and has served as a committee member and/or chair for the American Academy of Dermatology (AAD), ASDS, and the American Society for Laser Medicine and Surgery (ASLMS). No other relevant disclosures from other authors.

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REFERENCES

1. Li F, Wang F. TRPV1 in pain and itch. *Adv Exp Med Biol*. 2021;1349:249-273. doi:10.1007/978-981-16-4254-8_12
2. Xiao T, Sun M, Zhao C, Kang J. TRPV1: A promising therapeutic target for skin aging and inflammatory skin diseases. *Front Pharmacol*. 2023;14:1037925. doi:10.3389/fphar.2023.1037925
3. Marek-Jozefowicz L, Nedoszytko B, Grochowska M, et al. Molecular mechanisms of neurogenic inflammation of the skin. *Int J Mol Sci*. 2023;24(5):5001. doi:10.3390/ijms24055001
4. Goldsberry A, Hanke CW, Hanke KE. VISIA system: A possible tool in the cosmetic practice. *J Drugs Dermatol*. 2014;13:1312-1314.
5. Dobrev HP. A study of human skin mechanical properties by means of cutometer. *Folia Med*. 2001;44(3):5-10.
6. Kim SH, Lee SJ, Kim HJ, et al. Aging-related changes in the mid-face skin elasticity in East Asian women. *Arch Craniofac Surg*. 2019;20(3):158-163.
7. Alexander H, et al. Research techniques made simple: Transepidermal water loss measurement as a research tool. *J Invest Dermatol*. 2018;138(11):2295-2300.
8. Misery L, Loser K, Ständer S. Sensitive skin. *J Eur Acad Dermatol Venereol*. 2016;30(Suppl 1):2-8. doi:10.1111/jdv.13532
9. Constantin MM, Poenaru E, Poenaru C, et al. Skin hydration assessment through modern non-invasive bioengineering technologies. *Maedica (Bucur)*. 2014;9(1):33-38. PMID: 25553123
10. Andreev YA, Kozlov SA, Koshelev SG, et al. Analgesic compound from sea anemone *Heteractis crispa* is the first polypeptide inhibitor of vanilloid receptor 1 (TRPV1). *J Biol Chem*. 2008;283(35):23914-23921. doi:10.1074/jbc.M800776200
11. Ashrafi M, Baguneid M, Bayat A. The role of neuromediators and innervation in cutaneous wound healing. *Acta Derm Venereol*. 2016;96:587-594.
12. Southall MD, Li T, Gharibova LS, et al. Activation of epidermal vanilloid receptor-1 induces release of proinflammatory mediators in human keratinocytes. *J Pharmacol Exp Ther*. 2003;304:217-222.
13. Lee YM, Li WH, Kim YK, et al. Heat-induced MMP-1 expression is mediated by TRPV1 through PKCα signaling in HaCaT cells. *Exp Dermatol*. 2008;17:864-870.
14. Lee YM, Kang SM, Lee SR, et al. Inhibitory effects of TRPV1 blocker on UV-induced responses in the hairless mice. *Arch Dermatol Res*. 2011;303:727-736.
15. Lee YM, Kim YK, Chung JH. Increased expression of TRPV1 channel in intrinsically aged and photoaged human skin in vivo. *Exp Dermatol*. 2009;18:431-436.
16. Bagood MD, Isseroff RR. TRPV1: Role in skin and skin diseases and potential target for improving wound healing. *Int J Mol Sci*. 2021;22(11):6135. doi:10.3390/ijms22116135.

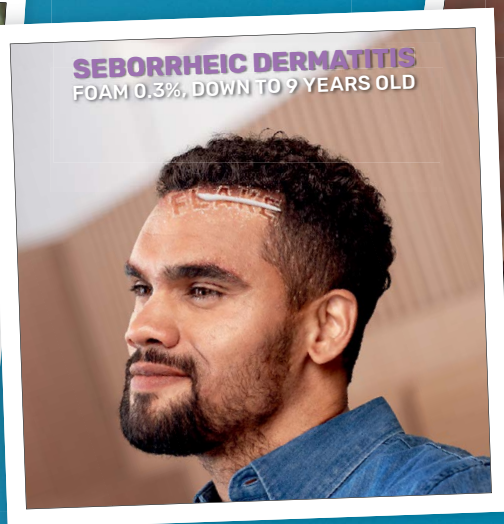
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ZORYVE® IT RELIEVE IT

The power and versatility
to be your everyday topical^{1,2,*†‡}



Symptoms illustrated. Not actual patients.

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use.^{1,2}

ZORYVE®
(roflumilast)

IMPORTANT SAFETY INFORMATION

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

Flammability: The propellants in ZORYVE foam are flammable. Avoid fire, flame, and smoking during and immediately following application.

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

The most common adverse reactions ($\geq 1\%$) for ZORYVE foam 0.3% for seborrheic dermatitis include nasopharyngitis (1.5%), nausea (1.3%), and headache (1.1%).

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

Please see accompanying brief summary of the full Prescribing Information for ZORYVE cream and ZORYVE foam.

INDICATIONS

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

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

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

THE FIRST AND ONLY STEROID-FREE TOPICAL APPROVED FOR 3 MAJOR INFLAMMATORY SKIN DISEASES³⁻⁶

ONCE-DAILY

STEROID-FREE

ATOPIC DERMATITIS

31% of patients achieved vIGA-AD Success at Week 4 with ZORYVE, some as early as Week 1 (vs 14% at Week 4 with vehicle).^{3,7*}

32% of patients achieved WI-NRS Success at Week 4 with ZORYVE, with results observed within 24 hours (vs 17% at Week 4 with vehicle).^{7*}

SEBORRHEIC DERMATITIS

77% of patients achieved IGA Success at Week 8, some as early as Week 2 (vs 53% at Week 8 with vehicle)^{2,3†}

PLAQUE PSORIASIS

40% of patients achieved IGA Success at Week 8, some as early as Week 4 (vs 7% at Week 8 with vehicle)^{8‡}



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about **ZORYVE**?



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Pivotal Study Designs

*Two Phase 3 multicenter, randomized, double-blind, vehicle-controlled studies (INTEGUMENT-1 & INTEGUMENT-2) evaluated 1337 participants with mild to moderate atopic dermatitis ages 6 years and older. Participants applied ZORYVE or vehicle once daily. Primary endpoint was vIGA-AD Success at Week 4; ZORYVE cream = 884, vehicle = 453. WI-NRS Success at Week 4 was a key secondary endpoint; ZORYVE cream = 542, vehicle = 271.¹

†Two multicenter, randomized, double-blind, vehicle-controlled studies (STRATUM and Trial 203) evaluated 683 participants with moderate to severe seborrheic dermatitis treated with ZORYVE or vehicle once daily for 8 weeks. STRATUM: ZORYVE foam = 304, vehicle = 153. Trial 203: ZORYVE foam = 154, vehicle = 72. Primary endpoint was IGA Success at Week 8.²

‡Two Phase 3 randomized, parallel, double-blind, vehicle-controlled, multicenter studies (DERMIS-1 and DERMIS-2) evaluated 881 participants with plaque psoriasis treated with ZORYVE or vehicle once daily for 8 weeks. ZORYVE = 576, vehicle = 305. Primary endpoint was IGA Success at Week 8.³

IGA Success/vIGA-AD Success = Achievement of Clear (0)/Almost Clear (1) and a ≥ 2 -grade improvement from baseline.

IGA = Investigator Global Assessment. vIGA-AD = Validated Investigator Global Assessment—Atopic Dermatitis.

WI-NRS Success defined as a ≥ 4 -point improvement for patients with a baseline score ≥ 4 . WI-NRS: 0 (no itch) to 10 (worst imaginable itch).

WI-NRS = Worst Itch Numeric Rating Scale.

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

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

INDICATIONS AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Wash hands after application.

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

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

CONTRAINDICATIONS

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

ADVERSE REACTIONS

Clinical Trials Experience

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

Plaque Psoriasis

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

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

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

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

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

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

Atopic Dermatitis

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

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

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

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

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

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

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

Seborrheic Dermatitis

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor and delivery

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

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (36 times the MRHD for ZORYVE cream and 30 times the MRHD for ZORYVE foam on a mg/m² basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (4 times the MRHD for ZORYVE cream and 3 times the MRHD for ZORYVE foam on a mg/m² basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (12 times the MRHD for ZORYVE cream and 10 times the MRHD for ZORYVE foam on a mg/m² basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (35 times the MRHD for ZORYVE cream and 29 times the MRHD for ZORYVE foam on a mg/m² basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (31 times the MRHD for ZORYVE cream and 26 times the MRHD for ZORYVE foam on a mg/m² basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (19 and 59 times the MRHD, respectively, for ZORYVE cream and 16 and 49 times the MRHD, respectively, for ZORYVE foam on a mg/m² basis). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (19 times the MRHD for ZORYVE cream and 16 times the MRHD for ZORYVE foam on a mg/m² basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (59 times the MRHD for ZORYVE cream and 49 times the MRHD for ZORYVE foam on a mg/m² basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (116 times the MRHD for ZORYVE cream and 97 times the MRHD for ZORYVE foam on a mg/m² basis).

Lactation

Risk Summary

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

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

Clinical Considerations

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

Data

Animal data

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

Pediatric Use

Plaque Psoriasis

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

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

Atopic Dermatitis

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

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

Seborrheic Dermatitis

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

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

Geriatric Use

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

Plaque Psoriasis

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

Atopic Dermatitis

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

Seborrheic Dermatitis

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

Hepatic Impairment

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

PATIENT COUNSELING INFORMATION

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

Flammability

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

Lactation

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

An Algorithm Integrating Acneceuticals Into the Management of Acne Vulgaris

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ABSTRACT

Background: Acne vulgaris is a common, chronic cutaneous disorder with numerous efficacious prescription and procedural treatments. Therapy, however, is hampered by medication intolerability and compromised by non-adherence. The use of acneceuticals is an effective way to improve patient outcomes.

Methods: A panel of 5 dermatologists met for a consensus conference in October 2023 to identify a practical acne treatment and maintenance algorithm integrating acneceuticals with prescription medications and procedures.

Results: The algorithm stratifies the use of acneceuticals first as monotherapy, adjunctive therapy, or maintenance therapy and then further diverges by skin phenotype (oily or dry/sensitive) and primary lesion morphology (comedonal or inflammatory). Finally, specific acneceuticals are recommended for each phenotypic description.

Conclusion: The algorithm is intended to serve as a guideline for integrating active nonprescription skin care into prescription acne therapy, improving efficacy, tolerability, and adherence, resulting in superior patient outcomes.

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INTRODUCTION

Although many quality prescription products exist for the treatment of acne, we continue to search for ways to improve patient care. Our patients search as well, often adding or substituting internet finds for proven regimens, occasionally with deleterious consequences. It is incumbent upon clinicians to be well-versed in ways in which nonprescription active skin care ingredients can improve patient outcomes. It is the clinician's responsibility to guide patients in their quest for self-care, helping them to choose quality products, improve safety and reduce cost.

In a previous study, the results of a modified Delphi consensus meeting were reported where the term "acneceutical" was coined to encompass nonprescription formulations with ingredients efficacious in acne.¹ A thorough literature search resulted in the identification of candidate ingredients that were divided into categories based on the pathophysiology of acne: sebum inhibitors, anti-inflammatory agents, antibacterial agents, keratolytic agents, and those that repair the deficient barrier (Table 1). These candidates were vetted for those that

were studied in patients with acne in double or single-blind, vehicle-controlled, or active-compared designs. Combination products and proprietary blends to which patients would not have access were omitted as were benzoyl peroxide and adapalene, viewing them as drugs, not acneceuticals.

In this paper, we present an algorithm incorporating these acneceuticals into acne management as monotherapy, adjunctive therapy (to pharmaceuticals or procedures), and maintenance therapy following discontinuation of prescription medications.

Algorithm Development

The algorithm focuses on integrating acneceuticals into an acne management and maintenance regimen. The algorithm went through numerous iterations as individual acneceuticals were evaluated for quality of data, proposed mechanism of action, and their likely role in acne care. This information guided the panel to crystallize the most salient subdivisions and branchpoints of the algorithm. The panel reviewed and edited the final algorithm in a consensus conference.

TABLE 1.

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

The proposed use of acneceuticals was based on an understanding of acne pathophysiology. Acne pathophysiology is traditionally tied to 4 pathogenic pillars: hyperkeratinization, hyper- and dysseborrhea, *Cutibacterium acne* (*C.acnes*) colonization, and a robust inflammatory response.^{2,3} Additional data implicates skin barrier impairment as a material contributor to the pathophysiology of acne.⁴ Based on these tenets of acne pathophysiology, acneceuticals were chosen for inclusion if they had in vitro or in vivo data indicating mechanisms of action that included keratolysis, inhibition of sebum production, antibacterial activity (specifically against *C. acnes*) and anti-inflammatory activity as well as barrier repair. Many acneceuticals have more than one potential area of efficacy and thus are included in more than one category.

It is well documented that when composing a treatment regimen for acne, combination therapy is the most effective; in particular, utilizing drugs that approach the acne pathogenic cascade from numerous directions.^{5,6} It is likely that in clinical practice, we will need to choose several acneceuticals with differing mechanisms of action to maximize efficacy.

The Algorithm (Figure 1)

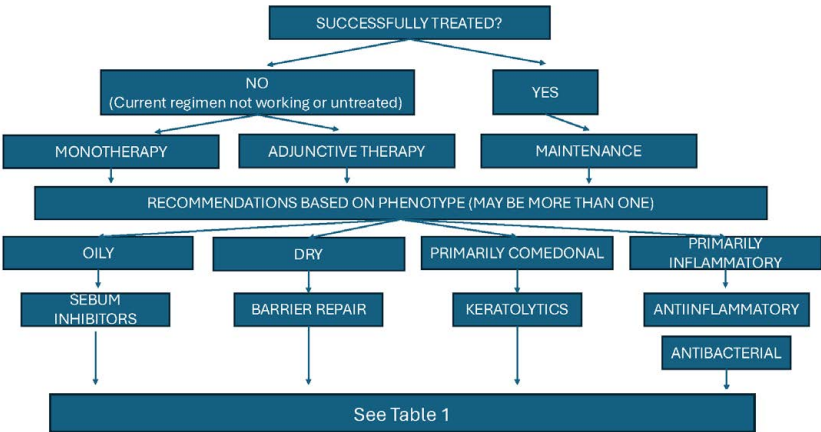
First Stratification

The first stratification of the algorithm is the choice of maintenance therapy for the successfully treated patient and monotherapy, or adjunctive therapy for the patient who needs continued care.

Monotherapy

Several acneceuticals had data demonstrating efficacy in acne as standalone treatments.¹ However, just as with prescription medications, it is expected that in clinical practice, combination therapy will be most effective. Simultaneous use of actives from categories with different mechanisms of action is recommended. Most monotherapy studies were conducted on subjects with mild disease; there is little data evaluating solo

FIGURE 1. Algorithm integrating acneceuticals into the management of acne vulgaris.



agents in patients with more severe disease.¹ It is likely that the use of acneceuticals as adjuncts to prescription medications or procedures will be better suited for more advanced disease.

Adjunctive Therapy

The utilization of acneceuticals for adjunctive therapy has been studied in two ways: the addition of an acneceutical to prescription care to augment effectiveness of therapy and the addition of a barrier repair acneceutical to improve prescription drug tolerability. Acne therapy is often drying, particularly during initial use. Symptoms including itch, sting, and burn can lead to non-adherent behavior and ultimate failure of the regimen.⁷⁻⁹ Barrier repair has been shown to reduce medication intolerability leading to consistent use of therapeutics and treatment success.¹⁰

Maintenance (Treatment Transition) Therapy

Treatment transition to alternate regimens is an inevitable necessity in acne care. Once satisfactory lesion clearance has been obtained, patients often become anxious to discontinue all or part of their therapy. As clinicians, we are aware that, with the exception of isotretinoin, acne therapy can best be described as a bandaid on the condition until acne naturally resolves; abrupt discontinuation of efficacious products results in rapid return of disease. Substitution of an appropriate acneceutical – one having the same mechanism of action as the drug itself – may aid in the transition: antibacterial for antibiotic, keratolytic for a retinoid.

Other reasons for treatment transition include cost of and access to medications and tolerability. Acneceuticals, almost without exception, are less expensive than pharmaceutical agents, are accessible to all, without the economic disparity that exists due to affordable access, available for children under the age of FDA approval and highly tolerable.

Lastly, the use of topical and oral antibiotics is associated with the development of antimicrobial resistance. The CDC warns us that antimicrobial resistance is one of the most important public health threats of our time and has called upon us to be better stewards of antibiotics.¹¹ Although antibiotics are highly effective in reducing *C. acnes* and thus improving inflammatory acne, durability of response is poor. Discontinuation results in inevitable recolonization of the follicle with the commensal *C. acnes* and return of disease, having brought about ecologic damage without ultimate gain. Acneceuticals, with the ability to accomplish microbiome modulation without evident antimicrobial resistance, are a readily available answer to this dilemma, allowing for continued therapy with less risk.

Second Stratification (Figure 1)

The second stratification of the algorithm involves determining the phenotypic description of the patient. Based on the

mechanism of action of the acneceuticals, the panel recognized four general phenotypes (realizing that the individual patient will often fall into more than one category): oily skin vs dry/sensitive skin and comedonal vs inflammatory acne. Although acknowledging that maximizing acne therapy is best accomplished by utilizing combination therapy, the panel stratified acneceuticals by determining for which phenotype each was best suited.

Oily Skin

Oily skin patients appreciate products that reduce the appearance of shine in addition to the potential therapeutic benefits that sebum inhibition could accomplish. Sebum excretion is known to be higher in acne patients. Additionally, sebum quality is altered; linoleic acid levels are reduced and squalene concentrations increased, contributing to subclinical inflammation.^{12,13} Reduction in sebum excretion is thus an important clinical and cosmetic endpoint that may be accomplished in part by the use of an acneceutical.

Dry and Sensitive Skin

Dry and sensitive skin patients can benefit from barrier repair. Yamamoto and co-workers demonstrated that acne patients have an inherent barrier dysfunction, noting a statistically significant reduction in ceramides and increase in transepidermal water loss.⁴ The deficiency was more significant in more severe disease. As barrier dysfunction is known to be accompanied by hyperkeratosis of the follicular epithelium, this suggests that acne should be added to the list of barrier deficiency disorders such as atopic dermatitis and psoriasis. Data suggest that quality skin care may result in acne improvement as monotherapy. We often see this when faced with unexpectedly good results in the vehicle arms of acne studies. Small studies have demonstrated that daily use of a mild facial cleanser and quality moisturizer can reduce acne lesions without aggravating epidermal barrier dysfunction, thereby reducing TEWL, mitigating aberrations of cutaneous pH, and fostering the growth of a diverse and healthy microbiome.¹³⁻¹⁵

In addition to resolving an inherent barrier deficiency, quality skin care improves pharmaceutical tolerability. The acne management paradigm is built on topical retinoids and benzoyl peroxide. Although effective acne drugs, these ingredients also increase cell turnover, induce stratum corneum thinning, and increase TEWL, often leading to xerosis, irritation, and even inflammation. When combined with acne treatment regimens, the use of gentle cleansers and quality moisturizers improves patient comfort, minimizing the adverse effects of dryness and irritation.^{14,15} Although there are many factors leading to poor compliance, skin irritation is a prominent factor.⁷⁻⁹ A double-blinded, randomized study compared the outcome of an acne treatment regimen consisting of a twice-daily skincare routine in addition to a nightly combination topical agent (adapalene

0.3%/BP 2.5%).¹⁰ Use of a ceramide-containing cleanser and moisturizer during the 12-week treatment period resulted in a statistically significant improvement in both primary endpoints: markers of skin barrier function and acne severity.¹⁰

Primarily Comedonal Acne

Comedonal acne responds most efficiently to topical retinoids which are comedolytic, anti-comedogenic, and anti-inflammatory. Many acneceuticals that are keratolytics also have anti-inflammatory activities (alpha and beta hydroxy acids, azelaic acid, retinol derivatives, and bakuchiol) and some also aid in barrier repair (alpha and beta hydroxy acids).¹ As such, keratolytic acneceuticals may accomplish or aid in the treatment of primarily comedonal acne.

Primarily Inflammatory Acne

The papules and pustules of acne are inflammatory lesions that respond particularly well to anti-inflammatory agents. Increased colonization of *C. acnes* within the pilosebaceous unit is a fundamental cause of the inflammatory process in acne. Several acneceuticals serve the dual roles of anti-inflammatory and antibacterial agents (niacinamide, bakuchiol, zinc, green tea, cannabidiol).¹

When utilizing acneceuticals with antibacterial activity, we are seeking agents that will modify the follicular microbiome, thereby encouraging a normal, balanced diversity to regain microbiome homeostasis. Commensal *C. acnes* plays an important role in skin health, acidifying the stratum corneum by producing free fatty acids from triglycerides and reducing colonization with pathogenic bacteria. Both the quantity and quality of follicular *C. acnes* are of clinical importance in the acne-prone follicular unit. Several phylotypes of *C. acnes* exist with an overabundance of phylotype IA1 associated with more severe acne and phylotype II associated with skin health.^{12,16,17} The overarching aim of therapy is to minimize IA1 rather than to eradicate the entire *C. acnes* community. There is some data demonstrating the ability to utilize isolated phylotype II *C. acnes* as a probiotic to improve skin health.¹⁸

Third Stratification (Figure 1 and Table 1)

The third stratification recognizes the acneceuticals most likely to accomplish the goals of therapy: sebum reduction, barrier repair, reduction of hyperkeratinization, *C. acnes* reduction, and reduced inflammation. As mentioned previously, these acneceuticals were vetted in an earlier publication as those agents with human, in vivo, single- or double-blinded, vehicle- or comparator-controlled trials.¹ Combination therapy chosen purposefully from each therapeutic goal is likely to be the most effective.

Limitations

In vetting acneceuticals for inclusion in this paper, the authors

endeavored to review actives with only the highest quality data. It cannot go without noting, however, that the rigor of nonprescription studies does not mirror that of prescription products. In many cases, studies were heterogeneous in design, differed in clinical endpoints, and had small numbers of subjects. Although data utilized to create this algorithm was not limited to any race or ethnicity, the majority of the studies either did not contain patients of varied backgrounds or did not indicate race or ethnicity. As such, it is difficult to draw definitive conclusions across diverse populations or skincare products.

CONCLUSION

Acne management focuses on the use of prescription medications and procedures that aim to target the 4 pillars of acne pathophysiology. More recently, however, our understanding of the interrelationship between acne, barrier health, and microbiome diversity has led us to examine more closely the importance of nonprescription actives (acneceuticals) as monotherapy as well as adjunctive therapy. Expert opinion and consensus papers have stressed the importance of quality skin care in acne management, but this advice has yet to make its way to treatment guidelines.

Although our pharmacologic treatments are highly efficacious, clinicians continue to search for better regimens with improved safety and tolerability. Our patients search, too – with or without our guidance. Some are looking for a more “natural” approach to skin care, others for affordable options, and still others seek the satisfying sense of control that can come from successful self-prescribing. Unfortunately, the internet is replete with recommendations that fall short of effective care and may have harmful consequences.¹⁹ Delay in acne therapy is associated with an increased risk of acne sequelae such as dyspigmentation and scarring, and uneducated postings can lead to permanent disfigurement.^{20,21} It is incumbent upon clinicians to be well-versed in the use of acneceuticals - nonprescription active skin care ingredients - which alone can treat mild acne and combined with prescription medications, optimize treatment regimens. Failure to discuss skin care at every acne visit is a missed opportunity to enhance patient outcomes.

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REFERENCES

1. Baldwin H, Bui H, Callender V, et al. The use of acneceuticals to improve acne care: introduction of a new term and review of the literature. *J Drugs Dermatol.* 2025;24(3):
2. Kircik L. Advances in the understanding of the pathogenesis of inflammatory acne. *J Drugs Dermatol.* 2016;15(Suppl 1):s7-10.
3. Zaenglein A, Pathy A, Schlosser B et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945-973.
4. Yamamoto A, Takenouchi K, Ito M. Impaired water barrier function in acne vulgaris. *Arch Derm Res.* 1995;287:214-218.
5. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2024;90:1006 e1-e30.
6. Corcoran L, Muller I, Layton A, et al. Systematic review of clinical practice guidelines for acne vulgaris published between January 2017 and July 2021. *Skin Health Dis.* 2023;3:e240.
7. Goh C-L, Wu Y, Welsh B, et al. Expert consensus on holistic skin care routine. *J Cosmet Dermatol.* 2023;22(1):45-54.
8. Fabbrocini G, Rossi G, Thouverin M et al. Fragility of the epidermis: Acne and post procedure lesional skin. *J Eur Acad Dermatol Venereol.* 2017;31 Suppl 6:3-18.
9. Jordan L, Baldwin H. Stratum corneum abnormality and disease-affected skin strategies for successful outcomes in inflammatory acne. *J Drugs Dermatol.* 2016;15(10):1170-1183.
10. Draelos ZD, Baalbaki N, Colon G, et al. Ceramide-containing adjunctive skin care for skin barrier restoration during acne vulgaris treatment. *J Drugs Dermatol.* 2023;22(6):554-558.
11. [www://http.cdc.gov/antimicrobial-resistance/data-research/threats/index.html](http://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html), accessed 11/20/2024.
12. Downing DR, Stewart ME, Wertz PW, et al. Essential fatty acids and acne. *J Am Acad Dermatol.* 1986;14(2 Pt 1):221-225.
13. Marson J, Bhatia N, Graber E et al. The role of epidermal barrier dysfunction and cutaneous microbiome dysbiosis in the pathogenesis and management of acne vulgaris and rosacea. *J Drugs Dermatol.* 2022; Sep 1;21(9).
14. Araviiskaia E, Dreno B. The role of topical dermocosmetics in acne vulgaris. *J Eur Acad Dermatol Venereol.* 2016;30(6):926-935.
15. Thiboutot D, Del Rosso J. Acne vulgaris and the epidermal barrier: Is acne vulgaris associated with inherent epidermal abnormalities that cause impairment of barrier functions? *J Clin Aesthet Dermatol.* 2013;6(2):18-24.
16. Paugem C, Corvec S, Saint-Jean M et al. Propionibacterium acnes phylotypes and acne severity: an observational prospective study. *J Eur Acad Dermatol Venereol.* 2017;31(9):e398-e399.
17. Dagnelie MA, Corvec S, Saint-Jean M et al. Decrease in diversity of Propionibacterium acnes phyloypes in patients with severe acne on the back. *Acta Derm Venereol.* 2018;98(2):262-267.
18. Rhee MS, Alqam ML, Jones BC. Characterization of a live Cutibacterium acnes subspecies defendens strain XYCM42 and clinical assessment as a topical regimen for general skin health and cosmesis. *J Cosmet Dermatol.* 2023;22(3):1031-1045.
19. Szeto MD, Mamo A, Afrin A, Militello M, Barber C. Social media in dermatology and an overview of popular social media platforms. *Curr Dermatol Rep.* 2021;10(4):97-104.
20. Goodman G. Acne and acne scarring. The case for active and early intervention. *Aust Fam Physician.* 2006;35:503-504.
21. Layton AM, Henderson CA, Cunliffe WJ. A Clinical evaluation of acne scarring and its incidence. *Clin Exp Dermatol.* 1994;19:303-308.

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The State of the Clinical Management Union: A Cross-Sectional Survey of Persons With Hidradenitis Suppurativa

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic autoinflammatory condition notable for a high psychosocial burden on patients. This burden is theorized to be linked to patient dissatisfaction due to the paucity of treatment options.

Objectives: This study assessed respondent perceptions of current and emerging HS treatments and their impact on quality of life.

Methods: An IRB-exempt (IRB#: NCR235179) survey was distributed via the HSconnect.org listserv for respondents ≥18 years old. Of 501 responses, 423 (84.4%) completed the entire survey.

Results: Less than 20% of respondents were satisfied or very satisfied with current treatment options (76/423). Of respondents with self-reported disease severity of Hurley stage II or III (51%, 244/483), only 39% were being treated with biologics and/or 26% hormone therapy, indicating undertreatment per current HS guidelines. Most respondents (74%) were unaware of Federal Drug Administration (FDA)-approved treatments and 56% reported that their dermatologist or healthcare provider had not discussed these options with them. More than half of respondents (60%, 254/423) felt it was important to have FDA-approved therapies, believing it would lead to improved physical health (86%), mental health (78%), and/or personal relationships (60%).

Conclusions: In a large cross-sectional survey of patients with HS, dissatisfaction with current treatment options was expressed by a minority of respondents and likely results from both undertreatment and gaps in knowledge of current FDA-approved therapies. Enhancing patient-provider education about off-label and FDA-approved therapies, including established and emerging treatment options, guidelines for use, and their adverse effects, can dramatically improve the quality of life for persons living with HS.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic auto-inflammatory condition characterized by the presence of fluctuant, painful papules and nodules that can evolve into sinus tracts and deforming scarring.¹ HS often follows an unpredictable, relapsing, and remitting disease course and has a significant negative impact on quality of life.¹ HS is associated with social isolation, challenges with intimate relationships, and increased rates of anxiety and depression.²⁻⁴ A variety of medications with variable efficacy are utilized for the treatment of HS, including topical and systemic antibiotics, anti-hormonal therapies, and immunosuppressants.¹ Many of these treatments are used off-label, and to date, only 2 US Food and Drug Administration (FDA)-approved biologic therapies are available—adalimumab and secukinumab.^{1,5} Other management strategies include surgical interventions, such as wide excision and derofing, which can be employed for the disfiguring sequelae but may involve extensive procedural aspects such as grafts and skin flaps.¹ Due to the impressive psychosocial and physical burden of HS, along with

the predominately off-label therapeutic armamentarium, this study aimed to assess patients' experiences and satisfaction with managing their HS. The study also sought to understand patient knowledge and perceptions of emerging FDA-approved therapies.

MATERIALS AND METHODS

An IRB-exempt (IRB#: NCR235179), 18-question survey was developed using the cloud-based survey tool SurveyMonkey and distributed via the HSconnect.org listserv for completion between November and December of 2023. Participation was optional; respondents were required to be 18 years of age or older and currently living with HS. Respondents not meeting eligibility criteria were excluded from participation. Demographic data collected included age, race and/or ethnicity, and gender. Responses were measured using free text, multiple-choice questions, and modified Likert scales. Survey responses were compiled for analysis using Fisher's exact tests and statistical significance was calculated using a standard 95% confidence interval, as well as ChatGPT to summarize free text responses.

RESULTS

Demographics

In total 501 survey responses were collected with 423 (84.4%) completing the entire survey. The average age of participants was 37.35 years old (SEM = +/- 0.51) (n=501). Most respondents (91.82%, 460/501) identified as women, while a minority identified as men (4.99%, 25/501), non-binary individuals (2.2%, 11/501), or chose to self-describe (0.2%, 1/501). Participants were given the option to select more than 1 racial and ethnic category with most participants identifying as white/Caucasian (58.88%, 295/501). Other represented racial and ethnic groups included persons identifying as African American (25.35%, 127/501), Black (10.38%, 53/501), Latinx (9.18%, 46/501), Native American or Alaska Native (2.99%, 15/501), Asian (2.40%, 12/501), other (2.20%, 11/501), African Caribbean (2%, 10/501) and Middle Eastern or North African (0.8%, 4/501). Demographics of survey participants can be found in Table 1.

Disease Characteristics

The average age of HS onset was 20 years old (SEM = +/- 0.48) (n=483), while the average age of formal diagnosis with HS

was 29 years old (SEM = +/- 0.57) (n=483). Most participants (93.17%, 450/483) were diagnosed with HS by a dermatologist or other healthcare provider and graded as either Hurley stage III (28.57%, 138/483), stage II (21.95%, 106/483) or stage I (6%, 29/483). Summarized disease characteristics are found in Table 1.

Management Strategies

Respondents utilized a variety of treatments for managing HS. The most utilized treatments including antimicrobial washes (ie, benzoyl peroxide, chlorhexidine) (69.03%, 292/423), antibiotics (ie, doxycycline, minocycline, trimethoprim-sulfamethoxazole) (54.85%, 232/423), and biologics (ie, adalimumab, infliximab) (28.84%, 122/423). Other treatments included anti-hormonal therapy (ie, birth control pills, spironolactone, finasteride) (24.82%, 105/423), corticosteroids (ie, triamcinolone) (18.91%, 80/423), diabetes medications (ie, metformin) (13.24%, 56/423), oral immunosuppressants (ie, methotrexate) (4.73%, 20/423), and other treatments not specified in the above categories (16.78%, 71/423). The mean number of treatments utilized per respondent was 2.36 (SEM = +/- 0.065) (n=423). Of those participants who utilized more than 1 treatment for disease

TABLE 1.

Demographics of Survey Respondents		
Demographics	Variable	Mean (SEM)
Age (y)	Current (N=501)	37.35 (0.51)
	HS onset (N=483)	19.60 (0.48)
	HS diagnosis (N=483)	28.57 (0.57)
Demographics	Variable	N (%)
Gender (N=501)	Woman	460 (91.82)
	Man	25 (4.99)
	Non-binary	11 (2.20)
	Prefer to self-describe	1 (0.20)
	Prefer not to answer	4 (0.80)
Race and/or ethnicity (N=501)	White/Caucasian	295 (58.8)
	African American	127 (25.35)
	Black	53 (10.58)
	Latinx	46 (9.18)
	Native American or Alaska Native	15 (2.99)
	Asian	12 (2.40)
	Other	11 (2.20)
	African Caribbean	10 (2.00)
	Middle Eastern or North African	4 (0.80)
	Prefer not to answer	5 (1.00)
Hurley Stage (N=483)	One (I)	29 (6.00)
	Two (II)	106 (21.95)
	Three (III)	138 (28.57)
	Unsure	210 (43.48)

management, the most frequent combination was antibiotics and antimicrobial washes (28.37%, 120/423).

Disease Management Satisfaction, FDA-Treatment Knowledge, and Related Challenges

In evaluating respondent satisfaction with their disease management strategy, only 17.97% of participants were satisfied or very satisfied (17.97%, 76/423). Additionally, most participants indicated that they were unaware of FDA-approved therapies (73.52%, 311/423) and had not discussed these options with their dermatologist or other healthcare provider (55.79%, 236/423). When asked to quantify how many of the treatments they currently utilized for the management of HS were FDA-approved, many respondents were unsure (48.94%, 207/423).

A sub-analysis of respondents grouped according to their Hurley stages (Hurley I-III only) found that patients with more severe disease were more likely to have discussed FDA-approved therapies with their dermatologist or healthcare provider ($P=0.00391$). However, neither knowledge nor current utilization of FDA-approved therapies was significantly different across Hurley stages ($P=0.5756$ and $P=0.1588$, respectively).

The greatest respondent-reported challenge in finding FDA-approved treatments to manage HS was a lack of awareness about options (48.46%, 205/423). Other challenges included an insufficient number of treatments (43.26%, 183/423), difficulty finding treatment for HS subtype (38.30%, 162/423), high cost (30.97%, 131/423), and lack of regular access to a dermatologist or other healthcare provider (21.75%, 92/423).

Perceptions and Impact of Secukinumab Approval

Despite many respondents reporting a lack of knowledge about FDA-approved options, most responses indicated it was important or extremely important to have FDA-approved options (60.04%, 254/423). Along with these findings, most respondents (71.37%, 304/423) expressed confidence to high confidence in the development of additional HS treatments given the recent approval of secukinumab. Greater disease severity (Hurley stage III) was statistically correlated with more respondents reporting either “moderate-to-high” or “little-to-none” confidence in the development of more FDA-approved therapies following the approval of secukinumab ($P=0.0289$) compared to Hurley stages I or II.

In evaluating the impact of more FDA-approved options for HS management, patients anticipated improved physical health (85.58%, 362/423), mental health (77.78%, 329/423), and personal relationships (59.81%, 253/423). Participants were also given 2 free-text response options to elaborate on the personal impact of FDA-approved options, as well as an opportunity to provide feedback related to secukinumab approval. Responses were condensed as artificial intelligence (AI)-generated summaries

and coded based on frequency of variables as assigned in the Dermatology Quality Life Index (DLQI).⁶ The most frequent DLQI variables in response to the personal impact of FDA-approved options were disease activity (119/296), self-confidence (78/296), and treatment effort and access (71/296). These data are represented in Figures 1-3.

FIGURE 1. Artificial Intelligence (AI)-generated summary of free-text responses to Q15: “If more FDA-approved treatment options are available for managing HS, what impact do you anticipate this will have for you personally?”¹⁰

If more FDA-approved treatment options were available for managing my hidradenitis suppurativa (HS), it would significantly improve my quality of life. HS currently makes me feel insecure, self-conscious, and isolated due to the pain, flare-ups, and odor, which affect my confidence and mental health. More effective treatments could help reduce my physical symptoms, making it easier to engage in social activities, work, and relationships. Having reliable options could also provide peace of mind, reduce my stress and anxiety, and help me regain control over my life, allowing me to live more comfortably and confidently.

FIGURE 2. Frequency of respondent’s free text responses to Q15 (“If more FDA-approved treatment options are available for managing HS, what impact do you anticipate this will have for you personally?”) describing the positive impact of a new treatment option categorized using variables assessed in the Dermatology Life Quality Index (DLQI).⁶

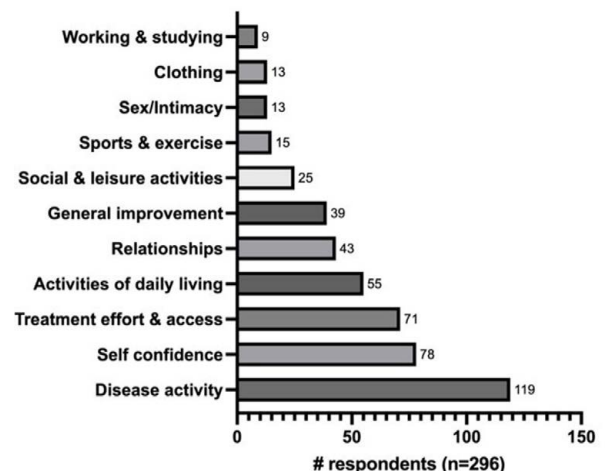


FIGURE 3. AI-generated summary of free-text responses to Q18: “Please share any thoughts or feedback related to the approval of secukinumab (Cosentyx) for HS and its impact on your overall well-being.”¹⁰

As a patient dealing with Hidradenitis Suppurativa (HS), I have mixed feelings about the approval of [Secukinumab] for HS. While I am hopeful that it may provide a new treatment option and improve my quality of life, I am also cautious due to concerns about potential side effects and the cost of the medication. Many patients in the HS community, including myself, are not yet familiar with [Secukinumab] and would like more information before trying it. Despite these uncertainties, the approval of new treatments gives me hope that there is ongoing research focused on HS, which could lead to more effective and accessible options in the future.

DISCUSSION

This national survey of individuals with HS provides insight into the current demographic landscape of HS and the treatment experience of those living with HS. Firstly, the results herein were consistent with the literature at the time of disease onset and diagnosis. Estimated disease onset according to published studies is after puberty with an associated 7- to 12-year delay in diagnosis.¹ Both of these observations were supported by responses with an average onset at approximately 20 years and diagnosis at approximately 29 years old. However, there were inconsistencies in the perceived prevalence of HS across different racial and ethnic groups. While current studies suggest that HS is more prevalent in Black and/or African American and Latinx women, most survey participants were white/Caucasian women which could attributed to the makeup of the listserv.¹⁻³

Notably, this study highlighted that a small minority of respondents are satisfied with current treatments available for HS, and many are unaware of FDA-approved options, with over half of respondents reporting that their dermatologist or other healthcare provider had not discussed FDA-approved options with them. Yet, most respondents indicated that it was important to have FDA-approved treatments for HS and believed that their use would lead to improved overall quality of life. Specifically, both the summaries of free text responses and DLQI frequency graph demonstrated that additional FDA therapies would have a pronounced impact on quality-of-life measures such as self-confidence and overall health. These findings emphasize the overwhelming potential to ease the tremendous psychosocial burden of HS on patients with the addition of more approved treatments. Additionally, our findings underscore the amount of work left to address gaps in patient education and employ adequate advertising strategies to enhance patient awareness of available treatments for their condition.

Survey findings provided insight that respondents are likely being undertreated with available systemic therapies. According to the North American clinical management guidelines for HS published in 2019, biologics (ie, adalimumab) are first-line treatments for managing moderate (Hurley stage II) to severe (Hurley stage III) HS.⁷ However, of these respondents, less than 1 quarter (23.58%, 25/106) of those in Hurley stage II and slightly over half (51.45%, 71/138) of those classified into Hurley stage III reported using biologics. This undertreatment is likely correlated with the high rates of dissatisfaction with management strategies, as supported by a recent qualitative study of HS treatment selection. In this study, Salame et al performed an investigation to explore factors affecting treatment decisions and demonstrated that respondents with HS who experienced increased pain and debilitation were more willing to incorporate a biologic medication compared to their counterparts.⁸ It was shown that patients perceived biologics as a last resort option for management of disease, influenced

by a combination of misunderstanding adverse risks, quality of information available on the internet, conversations with their dermatologist, advertisements, and the experiences of friends and family.⁸ Investigators called attention to the gaps in knowledge that dermatologists must help their patients fill to assist patients in making educated decisions focused on prevention of disease progression.

Another recent study by Tolson et al could also explain undertreatment and dissatisfaction of HS management in the context of dermatology versus non-dermatology clinicians. In this investigation, antibiotic prescribing patterns of dermatologists versus non-dermatologists were compared, and showed that 72% of HS visits were conducted by non-dermatology clinicians with antibiotics prescribed in 51.9% of these encounters. While there was no difference found between these groups in their likelihood to prescribe antibiotic therapies, dermatology clinicians most commonly prescribed tetracyclines, a first-line recommendation for systemic antibiotics in treatment of HS per guidelines, whereas non-dermatology clinicians most commonly prescribed penicillin/cephalosporins.⁹ While the respondents were not specifically questioned about whether or not a dermatologist manages their HS, treatment dissatisfaction rates expressed by respondents may be impacted by the care received from a non-dermatology provider who may be less familiar with HS-specific therapeutic options, treatment guidelines, and have varied levels of exposure and formal education in this area compared to their dermatologist counterparts.

Nearly 75% of respondents endorsed that the recent approval of secukinumab instills confidence in the development of future, more effective treatments for HS which are sorely lacking to date. While respondent-reported thoughts related to approval of secukinumab were of varied opinion, most concerns were related to insurance coverage and side effects. This suggests that the remaining hesitancy regarding confidence in the development of these treatments is primarily centered on issues of access and cost. Further supporting this, other responses indicated that respondents were cautiously optimistic about the general efficacy of secukinumab, noting that its recent approval is an encouraging step toward expanding treatment options in the near future. Interestingly, self-identified Hurley stage III respondents had polarized opinions, as they were statistically more likely to have either greater or lesser confidence compared to respondents with milder disease manifestations. This could in part be due to the notion that increased disease severity is associated with more 'failed' experiences with available therapeutic options, and as a result, linked with a greater degree of skepticism. For example, a respondent who has been on adalimumab and found it to be ineffective for their HS may be more apprehensive about the development of additional FDA therapies, especially if those treatments are in the same

medication category, such as in the case of adalimumab and secukinumab which are both biologics.

Limitations

Limitations of this study include its cross-sectional design and potential for sampling and response bias which limits generalizability. Additionally, accuracy of responses is limited by potential misinterpretation of question stems by respondents. Finally, in assessing free responses related to the approval of secukinumab, many respondents indicated little to no knowledge about its approval, potentially signaling a premature distribution of the survey and a missed opportunity to educate respondents.

CONCLUSION

These survey results provide invaluable insight into the high rates of respondent dissatisfaction with current HS treatment options, likely attributed to undertreatment with available therapies and gaps in respondent knowledge. Respondents were overwhelmingly unaware of FDA-approved options and reported that their dermatologist or other healthcare provider had not recommended these therapies for them, despite biologics being first-line therapies for moderate-to-severe HS. Apart from these sentiments, respondents expressed a strong desire for increased development and approval of FDA-approved therapies, which were strongly associated with a perceived positive impact on quality of life.

Future research and advocacy efforts should focus on increasing the number of FDA-approved therapies, while simultaneously addressing potential treatment inadequacies in patient care and knowledge. Future studies should further evaluate other underlying reasons such as barriers to care, advertising approaches, and utilize enhanced patient-provider communication strategies to address gaps in care, empower patients, and dispel misinformation.

DISCLOSURES

The authors have no conflicts of interest. Ethics statement: This study was declared IRB-exempt by the research ethics committee of The George Washington School of Medicine and Health Sciences IRB-Board (IRB#: NCR235179).

REFERENCES

- Okoye GA. Hidradenitis Suppurativa. In: Kang S, Amagai M, Bruckner AL, et al. eds. *Fitzpatrick's Dermatology*, 9e. McGraw-Hill Education; 2019. <https://accessmedicine.mhmedical.com/content.aspx?bookid=2570§ionid=210420511>. Accessed August 23, 2024.
- McMillan K. Hidradenitis suppurativa: number of diagnosed patients, demographic characteristics, and treatment patterns in the United States. *Am J Epidemiol*. 2014;179(12):1477-1483. doi:10.1093/aje/kwu078
- Kim WB, Sibbald RG, Hu H, et al. Clinical features and patient outcomes of hidradenitis suppurativa: a cross-sectional retrospective study. *J Cutan Med Surg*. 2016;20(1):52-57. doi:10.1177/1203475415602840

- Stergianou D, Kanni T, Damoulari C, et al. An evaluation of secukinumab for the treatment of moderate-to-severe hidradenitis suppurativa. *Expert Opin Biol Ther*. 2024;24(4):225-232. doi:10.1080/14712598.2024.2343112
- FDA approves Novartis Cosentyx® as the first new biologic treatment option for hidradenitis suppurativa patients in nearly a decade. <https://www.novartis.com/news/media-releases/fda-approves-novartis-cosentyx-first-new-biologic-treatment-option-hidradenitis-suppurativa-patients-nearly-decade>. Accessed January 1, 2024.
- Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216. doi:10.1111/j.1365-2230.1994.tb01167.x
- Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81(1):91-101. doi:10.1016/j.jaad.2019.02.068
- Salame N, Sow YN, Siira MR, et al. Factors affecting treatment selection among patients with hidradenitis suppurativa. *JAMA Dermatol*. 2024;160(2):179-186. doi:10.1001/jamadermatol.2023.5425
- Tolson H, Kikuchi R, Yamamoto RK, et al. Comparing antibiotic prescribing patterns for hidradenitis suppurativa between dermatology and non-dermatology ambulatory providers. *Skin Health Dis*. 2024;4(5):e451. doi:10.1002/ski.2.451
- OpenAI. (2024). ChatGPT (4o mini) [Large language model]. <https://chat.openai.com/>

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48

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Rituximab in the Treatment of Epidermolysis Bullosa Acquisita: A Systematic Review of the Literature

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ABSTRACT

Epidermolysis bullosa acquisita (EBA) is a rare autoimmune disorder characterized by blistering of the skin and mucous membranes. Current pathophysiology implicates autoantibodies targeting type VII collagen, which serves as a crucial component of anchoring fibrils that attach the epidermis to the dermis. Management of EBA remains challenging and relies on a combination of anti-inflammatory, immunosuppressive, and immunomodulating agents. Despite treatment, EBA is often chronic and relapsing, thus significantly impacting patients' quality of life.¹³ In this report, we aimed to systematically review the literature to provide an overview of the effectiveness of pharmacotherapy in treating cases of EBA with rituximab (RTX), specifically. We explore the efficacy of RTX as immunomodulator monotherapy and also its use in combination with other agents. A total of 51 patients were included over 20 studies and all studies were either case reports/series or retrospective chart reviews. The most utilized adjuvant therapies were glucocorticoids (n = 29) in the forms of methylprednisolone (MP), prednisolone (PL), and prednisone (P). RTX use in combination with PL had the best overall result; this regimen resulted in 15.7% (n = 8) of patients having clinical remission (CR) and 9.8% (n = 5) having well-controlled (WC) disease. Notably, the review elucidated that 4 patients had treatment with RTX alone and 100% of them achieved either CR or partial remission/control (PR/C). Our review highlights the relative efficacy of RTX in combination therapy and as monotherapy for the treatment of this rare condition, but more powerful research in the form of randomized clinical trials is imperative in order to obtain a more comprehensive understanding of its utility in the treatment of EBA.

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INTRODUCTION

Epidermolysis bullosa acquisita (EBA) is a rare autoimmune blistering disorder caused by autoantibodies targeting type VII collagen, which is a critical component of anchoring fibrils responsible for maintaining the integrity of the skin's dermo-epidermal junction. Clinically, EBA presents with tense blisters and erosions, primarily on trauma-prone areas such as the hands, feet, knees, and elbows. Diagnosis typically involves a combination of clinical examination, histopathological analysis, and immunofluorescence studies demonstrating linear deposition of immunoglobulin G and complement along the basement membrane zone.

Treatment of EBA involves a multi-faceted approach aimed at controlling the extent of blistering, reducing inflammation, and preventing complications. Due to its rarity, with a prevalence ranging from 0.08 to 0.5 per million individuals, and the variable efficacy of treatments among patients, there is currently no universally endorsed therapeutic regimen. Various modalities have been explored in addressing this condition, select ones are delineated in Table 1 along with their respective mechanisms of action.

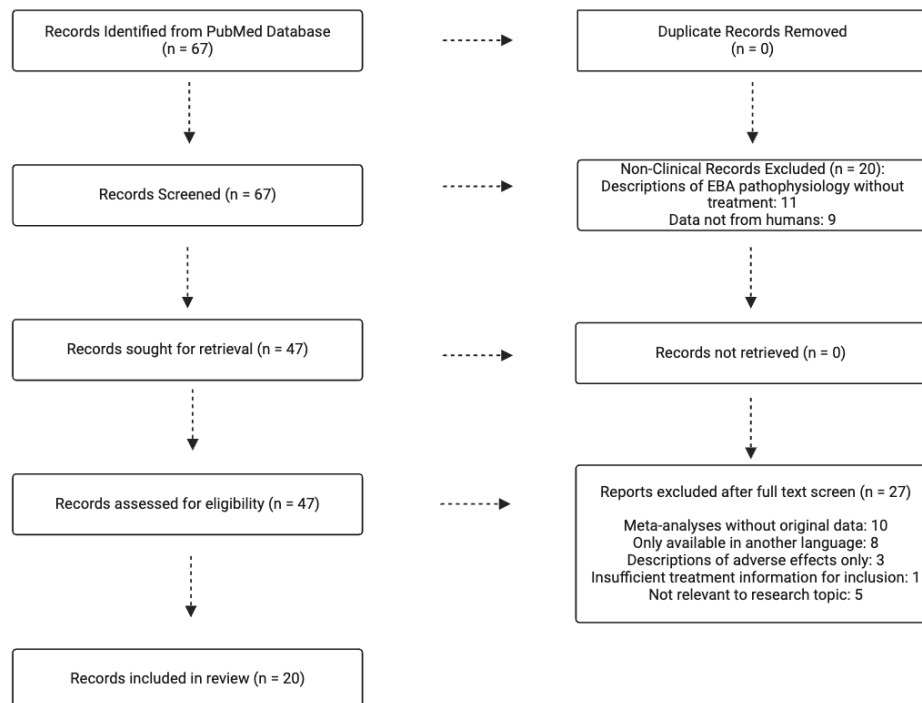
TABLE 1.

Treatment Modalities Used in the Management of Epidermolysis Bullosa Acquisita	
Outcome	n (%)
CR	1 (25%)
PR/C	3 (75%)

EBA presents significant challenges in management due to its chronic and debilitating nature, which impacts patients' quality of life and often requires long-term immunosuppressive therapy. Over the years, various treatment modalities have been explored in an effort to control disease activity and mitigate symptoms associated with EBA. Among these is rituximab (RTX), a monoclonal antibody targeting CD20-positive B cells, which has emerged as a promising therapeutic option. RTX works by depleting B cells and disrupting the production of pathogenic autoantibodies, thereby attenuating the autoimmune response underlying EBA.^{13, 14, 25}

When considering RTX for the treatment of EBA it is important to weigh the potential benefits against the associated risks. While rituximab has shown promise in managing EBA, particularly due

FIGURE 1. Flowchart of article selection process.



to its ability to target the underlying autoimmune processes, it can also lead to several side effects that are relevant to this patient population. Infusion-related reactions, such as fever, chills, and shortness of breath, are common and require close monitoring, especially since EBA patients may already be immunocompromised. Furthermore, the immunosuppressive nature of rituximab also increases the risk of infections, which could be particularly concerning for EBA patients, whose compromised skin integrity may predispose them to secondary infections. Additionally, the potential for serious side effects like progressive multifocal leukoencephalopathy (PML) or severe skin reactions, although rare, must be considered in the context of treating a condition as delicate as EBA. Therefore, although rituximab offers a valuable treatment option, its administration must be carefully managed to mitigate these risks in EBA patients.¹⁷

While RTX has demonstrated efficacy in the treatment of EBA, questions remain regarding its optimal use as monotherapy vs its incorporation into combination therapy regimens. This literature review aims to explore the existing evidence on the differences in treatment outcomes between RTX used as monotherapy and its use in combination therapy approaches for EBA. By synthesizing and analyzing available data from clinical studies, we seek to elucidate the comparative efficacy, safety profile, and outcomes associated with these treatment strategies.

MATERIALS AND METHODS

In the PubMed database, the query terms “epidermolysis bullosa acquisita AND rituximab” and “EBA AND rituximab” were used. One independent reviewer performed the initial search as well as independently screened articles and performed data extraction. Primary studies and case reports/series that studied the outcome of treatment with rituximab in cases of EBA malignancies were included. Articles were filtered for dates ranging from 2006 to December 31st, 2023, and for journal articles only. We excluded articles unavailable in the English language, articles without specific delineation of EBA, articles lacking rituximab utilization, and literature reviews without original data. The following data were extracted from all articles: study design, treatments utilized, total number of patients treated, patient characteristics, and results/outcomes of the treatment. Of note, one relevant study lacked specifics on treatment regimens and outcomes and one study was excluded due to an overlapping condition with EBA obscuring the clinical picture; although not included in the review, both of these studies will be summarized in the discussion section as they hold relevance to the research topic.

RESULTS

The initial search found 67 articles across PubMed. A manual review of these articles yielded 20 articles meeting the inclusion criteria. The article selection and review process are outlined in Figure 1. A summary of patient characteristics and outcomes of therapy is delineated in Table 2. Of the 20 studies, 3 were retrospective chart reviews and 17 were case reports/series.

TABLE 2.

Summary of Treatment Outcomes					
Authors	Number of Patients	Patient Age/Biological Sex	Adjuncts	Cycles of Rituximab	Outcome
Becker et al ¹	2	71, F	IV Ig, MMF, MP	2	P/RD
		46, M	D, IA, IV Ig	5	PR/C
Bevans et al ²	3	85, M	AZA, D, P	2	WC
		52, M	MMF, P	2	WC
		52, F	D, MMF, P	4	PR/C
Crichlow et al ³	1	58, F	MMF, PL	4	CR
Dasdar et al ⁴	15	72, M	MTX, PL	1	CR
		46, M	PL	1	CR
		43, M	PL	1	WC
		20, F	D, PL	1	WC
		47, F	PL	1	WC
		53, F	D, PL	1	PR/C
		88, M	MTX	1	CR
		45, F	--	1	CR
		54, M	D	1	WC
		54, M	D, MMF	2	PR/C
		29, F	D, MMF, PL	1	PR/C
		58, F	MTX, PL	1	WC
		57, F	PL	1	CR
		50, M	MTX, PL	1	WC
Kim et al ⁵	1	68, F	D, MMF, PL	1	PR/C
Kim et al ⁵	1	68, F	C, D, MP	4	CR
Kolesnik et al ⁶	1	71, F	D, IA, PL	4	CR
Kubisch et al ⁷	1	71, F	IA	4	CR
Lamberts et al ⁸	5	59, F	PL, TS	2	CR
		87, F	AZA, PL	2	DRD
		56, F	AZA, PL, TS	2	PR/C
		25, M	D, PL, TS	2	CR
		43, F	D, PL	2	P/RD
Le Roux-Villet et al ^{9*}	5	56, F	MTX	4	CR
		17, F	AZA, D, SZ	4	CR
		30, F	CS, P	4	CR
		79, F	D, SZ	4	CR
		70, M	D, P	4	CR
McKinley et al ¹¹	1	13, M	D	2	CR
Mendes et al ¹²	1	69, M	--	4	PR/C
Niedermeier et al ¹⁴	2	67, M	IA, MMF	4	PR/C
		42, M	IA, MMF	4	WC
Oktem et al ¹⁵	5	61, F	IV Ig	4	WC
		56, M	IV Ig	4	WC
		31, M	IV Ig, C	4	WC
		55, M	IV Ig	2	WC
		50, F	IV Ig	4	WC
Rousset et al ^{17*}	1	28, F	PL	2	DRD
Sadler et al ¹⁸	1	71, F	AZA	5	WC
Saha et al ¹⁹	1	54, F	MMF	12	CR
Schmidt et al ²²	1	46, M	AZA, C, PL	4	CR
Szymański et al ²³	2	73, F	P	2	WC
		25, M	--	4	PR/C
Wallet-Faber et al ²⁶	1	75, F	AZA, P	4	WC
Yang et al ²⁷	1	49, M	--	4	PR/C

*Mucomembranous sub-type of EBA. Treatment Key: AZA, azathioprine; C, colchicine; CS, cyclosporine; D, dapsone; IA, immunoadsorption; IV Ig, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; MP, methylprednisolone; P, prednisone; PL, prednisolone; TCS, topical steroid; SZ, sulfasalazine. Outcome Key: CR, clinical remission; DRD, disease-related death; PR/C, partial remission/control; P/RD, progressive/recurrent disease; WC, well-controlled.

A total of 51 patients with EBA treated with RTX were included. All patients received RTX therapy with an average number of 2.86 cycles (range: 1-12 cycles; SD 1.89). Of the 51 EBA cases in the studies, 6 (11.8%) were found to be mucomembranous sub-type (delineated with "*" in Table 2). The rest of the case subtypes were not specified. The mean age of patients was 53.7 years (range: 13-88 years; SD 18). In our review, patients identifying as females were more commonly affected (n = 29) as compared to patients identifying as males (n = 22). The number of patients treated with monotherapy was 4 and the number of patients treated with combo therapy was 47.

The mean time to clinical improvement was 9.2 months (range: 1-49 months; SD: 9.96), but this only included outcome information on 46 patients, not all 51. Furthermore, some of the studies did not delineate the true onset of improvement and only described what was seen on follow-up, thus resulting in a large standard deviation in the mean time to clinical improvement. As such, we did not formally conduct a data analysis to assess which treatment modalities led to a quicker onset of symptomatic improvement as the data reviewed is not representative of a true improvement timeline due to the heterogeneity in outcomes.

The overall outcomes of all patients are outlined in Table 3. The majority of patients (n = 47, 92.2%) had positive responses to their treatments. The overall percentage of complete remission (CR; n = 19) was 37.3%, and well-controlled (WC) disease was 33.33% (n = 17). 11 patients (21.6%) had partial remission/control, while 2 patients (3.9%) had progressive/recurrent disease and 2 patients (3.9%) suffered disease-related death.

TABLE 3.

Overall Outcomes of All Therapies	
Outcome	n (%)
CR	19 (37.3%)
WC	17 (33.3%)
PR/C	11 (21.6%)
PR/D	2 (3.9%)
DRD	2 (3.9%)

TABLE 4.

Positive Outcomes in Patients With Adjunct Treatment			
Outcomes	Most Common Adjuncts	n (%)	Average Number of RTX Cycles
CR	PL	8 (42.1%)	2.75
WC	PL	5 (29.4%)	3.6
	IVIg	5 (29.4%)	3.6
PR/C	D	6 (60%)	2.33

Adjunct Therapy

Discussion of positive treatment outcomes in patients with adjunct treatment are outlined in Table 4. We defined adjunct therapy as treatment with a modality other than RTX that was used concurrently during the duration of a patient's RTX therapy. Of those treated with combination therapy, glucocorticoids were the most common adjuvant treatment regimen used. 20 patients were on prednisolone (PL), 7 patients were on prednisone (P), and 2 patients were on methylprednisolone (MP). Combination with PL was the most common adjunct used in patients who achieved CR. The other adjunct treatments we reviewed did not showcase as impressive of an outcome as the combination of RTX with PL; using this combination, 8 patients had complete remission (CR) and 5 had disease that was well-controlled (WC). The average number of RTX cycles for patients achieving CR and WC with this regimen was 2.75 and 3.6, respectively. In patients who had PR/C, the most common adjunct was dapsone (D) (n = 6), with the average number of RTX cycles being 2.33.

Monotherapy

Only a small subset (4 out of 51) of patients received treatment with rituximab alone with outcomes detailed in Table 5. Of these patients, 1 patient achieved CR (25%) and 3 patients had PR/C (75%). Despite the limited number of cases, the success of rituximab monotherapy is noteworthy, as 100% of these patients had positive outcomes; RTX monotherapy success was shown to be higher when compared with the percentage of patients having positive outcomes with combination therapy (n = 43, 84.3%). The average number of RTX cycles for patients achieving CR and PR/C with this regimen was 1 and 3.33, respectively.

These findings underscore the potential of rituximab as a promising monotherapy option in EBA management, highlighting its ability to induce significant clinical responses in a considerable proportion of patients. These findings emphasize the potential of rituximab as a promising treatment option and warrant further investigation into its efficacy and safety in EBA management.

TABLE 5.

Assessment of RTX Monotherapy	
Outcome	n (%)
CR	1 (25%)
PR/C	3 (75%)

Study Without Treatment Specificity

There was 1 study that lacked specifics on treatment regimens and/or outcomes. However, the data included in this case series were useful to the overall understanding of rituximab utility. In Schauer et al's 2022 study, 2 patients were treated with RTX, but their adjunct treatments and outcomes were not well-defined, thus leading to exclusion. The patient in Case 1 was on RTX with adjunct IVIg, but it is unclear from the study if her previous therapies were continued. According to the study, the patient achieved stable disease, but it was unclear at what point, and no further description of what stability entails was provided. The patient in Case 2 was initially on RTX with adjunct IV Ig, prednisolone (PL), and topical corticosteroids (TCS). However, this patient had progressive/recurrent disease (P/RD), for which the flares were treated with mycophenolate mofetil (MMF), immunoadsorption (IA), and PL. The length of time to assessment of P/RD was unclear and it was also unclear if RTX was continued or discontinued during these flares. This patient did not develop disease-related death, but did end up having septic thromboembolism and bacterial septicemia.²²

Study With Overlapping Condition

There was 1 study that had the overlapping Brunsting-Perry variant of cicatricial pemphigoid in addition to EBA; since it was not solely EBA being treated, this case could not be included in the review. In Li et al's 2011 study, the patient received RTX and prednisone for their 2 conditions, which led to complete remission of both conditions at month 6. This case is significant in highlighting the difficulty that comes with diagnosing EBA. EBA has many clinical presentations and can often be mistaken for other conditions or overlap with other blistering conditions. Thus, it is important for clinicians to keep EBA on the differential as diagnostic delays can lead to worse prognoses and disease progression.¹⁰

DISCUSSION

This literature review provides a narrative analysis of the use of rituximab in the treatment of EBA, focusing on the comparison between rituximab monotherapy and combination therapy approaches, as well as investigating which adjuncts had the best outcomes. Despite the limited number of cases studied, rituximab monotherapy demonstrated material efficacy, with all patients experiencing positive outcomes. This is particularly noteworthy considering the challenging nature of EBA, a chronic autoimmune blistering disease that can be difficult to treat. However, it is important to recognize that while the evidence synthesized from various sources offers valuable insights into the efficacy, safety, and outcomes associated with these treatment strategies, several limitations need to be acknowledged. The quality of available evidence varies across studies, and heterogeneity in study designs and patient populations introduces challenges in drawing definitive conclusions.

The scarcity of high-quality randomized controlled trials (RCTs) directly comparing rituximab monotherapy and combination therapy regimens in EBA restricts the ability to make conclusive recommendations regarding treatment strategies. The temporal relevance of the included studies also warrants consideration, as new evidence may have emerged since the completion of this review.

Nevertheless, the review highlights the clinical relevance of exploring different treatment approaches involving rituximab and underscores the need for further research to address unanswered questions and refine treatment strategies in EBA. Understanding the relative merits and limitations of rituximab as monotherapy vs combination therapy is crucial for informing clinical decision-making and optimizing patient care for EBA. Thus, further research into the pathogenesis and targeted therapies is warranted to improve outcomes and advance the field toward more effective and personalized treatment approaches for individuals living with EBA.

The comparison between rituximab monotherapy and combination therapy sheds light on the relative efficacy of different treatment approaches. In this review, rituximab monotherapy appeared to offer certain advantages, including a higher observed success rate and possibly fewer side effects or complications. However, combination therapy remains a valuable approach, particularly in cases where synergistic effects with other agents may enhance disease control.

The analysis of adverse events is a crucial aspect of medication evaluation, yet not all studies included in this review provided detailed information on this topic. The lack of consistent reporting on adverse events can impact the overall understanding of a medication's safety profile and this gap somewhat limits the ability to make true comprehensive comparisons across studies. The reasons for this omission vary; some studies may have focused primarily on efficacy outcomes, while others may have encountered limitations in data collection, reporting standards, and methods of patient evaluation. In the combination group, side effects that were discussed included nausea, vomiting, immunosuppression, and post-inflammatory hyper-pigmentation. Only one study in the monotherapy group, Yang et al, discussed side effects; but these unfortunately did not pertain to rituximab, but rather to the previous modalities that the patient had tried in the past for his EBA. Despite these inconsistencies, the available data on adverse events revealed that in the group of patients treated with combination therapy, 2 patients experienced disease-related death, while in the rituximab monotherapy group, no such adverse effect occurred.

Another significant challenge in assessing the severe adverse effects of the medications is distinguishing whether these effects arise from the medications themselves, the severity of

the underlying disease, EBA sub-type, disease location, or a combination of some or all of these factors. This difficulty is exacerbated by the lack of standardization in disease descriptions across studies. Without a consistent framework for categorizing disease severity, it becomes challenging to determine the extent to which the adverse effects that patients experience are attributable to the medication vs the disease. This ambiguity can lead to varied interpretations and potentially misleading conclusions about the safety profile of the medications. To enhance the accuracy and reliability of future research, it is crucial to establish standardized criteria for disease descriptions and systematically report adverse effects. This approach would facilitate clearer distinctions between medication-induced and disease-related adverse effects, ultimately contributing to more robust and comparable study findings.

By examining the existing literature, we aimed to provide insights into the evolving landscape of therapeutic interventions for this challenging autoimmune condition, ultimately striving towards improved treatment strategies and better outcomes for individuals living with EBA. Comparing rituximab's efficacy as monotherapy to its role as an adjunct treatment offers valuable insights into optimizing treatment strategies for EBA. Investigating whether rituximab is more effective when used alone or in combination with other immunosuppressive agents can help clinicians tailor treatment regimens to individual patient needs, potentially improving disease control and quality of life. Moreover, using rituximab as an adjunct treatment may allow for the reduction of overall immunosuppressive burden, improving treatment tolerability while maintaining efficacy. Comparative studies evaluating rituximab's efficacy in different treatment contexts contribute to evidence-based decision-making in clinical practice, guiding clinicians in selecting the most appropriate treatment approach for individual patients. Overall, investigating rituximab's efficacy as both monotherapy and adjunct treatment offers a comprehensive understanding of treatment optimization and long-term disease management strategies in EBA, ultimately improving outcomes for affected individuals.

CONCLUSION

To our knowledge, this study is the first systematic review on rituximab outcomes specifically in patients with EBA; our study showcases the potential efficacy of rituximab therapy both as combination therapy and alone as a treatment option for this rare condition.

The management of EBA requires a comprehensive and individualized approach, taking into account the severity of disease, extent of involvement, and patient preferences. Close collaboration between dermatologists, immunologists, and other healthcare providers is essential in optimizing treatment outcomes and enhancing the quality of life for individuals living with EBA.

Moving forward, prospective studies with standardized protocols are warranted to provide higher-quality evidence and more robust conclusions regarding the comparative effectiveness of rituximab monotherapy vs combination therapy. Long-term follow-up studies are essential to assess the durability of treatment responses and potential adverse effects associated with rituximab therapy. Additionally, mechanistic studies focusing on the immunological pathways involved in EBA and the mechanisms of action of rituximab can deepen our understanding of disease pathogenesis and inform personalized treatment approaches. Furthermore, including adverse event data in studies and establishing a standardized criteria for disease descriptions will help provide a complete picture of a medication's effects, thus informing wholistic clinical decision-making.

Ultimately, ongoing research efforts aimed at addressing existing limitations, filling knowledge gaps, and advancing the field are crucial for improving outcomes and enhancing patient care in EBA.

DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES

1. Becker M, Schumacher N, Schmidt E, et al. Evaluation and comparison of clinical and laboratory characteristics of patients with IgA epidermolysis bullosa acquisita, linear IgA bullous dermatosis, and IgG epidermolysis bullosa acquisita. *JAMA Dermatol.* 2021;157(8):917-923. doi:10.1001/jamadermatol.2021.0762
2. Bevans SL, Sami N. The use of rituximab in treatment of epidermolysis bullosa acquisita: three new cases and a review of the literature. *Dermatol Ther.* 2018;31(6):e12726. doi:10.1111/dth.12726
3. Crichlow SM, Mortimer NJ, Harman KE. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol.* 2007;156(1):194-196. doi:10.1111/j.1365-2133.2006.07596.x
4. Dasdar S, Kianfar N, Tavakolpour S, et al. Rituximab for the treatment of epidermolysis bullosa acquisita: a large case series of 15 patients. *J Dtsch Dermatol Ges.* 2023;21(7):779-784. doi:10.1111/ddg.15108
5. Kim JH, Lee SE, Kim SC. Successful treatment of epidermolysis bullosa acquisita with rituximab therapy. *J Dermatol.* 2012;39(5):477-479. doi:10.1111/j.1346-8138.2011.01360.x
6. Kolesnik M, Becker E, Reinhold D, et al. Treatment of severe autoimmune blistering skin diseases with combination of protein A immunoabsorption and rituximab: a protocol without initial high dose or pulse steroid medication. *J Eur Acad Dermatol Venereol.* 2014;28(6):771-780. doi:10.1111/jdv.12175
7. Kubisch I, Diessenbacher P, Schmidt E, et al. Premonitory epidermolysis bullosa acquisita mimicking eyelid dermatitis: successful treatment with rituximab and protein A immunoapheresis. *Am J Clin Dermatol.* 2010;11(4):289-293. doi:10.2165/11533210-000000000-00000
8. Lamberts A, Euverman HJ, Terra JB, et al. Effectiveness and safety of rituximab in recalcitrant pemphigoid diseases. *Front Immunol.* 2018;9:248. doi:10.3389/fimmu.2018.00248
9. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. Rituximab for patients with refractory mucous membrane pemphigoid. *Arch Dermatol.* 2011;147(7):843-849. doi:10.1001/archdermatol.2011.54
10. Li Y, Foshee JB, Sontheimer RD. Sustained clinical response to rituximab in a case of life-threatening overlap subepidermal autoimmune blistering disease. *J Am Acad Dermatol.* 2011;64(4):773-778. doi:10.1016/j.jaad.2009.09.045
11. McKinley SK, Huang JT, Tan J, et al. A case of recalcitrant epidermolysis bullosa acquisita responsive to rituximab therapy. *Pediatr Dermatol.* 2014;31(2):241-244. doi:10.1111/pde.12006
12. Mendes SR, Coutinho I, Cardoso JC. Epidermolysis bullosa acquisita treated with rituximab. *BMJ Case Rep.* 2021;14(7):e243432. doi:10.1136/bcr-2021-243432

13. Miyamoto D, Gordilho JO, Santi CG, et al. Epidermolysis bullosa acquisita. *An Bras Dermatol.* 2022;97(4):409-423. doi:10.1016/j.abd.2021.09.010
14. Niedermeier A, Eming R, Pfütze M, et al. Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). *Arch Dermatol.* 2007;143(2):192-198. doi:10.1001/archderm.143.2.192
15. Oktem A, Akay BN, Boyvat A, et al. Long-term results of rituximab-intravenous immunoglobulin combination therapy in patients with epidermolysis bullosa acquisita resistant to conventional therapy. *J Dermatolog Treat.* 2017;28(1):50-54. doi:10.1080/09546634.2016.1179711
16. Paul F, Cartron G. Infusion-related reactions to rituximab: frequency, mechanisms and predictors. *Expert Rev Clin Immunol.* 2019;15(4):383-389. doi:10.1080/1744666X.2019.1562905
17. Pope E, Lara-Corrales I, Mellerio J, et al. A consensus approach to wound care in epidermolysis bullosa. *J Am Acad Dermatol.* 2012;67(5):904-917. doi:10.1016/j.jaad.2012.01.016
18. Rousset L, Bohelay G, Gille T, et al. Bronchial involvement in mucous membrane pemphigoid: 2 cases and a literature review. *Ann Dermatol Venerol.* 2023;150(1):64-70. doi:10.1016/j.annder.2022.08.009
19. Sadler E, Schaffleitner B, Lanschuetzer C, et al. Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol.* 2007;157(2):417-419. doi:10.1111/j.1365-2133.2007.08048.x
20. Saha M, Cutler T, Bhogal B, et al. Refractory epidermolysis bullosa acquisita: successful treatment with rituximab. *Clin Exp Dermatol.* 2009;34(8):e979-e980. doi:10.1111/j.1365-2230.2009.03608.x
21. Santi CG, Gripp AC, Roselino AM, et al. Consensus on the treatment of autoimmune bullous dermatoses: bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita – Brazilian Society of Dermatology. *An Bras Dermatol.* 2019;94(2 Suppl 1):33-47. doi:10.1590/abd1806-4841.2019940207
22. Schauer F, Nyström A, Kunz M, et al. Case report: diagnostic and therapeutic challenges in severe mechanobullous epidermolysis bullosa acquisita. *Front Immunol.* 2022;13:883967. doi:10.3389/fimmu.2022.883967
23. Schmidt E, Benoit S, Bröcker EB, et al. Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. *Arch Dermatol.* 2006;142(2):147-150. doi:10.1001/archderm.142.2.147
24. Szymański K, Kowalewski C, Pietrzyk E, et al. Case report: biological treatment of epidermolysis bullosa acquisita: report on four cases and literature review. *Front Immunol.* 2023;14:1214011. doi:10.3389/fimmu.2023.1214011
25. Tešanović Perković D, Bukvić Mokos Z, et al. Epidermolysis bullosa acquisita—current and emerging treatments. *J Clin Med.* 2023;12(3):1139. doi:10.3390/jcm12031139
26. Thomas RM, Colon A, Motaparthy K. Rituximab in autoimmune pemphigoid diseases: indications, optimized regimens, and practice gaps. *Clin Dermatol.* 2020;38(3):384-396. doi:10.1016/j.clindermatol.2019.07.023
27. Wallet-Faber N, Franck N, Batteux F, et al. Epidermolysis bullosa acquisita following bullous pemphigoid, successfully treated with the anti-CD20 monoclonal antibody rituximab. *Dermatology.* 2007;215(3):252-255. doi:10.1159/000106585
28. Yang A, Kim M, Craig P, Murrell DF. A case report of the use of rituximab and the epidermolysis bullosa Disease Activity Scoring Index (EBDASI) in a patient with epidermolysis bullosa acquisita with extensive esophageal involvement. *Acta Dermatovenereol Croat.* 2018;26(4):325-328.

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PSPECIAL PSITE PSORIASIS PEARLS: Picking the Right Combo Meal for your Patients



HOST
Dr. Adam Friedman, MD, FAAD



GUEST
PETER A. LIO, MD

What a time to be a psoriasis patient, decades into the golden age of management strategies. With an embarrassment of treatment riches, all patients are clear right? Slow your roll you say? The paradigm shift has occurred and for many of our established patients it's now about cleaning up the biologic leftovers, especially when located on far reaching and sensitive sites. How to do so? So glad you asked, as we are so fortunate Dr. Peter Lio, clinical assistant professor of dermatology and pediatrics at Northwestern, joined host Dr. Adam Friedman to provide his experiences to pick apart the NYC diner menu of topical option add-ons to our powerful buffet of advanced systemics. Make sure to come hungry!



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Single-Center, Open-Label Study to Evaluate Improvement of Hair Appearance With Novel Hair Growth Serum

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ABSTRACT

Background: REVIVV[®] is a topical hair growth serum with a proprietary formula of botanicals that addresses multiple factors involved in hair loss pathophysiology. This open-label, prospective, single-center study evaluated the efficacy of REVIVV[®], a topical hair growth serum, in 20 adults (10 male, 10 female) with mild to moderate hair loss over 6 months. Participants applied the serum twice daily, and assessments were conducted at baseline, 4, 12, and 24 weeks. Dermatologist evaluations and patient self-assessments of hair quality and growth were performed using a 7-point Likert scale. Results Investigator-rated improvements in hair quality and growth increased from 0.75 and 0.81 at 4 weeks to 1.73 and 1.83 at 24 weeks, respectively. Patient-reported assessments showed that 85% of participants noted improved hair quality and growth at 24 weeks, with 50% reporting great improvement. Patient satisfaction was high, with 80% of participants being moderately or greatly satisfied at 4 weeks, increasing to 95% at 24 weeks. No adverse events related to the serum were reported throughout the study. The results demonstrate that twice-daily application of REVIVV[®] over 6 months is associated with increased hair growth and improved hair quality suggesting that REVIVV[®] may be an effective, non-pharmacological option for individuals seeking to improve hair growth and quality.

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INTRODUCTION

Hair loss is a prevalent issue affecting both men and women, often leading to considerable psychological distress. The causes of hair loss are multifaceted, encompassing medical conditions, medications, emotional and physical stress, post-partum, hormonal changes, aging, damage from styling or processing, or all in combination.^{1,2} This process leads to an alteration in the hair cycle, with a shortening of the anagen phase, a lengthening of the latency period, and miniaturization of the hair shaft turning from terminal into vellus-like hair. Perifollicular inflammation and immune deposits have also been shown to contribute to the pathophysiology.³

Pharmacological treatments for hair loss like finasteride and minoxidil are available but have side effects and their mechanisms of action are not well understood. Vitamins, minerals, and other nutrients are frequently used in a large range of products claiming to be efficient against hair loss but data from prospective intervention studies remain scarce.⁴⁻⁸

REVIVV[®] is a topical serum supplement, containing vitamins, minerals, proteins, and nutraceutical-grade botanical bioactives designed to restore hair health. The formulation

of botanicals includes potent anti-inflammatory, anti-stress adaptogenic, antioxidant, and DHT-inhibiting properties tailored to the specific needs of men and women. A previous study demonstrated that twice daily application of REVIVV over 8 weeks resulted in a statistically significant increase in hair thickness in the crown and vertex of the scalp in both males and females with androgenetic alopecia. Results also showed high patient satisfaction. Given these findings, we were interested in exploring the benefits of prolonged use of REVIVV.⁹

The present study aimed to evaluate the degree of change in hair growth and hair quality observed by patients and physicians after using REVIVV hair growth serum for 6 months. Patient satisfaction, safety, and tolerability were also assessed.

MATERIALS AND METHODS

Study Design

This was an open-label, prospective, single-center study in adult subjects. The study was conducted in one dermatologic office in New York City from May 2023 to March 2024 and a total of 20 evaluable subjects were enrolled. This study was conducted in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki, and applicable national

laws and regulations. All subjects provided written, informed consent to use their information in the current study, including photography.

Patients

Enrolled subjects were male and female adults aged 18 to 65 years of age with mild to moderate hair loss. Subjects with a history of surgical correction of hair loss on the scalp, history of autoimmune disease, previous clinical diagnosis of alopecia areata, scarring forms of alopecia, or hair loss for other reasons in the treatment area were excluded. Use of anti-androgenic therapies and other products or devices purported to promote scalp hair growth within 30 days prior to the study and for the duration of the study was not permitted. If patients received low-level lasers within 6 months prior to study start, they were not included. Enrolled participants were instructed not to use medicated shampoos or conditioners, or other medications that could potentially cause hair loss or affect hair growth.

Treatment

Participants applied the REVIVV Hair Growth Serum to the scalp twice daily for 6 months, in accordance with the product's instructions for use.

Assessments

Adverse events were monitored throughout the study. A dermatologist completed live assessments and assessments of standardized photographs using a Canfield imaging system. Evaluation included global hair growth improvement and hair quality improvement at the baseline visit, and 4 weeks, 12 weeks, and 24 weeks after the baseline visit. These assessments were performed using a 7-point Likert scale (greatly increased/improved, moderately increased/improved, slightly increased/improved, no change, slightly decreased/worsened, moderately decreased/worsened, and greatly decreased/worsened).

Patient questionnaires were completed at 4 weeks, 12 weeks, and 24 weeks after the initiation of treatment. Participants assessed hair quality using a 7-point Likert scale (greatly increased/improved, moderately increased/improved, slightly increased/improved, no change, slightly decreased/worsened, moderately decreased/worsened, and greatly decreased/worsened). Satisfaction with the study treatment was also assessed using a 7-point Likert scale (extremely satisfied, moderately satisfied, slightly satisfied, no change, slightly unsatisfied, moderately unsatisfied, greatly unsatisfied).

Statistical Analysis

Qualitative and quantitative analyses were performed. Evaluations of mean change of parameters from baseline to follow-up were analyzed using Wilcoxon signed-rank test. Values of $P \leq 0.05$ were considered statistically significant.

RESULTS

Of the 20 patients enrolled in the study, 10 were female and 10 were males, with 22% of patients having Fitzpatrick skin type IV-VI. The average investigator-rated improvement for hair quality was 0.75, and for hair growth, 0.81 at 4 weeks post-baseline. Improvement continued to increase to 1.69, 1.53, and 1.73, 1.83 for hair quality and hair growth at weeks 12 and 24 weeks, respectively (Figure 1A).

Patient-reported assessments of improvement were also positive. After 4 weeks of twice-daily use, 70% ($n=9$) of patients reported their hair quality had improved and 77% ($n=10$) of patients noted their hair growth increased (slightly, moderately, or greatly). After 24 weeks 85% ($n=11$) of patients noted their hair quality and hair growth increased slightly (8%), moderately (34%), and greatly (50%) (Figure 1B).

FIGURE 1. (A) Investigator-rated improvement of hair quality and hair growth. (B) Patient-rated improvement of hair quality and hair growth.

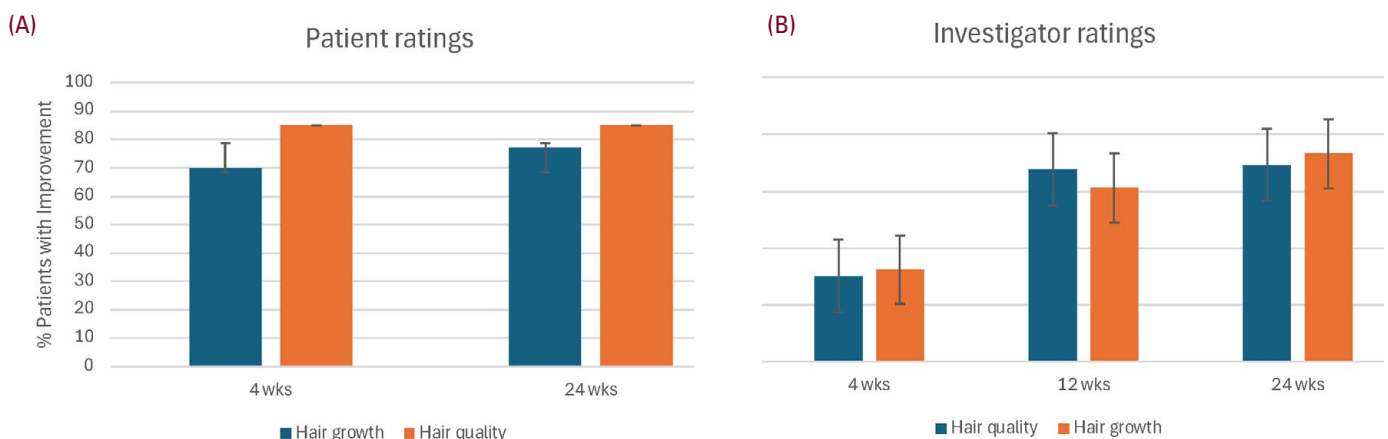


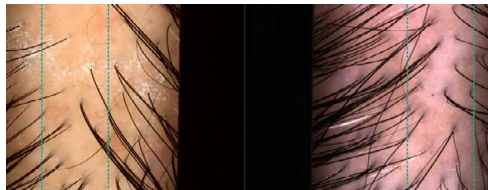
FIGURE 2. Global image of a 50-year-old male showing improvement in hair appearance at baseline and 24 weeks following use of REVIVV topical serum twice daily.



FIGURE 3. Global image of a 45-year-old female showing hair growth at baseline and 24 weeks following the use of REVIVV topical serum twice daily.



FIGURE 4. Trichoscopy showing improved hair appearance at 24 weeks post twice daily use of REVIVV from baseline.



Eighty percent of patients were moderately/greatly satisfied with the treatment at 4 weeks post-baseline and this number increased to 95% at the 24-week follow-up. Before and after photos from representative patients using twice daily REVIVV for 24 weeks are shown in Figures 2 to 4.

No adverse events or serious adverse events related to the REVIVV serum were reported. Subjects reported no signs of irritation, redness, or discomfort using the REVIVV serum during the duration of the study.

DISCUSSION

Twice-daily use of the REVIVV topical hair growth serum over 6 months led to improved global hair quality and growth, as demonstrated by both investigator and patient assessments. In this study, over half of participants observed an increase in hair growth after 4 weeks of twice-daily application and these results were sustained after 24 weeks of continuous use. High patient satisfaction ratings further validate the positive product feedback reported in the real-world study.

Although pharmacological agents for hair loss exist, patients are increasingly seeking non-pharmacological products with natural ingredients, as well as cost-effective therapies. Given the multifactorial nature of hair loss, employing a multipronged approach is crucial for achieving the most effective results.

The REVIVV topical hair growth serum's proprietary formula comprises botanicals with antiandrogenic properties tailored to the specific needs of men and women. It offers a high-compliance product that can be combined with oral medications or laser light therapies.

Limitations of this study include its completion at a single site, the lack of a placebo group, and a small sample size, which may limit the generalizability of the findings.

Future studies should investigate the reproducibility of these results with larger populations.

CONCLUSION

In conclusion, the proprietary formula of botanicals in the REVIVV hair serum addresses multiple factors involved in the complex pathophysiology of hair loss. These results demonstrate that twice-daily application of REVIVV over 6 months is associated with increased hair growth and improved hair quality, with no reported side effects.

DISCLOSURES

Dr Sadick is an advisor of WeThrivv. Dr Arruda, Dr Swearingen, Ms Elmadany, Ms Nakagama, Ms Lemoine, Ms Valmeus have nothing to disclose

REFERENCES

1. Coleman E. Types and treatment of hair loss in men and women. *Plast Surg Nurs.* 2020;40(4):222-235. doi:10.1097/PSN.0000000000000350
2. Sadick N, Arruda S. Understanding causes of hair loss in women. *Dermatol Clin.* 2021;39(3):371-374. doi:10.1016/j.det.2021.03.002
3. Sadick NS, Callender VD, Kircik LH, Kogan S. New insight into the pathophysiology of hair loss trigger a paradigm shift in the treatment approach. *J Drugs Dermatol.* 2017;16(11):s135-s140.
4. Deoghare S, Sadick NS. Combination therapy in female pattern hair loss. *J Cosmet Laser Ther.* 2023;25(1-4):1-6. doi:10.1080/14764172.2023.2222942
5. Kalhan V, Sadick N. The latest drugs and small molecule inhibitors for skin and hair. *J Drugs Dermatol.* 2017;16(12):1224-1228.
6. Kourosh AS, Santiago Mangual KP, Farah RS, et al. Platelet-rich plasma: advances and controversies in hair restoration and skin rejuvenation. *Dermatol Surg.* 2024;50(5):446-452. doi:10.1097/DSS.0000000000004115
7. Sadick NS. New-generation therapies for the treatment of hair loss in men. *Dermatol Clin.* 2018;36(1):63-67. doi:10.1016/j.det.2017.08.003
8. Sadick NS. The hair comeback. *Dermatol Clin.* 2021;39(3):ix. doi:10.1016/j.det.2021.04.005
9. Rapaport J, Sadgrove NJ, Arruda S, et al. Real-world, open-label study of the efficacy and safety of a novel serum in androgenetic alopecia. *J Drugs Dermatol.* 2023;22(6):559-564. doi:10.36849/JDD.7403

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Improvement in Skin Moisturization and Lack of Barrier Damage Following Treatment With Clascoterone Cream 1%

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ABSTRACT

Background: Topical medications commonly prescribed for the treatment of acne vulgaris may be limited by application-site dryness, which can result in skin barrier damage. This study aimed to evaluate the effects of clascoterone cream 1% on skin barrier properties in acne-prone individuals.

Methods: Participants ≥ 18 years of age with acne-prone skin were enrolled in a single-center, split-face study and randomized to twice-daily treatment with clascoterone cream 1% (approximately 0.5 g) to the right or left side of the face for 2 weeks. The primary and secondary endpoints were the changes in corneometry reading and transepidermal water loss (TEWL), respectively, between treated and untreated sides at week 2. Tolerability was evaluated from the severity of dryness, erythema, scaling, irritation, tightness, stinging, itching, and burning for each side using a 5-point scale from 0 (none) to 4 (severe).

Results: This study enrolled 50 participants (female, $n = 38$) with a mean $\pm$ standard deviation (SD) age of 31.1 ± 8.9 years. The mean $\pm$ SD corneometry reading was significantly higher for the treated vs untreated side at week 2 (131.3 ± 42.9 vs 113.9 ± 36.6 ; $P < 0.001$). There was no difference in TEWL between treated and untreated sides at any time point assessed. All tolerability parameters evaluated were rated as absent or minimal through week 2 for both sides.

Conclusion: Twice-daily treatment with clascoterone cream 1% for 2 weeks was associated with increased moisturization and maintenance of skin barrier function as assessed by corneometry and TEWL and was otherwise well tolerated.

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INTRODUCTION

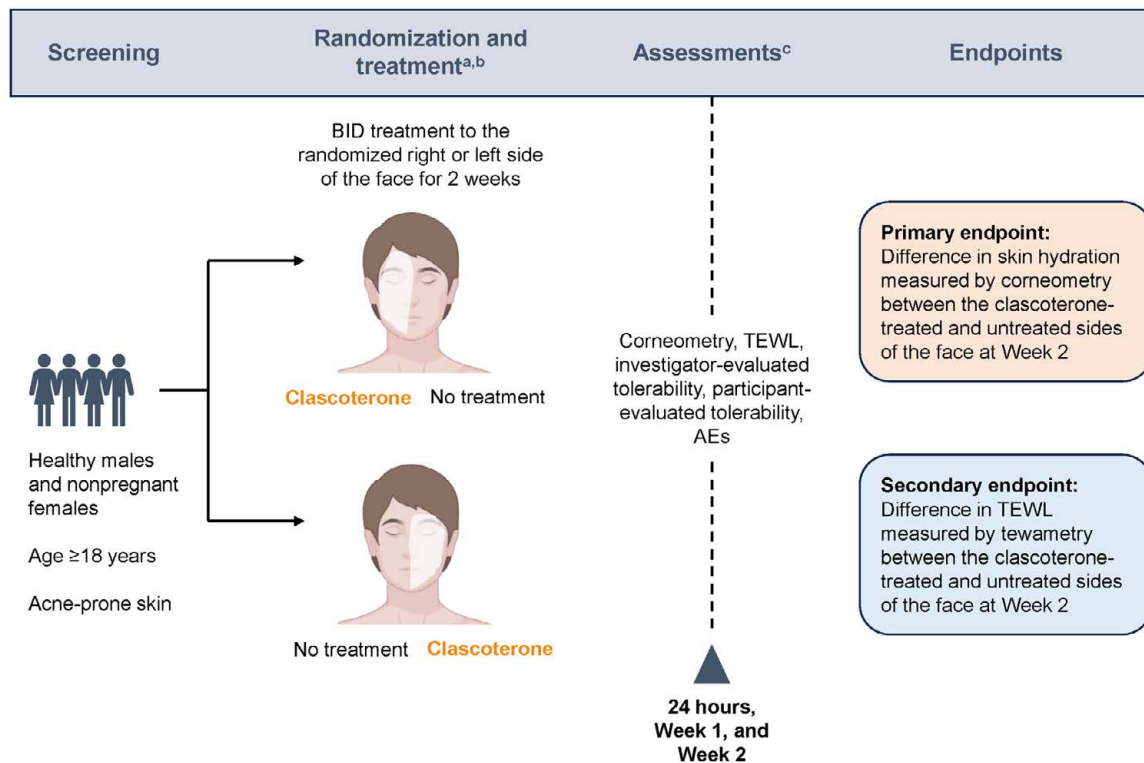
Acne vulgaris is one of the most prevalent dermatologic conditions in the US and worldwide.^{1,2} Although acne typically presents during adolescence, it is a chronic condition that can persist into adulthood.¹ The physical and psychological impacts of acne are often consequential for patients and can include pain, erythema, scarring, anxiety, and depression,^{3,4} highlighting the importance of early and effective treatment for patients with acne. Despite the range of acne treatments available, limitations in tolerability may contribute to the high rate of nonadherence to acne medications,⁵⁻⁷ which can impact efficacy and treatment success.⁸

As outlined in the American Academy of Dermatology guidelines, topical treatments are recommended as first-line agents in the treatment of acne vulgaris; however, therapies such as retinoids (eg, adapalene) and benzoyl peroxide may be limited by adverse effects, including dryness and irritation that can result in skin barrier damage and decreased patient

adherence.^{4,9-14} Topical agents with improved, less irritating vehicle formulations¹⁵ or concomitant use of moisturizers^{11,16} can improve tolerability and mitigate skin barrier damage during acne treatment, but adverse effects may still be a concern—particularly with combinations of 2 or more topical agents.¹⁷ Several new and effective topical treatment options for acne introduced within the past decade may provide better tolerability and therefore improve patient adherence.^{18,19}

Clascoterone cream 1%, a topical androgen receptor inhibitor, is a first-in-class therapy approved in the US in 2020 (with subsequent approvals in Canada and Australia) for the treatment of acne vulgaris in patients ≥ 12 years of age.²⁰⁻²³ The effect of clascoterone is attributed to competition with dihydrotestosterone for binding to androgen receptors within the skin, thereby preventing the transcription of androgen-responsive genes and decreasing sebum production.²⁴ The efficacy and safety of clascoterone cream 1% were established in two 12-week, randomized, double-blind, phase 3 clinical

FIGURE 1. Study design.



^aParticipants were not permitted to alternate application of clascoterone cream 1% between different sides of the face during the study.

^bParticipants were permitted to continue using a self-selected cleanser and sunscreen, which had been used for 30 days prior to study enrollment, with equal application to both sides of the face during the study.

^cCorneometry, TEWL, and tolerability assessments were also performed at baseline.
AE, adverse event; BID, twice daily; TEWL, transepidermal water loss.

trials and a 9-month extension study, in which adverse effects such as application-site pain, dryness, and irritation were not commonly reported.^{23,25} No head-to-head studies have been conducted to directly compare the efficacy and safety of clascoterone to those of other topical acne medications; however, the efficacy of clascoterone cream 1% was similar to that of topical retinoids including trifarotene and tazarotene in a recent meta-analysis.²⁶

Although low reported rates of dryness and cutaneous irritation in clinical trials of clascoterone cream 1% treatment suggest that it may have low potential for skin barrier disruption, the effect of clascoterone treatment on the integrity of the skin barrier has not been clinically evaluated. This study aimed to evaluate changes in skin barrier properties induced by treatment with clascoterone cream 1% in acne-prone individuals.

MATERIALS AND METHODS

Study Design and Participants

This single-center, split-face study evaluated changes in skin barrier properties following treatment with clascoterone cream 1% in participants with acne-prone skin. Male and nonpregnant female participants ≥18 years of age with all Fitzpatrick skin types who self-identified as having sensitive, acne-prone skin

and who were in generally good physical and mental health were eligible for enrollment. Individuals with any dermatologic disorder that in the investigator's opinion could interfere with the evaluation of skin characteristics, a previous hypersensitivity reaction to any of the ingredients in clascoterone cream 1%, clinically meaningful unstable medical disorders, a history of psychological illness or immunosuppressive/immune deficiency disorders, or who had planned surgeries and/or invasive medical procedures during the study were excluded, as were those who currently use or frequently used high doses of anti-inflammatory drugs or immunosuppressive medications.

The study was conducted in accordance with the principles described in the Declaration of Helsinki, Good Clinical Practice guidelines, and all local, legal, and regulatory requirements. Institutional review board (Allendale Institutional Review Board, Old Lyme, CT) approval was obtained for the study protocol and the informed consent form. All patients were required to provide written informed consent to participate in the study.

Treatments

Participants were randomized to treatment with clascoterone cream 1% twice daily to the right or left side of the face for 2 weeks, which represents 1 complete stratum corneum turnover cycle²⁷

(Figure 1). Participants were instructed to apply clascoterone cream 1% (approximately 0.5 g, half of the 1-g twice-daily recommended dose for the whole face in the clascoterone cream 1% Prescribing Information²⁰) to the entire right or left side of the face (including the forehead, cheek, and jawline) following cleansing every morning and evening and were not permitted to alternate application of clascoterone cream 1% between sides during the study. The assessing dermatologist was blinded as to which side of the face was receiving clascoterone cream 1% treatment. Participants were permitted to continue using a self-selected cleanser and sunscreen, which had been used for 30 days prior to study enrollment, with equal application to both sides of the face during the study; the use of any topical medications or facial skincare products other than sunscreen and cleanser was not allowed. Participants were not permitted to introduce any new colored cosmetics (lipstick, eye shadow, facial foundation, blush, or powder) during the study.

Assessments and Endpoints

All planned assessments were performed at baseline and during the treatment period at 24 hours, week 1, and week 2 (Figure 1). The primary endpoint was the difference in skin hydration measured by corneometry between the clascoterone-treated and untreated sides of the face at week 2. The secondary endpoint was the difference in transepidermal water loss (TEWL), a measure of epidermal barrier permeability, measured by tewametry between the clascoterone-treated and untreated sides of the face at week 2. Tolerability was evaluated by recording the severity of dryness, erythema, scaling, irritation, tightness, stinging, itching, and burning for each side of the face using a 5-point scale from 0 (none) to 4 (severe). Erythema, scaling, and irritation were assessed by the dermatologist investigator, whereas tightness, stinging, itching, and burning were assessed by the participant; dryness was assessed by both the investigator and the participant. Safety was also assessed by the monitoring of adverse events (AEs) at 24 hours, week 1, and week 2.

Statistical Analyses

No formal sample size calculations were performed due to the exploratory nature of this study. The sample size selected was based on the estimation of the number of participants required to achieve statistical significance. Ordinal tolerability assessment data were analyzed using Wilcoxon signed-rank test and sign test for paired comparisons at different time points; corneometry and tewametry data were confirmed to be normally distributed and then analyzed using paired *t*-tests performed using Microsoft Excel. No transformations were applied to the data. All statistical tests were 2-sided, and $P < 0.05$ was accepted as significant with no adjustment for multiple comparisons. Statistical analyses included all enrolled participants; missing data were not imputed.

RESULTS

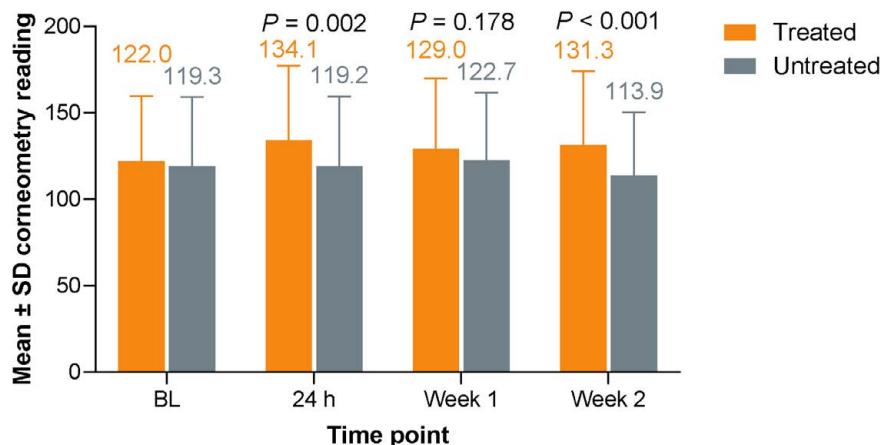
Patient Demographics

The study enrolled 50 participants (male, $n = 12$; female, $n = 38$), of whom 49 completed the study. The mean $\pm$ standard deviation (SD) age was 31.1 ± 8.9 (range, 19–45) years. Most of the participants were White (60%), 38% were Black or African American, and 2% were Hispanic.

Efficacy Outcomes

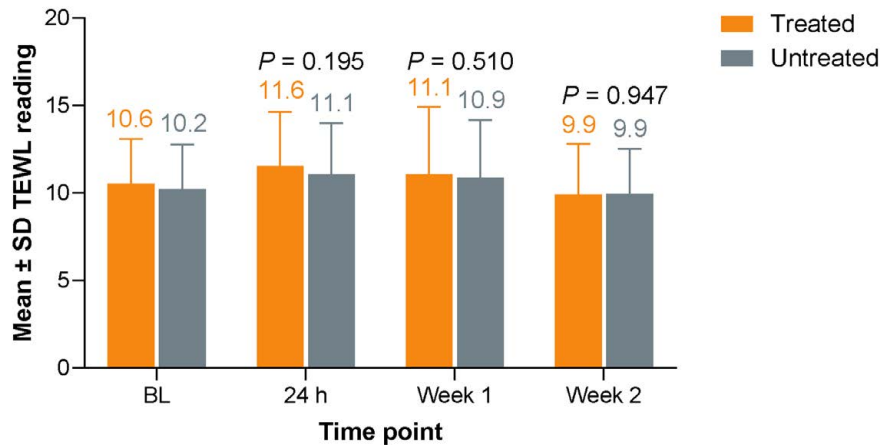
From baseline to week 2, the mean $\pm$ SD corneometry reading for the clascoterone-treated side of the face increased from 122.0 ± 37.7 to 131.3 ± 42.9 , whereas it decreased for the untreated side from 119.3 ± 39.7 to 113.9 ± 36.6 (Figure 2). The difference in corneometry reading for the clascoterone-treated vs untreated side was 15.0 ($P = 0.002$) at 24 hours, 6.3 ($P = 0.178$) at week 1, and 17.3 ($P < 0.001$) at week 2 of treatment. Consistent with these findings, the treatment difference in the change from baseline in corneometry reading favored the clascoterone-treated vs untreated side at 24 hours (12.3; $P = 0.041$), week 1 (3.6; $P = 0.531$), and week 2 (14.8; $P = 0.004$) of treatment. The mean $\pm$ SD TEWL readings for the clascoterone-treated side were 10.6 ± 2.5 at

FIGURE 2. Facial corneometry readings by visit from baseline to week 2.



BL, baseline; h, hours; SD, standard deviation.

FIGURE 3. Facial TEWL readings by visit from baseline to week 2.



BL, baseline; h, hours; SD, standard deviation; TEWL, transepidermal water loss.

baseline and 9.9 ± 2.9 at week 2, which were similar to those for the untreated side (10.2 ± 2.6 at baseline and 9.9 ± 2.6 at week 2; Figure 3). There was no statistically significant difference in mean TEWL between the clascoterone-treated and untreated sides of the face at 24 hours (0.5; $P=0.195$), week 1 (0.2; $P=0.510$), or week 2 (0.02; $P=0.947$) of treatment.

Tolerability Assessments

There was no statistically significant difference in any of the investigator-evaluated tolerability parameters (dryness, erythema, scaling, and irritation) between the clascoterone-treated and untreated sides of the face, all of which were rated as 0 (not present) at 24 hours, week 1, and week 2. Similarly, the mean severity rating for each of the participant-assessed

TABLE 1.

Summary of Participant-Evaluated Tolerability Assessments			
	24 hours N = 50	Week 1 N = 50	Week 2 N = 49
Dryness			
Treated	0.08 ± 0.27	0.06 ± 0.24	0
Untreated	0.14 ± 0.40	0.12 ± 0.33	0.08 ± 0.28
P-value	0.502	0.311	0.058
Tightness			
Treated	0.04 ± 0.20	0.02 ± 0.14	0.02 ± 0.14
Untreated	0.02 ± 0.14	0	0
P-value	0.596	0.436	0.436
Stinging			
Treated	0	0.02 ± 0.14	0
Untreated	0	0	0
P-value	1.000	0.436	1.000
Itching			
Treated	0.04 ± 0.28	0.04 ± 0.28	0
Untreated	0.02 ± 0.14	0	0
P-value	0.990	0.436	1.000
Burning			
Treated	0	0.02 ± 0.14	0
Untreated	0	0	0
P-value	1.000	0.436	1.000

Data are shown as mean ± SD. Responses to each parameter were scored on a 5-point scale from 0 (not present) to 4 (severe) for each side of the face. Data were analyzed using Wilcoxon signed-ranked test and sign test for paired comparisons at different time points. SD, standard deviation.

tolerability parameters (dryness, tightness, stinging, itching, and burning) ranged from 0 to 0.14 through week 2, with no statistically significant differences between the clascoterone-treated and untreated sides of the face (all $P>0.05$; Table 1).

Safety Outcomes

One AE of a fever, suspected to be from COVID-19, was reported in 1 participant; the participant was discontinued at the final study visit due to concerns about transmission to other study participants.

DISCUSSION

This study provides the first clinical evaluation of the effects of clascoterone cream 1% on skin barrier function in acne-prone individuals. Corneometry readings increased with no change in TEWL readings for the side of the face treated with clascoterone cream 1% twice daily for 2 weeks compared with the untreated side of the face, indicating increased moisturization and maintenance of skin barrier function, respectively, during treatment. The severity of each of the tolerability parameters was rated as none to minimal by the investigators and/or participants throughout the 2-week study period. These findings demonstrate that treatment with clascoterone cream 1% for 2 weeks did not disrupt the skin barrier in individuals with acne-prone skin and was otherwise well tolerated.

The term “epidermal barrier” generally refers to the ability of the stratum corneum to retain moisture, regulate and adapt to changes in TEWL, and maintain the selective permeability of the skin to exogenous and endogenous substances.²⁸ TEWL, a measure of epidermal barrier disruption, is significantly increased in patients with acne compared with healthy controls.²⁹ Topical acne medications such as benzoyl peroxide and topical retinoids can further exacerbate barrier disruption, leading to cutaneous side effects such as peeling, scaling, and erythema.⁹⁻¹⁴ These side effects may contribute to poor adherence to acne medications.⁶ Several randomized controlled trials have demonstrated that the concomitant use of moisturizers or other adjunctive products can limit the extent of skin barrier damage and reduce the severity of cutaneous side effects during acne treatment.^{11,16,30} However, the impact of adjuvant barrier repair therapies on clinical outcomes in acne treatment is contingent upon good adherence to both the medication and adjuvants,⁸ and the use of more complex treatment regimens (eg, involving a higher number of medications) may negatively impact patient adherence.^{31,32}

Improvements in vehicle design (eg, creams vs gels or the addition of emollients) have helped to mitigate the negative barrier impacts and cutaneous side effects of topical acne medications.^{15,33} Differences in tolerability and patient satisfaction following treatment with 2 distinct formulations of tretinoin—a 0.05% lotion and a 0.05% generic cream—were

evaluated in a split-face study in patients ≥ 18 years of age with acne.¹⁵ Following 2 weeks of once-daily treatment, tretinoin lotion produced significantly less irritation and was associated with higher rates of patient satisfaction compared with tretinoin cream.¹⁵ These findings highlight the importance of well-designed formulations to the development of topical acne medications, as the formulation can have a significant impact on tolerability and patient satisfaction and, in turn, adherence to medication.¹⁵

A limitation of this study is the comparison of changes in corneometry and TEWL between clascoterone cream 1% and no treatment, rather than a comparator, which would allow for direct comparison of the barrier properties of clascoterone vs other topical formulations. Nonetheless, the results of the current study demonstrate that clascoterone cream 1% provides a well-tolerated treatment option for patients with acne vulgaris, with a low potential for skin barrier damage and without the need for concomitant moisturizers or adjunctive barrier repair therapies. These properties increase the likelihood that patients will demonstrate good adherence to treatment with clascoterone cream 1%. However, future studies are needed to demonstrate adherence and patient satisfaction with clascoterone cream 1% treatment.

CONCLUSION

Twice-daily treatment with clascoterone cream 1% was associated with increased moisturization and maintenance of skin barrier function through 2 weeks of treatment in acne-prone individuals. Clascoterone cream 1% provides a treatment option for patients with acne vulgaris that is well tolerated and has low potential for skin barrier disruption, which may increase patient adherence.

DISCLOSURES

ZDD was an investigator on this study and received a grant from Sun Pharma. KK and NS are employees of Sun Pharmaceutical Industries, Inc.

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REFERENCES

1. Chen H, Zhang TC, Yin XL, et al. Magnitude and temporal trend of acne vulgaris burden in 204 countries and territories from 1990 to 2019: an analysis from the Global Burden of Disease Study 2019. *Br J Dermatol*. 2022;186(4):673-683.
2. Lim HW, Collins SAB, Resneck JS, Jr, et al. The burden of skin disease in the United States. *J Am Acad Dermatol*. 2017;76(5):958-972.e2.
3. Samuels DV, Rosenthal R, Lin R, et al. Acne vulgaris and risk of depression and anxiety: a meta-analytic review. *J Am Acad Dermatol*. 2020;83(2):532-541.
4. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2024;90(5):1006.e1-1006.e30.

5. Grada A, Perche P, Feldman S. Adherence and persistence to acne medications: a population-based claims database analysis. *J Drugs Dermatol.* 2022;21(7):758-764.
6. Dreno B, Thiboutot D, Gollnick H, et al. Large-scale worldwide observational study of adherence with acne therapy. *Int J Dermatol.* 2010;49(4):448-456.
7. Sevimli Dikicier B. Topical treatment of acne vulgaris: efficiency, side effects, and adherence rate. *J Int Med Res.* 2019;47(7):2987-2992.
8. de Lucas R, Moreno-Arias G, Perez-Lopez M, et al. Adherence to drug treatments and adjuvant barrier repair therapies are key factors for clinical improvement in mild to moderate acne: the ACTUO observational prospective multicenter cohort trial in 643 patients. *BMC Dermatol.* 2015;15:17.
9. Goreschi R, Samrao A, Ehst BD. A double-blind, randomized, bilateral comparison of skin irritancy following application of the combination acne products clindamycin/tretinoin and benzoyl peroxide/adapalene. *J Drugs Dermatol.* 2012;11(12):1422-1426.
10. Ting W. Randomized, observer-blind, split-face study to compare the irritation potential of 2 topical acne formulations over a 14-day treatment period. *Cutis.* 2012;90(2):91-96.
11. Chularojanamontri L, Tuchinda P, Kulthanan K, et al. A double-blinded, randomized, vehicle-controlled study to assess skin tolerability and efficacy of an anti-inflammatory moisturizer in treatment of acne with 0.1% adapalene gel. *J Dermatolog Treat.* 2016;27(2):140-145.
12. Kircik LH, Bhatt V, Martin G, et al. Randomized, double-blind, split-face study to compare the irritation potential of two topical acne formulations over a 21-day treatment period. *J Drugs Dermatol.* 2016;15(2):178-182.
13. Aschoff R, Moller S, Haase R, et al. Tolerability and efficacy of clindamycin/tretinoin versus adapalene/benzoyl peroxide in the treatment of acne vulgaris. *J Drugs Dermatol.* 2021;20(3):295-301.
14. Zhou L, Chen L, Liu X, et al. The influence of benzoyl peroxide on skin microbiota and the epidermal barrier for acne vulgaris. *Dermatol Ther.* 2022;35(3):e15288.
15. Draelos Z, Tanghetti E, Guenin E. Vehicle formulation impacts tolerability and patient preference: comparison of tretinoin branded lotion and generic cream. *J Drugs Dermatol.* 2022;21(8):875-880.
16. Draelos ZD, Baalbaki N, Colon G, et al. Ceramide-containing adjunctive skin care for skin barrier restoration during acne vulgaris treatment. *J Drugs Dermatol.* 2023;22(6):554-558.
17. Stuart B, Maund E, Wilcox C, et al. Topical preparations for the treatment of mild-to-moderate acne vulgaris: systematic review and network meta-analysis. *Br J Dermatol.* 2021;185(3):512-525.
18. Drake L, Reyes-Hadsall S, Barbieri JS, et al. New developments in topical acne therapy. *Am J Clin Dermatol.* 2022;23(2):125-136.
19. Han JJ, Faletsky A, Barbieri JS, et al. New acne therapies and updates on use of spironolactone and isotretinoin: a narrative review. *Dermatol Ther (Heidelb).* 2021;11(1):79-91.
20. WINLEVI® (clascoterone cream 1%). Full Prescribing Information. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2022.
21. WINLEVI® (clascoterone cream 1%). Product Monograph. Brampton, Ontario: Sun Pharma Canada Inc.; 2023.
22. Cosmo Pharmaceuticals announces approval of WINLEVI® in Australia. News release. Cosmo. Published March 19, 2024. Accessed February 10, 2025. <https://www.cosmopharma.com/news/cosmo-pharmaceuticals-announces-approval-of-winlevi-in-australia>
23. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. *JAMA Dermatol.* 2020;156(6):621-630.
24. Rosette C, Agan FJ, Mazzetti A, et al. Cortexolone 17alpha-propionate (clascoterone) is a novel androgen receptor antagonist that inhibits production of lipids and inflammatory cytokines from sebocytes in vitro. *J Drugs Dermatol.* 2019;18(5):412-418.
25. Eichenfield L, Hebert A, Gold LS, et al. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. *J Am Acad Dermatol.* 2020;83(2):477-485.
26. Shergill M, Ali MU, Abu-Hilal M. Comparison of the efficacy of clascoterone, trifarotene, and tazarotene for the treatment of acne: a systematic literature review and meta-analysis. *Dermatol Ther (Heidelb).* 2024;14(5):1093-1102.
27. Takahashi M, Machida Y, Marks R. Measurement of turnover time of stratum corneum using dansyl chloride fluorescence. *J Soc Cosmet Chem.* 1987;38:321-331.
28. Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease-affected skin. *J Clin Aesthet Dermatol.* 2011;4(9):22-42.
29. Zhou L, Liu X, Li X, et al. Epidermal barrier integrity is associated with both skin microbiome diversity and composition in patients with acne vulgaris. *Clin Cosmet Investig Dermatol.* 2022;15:2065-2075.
30. Draelos ZD, Ertel KD, Berge CA. Facilitating facial retinization through barrier improvement. *Cutis.* 2006;78(4):275-281.
31. Pantuzza LL, Ceccato M, Silveira MR, et al. Association between medication regimen complexity and pharmacotherapy adherence: a systematic review. *Eur J Clin Pharmacol.* 2017;73(11):1475-1489.
32. Anderson KL, Dothard EH, Huang KE, et al. Frequency of primary nonadherence to acne treatment. *JAMA Dermatol.* 2015;151(6):623-626.
33. Jordan L, Baldwin HE. Stratum corneum abnormalities and disease-affected skin: strategies for successful outcomes in inflammatory acne. *J Drugs Dermatol.* 2016;15(10):1170-1173.

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Top Chief Complaints and Diagnoses for Outpatient Dermatology Patients of Color

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ABSTRACT

Background: By 2044, people with skin of color (SOC) in the United States are projected to become the majority of the population, yet research and practice gaps remain regarding the dermatologic conditions most common and concerning to populations with SOC.^{1,2}

Objective: To investigate the most common outpatient dermatologic chief complaints and diagnoses in patients with SOC.

Methods: A retrospective chart review was conducted investigating the top chief complaints and diagnoses in children and adult patients with SOC seen at the University of Southern California outpatient dermatology clinics over 10 years, from 2009 to 2019.

Results: A total of 4572 individuals were identified (2326 [58.9%] female; mean age [SD]: 46.0 [19.9] years). The 5 most common skin concerns were skin examination (21.5%), bumps/growths (20.8%), rash (19.8%), acne (10.0%), and skin discoloration (8.5%). The 5 most common diagnoses were benign nevi/neoplasm (38.8%), followed by dermatitis (20.8%), acne (13.3%), eczema and/or xerosis (9.0%), and dyspigmentation (7.7%). Differences were observed across racial/ethnic, age, and gender groups.

Conclusion: Findings from this study contribute valuable insights regarding the potential motivations for seeking dermatologic care across various demographical groups, underscoring the importance of patient-centered, evidence-based, and culturally competent care in the diagnosis and treatment of dermatological disease across diverse populations.

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INTRODUCTION

While people with skin of color in the United States (US) are projected to become the majority of the population by 2044, research and practice gaps remain regarding the dermatologic conditions most concerning to populations with skin of color (SOC).^{1,2} It is known that dermatologic conditions can present differently in people with SOC. In addition, the sequelae of inflammatory skin diseases, such as post-inflammatory hyperpigmentation (PIH), can be more noticeable in patients with SOC.² Increased knowledge of the skin concerns most frequently reported among populations with SOC may improve understanding of the dermatologic needs and goals amongst increasingly diverse populations.

To our knowledge, this is the first study examining both the leading dermatologic diagnoses and chief complaints in patients with SOC in Los Angeles (LA). LA county represents the nation's most populated county and is one of the most diverse counties.^{3,4} The majority of the LA county population (74.8%) is

composed of people with SOC.⁵ In addition to its racial/ethnic diversity, over one-third of individuals in LA are born outside of the US.⁵ This study sought to characterize the top patient-reported chief complaints and diagnoses amongst this diverse population.

MATERIALS AND METHODS

This was a multi-site, retrospective chart review investigating the most common chief complaints and dermatologic diagnoses in patients with SOC. Patients meeting criteria included those ages 0 years and above and identified as Black/African American, Hispanic/Latino, Native American/Alaskan Native, Pacific Islander/Native Hawaiian, Asian, Middle Eastern, biracial, and/or multiracial. Patients were seen at the University of Southern California (USC) Keck Medicine outpatient dermatology clinics over 10 years, from January 1, 2009, to December 31, 2019. This study obtained ethical approval from the USC Institutional Review Board (IRB).

The ICD-9 and ICD-10 codes and clinical diagnoses were collected for each individual in addition to the year of their outpatient visit, past medical history, FST (if reported), and demographics, including race/ethnicity, age, and gender. For patients with multiple visits, the chief complaint and the dermatological diagnosis were obtained from the individual's first outpatient dermatological visit.

Descriptive statistics for the top 10 chief complaints and diagnoses were presented using frequencies for categorical variables and mean for continuous variables. The data was stratified by race, gender, and age. Associations between categorical variables were evaluated using Pearson's chi-squared or Fisher's exact test, as appropriate. To account for multiple comparisons, the Benjamini-Hochberg correction was used to adjust all *P*-values. All tests were 2-sided, and a *P*-value ≤ 0.05 was considered statistically significant (R, version 4.2.1).

RESULTS

A total of 4572 individuals were identified. The average age was 46.0 ± 19.9 years, with 58.9% female patients ($n=2326$). The largest racial/ethnic group was Asian (54.8%, $n=2507$), followed by Other (19.9%, $n=913$), Black/African American (15.2%, $n=696$), mixed/multiple race (9.6%, $n=440$), and Hispanic/Latino ($<1\%$, $n=16$). For this study, the "Other" racial group was not analyzed.

The top 10 most common diagnoses established in all patients with SOC were benign nevi/neoplasm (38.8%), dermatitis (20.8%), acne (13.3%), eczema and/or xerosis (9.0%), dyspigmentation (7.7%), neoplasm of uncertain behavior (6.2%), hypertrophic scars or keloids (4.6%), alopecia (4.4%), seborrheic dermatitis (3.6%), and psoriasis (3.4%; Figure 1).

The top 10 chief complaints amongst all patients with SOC were skin examination (21.5%), bumps/growths (20.8%), rash (19.8%), acne (10.0%), skin discoloration (8.5%), eczema and/or dry skin (7.0%), itching (5.0%), hair loss (4.1%), keloids/scars (2.9%), and nail discoloration (1.5%; Figure 2).

Race/ethnicity Sub-analyses

When sub-stratified by race/ethnicity, amongst Black/African American patients, the top 3 chief complaints were bumps/growths (24.4%), rash (21.0%), and skin examination (17.9%). In Asian patients, bumps/growths (22.8%) and rash (22.8%) were tied as the top diagnosis, followed by skin examination (21.5%), and acne (10.7%). The top 3 chief complaints in patients of mixed/multiple races were skin examination (28.9%), bumps/growths (24.8%), and rash (15.7%). In Hispanic/Latino patients, skin check (18.8%), rash (18.8%), and acne (18.8%) were tied as the first chief complaint, followed by itching (12.5%), skin discoloration (6.3%), keloids/scars (6.3%), and nail discoloration (6.3%).

FIGURE 1. Top 10 diagnoses in patients with skin of color.

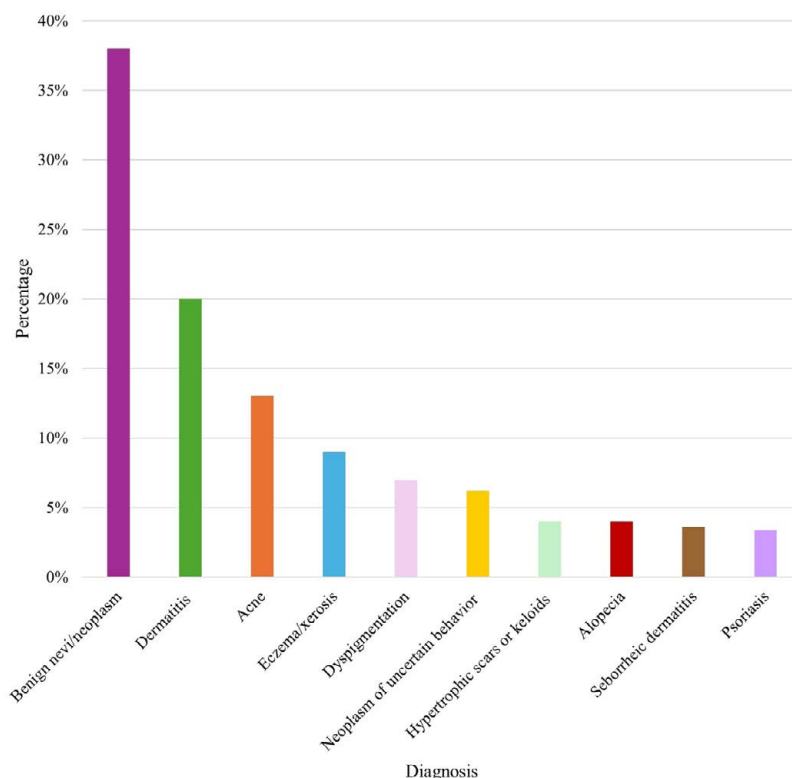
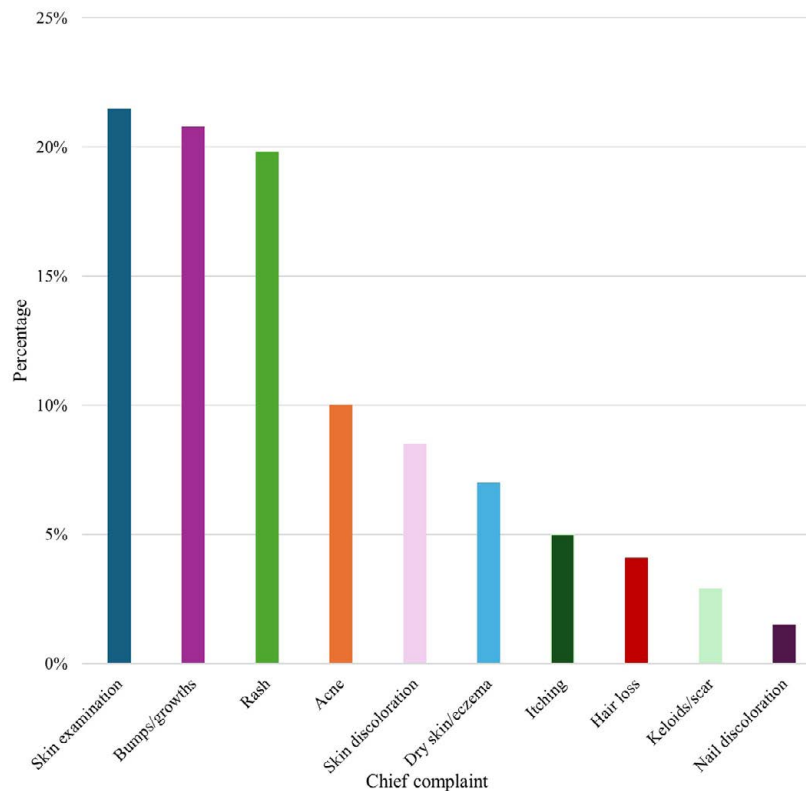


FIGURE 2. Top 10 chief complaints in patients with skin of color.



The 3 most common diagnoses for Black/African American patients included benign nevi/neoplasm (34.1%), dermatitis (20.1%), and dyspigmentation (15.6%; Table 1). In Asian patients, the 3 most frequent diagnoses were benign nevi/neoplasm (39.9%), dermatitis (23.6%), and acne (13.1%). Amongst patients of mixed/multiple races, the top 3 diagnoses were benign nevi/growth (42.3%), dermatitis (15.9%), and acne (15.7%). In Hispanic/Latino patients, benign nevi/neoplasm (31.3%), and acne (31.3%) were tied in first place for most frequent diagnosis, followed by dermatitis (12.5%), eczema and/or xerosis (12.5%), and psoriasis (12.5%).

Age Sub-analyses

When sub-stratified by age, amongst all patients with SOC, dermatitis ($P<0.001$), acne ($P<0.001$), eczema, and/or xerosis ($P=0.006$) were among the most common diagnoses in children. Between ages 19 to 39 years, individuals were most frequently diagnosed with acne ($P<0.001$), keloids/scarring ($P=0.014$), alopecia ($P=0.001$), and seborrheic dermatitis ($P=0.002$). As expected, compared to their younger counterparts, individuals ages 40 to 65 years were more often diagnosed with benign nevi/neoplasm ($P<0.001$). Further, among elderly patients (older than 65 years), eczema and/or xerosis ($P=0.006$), benign

nevi/neoplasm ($P<0.001$), and neoplasm of uncertain behavior ($P=0.002$) were more common diagnoses (Table 2).

The most common chief complaints among pediatric patients included eczema and/or dry skin ($P<0.001$) and acne ($P<0.001$) compared to hair loss ($P=0.013$) and keloids/scarring ($P=0.010$) in those 19 to 39 years, discoloration ($P<0.001$) and skin examination ($P=0.005$) in those 40-65 years, and rash ($P=0.002$) and itching ($P<0.001$) for those older than 65 years.

Gender Sub-analyses

When sub-stratified by gender, amongst all patients with SOC, the most common diagnosis in both males and females was benign nevi/neoplasm (Table 3). Further, female gender was associated with the diagnoses of acne ($P=0.010$), dyspigmentation ($P=0.012$), and alopecia ($P=0.011$). Male gender was not significantly associated with any dermatological diagnosis.

The top chief complaint in males was bumps/growths (26.3%), whereas skin examination was the most common chief complaint in females (22.1%). Male gender was associated with bumps/growths ($P<0.001$), whereas female gender was associated with acne ($P=0.003$), hair loss ($P=0.002$), and keloids/scars ($P=0.010$).

TABLE 1.

Top Chief Complaints and Diagnoses Among Skin of Color Patients Stratified by Race/Ethnicity					
Variable	All SOC (n=4,572)	Black/AA (n=696)	Asian (n=2,507)	Mixed/Multiple (n=440)	Hispanic/Latino (n=16)
Chief Complaint					
Skin Examination	979 (21.5%)	124 (17.9%)	539 (21.5%)	127 (28.9%)	3 (18.8%)
Bumps/Growths	948 (20.8%)	169 (24.4%)	570 (22.8%)	109 (24.8%)	0
Rash	903 (19.8%)	146 (21.0%)	571 (22.8%)	69 (15.7%)	3 (18.8%)
Acne	455 (10.0%)	61 (8.8%)	267 (10.7%)	50 (11.4%)	3 (18.8%)
Skin Discoloration	386 (8.5%)	87 (12.5%)	232 (9.3%)	38 (8.7%)	1 (6.3%)
Eczema and/or Dry Skin	321 (7.0%)	41 (5.9%)	206 (8.2%)	37 (8.4%)	0
Itching	230 (5.0%)	43 (6.2%)	143 (5.7%)	23 (5.2%)	2 (12.5%)
Hair Loss	187 (4.1%)	41 (5.9%)	91 (3.6%)	20 (4.6%)	0
Keloids/Scar	139 (2.9%)	33 (4.8%)	69 (2.8%)	6 (1.4%)	1 (6.3%)
Nail Discoloration	68 (1.5%)	16 (2.3%)	44 (1.8%)	2 (0.5%)	1 (6.3%)
Diagnosis					
Benign Nevi/Neoplasm	1,688 (38.8%)	232 (34.1%)	975 (39.9%)	183 (42.3%)	5 (31.3%)
Dermatitis	905 (20.8%)	137 (20.1%)	577 (23.6%)	69 (15.9%)	2 (12.5%)
Acne	580 (13.3%)	91 (13.4%)	321 (13.1%)	68 (15.7%)	5 (31.3%)
Eczema and/or Xerosis	392 (9.0%)	70 (10.3%)	232 (9.5%)	27 (6.2%)	2 (12.5%)
Dyspigmentation	336 (7.7%)	106 (15.6%)	166 (6.8%)	21 (4.9%)	0
Neoplasm of Uncertain Behavior	270 (6.2%)	30 (4.4%)	150 (6.1%)	43 (9.9%)	0
Hypertrophic Scar/Keloid	201 (4.6%)	43 (6.3%)	104 (4.3%)	11 (2.5%)	0
Alopecia	189 (4.4%)	42 (6.2%)	86 (3.5%)	17 (3.9%)	0
Seborrheic Dermatitis	158 (3.6%)	24 (3.5%)	85 (3.5%)	27 (6.2%)	0
Psoriasis	149 (3.4%)	12 (1.8%)	91 (3.7%)	12 (2.8%)	2 (12.5%)

Numbers represent frequency (column percent). *Significant at $P \leq 0.05$ (Pearson's chi-squared). ¹Adjusted using Benjamini-Hochberg correction. Of note, for the purposes of this study, "Other" racial group was not stratified in the analysis. This group was composed of 913 out of the total n=4,572 sample.

TABLE 2.

Top 10 Chief Complaints and Diagnoses Among Skin of Color Patients by Age Group					
Variable	Age Group				Adjusted <i>P</i> -value ¹
	0-18 years (n=222)	19-39 years (n=1,486)	40-65 years (n=1,437)	>65 years (n=832)	
Chief Complaint					
Skin Examination	34 (15.3%)	344 (23.2%)	354 (24.6%)	166 (20.0%)	0.005*
Bumps/Growths	39 (17.6%)	322 (21.7%)	344 (23.9%)	210 (25.3%)	0.043*
Rash	45 (20.3%)	284 (19.1%)	298 (20.7%)	219 (26.4%)	0.002*
Acne	50 (22.5%)	301 (20.3%)	52 (3.6%)	11 (1.3%)	<0.001*
Skin Discoloration	19 (8.6%)	103 (6.9%)	167 (11.6%)	86 (10.4%)	<0.001*
Eczema and/or Dry Skin	45 (20.3%)	126 (8.5%)	89 (6.2%)	46 (5.5%)	<0.001*
Itching	6 (2.7%)	51 (3.4%)	86 (6.0%)	80 (9.6%)	<0.001*
Hair Loss	10 (4.5%)	74 (5.0%)	67 (4.7%)	18 (2.2%)	0.013*
Keloids/Scar	3 (1.4%)	57 (3.8%)	40 (2.8%)	13 (1.6%)	0.010*
Nail Discoloration	0	21 (1.4%)	24 (1.7%)	19 (2.3%)	0.068
Diagnosis					
Benign Nevi/Neoplasm	43 (19.5%)	504 (34.8%)	620 (44.0%)	371 (45.6%)	<0.001*
Dermatitis	73 (33.0%)	273 (18.9%)	292 (20.7%)	196 (24.1%)	<0.001*
Acne	58 (26.2%)	392 (27.1%)	73 (5.2%)	6 (0.7%)	<0.001*
Eczema and/or Xerosis	22 (10.0%)	109 (7.5%)	116 (8.2%)	103 (12.7%)	0.006*
Dyspigmentation	14 (6.3%)	119 (8.2%)	120 (8.5%)	61 (7.5%)	0.64
Neoplasm of Uncertain Behavior	1 (0.5%)	92 (6.4%)	91 (6.5%)	64 (7.9%)	0.002*
Hypertrophic Scar/Keloid	5 (2.3%)	80 (5.5%)	59 (4.2%)	24 (3.0%)	0.014*
Alopecia	6 (2.7%)	75 (5.2%)	65 (4.6%)	14 (1.7%)	0.001*
Seborrheic Dermatitis	9 (4.1%)	77 (5.3%)	41 (2.9%)	21 (2.6%)	0.002*
Psoriasis	1 (0.5%)	53 (3.7%)	51 (3.6%)	22 (2.7%)	0.06

Numbers represent frequency (column percent). *Significant at $P \leq 0.05$ (Pearson's chi-squared). ¹Adjusted using Benjamini-Hochberg correction. 595 individuals not included in the age sub-stratification had missing data.

TABLE 3.

Top 10 Chief Complaints and Diagnoses Among Skin of Color Patients by Gender			
Variable	Gender		Adjusted <i>P</i> -value ¹
	Male (n=1,623)	Female (n=2,326)	
Chief Complaint			
Skin Check	362 (22.3%)	532 (22.9%)	0.685
Bumps/Growths	426 (26.3%)	482 (20.7%)	<0.001*
Rash	322 (19.9%)	520 (22.4%)	0.118
Acne	138 (8.5%)	274 (11.8%)	0.003*
Skin Discoloration	138 (8.5%)	234 (10.1%)	0.168
Eczema and/or Dry Skin	118 (7.3%)	185 (8.0%)	0.54
Itching	98 (6.1%)	124 (5.3%)	0.484
Hair Loss	46 (2.8%)	119 (5.1%)	0.002*
Keloids/Scar	32 (2.0%)	82 (3.5%)	0.010*
Nail Discoloration	28 (1.7%)	36 (1.6%)	0.685
Diagnosis			
Benign Nevi/Neoplasm	639 (40.2%)	887 (39.9%)	0.561
Dermatitis	318 (20.0%)	509 (22.4%)	0.16
Acne	180 (11.3%)	345 (15.2%)	0.010*
Eczema and/or Xerosis	148 (9.3%)	199 (8.8%)	0.6
Dyspigmentation	105 (6.6%)	207 (9.1%)	0.012*
Neoplasm of Uncertain Behavior	112 (7.1%)	134 (5.9%)	0.242
Hypertrophic Scars/Keloids	66 (4.2%)	102 (4.5%)	0.626
Alopecia	47 (3.0%)	110 (4.8%)	0.011*
Seborrheic Dermatitis	56 (3.5%)	91 (4.0%)	0.561
Psoriasis	63 (4.0%)	64 (2.8%)	0.12

Numbers represent frequency (column percent). *Significant at P≤0.05 (Pearson's chi-squared). ¹Adjusted using Benjamini-Hochberg correction. 626 individuals not included in the gender sub-stratification had missing data.

DISCUSSION

Limited studies in the US have investigated the leading chief complaints and dermatologic diagnoses among populations with SOC. In the US, these studies have been conducted in Washington, DC, Southeast Michigan, Miami, and New York City, as well as nationally by utilizing the National Ambulatory Medical Care Survey (NAMCS).⁶⁻¹⁹ There are also few international studies investigating common dermatologic diagnoses in patients of color.²⁰⁻²⁷ To our knowledge, this is the first study examining both the leading dermatologic diagnoses and chief complaints in patients with SOC in Los Angeles, a major urban population, with findings sub-stratified by age, race/ethnicity, and gender. Almost 90% of all visits amongst all patients with SOC were for the diagnoses of benign nevi/neoplasm, dermatitis, acne, eczema and/or xerosis, and dyspigmentation. Similarly, approximately 80% of all visits were for the top chief complaints of skin exam, bumps/growths, rash, acne, and skin discoloration.

Amongst all patients with SOC seen at our outpatient centers, the most frequent diagnosis was benign nevi/neoplasm. This diagnosis category included conditions such as seborrheic keratosis, acrochordons, verruca, and cysts. In patients with SOC, particularly among Black and Asian patients, seborrheic

keratoses may present as a variant known as dermatosis papulosa nigra (DPNs).^{28,29} It is estimated that DPNs present in roughly one-third of African Americans, and are also frequently encountered in other populations with SOC.²⁸ A Parisian study involving 836 adults of African or West Indian origin, DPNs, benign tumors/cysts, and warts were each identified among the top 20 dermatological diagnoses.²¹ Similarly, a cross-sectional analysis utilizing the NAMCS, between 2007 and 2016, reported epidermoid cyst among the top 5 dermatological diagnoses in Black/African American, Asian, and Hispanic patients.¹³

Acne and eczema and/or xerosis were among the top 5 diagnoses in patients with SOC in this study. This is consistent with prior studies involving African American, South Asian American, Hispanic/Latino, African, Afro-Caribbean, mixed-race, and Arab American patients, also reporting acne and eczema as the leading dermatologic diagnoses in populations with SOC.^{6, 9,11,14,15,18,20,22} In this study, the diagnosis of acne was associated with female gender, consistent with prior findings, suggesting an increased tendency among female patients to seek dermatological care for this condition.^{22,30-32} This was also a more frequent diagnosis among pediatric and young adult patients (19-39 years).

Atopic dermatitis has a multifactorial pathogenesis involving skin barrier impairment, environmental factors, genetic predisposition, and immune dysregulation.³³ Prior studies have indicated that atopic dermatitis occurs more frequently and is more severe in populations with SOC.^{33,34} In particular, studies have shown that Black, Latino, and Indigenous individuals in our country are disproportionately affected by atopic dermatitis.^{35,36} In regard to social determinants of health, disproportionate exposure to substandard housing, environmental pollutants, and workplace hazards contribute to the higher burden of atopic dermatitis among Black and Brown populations.³⁵⁻³⁹ In this cohort, the diagnosis of eczema and/or xerosis was most frequently observed in pediatric and older adult patients (older than 65 years).

This study showed dyspigmentation to be the fifth most common dermatological diagnoses among patients with SOC, consistent with prior literature findings.^{8,9,10,12,14,15,20-27} Pigmentary disorders such as melasma have been observed to occur more often among Hispanics/Latinos, Asians, Blacks/African Americans, and Arab Americans.^{9,20} Further, melasma affects diverse racial/ethnic groups worldwide, with epidemiological studies demonstrating a higher prevalence of melasma among East Asian, Indian, Pakistani, Middle Eastern, Mediterranean-African, and Brazilian populations.⁴⁰ A study by Alexis et al involving 1421 Black adults and children in New York City reported dyschromia (including PIH and melasma) to be the second most frequent dermatological diagnosis in these patients.¹⁰ Similarly, in an Afro-Caribbean population in Jamaica, pigmentary disorders ranked as the third most common dermatological diagnosis observed.²³ In our cohort, dyspigmentation was more frequently diagnosed in female patients, consistent with the female predilection observed for certain pigmentary disorders, including melasma, lichen planus pigmentosus, erythema dyschromicum perstans, and pigmented contact dermatitis.^{41,42}

Similar to this study, prior studies involving Black adult and pediatric patients in the US and internationally have also reported keloids to be among the leading dermatological diagnoses.^{8,9,10,12,15,20,21,23,26,27} In addition, similar to this study, other US and international studies have also demonstrated dermatitis, alopecias, seborrheic dermatitis, psoriasis, and neoplasm of uncertain behavior as frequent dermatological diagnoses among patients with SOC.^{6,8,10,12-15,20-27} Other leading diagnoses frequently reported in prior studies involving patients with SOC that were not in the top 10 diagnoses in our cohort were folliculitis, pseudofolliculitis, hirsutism, vitiligo, lichen planus, superficial mycoses, pityriasis rosea, urticaria, and keratosis pilaris.^{8-12,15,20,21,23-26}

Top Chief Complaints in SOC

This study was also unique in not only examining the top chief complaints in patients with SOC but also the top diagnoses

made by dermatologists. In this cohort, eczema and/or dry skin, hair loss, discoloration, and acne were among the top 10 chief complaints observed, consistent with prior literature findings. In a study conducted in the New York City area involving 190 South Asian adults, the top 5 patient-reported skin concerns included dry skin, hair loss, uneven skin tone, dark spots, and acne.¹¹ In Southeast Michigan/Detroit, a study involving 401 Arab Americans reported uneven skin tone, skin discoloration, dry skin, and acne as the top patient-reported skin concerns.⁹

In our cohort, other common chief complaints besides dyspigmentation in patients with SOC included skin exams, bumps/growths, rash, and itching. These conditions have also previously been reported as leading skin concerns in populations with SOC. A study utilizing the NAMCS, from 2007-2018, showed that the most common physician-reported chief complaints for Black and Other race patients were acne, skin rash, discoloration/abnormal pigmentation, skin lesion, cyst, eczema and dermatitis, dryness, itching, and skin cancer screening.¹⁹ Further, a prior study reported facial hair as a top chief complaint amongst patients with SOC, which was not observed in our cohort.¹¹ Interestingly, leading chief complaints in our patients that were not reported in these prior studies were keloids and nail discoloration.

Limitations of this study include its retrospective nature and incomplete electronic medical record documentation. When demographics were categorized by race/ethnicity, it is possible that Hispanic/Latino patients identifying as “White” race or “Other” were categorized into the non-SOC category and subsequently excluded from analysis. We believe this may account for the limited data collected for Hispanic/Latino patients. Additionally, this study did not include the USC-affiliated children’s hospital, thus most patients included were adults. Furthermore, the population of patients visiting USC’s Keck facilities may not be generalizable to other populations and settings.

CONCLUSION

It is known that many communities of color underutilize dermatology as a subspecialty.^{43,44} In particular, Black/African American and Hispanic/Latino patients are less likely to seek dermatologic care.¹⁴ Not seeking care or delaying care can exacerbate existing health disparities in dermatology for racial/ethnic minority groups. Findings from this study contribute valuable insights regarding the potential motivations for patients with SOC seeking dermatologic care across various demographic groups as well as the most common diagnoses among populations with SOC. Findings from this study may also promote further research and improvement of practice gaps in these chief complaints and diagnoses. Advancements in these areas can help improve the culturally competent and evidence-based dermatologic care of diverse populations.

DISCLOSURES

Dr Elbuluk has served as a consultant, advisory board member, and/or speaker for Avita, Scientis, Incyte, VisualDx, La Roche Posay, Beiersdorf, Unilever, Eli Lilly, Galderma, Pfizer, L'Oreal, McGraw Hill, Dior, Medscape, Abbvie, Takeda, Sanofi. She has received royalties from McGraw-Hill. She has stock options in VisualDx. The remaining authors have no disclosures to report.

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REFERENCES

- Colby SL, Jennifer JO. Projections of the size and composition of the U.S. population: 2014 to 2060. US Department of Commerce, Economics and Statistics and Administration, Bureau of the Census. Accessed July 30, 2024. <https://www.census.gov/library/publications/2015/demo/p25-1143.html>
- Montgomery SNB, Elbuluk N. A quantitative analysis of research publications focused on the top chief complaints in patients with skin of color. *J Am Acad Dermatol*. 2021;85(1):241-242.
- U.S. Census Bureau. 2020 Census Statistics Highlight Local Population Changes and Nation's Racial and Ethnic Diversity. Accessed January 26, 2024. <https://lacounty.gov/government/about-la-county/about/>
- County of Los Angeles Anti-Racism, Diversity, and Inclusion Initiative. Los Angeles County Racial Equity Strategic Plan. Accessed January 26, 2024. <https://ceo.lacounty.gov/ardi/racial-equity-strategic-plan/>
- U.S. Census Bureau. QuickFacts Los Angeles County, California. Accessed January 26, 2024. <https://www.census.gov/quickfacts/fact/table/losangelescountycalifornia/PST045223>
- Gaulding JV, Gutierrez D, Bhatia BK, et al. Epidemiology of skin diseases in a diverse patient population. *J Drugs Dermatol*. 2018;17(10):1032-1036.
- Taylor SC. Epidemiology of skin diseases in ethnic populations. *Dermatol Clin*. 2003;21(4):601-607.
- Henderson MD, Abboud J, Cogan CM, et al. Skin-of-color epidemiology: a report of the most common skin conditions by race. *Pediatr Dermatol*. 2012;29(5):584-589.
- El-Essawi D, Musial JL, Hammad A, et al. A survey of skin disease and skin-related issues in Arab Americans. *J Am Acad Dermatol*. 2007;56(6):933-8.
- Alexis AF, Sergay AB, Taylor SC. Common dermatologic disorders in skin of color: a comparative practice survey. *Cutis*. 2007;80(5):387-394.
- Shah SK, Bhanusali DG, Sachdev A, et al. A survey of skin conditions and concerns in South Asian Americans: a community-based study. *J Drugs Dermatol*. 2011;10(5):524-528.
- Ho T, Taylor MT, Marathe KS, et al. Most common pediatric skin conditions managed in outpatient dermatology clinics in the United States stratified by race and ethnicity. *Pediatr Dermatol*. 2021;38 Suppl 2:129-131.
- Grada A, Muddasani S, Fleischer AB Jr, et al. Trends in office visits for the 5 most common skin diseases in the United States. *J Clin Aesthet Dermatol*. 2022;15(5):E82-E86.
- Davis SA, Narahari S, Feldman SR, et al. Top dermatologic conditions in patients of color: an analysis of nationally representative data. *J Drugs Dermatol*. 2012;11(4):466-73.
- Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. *Cutis*. 1983;32(4):388, 390.
- Gaulding JV, Gutierrez D, Bhatia BK, et al. Epidemiology of skin diseases in a diverse patient population. *J Drugs Dermatol*. 2018;17(10):1032-1036.
- Schachner L, Ling NS, Press S. A statistical analysis of a pediatric dermatology clinic. *Pediatr Dermatol*. 1983;1(2):157-164.
- Sanchez MR. Cutaneous diseases in Latinos. *Dermatol Clin*. 2003;21:689-97.
- Peck GM, Roberson FA, Feldman SR. Reasons for visits to the dermatologist stratified by race. *South Med J*. 2022;115(10):780-783.
- Child FJ, Fuller LC, Higgins EM, et al. A study of the spectrum of skin disease occurring in a black population in south-east London. *Br J Dermatol*. 1999;141(3):512-517.
- Arsouze A, Fitoussi C, Cabotin PP, et al. Motifs de consultation en dermatologie des sujets de peau noire d'origine africaine et antillaise: enquête multicentrique en région parisienne [Presenting skin disorders in black Afro-Caribbean patients: a multicentre study conducted in the Paris region]. *Ann Dermatol Venerol*. 2008;135(3):177-182.
- Dlova NC, Mankahla A, Madala N, et al. The spectrum of skin diseases in a black population in Durban, KwaZulu-Natal, South Africa. *Int J Dermatol*. 2015;54(3):279-285.
- Dunwell P, Rose A. Study of the skin disease spectrum occurring in an Afro-Caribbean population. *Int J Dermatol*. 2003;42(4):287-289.
- Goh CL, Akarapant R. Epidemiology of skin disease among children in a referral skin clinic in Singapore. *Pediatr Dermatol*. 1994;11(2):125-128.
- Chua-Ty G, Goh CL, Koh SL. Pattern of skin diseases at the National Skin Centre (Singapore) from 1989-1990. *Int J Dermatol*. 1992;31(8):555-559.
- Banner A, Dinsey M, Ezzedine K, et al. The spectrum of skin diseases occurring in a multiethnic population in north-west London, U.K.: findings from a cross-sectional descriptive study. *Br J Dermatol*. 2017;176(2):523-525.
- East-Innis ADC, Chung-Stanley MM, et al. The spectrum of skin diseases seen in a Jamaican tertiary academic medical center. *JAAD Int*. 2021;4:59-64.
- Chatrath S, Bradley L, Kentosh J. Dermatologic conditions in skin of color compared to white patients: similarities, differences, and special considerations. *Arch Dermatol Res*. 2023;315(5):1089-1097.
- Xiao A, Muse ME, Ettefagh L. Dermatitis Papulosa Nigra. StatPearls. Accessed July 30, 2024. <https://www.ncbi.nlm.nih.gov/books/NBK534205/>
- Pathmarajah P, Peterknecht E, Cheung K, et al. Acne vulgaris in skin of color: a systematic review of the effectiveness and tolerability of current treatments. *J Clin Aesthet Dermatol*. 2022;15(11):43-68.
- Chang J, Nock MR, Cohen JM, et al. Acne accounts for an almost 2.5-fold higher proportion of dermatology visits among adult females compared to adult males in the United States: A study of the national ambulatory medical care survey from 2002-2016. *PLoS One*. 2023;18(9):e0290763.
- Skroza N, Tolino E, Mambrin A, et al. Adult acne versus adolescent acne: a retrospective study of 1,167 patients. *J Clin Aesthet Dermatol*. 2018;11(1):21-25.
- Kantor R, Silverberg JL. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol*. 2017;13(1):15-26.
- Davis CM, Flohr C, Gupta MR, et al. Managing atopic dermatitis in patients with skin of color. *J Allergy Clin Immunol Pract*. 2023;11(5):1376-1383.
- Croce EA, Levy ML, Adamson AS, Matsui EC. Reframing racial and ethnic disparities in atopic dermatitis in Black and Latinx populations. *J Allergy Clin Immunol*. 2021;148(5):1104-1111.
- Martinez A, de la Rosa R, Mujahid M, et al. Structural racism and its pathways to asthma and atopic dermatitis. *J Allergy Clin Immunol*. 2021;148(5):1112-1120.
- Bailey ZD, Feldman JM, Bassett MT. How structural racism works - racist policies as a root cause of U.S. Racial Health Inequities. *N Engl J Med*. 2021;384(8):768-773.
- Nardone A, Casey JA, Morello-Frosch R, et al. Associations between historical residential redlining and current age-adjusted rates of emergency department visits due to asthma across 8 cities in California: an ecological study. *Lancet Planet Health*. 2020;4(1):e24-e31.
- Rosenbaum E. Racial/ethnic differences in asthma prevalence: the role of housing and neighborhood environments. *J Health Soc Behav*. 2008;49(2):131-145.
- Del Bino S, Duval C, Bernerd F. Clinical and biological characterization of skin pigmentation diversity and its consequences on UV Impact. *Int J Mol Sci*. 2018;19(9):2668.
- Vinay K, Bishnoi A, Kamat D, et al. Acquired dermal macular hyperpigmentation: an update. *Indian Dermatol Online J*. 2021;12(5):663-673.
- Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. *An Bras Dermatol*. 2014;89(5):771-782.
- Narla S, Heath CR, Alexis A, Silverberg JL. Racial disparities in dermatology. *Arch Dermatol Res*. 2023;315(5):1215-1223.
- Tripathi R, Knusel KD, Ezaldein HH, et al. Association of demographic and socioeconomic characteristics with differences in use of outpatient dermatology services in the United States. *JAMA Dermatol*. 2018;154(11):1286-1291.

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Artificial Intelligence-Generated Educational Curriculum on Facial Neurotoxin Injections: Assessment of Educational Content, Curriculum Structure, and Course Logistics

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ABSTRACT

Background: Large language models (LLMs) have revolutionized the way physicians access and leverage artificial intelligence (AI). The potential role of AI in facilitating aesthetic medical education remains to be established.

Objectives: The present study aims to assess AI's ability in developing an educational curriculum for the purpose of training physician and nurse injectors in facial botulinum toxin injections.

Methods: An AI model was leveraged in line with the study's objectives; five expert injectors and educators validated its performance.

Results: Ten suggested steps for curriculum design and implementation were proposed by AI. A list of 12-course learning objectives and a suggested curriculum overview were provided. A 2-day schedule with appropriate session allocations was created, along with a 49-paged curriculum compendium generated entirely by AI. A 9-step approach towards implementation of hands-on practice sessions was provided, complete with quantities of equipment needed. Rubrics evaluating trainees' practical performance, and a form soliciting feedback were created. Budget estimates for anticipated costs and finances were also provided, along with 12 target cities with potential dates and venues, 12 suggested instructors, guidelines for obtaining sponsorships, draft sponsorship packages, and a list of potential sponsors.

Conclusion: Validation of AI performance in the development of an educational course for facial toxin injections demonstrated promising utility for course design and implementation logistics. While AI performance remains imperfect and can never replace human educators, AI can provide a practical framework for physicians in the development and implementation of large-scale educational endeavors in aesthetic medicine and beyond.

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INTRODUCTION

ChatGPT (OpenAI, San Francisco, California) is a novel artificial intelligence (AI) large language model (LLM) that has garnered significant attention in the literature as of late.¹⁻³ With potential to significantly improve efficiency and human productivity, interest in the integration of AI into different sectors, including healthcare, is on the rise.⁴⁻¹⁰ Within medical education, LLMs have demonstrated a remarkable ability to answer standardized pre-medical and medical examination questions, including from the Biomedical Admissions Test (BMAT)¹¹ and United States Medical Licensing Examinations (USMLE).¹²⁻¹⁴ In plastic surgery, ChatGPT has scored similarly to first-year residents on the American Society

of Plastic Surgeons (ASPS) in-service training examination, while also successfully answering board-examination questions from an array of different medical and surgical subspecialties.¹⁵⁻²⁰

The potential role of AI in facilitating medical education and training in aesthetic surgery may thus warrant investigation. In parallel to the growing number of physician and nurse aesthetic injectors observed as of late, reports on preventable complications from unsafe injection practices are also on the rise. This accentuates the importance of medical education in injectables and aesthetic medicine.²¹⁻²³ Furthermore, several previous studies have identified a need for specialized training

in non-surgical facial aesthetics among post-graduate training programs.²⁴ With facial botulinum toxin injections representing the most commonly-performed aesthetic non-surgical procedure yearly by plastic surgeons,²⁵ the authors aim to assess AI's ability in developing an educational curriculum, in its entirety, for the purpose of training and assessment of physician and nurse injectors in facial botulinum toxin injections. Educational content, curriculum structure, and course implementation logistics are evaluated and validated by expert injectors and educators. By investigating and rigorously validating AI performance, the authors aim to elucidate the role this technology may have in enriching, advancing, and supplementing the educational landscape within aesthetic medicine and surgery.

MATERIALS AND METHODS

ChatGPT was prompted to design a weekend-long course to train aesthetic physicians and nurse injectors in facial botulinum toxin injections. Ten fundamental steps required for implementation of the proposed task were suggested, in response, by ChatGPT (Figure 1). Serial iterations of interactions between the bot and the study's authors ensued in order to prompt ChatGPT to expand upon all of the aforementioned steps for course development and implementation (Supplementary Document 1). At no time was new information suggested to ChatGPT, nor alternative instructions provided. A single author performed all queries of the bot within the same chat and on the same computer (Apple MacBook Pro, Apple, Inc. California) running ChatGPT-3 (OpenAI, San Francisco, California). Information gathered was compiled for subsequent evaluation and analysis.

Assessment

Five expert aesthetic injectors and educators (FN, MG, AN, MA, SS) evaluated the collected information, and an objective assessment of responses was performed using standardized 10-point evaluation rubrics (Supplementary Document 2). Curriculum outline, course objectives, educational content, budgeting, sponsorships, target cities, potential venues, suggested dates, faculty recommendations, scheduling, hands-on training session design, and curriculum feedback strategies were all assessed individually. Educational content was broken down into 6 sections for individual assessment of accuracy, comprehensiveness, relevance, clarity, and safety. Supplemental materials for this manuscript can be found at: <https://s3.us-east-1.amazonaws.com/dl.jddonline.com/pdfs/M8331+Supplementary+Materials+Compiled.pdf>

RESULTS

The 10 suggested steps for curriculum design and implementation included: identification of course learning objectives; planning of curriculum content; scheduling of educational sessions; recruitment of experienced faculty; arrangement of hands-on practice sessions; incorporation of interactive learning techniques; provision of reference materials; assessment of

FIGURE 1. Ten fundamental steps recommended by AI for the planning and implementation of a neurotoxin injection training course.

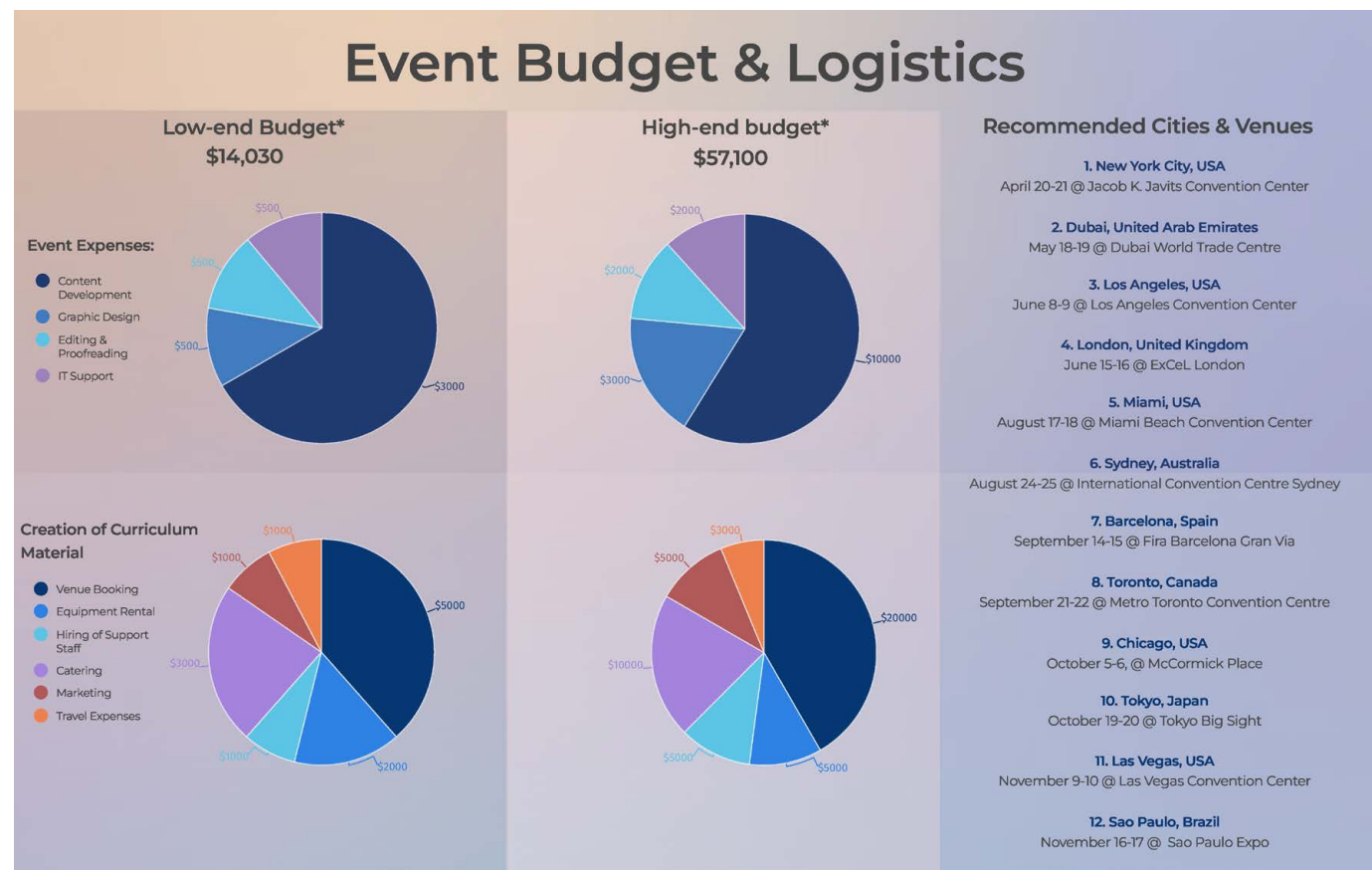


participants' competence; offering of continuous support to trainees; and soliciting feedback on training provided (Figure 1).

Logistics

ChatGPT provided budget estimates with detailed breakdowns of anticipated costs for both curriculum creation as well as event expenses. Twelve target cities along with potential venues and dates were suggested (Figure 2). ChatGPT recommended

FIGURE 2. Event implementation logistics. This Figure summarizes information provided by AI regarding event budget, list of proposed cities, venues, and target dates



*Budget estimations were generated using New York City as a sample target city.

3 dermatologists, 3 plastic surgeons, 3 aesthetic nurses, and 3 aesthetic physicians as potential instructors. It gave step-by-step instructions for obtaining sponsorships to offset anticipated costs of the event, drafted sample sponsorship packages, and provided 10 target industries, with specific companies from within each, as potential sponsors (Figure 3, Supplementary Document 3).

Course Design and Implementation

ChatGPT provided a list of 12-course learning objectives, presented in Table 1. Suggested curriculum overview is presented in Table 2. A 2-day schedule with time allocations for each educational session was generated (Table 3). A 49-page curriculum compendium was also created entirely by ChatGPT, presented in its original form in Supplementary Document 4. The corrected version of the compendium is presented in Supplementary Document 5, with a summary of all errors, and corrections made to the AI-generated material, presented in Supplementary Table 1.

A 9-step approach towards implementation of ancillary hands-on practice sessions, complete with quantities of equipment needed, was also provided (Figure 4). A suggested written exam evaluating trainees on material covered was generated, including multiple-choice, scenario-based, and short answer questions complete with answer keys. A rubric evaluating trainees’ performance during the practical exam was also generated (Supplementary Document 6). Finally, a form soliciting feedback following completion of the educational course was also generated by ChatGPT (Supplementary Document 7).

Validation of Performance

Five expert aesthetic surgeon injectors and educators objectively evaluated the AI-generated material, for the purpose of content validation, using standardized assessment rubrics (Supplementary Document 2). A detailed breakdown of scores for each assessment category is presented in Table 4. Overall, information relating to logistics of implementation was scored at 7.6/10 ± 1.3, and curriculum content at 7.5/10 ± 0.8.

FIGURE 3. Sponsorship package and proposal overview.



AI suggested 4 levels of sponsorship, including Platinum, Gold, Silver, and Bronze. A list of 10 industry sectors from which potential sponsors may be recruited were provided, along with specific companies from within each: 1. Pharmaceutical companies: Allergan (Allergan, Dublin, Ireland), Galderma (Galderma, Lausanne, Switzerland), Merz Aesthetics (Merz Aesthetics, Frankfurt, Germany). 2. Medical device manufacturers: Cynosure (Cynosure LLC, Massachusetts, USA), Syneron Candela (Syneron Candela, Massachusetts, USA), Cutera (Cutera Inc., California, USA). 3. Cosmetic brands: L'Oréal (L'Oréal, Clichy, France), Estée Lauder (Estée Lauder Companies Inc., New York, USA). 4. Skincare companies: SkinCeuticals (L'Oréal, Clichy, France), Obagi (Obagi Medical Products, California, USA). 5. Aesthetic equipment providers: Sciton (Sciton, California, USA), InMode (InMode Ltd., Yokneam Illit, Israel) 6. Professional organizations: American Society for Aesthetic Plastic Surgery (ASAPS, New York, USA), American Academy of Dermatology (AAD, Illinois, USA, American Society for Laser Medicine and Surgery (ASLMS, Wisconsin, USA). 7. Medical technology companies: Medtronic (Medtronic plc., Dublin, Ireland), Stryker (Stryker Corporation, Michigan, USA). 8. Insurance providers: Medical malpractice insurance companies that specialize in aesthetic medicine coverage 9. Health and wellness brands: Fitness centers, nutrition companies, wellness retreats 10. Event and media sponsors: Local media outlets, event management companies, audiovisual and production companies

TABLE 1.

Neurotoxin Injection Training Course Curriculum Objectives Generated by AI
Curriculum Objectives
1. "Understand the facial anatomy relevant to Botulinum toxin injection, including the key muscles, nerve pathways, and blood supply."
2. "Identify and assess appropriate candidates for Botulinum toxin treatment, considering factors such as patient history, facial analysis, and aesthetic goals."
3. "Demonstrate proficiency in the proper preparation, reconstitution, and storage of Botulinum toxin, adhering to recommended guidelines and safety protocols."
4. "Describe the mechanism of action of Botulinum toxin and its effects on neuromuscular activity and wrinkle reduction."
5. "Apply knowledge of injection techniques, including needle selection, correct placement, and depth, to administer Botulinum toxin injections accurately and safely."
6. "Calculate and determine the appropriate dosage of Botulinum toxin for specific treatment areas based on patient characteristics and desired outcomes."
7. "Evaluate and manage potential complications and adverse reactions associated with Botulinum toxin injections, including knowledge of contraindications, precautions, and emergency procedures."
8. "Implement appropriate patient assessment and communication skills to educate patients about the expected outcomes, potential risks, and necessary follow-up care."
9. "Demonstrate competence in achieving desired aesthetic outcomes through Botulinum toxin injection, including the reduction of wrinkles, fine lines, and facial asymmetry."
10. "Develop proficiency in the treatment of various facial areas using Botulinum toxin, including glabellar lines, forehead lines, crow's feet, bunny lines, lip lines, and other targeted regions."
11. "Understand the duration of Botulinum toxin effects and the need for maintenance treatments, and provide appropriate guidance to patients regarding treatment frequency and long-term care."
12. "Stay updated with the latest research, advancements, and best practices in Botulinum toxin injection techniques, safety protocols, and patient management."

TABLE 2.

Neurotoxin Injection Training Course Curriculum Overview. General outline of the curriculum contents generated by AI. The bot was subsequently queried serially to expand upon each of these points in increasing detail to craft the full curriculum.	
1. Introduction to Aesthetics and Botulinum Toxin:	• Overview of aesthetic medicine and the role of botulinum toxin injections. • Understanding facial anatomy relevant to botulinum toxin injections. • History, development, and types of botulinum toxin products.
2. Indications and Contraindications:	• Identifying suitable candidates for botulinum toxin injections. • Common aesthetic concerns and indications for treatment. • Recognizing contraindications and potential complications.
3. Product Selection and Preparation:	• Understanding different botulinum toxin products and their characteristics. • Proper storage, reconstitution, and preparation techniques. • Dosage calculations and dilution guidelines.
4. Injection Techniques and Treatment Areas:	• Detailed instruction on injection techniques for different facial areas. • Upper face • Mid-face • Lower face
5. Safety Considerations and Complications:	• Recognizing and managing potential adverse events and complications. • Strategies for avoiding complications and achieving optimal outcomes. • Emergency protocols and management of adverse reactions.
6. Patient Assessment and Consultation:	• Comprehensive patient assessment and consultation skills. • Understanding patient expectations and setting realistic goals. • Informed consent and documentation procedures.
7. Hands-on Training and Practical Experience:	• Supervised practical sessions with experienced trainers. • Live patient demonstrations and observation of experienced practitioners. • Guided practice on mannequins or simulation models.
8. Clinical Practice and Case Studies:	• Opportunities for participants to gain real-world experience. • Clinical rotations or internships in aesthetic clinics or supervised settings. • Reviewing and discussing case studies to enhance decision-making skills.

TABLE 3.

Proposed Two-Day Schedule for Neurotoxin Injection Training Course. A table generated entirely by AI in which all topics of the curriculum were divided over 2 days of training, with sensible estimated time allocations for each. Each day begins at 9:00 AM and ends at 5:30 PM, with mid-morning, noon, and mid-afternoon break times included. Time for hands-on training sessions, group discussions, written and practical exam, a question & answer period, as well as feedback sessions, were included.		
Course Schedule		
Time	Day 1	Day 2
9:00 AM – 9:30 AM	Registration and Welcome	Recap of Day 1 and Overview of Day 2 Agenda
9:30 AM – 10:00 AM	Introduction to Botulinum Toxin and its Applications	Workshop of Informed Consent Process and Documentation
10:00 AM – 11:00 AM	Overview of Facial Anatomy Relevant to Botulinum Toxin Treatment	Written Exam on Botulinum Toxin Knowledge and Best Practices
11:00 AM – 11:15 AM	Break	Break
11:15 AM – 12:00 PM	Patient Assessment: Identifying Aesthetic Concerns and Setting Goals	Hands-on Training Session: Applying Injection Techniques on Live Models (supervised by instructors)
12:00 PM – 12:45 PM	Overview of Different Botulinum Toxin Injection Techniques	Lunch Break
12:45 PM – 1:30 PM	Lunch Break	Lunch Break
1:30 PM – 2:30 PM	Understanding Safety Considerations in Botulinum Toxin Administration	Group Discussion and Feedback on Hands-on Practice
2:30 PM – 3:30 PM	Recognizing and Managing Potential complications	Open Q&A Session: Addressing Participant Questions and Concerns
3:30 PM – 3:45 PM	Break	Break
3:45 PM – 5:00 PM	Hands-on Training Session: Practicing Injection Techniques on Simulation Models	Summary of Key Learnings and Closing Remarks
5:00 PM – 5:30 PM	Wrap-up, Summary, and Day 1 Closing Remarks	Distribution of Certificates and Event Conclusion

DISCUSSION

The present study aims to evaluate AI’s potential application in facilitating medical education within aesthetic medicine and surgery.^{26,27} Validation of LLM performance in the development of an educational course on facial botulinum toxin injections demonstrated promising utility of AI in this context (Table 5). While AI performance remains imperfect and can never be used to replace human physicians and educators, the present study demonstrates that LLMs may be best leveraged to provide a practical groundwork for aesthetic surgeons to use in the development and implementation of their educational endeavors.

Logistics of Educational Course Implementation

Budget and Finances

ChatGPT successfully provided a breakdown of anticipated costs for development and implementation of a proposed course of this caliber. The budget was broken down according to event expenses (including venue booking, equipment rental, hiring of support staff, catering, marketing, and travel expenses), as well as budgetary estimates for the creation of curriculum material, including educational content development, editing, graphic design, and publishing. Given the multitude of factors influencing overall projected costs, the authors encountered challenges obtaining a gross budget estimate from ChatGPT; however, when prompted with more specific details, such as a target city of New York, for example, ChatGPT provided two different “low-end” or “high-end” budgets, priced at \$14,030 or \$57,100, respectively (Figure 2). Similarly, detailed proposed estimates for registration prices and target number of attendees (in order to appropriately finance the event) were challenging to obtain, with ChatGPT again naming several influencing factors, such as quality of the educational content, reputation of the speakers, exclusivity of the event, and perceived value by the target audience. Following further prompting, the bot suggested a \$1500 to \$3000 ticket price, per person, and a target number of 100 attendees. This represents a gross profit margin of \$92,900 to \$285,970, given the anticipated expenses. The bot stated that it would be important to assess market demand, size of target audience, and goal profit margin in order to decide on the final ticket price.

Cities, Dates, Venues, and Expert Faculty

When asked to provide a list of cities and venues with dates available in 2024, ChatGPT listed 12 potential cities: 5 in the United States, one in Canada, one in South America, 2 in Europe, 2 in Asia, and one in Australia. For each city, notable convention centers were recommended as potential venues, with weekends between April and December 2024 suggested, among which none overlapped (Figure 2). It remains unclear how ChatGPT is able to deduce availability; more specifically, whether LLMs are able to access relevant registries, or by process of elimination, deduce possible dates based on what is already booked and advertised on the internet.

TABLE 4.

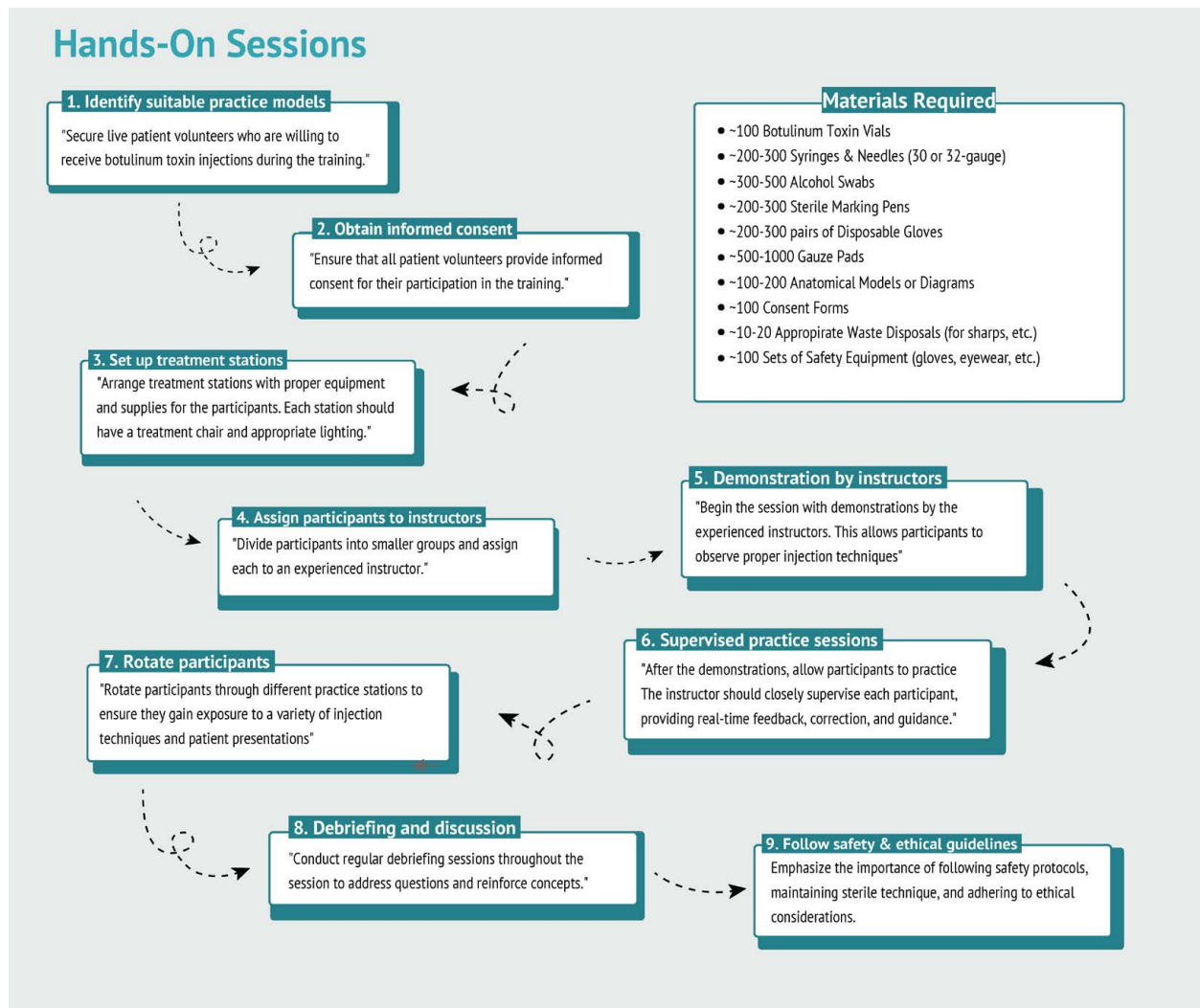
Evaluation Results of Neurotoxin Injection Course Components. Course components were evaluated by 5 expert aesthetic injectors and educators using standardized 10-point evaluation rubrics. The assessment covered both the organization and implementation logistics and the curriculum contents.	
Categories	Expert Assessment Score
Logistics	
Curriculum Outline	8.2 ± 0.8
Course Objectives	8.0 ± 1.4
Curriculum Scheduling	8.2 ± 1.6
Hands on Session Design	8.8 ± 0.8
Curriculum Evaluation & Feedback	8.5 ± 0.6
Budgeting	6.6 ± 1.7
Sponsorship	8.0 ± 0.7
Cities, Venues & Dates	7.6 ± 2.7
Faculty Recommendations	4.6 ± 1.5
Logistics Average Score	7.6 ± 1.3
Curriculum Content	
Introduction & Overview of botulinum toxin	8.0 ± 2.2
Patient Consultation & Consent	8.6 ± 1.5
Facial Anatomy	7.8 ± 1.9
Injection Technique	7.4 ± 1.9
Safety Considerations & Complications	6.8 ± 2.7
Case Studies	6.2 ± 1.9
Attendee Evaluation & Exam	7.4 ± 0.9
Curriculum Content Average Score	7.5 ± 0.8

The bot suggested that experienced dermatologists, plastic surgeons, aesthetic nurses, aesthetic physicians, and trainers from pharmaceutical companies be recruited to lead the teaching sessions and, when prompted for specific names, 3 suggested experts from each of the aforementioned categories were named. Upon verification by the authors, it was noted that the stated specialties for suggested experts were not always accurate. A plastic surgeon was listed in the aesthetic physician category, whereas one aesthetician was listed as a registered nurse. With an ever-increasing emphasis on credentials and appropriate training in aesthetics and injectables, this represents a marked limitation of LLMs and accentuates the need to verify all information that these models may assist in providing.

Sponsors

Step-by-step instructions for obtaining sponsors were impressively provided by ChatGPT, which began by identification of potential sponsors, creation of sponsorship packages, and drafting of sponsorship proposals. When asked to name and identify potential sponsors with relevance

FIGURE 4. Hands-on practice sessions. Nine essential steps for planning and implementation of hands-on practice sessions were generated by AI. Through these sessions, trainees would gain practical experience and confidence in performing neurotoxin injections while under the supervision of experienced instructors.



to the course at hand, ChatGPT listed 10 potential industry sectors, with specific examples of companies from within each. These included pharmaceutical companies, medical device manufacturers, cosmetic and skincare companies, and professional organizations, as well as wellness brands. ChatGPT drafted sponsorship packages in their entirety, which it classified as Platinum, Gold, Silver, and Bronze, according to respective contributions, and drafted written proposals and email templates which may be used to reach out to target companies (Figure 3; Supplementary Document 3). While the LLMs omitted any discussion of Continuing Medical Education (CME) credits in the context of course sponsorship, it would be worthwhile to highlight to the course organizers and participants that any sponsored talks would not be amenable for CME credits.

Scheduling of Teaching Sessions

ChatGPT was able to break the curriculum content down into a sensible 2-day schedule, with an appropriate chronology and time allotted for each section. Sessions ranged between 45 minutes and 1 hour per topic, with several 45 minute breaks for lunch and refreshments, time for live patient demonstrations, attendee evaluation, and a feedback session. When discussing the hands-on teaching sessions, ChatGPT provided a comprehensive list of materials needed with consideration of the need for sterility and waste disposal. The importance of obtaining informed consent from patients participating as models prior to the live injection sessions was also emphasized, and, when prompted, the bot drafted a consent form for use with patient models, though it accentuated the need to consult with legal professionals. The

TABLE 5.
Outline of Standardized Questions posed to the LLM for Curriculum Design. General summary of answering capabilities presented. Wording of some questions are marginally altered for brevity and grouping. All original questions posed to the AI model and responses within each of the three simulated patient interactions are presented, in original form, within Supplementary Document 1.

Questions	Answering Capabilities
Curriculum Design and Structure	
“I want to develop a curriculum to hold a weekend long session to teach aesthetic physicians and nurses how to perform botulinum toxin injections. - How would you suggest I design this?” “Can you please identify learning objectives for the curriculum?” “How would you design a comprehensive curriculum?”	- Created a 10-step guide of all aspects that should be considered for both creation of curriculum content and implementation of event logistics. - Able to identify 12 learning objectives. - Created an overview of 8 sub-sections to be covered in the curriculum.
“Can you make a 2-day schedule with estimated time allocations for the event?”	Able to break the curriculum content down into a 2-day schedule, with a sensible chronology and with appropriate time allotted to each teaching section.
Curriculum Content	
1. Introduction and Overview of botulinum toxin	
“Can you write about the historical context and evolution of Botulinum toxin?” “Can you expand on patient aesthetic concerns and motivations?” “Can you expand upon patient treatment goals and outcomes?”	- Discussed key milestones and developments from discovery of clostridium botulinum in the 18th century to its FDA approval and expanding indications and applications were summarized. - Aesthetic concerns as well as patient motivation and expectations were discussed.
“Can you explain the mechanism of action, pharmacology, and effects of Botulinum toxin?” “What are the FDA indications for Botulinum toxin? What are contraindications to Botulinum toxin?”	- The mechanism of action and pharmacology of Botulinum toxin was explained in adequate detail. - Knowledge cut-off in September 2021 and limitations with respect to current FDA indications was stated.
“Can you compare the following brands of botulinum toxin A? 1. Botox, 2. Dysport, 3. Xeomin, 4. Jeuveau?” “How should they be stored, reconstituted, prepared, and how should dosage and dilution be calculated?”	- Provided a detailed comparison of the formulation, dosage, onset and duration of action and clinical uses of each, in concordance with official manufacturer guidelines. - Encouraged review of the guidelines provided by the manufacturers.
2. Patient consultation, assessment, and consent process	
“How should injectors assess and identify suitable candidates for Botulinum toxin?” “How should evaluation of muscle movement, and presence of static or dynamic wrinkles be performed?” “What are these the potential benefits and limitations of botulinum toxin injections?” “How should injectors education patients about expected outcomes, duration of results, potential side effects, and need for maintenance treatments?” “Can you prepare a consent form for patients who are receiving Botulinum toxin?” “How would you instruct physicians to acquire patient consent for Botulinum toxin?”	- Provided a step-by-step approach to assessing patients at the initial consultation, including evaluation of aesthetic concerns, facial examination, explanations to the patient (including treatment options, potential benefits, limitations, outcomes, and side effects of Botulinum toxin) - The importance of setting realistic treatment goals and discussing limitations and potential outcomes of Botulinum toxin were highlighted. - Emphasized that the consent form should be tailored to meet specific requirements/regulations of the practice and jurisdiction - Presented a step-by-step approach for obtaining patient consent.
3. Facial Anatomy for Botulinum toxin	
“Can you provide an overview of the relevant facial anatomy for Botulinum toxin injection?” “What are the origins, insertions, and orientations of these facial muscles?” “Can you expand on facial anatomy variations?” “Can you expand on relevant neural anatomy? Can you describe the course of the facial nerve, and explain what precautions injectors can take to avoid complications involving these nerves?”	- Provided an overview of muscles of facial expression, injection sites/targeted areas and neural anatomy. - Had difficulty identifying correct muscular origins and insertions - Emphasized that individual anatomy can vary, thus impacting dosing - Provided an accurate overview of the facial nerve and its branches
“What are danger zones for injection and how can these areas be avoided?” “How can injectors avoid [brow ptosis, diplopia, elevation of the eyebrow tail, eyelid ptosis, asymmetric smile and lip droop] when injecting botulinum toxin? What anatomical landmarks should be kept in mind?”	- Had trouble identifying relevant danger zones. - However, when prompted specifically on how to avoid certain side effects, the bot was able to provide general guidelines for safe injection. - Did not provide any unsafe recommendations; however, explanation anatomic landmarks could have been more specific.
4. Injection Techniques and Treatment Areas	
“What type of needle should be used for injection?” “How many injection points should be performed to treat the [glabella, frontalis, crow’s feet, bunny lines, vertical lip lines, mentalis, platysmal bands]?” “What is the recommended dosing, and how deep should injections be? What is the recommended dosing in males and females respectively?” “What areas should be avoided when injecting to avoid complications/side effects?”	- Provided accurate information concerning needle selection. - Depth of injection was generally accurate, however certain details and strategies were omitted (e.g: creation of intradermal blebs when injecting orbicularis oculi) - Frequent underestimation of number of injection points. - Provided mostly correct or underestimated dose estimations. - Provided dosing recommendations for males vs. females (where relevant).
“What post-procedural instructions should be given to patients?” “When should follow up be done?”	- Provided accurate post-procedural and follow-up instructions with no unsafe recommendations. - Adverse reactions that, if noted by the patient, should be reported to healthcare professionals were outlined.
5. Safety Considerations and Complications	
“Can you elaborate on potential adverse outcomes and how they should be managed?” “What are some strategies for avoiding complications?” “Are there any medical emergencies that could happen?”	- Provided an overview of potential complications from Botulinum toxin, with recommendations for both injectors and patients to avoid and manage these complications. - Adverse reactions were addressed, with appropriate deferral to emergency medical assistance when relevant.

TABLE 5. CONTINUED)

Outline of Standardized Questions posed to the LLM for Curriculum Design. General summary of answering capabilities presented. Wording of some questions are marginally altered for brevity and grouping. All original questions posed to the AI model and responses within each of the three simulated patient interactions are presented, in original form, within Supplementary Document 1.

Questions	Answering Capabilities
Curriculum Design and Structure	
6. Case Studies	
“Can you design some case studies to go over tough cases/complications of Botulinum toxin?” “Can you create an answer guide for these case studies?”	5 Case Studies were provided, topics chosen as relevant by ChatGPT were: Ptosis management, overcorrection of Crow’s Feet, Nerve Injury in Lip augmentation, Allergic Reaction management, and Uneven Brown Position - An answer guide to each was provided.
Attendee Exam & Evaluation	
“Can you design an exam to evaluate the attendees of the curriculum?” “What’s the answer key for this exam?” “Can you design an evaluation rubric for the practice sessions?”	- Provided an exam containing 4 multiple-choice questions, 2 scenario-based questions, 3 short-answer questions. - Suggested that a last section for practical exam be conducted. - An accurate answer key for all sections and a rubric that could be used to evaluate attendees during the practical exam was provided.
Hands on Session	
“How would you arrange these hands-on practice sessions?” “What materials (and approximately how many of each) should I have on hand at each station?” “Can you prepare a consent form for the patient models?”	- Provided a 9-step approach for planning hands-on sessions. - Provided a list (and estimated quantity) of important items and equipment to have for the sessions. - Step 2 of the hands-on practice was to obtain informed consent from the patient models; when prompted, it provided a sample consent form. - Emphasized that the consent form should be tailored to meet specific requirements and regulations of the practice and jurisdiction.
Curriculum Evaluation and Feedback	
“Can you design a feedback form for attendees to evaluate our course?”	A feedback form was provided with sections concerning content coverage, structure and organization, faculty and presenters, hands-on practice sessions, training materials and resources, and overall experience, as well as a section for additional comments.
Event Logistics and Budget	
“What would be the anticipated budget for this curriculum creation and event? For one weekend of it for example?” “Can you try to make an estimate if it was held in New York City, for example?” “In this context what should be my target number of attendees be and what should we charge per ticket?”	- Provided a breakdown of anticipated costs for both curriculum creation as well as event expenses. - With considerable prompting, and after it was given an example of a specific city where it would be held (New York), ChatGPT provided a sample budget, provided as a breakdown by category, in a range from low to high end (Figure 3) - With considerable prompting (specified that this would be an in-depth course from experts in the field to create a high-end networking event) ChatGPT provided an ticket price and guest estimate (\$1500-\$3000 per person, for 100 attendees).
“What cities do you think this course should be held (where there would be a lot of healthcare practitioners interested in aesthetics)?” “Can you find a good venue for each city, and a weekend in 2024 where it would be available?”	12 cities provided: 5 in the USA, 1 in Canada, 1 in South America, 2 in Europe, 2 in Asia and one in Australia. - Each city provided included a potential venue (large convention/ exhibition center), and a suggested weekend in 2024 from April- December 2024. None of the weekends overlapped.
“How can I offset costs for this event?” “How could I get sponsorships for this event? Can you identify some potential sponsors to reach out to, and can you create me a sponsorship package?” “Can you draft a proposal and a template email?”	- Several ideas were advanced, the first being sponsorships. - Provided step-by-step instructions for obtaining sponsors, listed 10 categories of potential sponsors in related industries, with examples of companies from each industry (Pharmaceuticals, medical device manufacturers, cosmetics and skincare companies, professional organizations, etc.) - Provided a detailed sponsorship package with prices for Platinum, Gold, Silver, and Bronze levels - Provided a detailed proposal as well as a shorter email proposal.
“Who are some experience faculty you would consider recruiting to lead the training sessions?”	- Suggested that experienced dermatologists, plastic surgeons, aesthetic nurses, aesthetic physicians, and trainers from pharmaceutical companies be recruited. - When prompted to name specific examples, was able to give 3 names from each category - However these were not always accurately categorized according to their true profession (e.g an aesthetician was categorized as a registered nurse)

bot emphasized the need for instructors to comply with all legal and regulatory requirements related to facial toxin injections, as well as safety and ethical protocols while working with patients (Table 3, Supplementary Document 4).

Educational Content – Pearls

The 49-paged course compendium drafted by ChatGPT was broken down into 6 subsections. These included an introduction to botulinum toxin, guide to patient consultation and assessment, overview of facial anatomy, description of injection techniques, discussion of safety considerations and complications, and case studies. Within the introduction to neurotoxins, ChatGPT discussed key milestones in the development of Botulinum toxin, from the discovery of *Clostridium botulinum* in the 18th century, to its FDA approval as a medical product in 2002.²⁸ The mechanism of action of botulinum toxin was clearly explained; and, with prompting, ChatGPT was able to discuss details of its pharmacologic action at levels appropriate for clinicians and nurses (binding of toxin to the SNAP-25 receptor & targeting of the SNARE complex, for example).²⁸ A detailed comparison of formulations, dosages, reconstitution, onset, duration of action, clinical indications, and storage of different products was provided, including Botox, Dysport, Xeomin, and Jeuveau. Of note, Daxxify was omitted, given that it was launched after September 2021, the cutoff date for data on which ChatGPT was trained.

Information and recommendations provided were generally accurate, though some important omissions were noted (Supplementary Table 1). For example, while recent studies have demonstrated that the potency of Botox may be maintained up to 6 weeks following reconstitution if appropriately stored, ChatGPT reported that the product should be used within 4 hours of reconstitution, which is line with the recommendations of the product's manufacturer.^{29,30} Similarly, ChatGPT emphasized that botulinum toxin should be reformulated only with preservative-free sodium chloride, despite many expert injectors advising that preserved sodium chloride is not only safe but preferred, due to reduced pain during the injection process.^{30,31} Therefore, while ChatGPT excels in delivering accurate, "textbook-based" information, it may fall short in capturing crucial nuances derived from new studies, innovations, and practical experience. Nonetheless, ChatGPT repeatedly encouraged review of instructions and guidelines to supplement the information it shared (Supplementary Documents 4 and 5).

ChatGPT provided a comprehensive approach for the initial patient consultation, including evaluation of perceived aesthetic concerns, motivation for seeking neurotoxin treatment, and an assessment of facial animation and muscle activity. Additional sections covered a discussion of both benefits and limitations of neurotoxin, expected outcomes, and potential adverse events. The importance of setting realistic goals

and maintaining patients' natural facial expressions were emphasized. It presented an excellent step-by-step approach for obtaining informed consent, including a thorough explanation of the procedure, and discussion of potential complications, such as bruising, swelling, headache, ptosis, asymmetry, temporary muscle weakness, flu-like symptoms, and allergic reactions. Additionally, it discussed serious adverse effects that should prompt immediate medical attention, such as difficulty swallowing, speaking, or breathing, persistent pain at the injection site, excessive or spreading muscle weakness, vision changes, or allergic reactions. It discussed principles of patient confidentiality and autonomy and emphasized the importance of judicious documentation, as well as the use of clear and concise language to communicate with patients, with avoidance of medical jargon. (Supplementary Documents 4 and 5).

With relevance to anatomy, ChatGPT provided a general overview of the relevant muscles of facial expression, before outlining injection techniques for treatment of the glabellar complex, frontalis, crow's feet, bunny lines, vertical lip lines, mentalis, and platysma. The bot provided accurate guidance on needle gauge and length selection. Dose estimations were provided for each of the above treatment areas, and the bot distinguished between dosing in males and females. It provided accurate and comprehensive post-procedural instructions, with no unsafe recommendations. Accurate intervals for post-injection follow-ups of 1 to 2 weeks were also mentioned.^{30,32} Finally, ChatGPT provided 5 clinical cases to guide group discussion on possible complications, along with an answer guide for each, including eyelid ptosis, overcorrection of crow's feet, nerve injury, allergic reaction, and uneven brow position. Albeit discussing relevant complications, suggested management was vague, and strategies for their avoidance were incompletely discussed.

Educational Content – Pitfalls

Although ChatGPT performed well overall in providing a general and comprehensive overview of essential educational content, its performance on some sections accentuated the need for oversight by experienced faculty, especially in the development of educational content. With respect to anatomy, it generally failed to correctly identify the origins and insertions of important facial muscles, and had difficulty identifying anatomical danger zones³³ relevant for toxin injections, focusing instead on those for vascular complications and fillers. Its inability to provide anatomic diagrams and images represent added limitations. While it thoroughly discussed all possible complications associated with toxin injections, it provided incomplete guidelines on how to avoid them. Further omissions included important practice recommendations such as treating the frontalis and glabellar complex together in order to avoid unopposed action of the depressors and brow tail elevation,^{30,33} for example (Supplementary Table 1).

Generally, recommendations for injection points and dosing were safe, although not always in line with practice standards. ChatGPT typically underestimated the number of required injection points, such as limiting glabellar injections to 3 points, instead of 5 to 7,³⁰ or treatment of vertical lip lines with 2 to 4 injection points, rather than 5 to 6.³⁰ Description of injection depths was adequate, although certain details helpful for learners were omitted, such as the importance of superficial injection to create intradermal blebs in the treatment of Crow's feet.³⁰ The bot did not suggest grasping the platysmal bands prior to their injection, with the goal of avoiding potential dysphagia, dysphonia, and neck weakness from inadvertent injection of the strap muscles.^{30,34} Doses were typically within correct ranges, or slightly underestimated; however, some exceptions included an overestimation of the dose required for treatment of nasalis, at 4 to 8 units vs the recommended 2 to 5 units,³⁰ as well as the platysma at 25 to 100 units vs the recommended 10 to 40 units.³⁰ While these doses may not be unsafe and may be indicated in some patients, it would be more prudent for trainees to practice more conservative dosing at initial treatments³⁰ (Supplementary Table 1).

Attendee Exam and Curriculum Evaluation

ChatGPT highlighted the importance of incorporating time for trainee assessment in its proposed curriculum. When prompted, the bot provided a sample written exam and answer key with 4 multiple-choice, 2 scenario-based, and 3 short answer questions, complete with their answer keys (Supplementary Document 6). It also suggested a practical assessment of trainee performance, providing a rubric with a numerical grading system evaluating injection technique, injection point placement, knowledge of anatomy, communication, safety practices, and overall skill and confidence. A feedback form was also created covering content discussed, course structure, faculty, hands-on sessions, training materials, resources, and overall experience, with a section for additional comments. The provided rating schemes, representing 3- and 5-point Likert scales, were simple and intuitive (Supplementary Document 7).

Study Limitations and Next Steps

Internet resources used by LLMs are suboptimal for postgraduate medical education. Future iterations of LLM technology that may be trained on more reputable educational resources may prove more effective. While diagrams in the present study were created by the authors for the purpose of visually depicting the breadth of textual information provided by ChatGPT, newer versions of LLM technology, boasting computer vision capabilities, may be able to interpret and possibly produce images and diagrams in addition to textual outputs. Limitations pertaining to the present study design, reporting on how humans may subjectively interact with LLMs in a serial and sequential fashion to develop an educational curriculum of this caliber, is certainly prone to bias. Nonetheless, the authors standardize and objectify

their methodology within the bounds of the restrictions set by the study design and objectives, aiming to demonstrate the capabilities of this technology if leveraged appropriately. Future studies may seek to implement this proposed course and validate its educational utility as well as proposed logistics for implementation, in order to supplement the expert evaluation provided herein.

CONCLUSION

The present study demonstrates that LLMs may represent valuable tools for medical education in aesthetic surgery. While AI can never replace human physicians and educators, at minimum, AI can provide a practical framework that aesthetic surgeons may use to develop and implement large-scale educational initiatives. LLMs' greatest utility appears to be related to logistics of implementation. Given the advanced degree of medical and anatomical knowledge required for safe injection practices, a significant degree of human oversight in the development of educational content remains necessary.

DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES

1. Eysenbach G. The role of ChatGPT, generative language models, and artificial intelligence in medical education: a conversation with ChatGPT and a call for papers. *JMIR Med Educ.* 2023;9:e46885. doi:10.2196/46885
2. Abi-Rafeh J, Xu HH, Kazan R, et al. Medical applications of artificial intelligence and large language models: bibliometric analysis and stern call for improved publishing practices. *Aesthet Surg J.* 2023;doi:10.1093/asj/sjad277
3. Abi-Rafeh J, Xu HH, Kazan R, et al. Large language models and artificial intelligence: a primer for plastic surgeons on the demonstrated & potential applications, promises, and limitations of ChatGPT. *Aesthet Surg J.* 2023;doi:10.1093/asj/sjad260
4. George AS, George AH. A review of ChatGPT AI's impact on several business sectors. *PUIJ.* 2023;1(1):9-23.
5. Alshater MM. Exploring the role of artificial intelligence in enhancing academic performance: a case study of ChatGPT. *Available at SSRN.* 2022. <http://dx.doi.org/10.2139/ssrn.4312358>
6. Liu Y, Han T, Ma S, et al. Summary of Chatgpt/GPT-4 research and perspective towards the future of large language models. 2023. *arXiv Preprint. arXiv:230401852.*
7. Dwivedi YK, Pandey N, Currie W, Micu A. Leveraging ChatGPT and other generative artificial intelligence (AI)-based applications in the hospitality and tourism industry: practices, challenges and research agenda. *Int J Contemp Hosp Manag.* 2023;36(1). doi:10.1108/IJCHM-05-2023-0686.
8. Sallam M. The utility of ChatGPT as an example of large language models in healthcare education, research and practice: systematic review on the future perspectives and potential limitations. *medRxiv.* 2023;2023.02. doi:<https://doi.org/10.1101/2023.02.19.23286155>.
9. Patel SB, Lam K. ChatGPT: The future of discharge summaries? *Lancet Dig Health.* 2023;5(3):e107-e108.
10. Peikos G, Symeonidis S, Kasela P, et al. Utilizing ChatGPT to enhance clinical trial enrollment. *arXiv preprint arXiv:230602077.* 2023. <https://doi.org/10.48550/arXiv.2306.02077>.
11. Giannos P, Delardas O. Performance of ChatGPT on UK standardized admission tests: insights from the BMAT, TMUA, LNAT, and TSA examinations. *JMIR Med Educ.* 2023;9(1):e47737.
12. Cancarevic I. The US medical licensing examination. *International Medical Graduates in the United States: A Complete Guide to Challenges and Solutions.* 2021:371-377. 10.1007/978-3-030-62249-7_23.
13. Gilson A, Safranek CW, Huang T, et al. How does ChatGPT perform on the United States medical licensing examination? The implications of large language models for medical education and knowledge assessment. *JMIR Med Educ.* 2023;9(1):e45312.

14. Sillos C, Leon L, Elepaño C, et al. Performance of ChatGPT on USMLE: potential for AI-assisted medical education using large language models. *PLoS Digit Health*. 2023;2:e0000198.
15. Buvat I, Weber W. Nuclear medicine from a novel perspective: buvat and weber talk with OpenAI's ChatGPT. *J Nucl Med*. 2023;64(4):505-507.
16. Thirunavukarasu AJ, Hassan R, Mahmood S, et al. Trialling a large language model (ChatGPT) in general practice with the Applied Knowledge Test: observational study demonstrating opportunities and limitations in primary care. *JMIR Med Educ*. 2023;9(1):e46599.
17. Alberts IL, Mercolli L, Pyka T, et al. Large language models (LLM) and ChatGPT: what will the impact on nuclear medicine be? *Eur J Nucl Med Mol Imaging*. 2023;50(6):1549-1552.
18. Li SW, Kemp MW, Logan SJS, et al. ChatGPT outscored human candidates in a virtual objective structured clinical examination in obstetrics and gynecology. *Am J Obstet Gynecol*. 2023;229(2):172.e1-172.e12.
19. Mihalache A, Popovic MM, Muni RH. Performance of an artificial intelligence chatbot in ophthalmic knowledge assessment. *JAMA Ophthalmol*. 2023;141(6):589-597.
20. Hopkins BS, Nguyen VN, Dallas J, et al. ChatGPT versus the neurosurgical written boards: a comparative analysis of artificial intelligence/machine learning performance on neurosurgical board-style questions. *J Neurosurg*. 2023;1-8. doi:10.3171/2023.2.Jns23419
21. Sethi N, Singh S, DeBoulle K, et al. A review of complications due to the use of botulinum toxin A for cosmetic indications. *Aesthetic Plast Surg*. 2021;45:1210-1220.
22. Zargaran D, Zoller F, Zargaran A, et al. Complications of cosmetic botulinum toxin A injections to the upper face: a systematic review and meta-analysis. *Aesthetic Surg J*. 2022;42(5):NP327-NP336.
23. Nishikawa A, Aikawa Y, Kono T. Current status of early complications caused by hyaluronic acid fillers: insights from a descriptive, observational study of 41,775 cases. *Aesthet Surg J*. 2023;43(8):893-904. doi:10.1093/asj/sjad039
24. Kumar N, Rahman E. Global needs-assessment for a postgraduate program on nonsurgical facial aesthetics. *Aesthet Surg J*. 2021;41(4):501-510. doi:10.1093/asj/sjaa054.
25. Kazan R, Abi-Rafeh J, Viezel-Mathieu A, et al. Identification of essential assessment criteria in facial botulinum toxin injections. *J Plast Reconstr Aesthet Surg*. 2022;75(3):1209-1214. doi:10.1016/j.bjps.2021.11.040.
26. Abi-Rafeh J, Xu HH, Kazan R. Preservation of human creativity in plastic surgery research on ChatGPT. *Aesthet Surg J*. 2023;43(9):NP726-NP727. doi:10.1093/asj/sjad162.
27. Bassiri-Tehrani B, Cress PE. Unleashing the power of ChatGPT: revolutionizing plastic surgery and beyond. *Aesthet Surg J*. 2023;doi:10.1093/asj/sjad135.
28. Carruthers A, Carruthers J. *Botulinum Toxin E-Book: Procedures in Cosmetic Dermatology Series*. Elsevier Health Sciences; 2012.
29. Hexsel DM, De Almeida AT, Rutowitsch M, et al. Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted up to six consecutive weeks before application. *Dermatol Surg*. 2003;29(5):523-529.
30. Carruthers J, Fagien S, Matarasso SL, et al. Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. *Plast Reconstr Surg*. 2004;114(6):1S-22S.
31. Alam M, Dover JS, Arndt KA. Pain associated with injection of botulinum A exotoxin reconstituted using isotonic sodium chloride with and without preservative: a double-blind, randomized controlled trial. *Arch Dermatol*. 2002;138(4):510-514.
32. Jia Z, Lu H, Yang X, et al. Adverse events of botulinum toxin type a in facial rejuvenation: a systematic review and meta-analysis. *Aesthetic Plast Surg*. 2016;40(5):769-77. doi:10.1007/s00266-016-0682-1.
33. Borba A, Matayoshi S, Rodrigues M. Avoiding complications on the upper face treatment with botulinum toxin: a practical guide. *Aesthetic Plast Surg*. 2022;46(1):385-394. doi:10.1007/s00266-021-02483-1.
34. Rohrich RJ, Savetsky IL, Cohen JM, et al. Effective treatment of platysma bands with neurotoxin. *Plast Reconstr Surg Glob Open*. 2020;8(6):e2812. doi:10.1097/gox.0000000000002812.

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Improvement of Hailey-Hailey Disease Following Administration of Dupilumab

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ABSTRACT

Hailey-Hailey disease (HHD) is a rare, chronic skin disorder characterized by recurrent inflammatory plaques with painful blisters, erosions, and macerations. We report a case of a 40-year-old female with clinical and pathological findings consistent with HHD. After numerous unsuccessful treatments, including the use of antiseptic washes, topical and oral medications, and injections, the patient was started on dupilumab (300 mg/2 mL syringes every 2 weeks). After 4 months of treatment, there was a clearance of plaques and resolution of pain with only minimal residual erythema. This response was maintained with no reported side effects. Dupilumab may be an effective and safe treatment option for refractory HHD, but it necessitates further research.

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INTRODUCTION

Hailey-Hailey disease (HHD), also called benign familial pemphigus or benign chronic pemphigus, is a rare, autosomal dominant disorder that affects the adhesion of epidermal keratinocytes. This chronic, relapsing condition is characterized by recurrent painful blistering, erosions, maceration, and frequent secondary infections in the intertriginous and flexural areas. HHD is caused by loss-of-function variants in the ATP2C1 gene at 3q22.1, which encodes the ATP-powered, magnesium-dependent calcium pump protein hSPCA1. Its function is to maintain normal intracellular concentrations of free calcium by sequestering calcium into the Golgi apparatus.¹ While the precise mechanism is not completely understood, the genetic defect causes high cytosolic calcium levels, resulting in altered cellular connections within the epidermis. HHD can also be exacerbated by trauma, friction, sweat, and secondary infections. Although rare, HHD is a chronic and painful condition that can impact a patient's physical and psychological well-being.

Currently, there is no cure for the disease. The mainstay of existing treatments focuses on the management of the disease and avoidance of moisture, which is largely based on case reports and small observational studies. Topical therapies are considered first-line for mild manifestations of the disease and include topical antibiotics, antifungals, corticosteroids, and calcineurin inhibitors.² Patients with severe disease manifestations have shown improvement with the addition of systemic treatments such as oral antibiotics and/or intralesional

botulinum toxin injections.³ Last-line treatments include surgical excision, ablation, or radiation therapy.⁴

Dupilumab, or Dupixent, is a human monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling and has been approved for use in conditions such as atopic dermatitis, asthma, and prurigo nodularis. Dupilumab has shown long-term safety and efficacy in treating atopic dermatitis. This drug has a favorable safety profile with the most common adverse events including nasopharyngitis, conjunctivitis, and injection-site reactions.⁵ This report documents a case of successful treatment of refractory Hailey-Hailey disease with dupilumab.

CASE REPORT

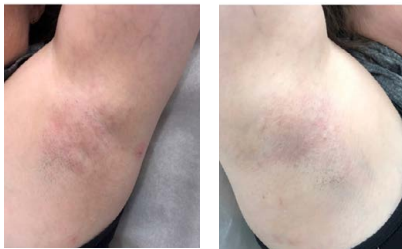
A 40-year-old female with a past medical history of hypothyroidism and atopic dermatitis presented to the clinic with a chief complaint of recurrent skin lesions and erosions to the bilateral axilla for four years. The patient reported intermittent burning and soreness associated with the rash. She also had a history of methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections in the areas, which were treated with Bactrim courses by her primary care physician. The patient denied a family history of blistering cutaneous disease.

On physical exam, there were well-defined, erythematous, scaly papules and plaques with linear erosions and yellow crusting in the bilateral axillary vaults (Figure 1). A biopsy of the right axilla demonstrated full-thickness suprabasilar acantholysis

FIGURE 1. Erythematous, scaly papules and plaques with linear erosions on bilateral axillae prior to dupilumab treatment.



FIGURE 2. Clearance of plaques with only minimal residual erythema after 4 months of dupilumab treatment.



with overlying hyperkeratosis, consistent with Hailey-Hailey disease. The patient tried numerous treatments without clinical improvement, including antiseptic washes, topical tacrolimus ointment, topical and intralesional steroids, oral antifungals, oral antibiotics, glycopyrrolate, naltrexone, and botulinum toxin injections. The patient later began to develop papules and plaques in the groin and inframammary folds. After many failed therapies, the treatment team and patient decided to trial dupilumab (300 mg/2 mL syringes every 2 weeks). Within 4 months of beginning dupilumab, the patient had clearance of plaques with only minimal residual erythema left to bilateral axillae (Figure 2). The patient also reported resolution of pain and significant improvement in quality of life. This response was maintained with no reported side effects.

DISCUSSION

Our patient with HHD, supported by clinical and biopsy findings, was successfully treated with dupilumab. Lesions were cleared with only minimal residual erythema after 4 months of treatment and no notable side effects.

There have been many recent reports using dupilumab off-label to successfully treat a wide range of inflammatory cutaneous diseases, including bullous pemphigoid, acquired perforating dermatosis, palmoplantar pustulosis, and HHD. One case series

TABLE 1.
Response After Administration of Dupilumab in Hailey-Hailey Disease

Author (Year) PMID	Age (Years)/ Gender	Duration of Symptoms Prior to Dupilumab Treatment (Years)	Previous Treatments	Outcome of Dupilumab Course	Concomitant Treatments
Alzahrani et al ⁶ (2021) PMID: 33971025	50s/F	20+	A, Abx, AH, CLI, CLOT, CsA, E, I, LDN, Pred, SS, TCS, 5FU, and various OTC supplements	Significant improvement after an average of 2 months; improvement sustained at 21 months follow-up	None
Alzahrani et al ⁶ (2021) PMID: 33971025	50s/M	5	A, GLY, LDN, TCS	Significant improvement after an average of 2 months; improvement sustained at 25 months follow-up	Betamethasone valerate cream
Alzahrani et al ⁶ (2021) PMID: 33971025	70s/M	33	BTX, ILS, and numerous unspecified topical therapies	Significant improvement after an average of 2 months; improvement sustained at 17 months follow-up	Topical desonide lotion and antiperspirant
Alamon-Reig et al ⁷ (2022) PMID: 35734956	56/F	10	A, AH, AP, CsA, D, DS, Fluc, HCQ, LDN, Min, MTX, Ox, Pred, S, TCS, TT	Significant improvement after 2 months of treatment	Topical clobetasol propionate ointment
Alamon-Reig et al ⁷ (2022) PMID: 35734956	52/M	12	A, AP, CO2 laser, D, LDN, Min, MMp, Ox, Pred, TCS	No improvement reported	Topical fusidic acid, hydrocortisone ointment and Ox 5mg/day
Alamon-Reig et al ⁷ (2022) PMID: 35734956	59/M	25	A, AH, AP, DS, LDN, Min, Pred, TCS	Significant improvement after 5 months of treatment	Antihistamine as needed
Present Case	40/F	4	Abx, AW, BTX, GLY, ILS, LDN, OAF, TCS, TT	Clearance of plaques with only minimal residual erythema after 4 months of treatment	None

A, acitretin; Abx, oral antibiotics; AH, antihistamines; AP, apremilast; AW, antiseptic washes; BTX, botulinum toxin injections; CLI, topical clindamycin; CLOT, clotrimazole; CO2 laser, carbon dioxide laser; CsA, cyclosporine; D, doxycycline; DS, dapsone; E, etanercept; F, female; Fluc, fluconazole; GLY, glycopyrrolate; HCQ, hydroxychloroquine; I, isotretinoin; ILS, intralesional steroids; LDN, low-dose naltrexone; M, Male; Min, Minocycline; MMp, mofetil mycophenolate; MTX, methotrexate; OAF, oral antifungals; OTC, over-the-counter; Ox, oxybutynin; Pred, prednisone; S, sulfone; SS, silver sulfadiazine; TCS, topical corticosteroids; TT, topical tacrolimus; 5FU, topical fluorouracil.

of 3 patients with recalcitrant HHD showed significant clinical response to treatment with dupilumab.⁶ Another case series described lower response rates in the use of dupilumab in three patients with HHD, with only two patients maintaining significant clinical improvement.⁷ These 2 case studies are limited by the number of participants and the lack of a universal assessment scale for this disease. This is only the 7th known case, to the best of our knowledge, of recalcitrant HHD treated with dupilumab that has been reported in the literature (Table 1). This case highlights a potentially exciting new alternative therapy for patients with refractory moderate to severe Hailey-Hailey disease, necessitating further research.

CONCLUSION

Our patient with Hailey-Hailey disease was successfully treated with dupilumab after failing all other current treatments, with a near-complete resolution of lesions and no notable adverse effects. Further studies of IL-4 receptor antagonist use in Hailey-Hailey disease can improve our understanding of the drug's therapeutic potential. Future studies could also examine its use in similar acantholytic diseases, such as Darier disease, to gain a better understanding of the treatment potential and range of dupilumab.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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REFERENCES

1. Hu Z, Bonifas JM, Beech J, et al. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. *Nat Genet.* 2000;24(1):61-5. doi: 10.1038/71701. PMID: 10615129.
2. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. *Br J Dermatol.* 1992;126(3):275-82. doi: 10.1111/j.1365-2133.1992.tb00658.x. PMID: 1554604.
3. Koeyers WJ, Van Der Geer S, Krekels G. Botulinum toxin type A as an adjuvant treatment modality for extensive Hailey-Hailey disease. *J Dermatolog Treat.* 2008;19(4):251-4. doi: 10.1080/09546630801955135. PMID: 18629693.
4. Farahnik B, Blattner CM, Mortazie MB, et al. Interventional treatments for Hailey-Hailey disease. *J Am Acad Dermatol.* 2017;76(3):551-558.e3. doi: 10.1016/j.jaad.2016.08.039. PMID: 27745906.
5. Deleuran M, Thaçi D, Beck LA, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol.* 2020;82(2):377-388. doi: 10.1016/j.jaad.2019.07.074. Epub 2019 Jul 30. PMID: 31374300.
6. Alzahrani N, Grossman-Kranseler J, Swali R, et al. Hailey-Hailey disease treated with dupilumab: a case series. *Br J Dermatol.* 2021;185(3):680-682. doi: 10.1111/bjd.20475. Epub 2021 Jul 5. PMID: 33971025.
7. Alamon-Reig F, Serra-Garcia L, Bosch-Amate X, et al. Dupilumab in Hailey-Hailey disease: a case series. *J Eur Acad Dermatol Venereol.* 2022;36(10):e776-e779. doi: 10.1111/jdv.18350. Epub 2022 Jul 4. PMID: 35734956.

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A Retrospective Comparative Analysis of Cutaneous Adverse Reactions in GLP-1 Agonist Therapies

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) agonists are used to treat type 2 diabetes mellitus (T2DM) and have recently gained approval and popularity for treating obesity and weight loss. There is a lack of data evaluating the types of reactions associated with this medication class, and this study aimed to characterize the types of cutaneous reactions seen across different GLP-1 agonists, and whether differences exist in reactions based on the reason for medication use. Through a retrospective review of cutaneous adverse events associated with semaglutide, dulaglutide, tirzepatide, lixisenatide, liraglutide, and exenatide in the FDA Adverse Event Reporting System, it was found that the 5 most common cutaneous reactions associated with GLP-1 agonists were eczematous, pruritus, drug eruptions, hyperhidrosis, and alopecia. Life-threatening cutaneous adverse events accounted for 2.17% of all cutaneous reactions, with no statistically significant differences observed between drug types. It was also found that GLP-1 agonist use for T2DM exhibited significantly higher rates of alopecia ($P=0.000$) and hyperhidrosis ($P=0.000$) in comparison to use for weight management.

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) agonists are used to treat type 2 diabetes mellitus (T2DM) and have recently gained approval and popularity for treating obesity and weight loss. With the recent increase in prescriptions,¹ a notable gap in the literature still exists regarding comprehensive evaluations and comparisons of cutaneous reactions in this medication class. This study aimed to characterize the types of cutaneous reactions seen across different GLP-1 agonists and to determine whether differences exist in reactions based on the reason for medication use.

Cutaneous adverse events (CAEs) to GLP-1 agonists were retrospectively reviewed using the FDA Adverse Event Reporting System (FAERS).² Medications reviewed included: semaglutide, dulaglutide, tirzepatide, lixisenatide, liraglutide, and exenatide. Adverse events (AEs) reviewed were limited to those categorized as “Skin and Subcutaneous Tissue Disorders” reactions with a single suspected offending drug from the previously listed medications. Reactions were grouped into categories such as life-threatening, drug eruptions, eczematous reactions, etc, (Table 1). CAEs were then filtered and grouped into the reason for use in the following groups: T2DM, weight management (WM), and T2DM+WM. Chi-Square (or Fisher’s

TABLE 1.

Reaction Groupings
Reactions
Life-threatening (includes Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, Angioedema, and Pemphigus)
Drug eruptions (includes urticaria, erythema, erythema multiforme, erythema nodosum, pemphigoid, and fixed drug eruptions)
Eczematous (includes Rash, Dry Skin, and Dermatitis)
Alopecia
Hyperhidrosis
Pruritus
Acne
Photosensitivity Reactions
Discoloration
Purpura and Petechiae
Nail Changes
Psoriasis
Hidradenitis Suppurativa
Skin Laxity
Mucosal Blistering

Exact Test as appropriate) with Bonferonni adjusted *P*-values was utilized to determine the relative rates of reactions and to compare these rates amongst medications and reasons for use. This study utilized publicly available data and therefore was exempt from IRB approval.

CAEs accounted for approximately 5% (n=10,926) of the total reported AEs (n=220,872). 11,576 reactions were reported within the 10,926 CAEs (multiple reactions listed for some events). Of the total reported reactions, exenatide accounted for the largest proportion (42.4%, n=4,904) followed by dulaglutide (20.1%, n=2,331). The five most common reaction types were eczematous (27.0%, n=3,127), pruritus (22.3%, n=2,587), drug eruptions (19.1%, n=2,207), hyperhidrosis (15.2%, n=1,759), and alopecia (10.0%, n=1,162) (Table 2). Life-threatening CAEs accounted for 2.17% (n=251) of reactions, with no statistically significant differences observed between drug types (Table 2). Significant differences existed between drug types for eczematous reactions (*P*=0.000), pruritus (*P*<0.001), drug eruptions (*P*=0.000), hyperhidrosis (*P*=0.000), alopecia

(*P*=0.000), discoloration (*P*=0.014), and acne (*P*=0.028) (Table 2). CAEs were then filtered by reason for use. 7,803 reactions were related to GLP-1 agonist use for T2DM (90.03%, n=7,025), WM (9.16%, n=715), and T2DM+WM (0.81%, n=63) (Table 3). Of note, alopecia (*P*=0.000) and hyperhidrosis (*P*=0.000) reactions were significantly more likely to be associated with use of T2DM in comparison to WM.

To our knowledge, there is limited data that quantifies and characterizes CAEs associated with GLP-1 agonist use. Our study found that patients may experience pruritus, eczematous reactions, drug eruptions, hyperhidrosis, and alopecia when taking GLP-1 agonists. Additionally, even though hair loss has been associated with rapid weight loss and nutritional deficiencies,^{3,4} alopecia was more significantly associated with T2DM. As the prescriptions of GLP-1 agonists continue to increase, providers should be aware of associated CAEs and equipped to counsel and manage patients accordingly. More research is needed to determine whether CAEs from GLP-1 agonists are a significant concern.

TABLE 2.
Associated Reactions With GLP-1 Agonists Grouped by Medication

	Semaglutide	Dulaglutide	Tirzepatide	Liraglutide	Exenatide	Lixisenatide	Total reactions (n, % within total reactions)	P-value
Life-threatening	43	59	7	49	93	0	251 (2.17%)	0.083
Eczematous	533 ^{a,b}	769 ^b	183 ^{a,c}	580 ^{a,b}	1059 ^c	3 ^{a,b,c}	3127 (27.0%)	0.000*
Pruritus	401 ^{a,b}	515 ^{a,b}	130 ^b	409 ^{a,b}	1127 ^a	5 ^c	2587 (22.3%)	<0.001*
Drug eruptions	228 ^a	422 ^b	151 ^{b,c}	351 ^b	1052 ^c	3 ^{a,b,c}	2207 (19.1%)	0.000*
Hyperhidrosis	164 ^a	238 ^{a,b}	39 ^c	237 ^b	1081 ^d	0 ^{a,b,c,d}	1759 (15.2%)	0.000*
Alopecia	239 ^a	239 ^b	155 ^c	251 ^{a,b}	278 ^d	0 ^{a,b,c,d}	1162 (10.0%)	0.000*
Discoloration	28 ^{a,b}	30 ^{a,b}	8 ^{a,b}	21 ^b	103 ^a	0 ^{a,b}	190 (1.64%)	0.014*
Acne	12 ^a	20 ^a	5 ^a	21 ^a	27 ^a	1 ^b	86 (0.74%)	0.028*
Nail changes	10	8	3	13	37	0	71 (0.61%)	0.281
Psoriasis	9	15	4	15	18	0	61 (0.53%)	0.279
Photosensitivity reaction	6	8	4	6	16	0	40 (0.35%)	0.855
Purpura and Petechiae	3	5	0	2	8	0	18 (0.16%)	0.853
Hidradenitis Suppurativa	3	0	0	1	2	0	6 (0.05%)	0.206
Mucosal Blistering	1	2	0	1	2	0	6 (0.05%)	0.954
Skin laxity	1	1	1	1	1	0	5 (0.04%)	0.365
Total reactions associated with drug type (n, % within total reactions)	1681 (14.5%)	2331 (20.1%)	690 (5.96%)	1958 (16.9%)	4904 (42.4%)	12 (0.10%)	11576	--

**P*-value ≤ 0.05 was considered statistically significant. Differing lettered subscripts across reaction rows indicate statistical significance between drug types.

TABLE 3.

Associated Reactions With GLP-1 Agonists Grouped by Reason for Medication Use					
	Type 2 Diabetes Mellitus	Weight Management	T2DM + Weight Management	Total reactions (n, % within total reactions)	P-value
Life-threatening	151	14	1	166 (2.13%)	0.901
Eczematous	1696	161	15	1872 (24.0%)	0.118
Pruritus	1604	156	13	1773 (22.7%)	0.159
Drug eruptions	1361	133	14	1508 (19.3%)	0.446
Hyperhidrosis	1373 ^a	100 ^b	9 ^{a,b}	1482 (19.0%)	0.000*
Alopecia	542 ^a	121 ^b	10 ^{a,b}	673 (8.62%)	0.000*
Discoloration	123	10	0	133 (1.70%)	0.476
Acne	44	10	0	54 (0.69%)	0.100
Nail changes	47	6	1	54 (0.69%)	0.444
Psoriasis	36	3	0	39 (0.50%)	1.000
Photosensitivity reaction	23	1	0	24 (0.31%)	0.782
Purpura and Petechiae	14	0	0	14 (0.18%)	0.468
Hidradenitis Suppurativa	3	0	0	3 (0.04%)	1.000
Mucosal Blistering	4	0	0	4 (0.05%)	1.000
Skin laxity	4	0	0	4 (0.05%)	1.000
Total reactions associated with the reason for use (n, % within total reactions)	7025 (90.03%)	715 (9.16%)	63 (0.81%)	7803	--

*P-value ≤ 0.05 was considered statistically significant. Differing lettered subscripts across reaction rows indicate statistical significance between reason for use.

DISCLOSURES

The authors have no conflict of interest to disclose.

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REFERENCES

- Dzaye O, Berning P, Razavi AC, et al. Online searches for SGLT-2 inhibitors and GLP-1 receptor agonists correlate with prescription rates in the United States: an infodemiological study. *Front Cardiovasc Med.* 2022;9:936651. doi:10.3389/fcvm.2022.936651
- Food and Drug Administration. FDA AEs reporting system (FAERS) public dashboard. <https://www.fda.gov/Drugs/GuidanceComplianceRegulatory-Information/Surveillance/AdverseDrugEffects/ucm070093.htm>. Accessed November 28, 2023.
- Rushton DH. Nutritional factors and hair loss. *Clin Exp Dermatol.* 2002;27(5):396-404. doi:10.1046/j.1365-2230.2002.01076.x
- Zhang W, Fan M, Wang C, et al. Hair loss after metabolic and bariatric surgery: a systematic review and meta-analysis. *Obes Surg.* 2021;31(6):2649-2659. doi:10.1007/s11695-021-05311-2

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Effects of a Moisturizer Containing Colloidal Oatmeal and Filaggrin Technology on *Staphylococcus* Species In Vitro

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ABSTRACT

The pathophysiology of atopic dermatitis (AD) is multifactorial, with genetic predisposition, environmental exposures, and dysbiosis of the skin microbiome all associated with disease activity. Colonization by *Staphylococcus aureus* (*S. aureus*) is specifically associated with AD, and modifying the skin microbiota through topical skincare products may play a role in AD management. A moisturizer containing colloidal oatmeal, a patented filaggrin technology, niacinamide, and tocopheryl acetate was assessed for its impact on the growth, biofilm formation, and bacterial mix adhesion of *S. aureus* and/or *S. epidermidis* on reconstructed human epidermis (RHE). Compared to control conditions, the bacterial growth and adhesion of *S. aureus* were decreased compared to *S. epidermidis* in the presence of the moisturizer. Additionally, the moisturizer did not significantly induce nor inhibit the formation of *S. aureus* biofilm relative to control. Overall, the moisturizer improved the growth ratio of *Staphylococcus* species, shifting the predominant species from pathogenic *S. aureus* to commensal *S. epidermidis*, which may be clinically beneficial in the management of AD.

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INTRODUCTION

Atopic dermatitis (AD) is a multifactorial disease associated with both genetic risk factors and environmental stimuli. AD is also associated with dysbiosis, notably increased colonization by *Staphylococcus aureus*, and the degree of colonization correlates with disease severity.¹ Topical skincare products may be beneficial in improving bacterial diversity resulting from barrier dysfunction.²

A moisturizer specifically designed for AD (Moisturizer 1642) containing colloidal oatmeal, a patented filaggrin technology (RestoradermTechnology™, sodium pyrrolidone carboxylic acid [PCA], and arginine), niacinamide, and tocopheryl acetate was evaluated for its effect on bacterial growth, biofilm formation, and bacterial mix adhesion on reconstructed human epidermis (RHE).

MATERIALS AND METHODS

The growth of two bacteria strains (*S. aureus* and *S. epidermidis*) cultured without hydrocortisone or antibiotics at 37°C with 5% CO₂ was evaluated in the absence (control) and presence of Moisturizer 1642 at 8 concentrations from 0.004% to 0.5% by measuring optical density (OD) at 600 nanometers (nm)

kinetically for 24 hours. Bacterial enumeration and adhesion were measured by colony counting of untreated (control) and pre-treated RHE seeded with a bacterial mix of 50% *S. aureus* and 50% *S. epidermidis* (1.67x10⁷ CFU/ml of each strain). Biofilm formation of *S. aureus* was performed according to the Helaly et al protocol³ and was assessed by the fixation of crystal violet measured by optical density at 590 nm. Experimental data was standardized to control for color interference with OD measurements. All experiments were performed in triplicate.

Statistical analyses were performed using Microsoft Excel and GraphPad PRISM software. The inter-group comparisons were performed using unpaired Student's t-tests.

RESULTS

Bacterial Growth

Individual growth curves for each bacterial strain showed that under control conditions (n=3), *S. aureus* and *S. epidermidis* growth plateaued after approximately 12 and 8 hours of incubation, respectively. Following treatment with Moisturizer 1642 (n=3), no significant inhibition or promotion of either bacterial strain was observed.

Evaluation of bacterial growth following incubation of a bacterial mix found growth of both *S. aureus* and *S. epidermidis* after 6 hours under control conditions (n=3); however, *S. aureus* grew faster than *S. epidermidis* after 24 hours of incubation (1000% versus 372% of the control at baseline [T0]). Following treatment with Moisturizer 1642 (n=3), no difference in bacterial enumeration of *S. aureus* and *S. epidermidis* was observed at T0 (Figure 1A). At 0.05%, 0.15%, and 0.5% concentrations of the moisturizer, the growth of *S. aureus* was inhibited, whereas the growth of *S. epidermidis* was promoted over time compared to the control, thus rebalancing the ratio of bacterial strain growth (Figure 1A and 1B).

Bacterial Adhesion

Under control conditions (n=5), 70.7% of *S. aureus* and 2.1% of *S. epidermidis* within the bacterial mix adhered to the surface of RHE, corresponding to 97% and 3% of adhered bacteria, respectively (Figure 2A). Application of Moisturizer 1642 (n=5)

significantly decreased *S. aureus* adhesion by 79% and strongly promoted *S. epidermidis* adhesion to 1988% of the control ($P<0.001$; Figure 2B).

Biofilm Formation

At concentrations 0.004% to 0.125%, the application of Moisturizer 1642 (n=3) resulted in 95-111% biofilm formation compared to control (n=6) following 24 hours of incubation. Thus, the moisturizer did not significantly induce nor inhibit the formation of *S. aureus* biofilm relative to control.

DISCUSSION

In the presence of Moisturizer 1642, the bacterial growth and adhesion of *S. aureus* were decreased to the benefit of *S. epidermidis*. This rebalancing effect could be particularly beneficial in dysbiotic skin disease associated with aberrant *S. aureus* colonization. The ingredients of Moisturizer 1642 likely contributed to these results. Colloidal oatmeal has demonstrated

FIGURE 1. *S. aureus* and *S. epidermidis* (A) bacterial enumeration and (B) ratio versus total bacteria in mix immediately (T0), and after 6 hours (T6) and 24 hours (T24) of incubation in well-plates. Compared to control, treatment with Moisturizer 1642 tended to slow the growth of *S. aureus* and promote the growth of *S. epidermidis*, thus rebalancing the ratio of bacterial species. These effects were greatest at 0.015% of the moisturizer.

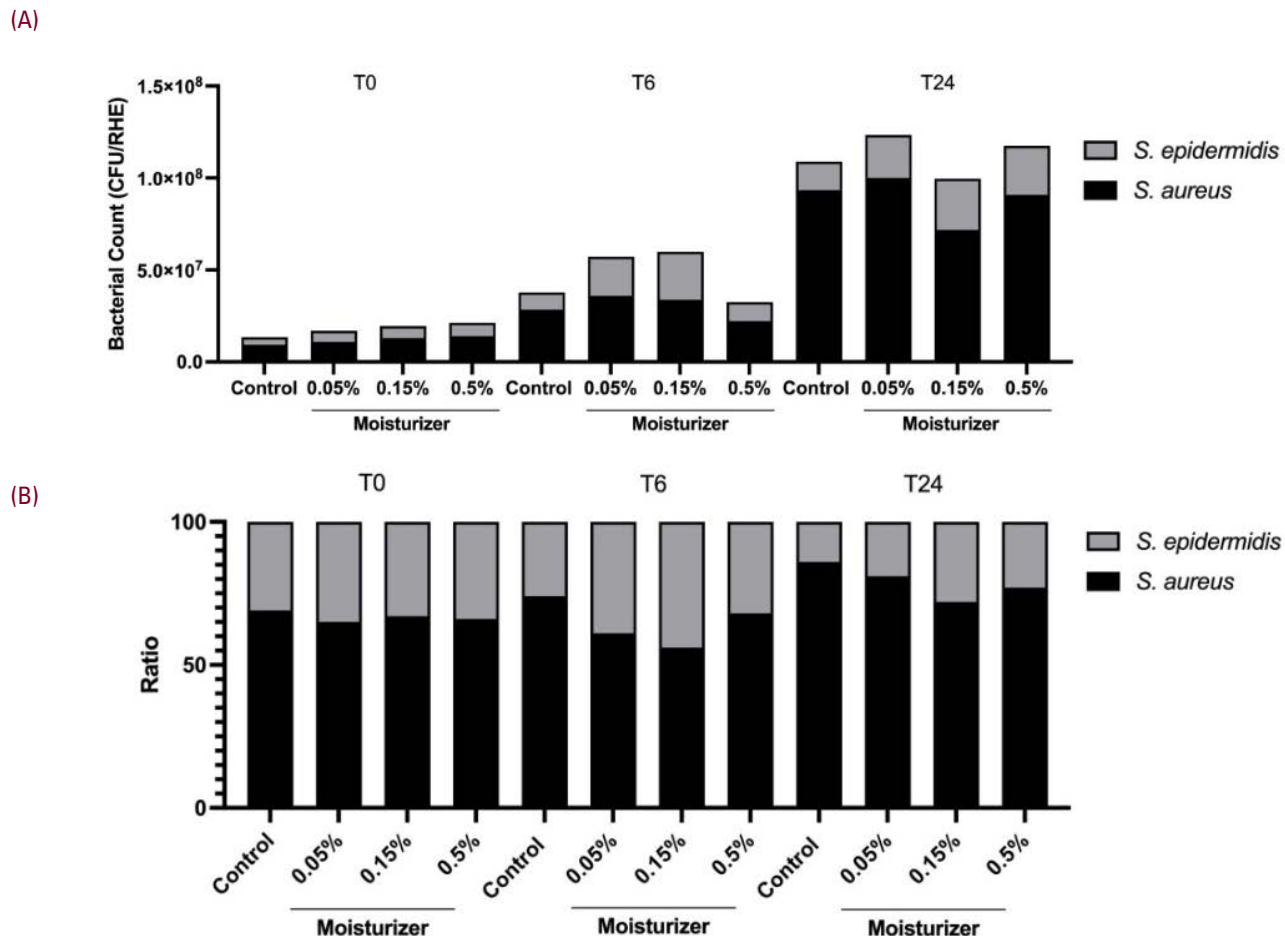
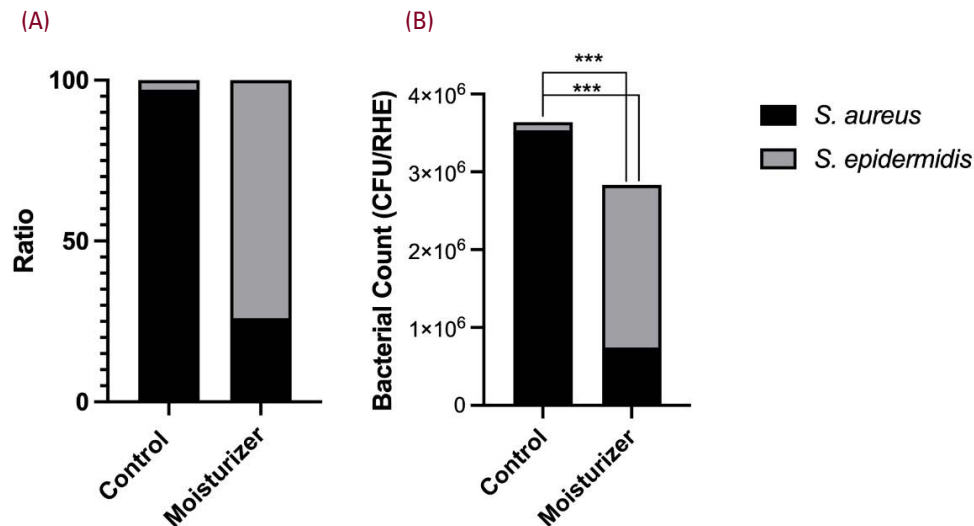


FIGURE 2. (A) Ratio and (B) quantification of *S. aureus* and *S. epidermidis* adhesion on reconstructed human epidermis after application of Moisturizer 1642 compared to control. In control conditions, the majority of bacteria adhered was *S. aureus*, while in the presence of Moisturizer, 1642 *S. epidermidis* predominated.



(n=5; *** $P<0.001$)

prebiotic properties.⁴ In vitro studies by Liu-Walsh et al showed that 1% colloidal oat significantly increases the growth of *S. epidermidis* versus *S. aureus*.⁵ Significant upregulation of *S. epidermidis* dltA gene, which confers reduced susceptibility of bacteria to cationic antimicrobial peptides on the skin was also shown, possibly explaining *S. epidermidis* outcompeting *S. aureus*.^{5,6} Another key ingredient of Moisturizer 1642 is filaggrin technology containing pyrrolidone carboxylic acid (PCA), a filaggrin breakdown product. Reduced expression of *FLG*, the gene encoding filaggrin, is observed in AD skin through multiple mechanisms. PCA is a main component of epidermal natural moisturizing factor (NMF) which helps maintain hydration and a mildly acidic pH of the stratum corneum.⁷ Under mildly acidic conditions created by physiologic concentrations of NMFs, *S. aureus* growth rate and its production of proteins responsible for colonization and immune evasion were decreased. Thus, the presence of PCA in Moisturizer 1642 may have deterred *S. aureus* growth and colonization through acidification of the epidermal environment. The improvement of *Staphylococcal* species growth ratio in the presence of Moisturizer 1642 may be beneficial clinically as *S. aureus* predominance is associated with more severe disease and *S. epidermidis* with less.⁸

This study was limited by its vitro design, as these results may not accurately reflect the dynamic and diverse microbiome of normal and atopic skin in humans. Future clinical studies using this moisturizer, particularly in AD, are warranted.

CONCLUSION

A moisturizer containing ingredients beneficial to AD significantly impacted the growth and adhesion of pathogenic *S. aureus* to the benefit of commensal *S. epidermidis*.

DISCLOSURES

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REFERENCES

- Williams MR, Gallo RL. Evidence that human skin microbiome dysbiosis promotes atopic dermatitis. *J Invest Dermatol.* 2017;137(12):2460-2461. doi:10.1016/j.jid.2017.09.010
- Baldwin HE, Bhatia ND, Friedman A, et al. The role of cutaneous microbiota harmony in maintaining a functional skin barrier. *J Drugs Dermatol.* 2017;16(1):12-18.
- Ghada F, Helaly, Abd El-Aziz AA, Sonbol FI, et al. Dexpanthenol and propolis extract in combination with local antibiotics for treatment of *Staphylococcal* and *Pseudomonas* wound infections. *iMedPub Journals.* 2011;2(4:3).
- Allais B, Friedman A. ARTICLE: Colloidal oatmeal part i: history, basic science, mechanism of action, and clinical efficacy in the treatment of atopic dermatitis. *J Drugs Dermatol.* 2020;19(10):s4-s7.
- Liu-Walsh F, Tierney NK, Hauschild J, et al. Prebiotic colloidal oat supports the growth of cutaneous commensal bacteria including *S. epidermidis* and enhances the production of lactic acid. *Clin Cosmet Investig Dermatol.* 2021;14:73-82. doi:10.2147/CCID.S253386
- Simanski M, Gläser R, Köten B, et al. *Staphylococcus aureus* subverts cutaneous defense by D-alanylation of teichoic acids. *Exp Dermatol.* 2013;22(4):294-296. doi:10.1111/exd.12114
- Moosbrugger-Martinez V, Leprince C, Méchin MC, et al. Revisiting the roles of filaggrin in atopic dermatitis. *Int J Mol Sci.* 2022;23(10):5318. doi:10.3390/ijms23105318
- Byrd AL, Deming C, Cassidy SKB, et al. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med.* 2017;9(397):eaal4651. doi:10.1126/scitranslmed.aal4651

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Acetyl Hexapeptide-8 as a Topical Alternative to Botulinum Toxin: A Review of the Literature

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INTRODUCTION

Acetyl hexapeptide-8, marketed as Argireline[®] (Lipotec, Barcelona, Spain), is a six-amino-acid biomimetic of botulinum toxin promoted as a wrinkle-reducing compound. It entered the market in 2001 and has grown in popularity, as evidenced by a progressively increasing volume of Google searches from 2013 to 2023.¹

Acetyl hexapeptide-8 is applied topically as a cream or serum and is marketed as a less invasive and less expensive alternative to botulinum toxin. Compared to botulinum toxin, acetyl hexapeptide-8 is both less potent (12 vs 0.003 AAUs) and less toxic (2000 mg/kg vs 20 ng/kg).² Additionally, consumers may pay from \$10 to \$30 per ounce for drugstore products to \$100 to \$300 per ounce for premium formulations containing acetyl hexapeptide-8.³ Comparatively, full-face applications of botulinum toxin can cost \$1000 to 3000.³ Our objective was to review the current literature on acetyl hexapeptide-8 and its efficacy in wrinkle minimization.

MATERIALS AND METHODS

A literature search was conducted in August 2024 utilizing PRISMA guidelines using the PubMed, Cochrane Library, and Embase databases with search terms, “acetyl hexapeptide-8” OR “acetyl hexapeptide-3” OR “argireline”. Inclusion criteria included human studies evaluating cutaneous effects of acetyl hexapeptide-8. Exclusion criteria included non-human studies, non-English studies, studies not analyzing the cutaneous effects of acetyl hexapeptide-8, and articles without available full text.

RESULTS

Ten studies (302 females, and 10 males) met our inclusion criteria (Table 1).⁴⁻¹² Four studies⁴⁻⁷ analyzed the isolated effect

of acetyl hexapeptide-8. Five studies⁸⁻¹² explored the efficacy of multi-ingredient formulations, and 1 study¹³ assessed both its isolated effects and in combination with other compounds. All 10 studies reported decreases in wrinkle and scar prominence although significance varied. No significant adverse effects were reported in any trial.

All 4 studies describing the isolated effects of acetyl hexapeptide-8 reported significant changes in wrinkle appearance. Blanes-Mira et al⁴ used Confocal Microscopy and 3D analyses to measure topography. Ruiz et al⁵ measured skin hydration and wrinkle size using Clinipro Antiaging SD with the IMAGE DB system. Wang et al⁶ measured topography with Skin-Visioline VL 650[®] and SPSS 17.0 software. Tadini et al⁷ used the Corneometer[®] CM for skin hydration, and the CutometerSEM 575 and ReviscometerRV600 for anisotropy.

Four of 5 studies that utilized multi-ingredient formulations showed statistically significant changes in wrinkle and scar appearance. An et al⁸ utilized Antera 3D[®] (Miravex, Ireland). Henseler⁹ created wrinkle scores and biologic age comparisons with the Visia[®] Complexion Analysis camera. Palmieri et al¹⁰ measured scar hydration (DermaLabR USB), skin elasticity (ElastiMeter R), sebum levels (Sebumeter SM 815), and used photos and SF-36 quality of life questionnaires. Li et al¹¹ used the Corneometer CM825, Skin Elastometer MPA580, PRIMOS CR technique, and self-assessment questionnaires. Draelos et al¹² used investigator evaluations, subject evaluations, and facial photographs. Raikou et al¹³ measured both the isolated and adjunctive effects of acetyl hexapeptide-8 on microtopography (Skin Visioscan VC98) and transepidermal water loss (tewameter).

TABLE 1.

Summary of Clinical Studies Describing the Cutaneous Effects of Topical Acetyl Hexapeptide-8									
Study	Demographics			Study Characteristics				Outcomes	Severe Adverse Effects
	n	Sex (% F)	Age Range; Mean (y)	Type	Active Ingredients	Location	Follow-up (d)		
Blanes-Mira et al ^{4a}	10	100	NA	Prospective	10% AH-8 (O/W emulsion)	Periorbital	30	30% decrease in wrinkle depth and texture*	None reported
Ruiz et al ^{5a}	20	100	40-57	RCT	AH-8 O/W gel and cream	Full face	30	Decreased wrinkle depth*; Decreased wrinkle width	None reported
Wang et al ^{6a}	60	83.3	25-60	RCT	10% AH-8 (O/W emulsion)	Periorbital	28	Decreased wrinkle height*; Subjective wrinkle improvement in 48.9% patients	None
Tadini et al ^{7a}	40	100	33-55	RCT	10% AH-8 (W/W)	Ventral forearm, full face	28	Decreased anisotropy of facial skin*; Increased facial stratum corneum water content*	None reported
An et al ⁸	52	100	37-57; 45.02±4.85	RCT; split-face	0.005% AH-8 (W/W) and hyaluronic acid-based microneedle patch	Perioral, periorbital	29	Decreased wrinkle severity*	None
Henseler ⁹	19	100	24-68; 51.1±10.4	RCT; split-face	10% AH-8 in triple hyaluronic acid serum	Hemiface	28	Decreased wrinkle score	None
Palmieri et al ¹⁰	26	100	23-63	Retro-spective	10% AH-8, magnesium aluminum silicate, and sodium silicate	Chin, neck, forehead, malar area	NA	Increased scar elasticity*; Reduced sebum levels*; Decreased hydration of affected area*; Increased QOL*	None
Li et al ¹¹	32	100	20-45; 28.5	Pro-spective	10% AH-8, 4% combination of palmitoyltetrapeptide-7 and palmitoyl tripeptide-1, and 2% combination of dipeptide-2, palmitoyl tetrapeptide-7, and hesperidin methyl chalcone	Periorbital	28	Decreased wrinkle number, depth, and volume*; Subjective wrinkle improvement in 75% patients	None
Draelos et al ¹²	29	100	35-60; 47±6.6	Pro-spective	Serum containing gamma-aminobutyric acid and 7 peptides including AH-8, acetyl octapeptide-3, dipeptide diamino-butyroyl benzylamide diacetate, tri-fluoroacetyl tripeptide-2, and palmitoyl tetrapeptide-7	Crow's feet, glabella, forehead	98	Decreased severity of facial lines, facial wrinkles, eye lines, eye wrinkles*	None
Raikou et al ^{13a}	24	100	30-60; 45±5	RCT	10% AH-8 (W/W); 10% AH-8 (W/W) and 5% tripeptide-10 citrulline (W/W)	Forehead, periorbital	60	Decreased cR2 & cR3 in both formulations; Decreased TEWL in isolated formulation*; Increased TEWL in multi-serum formulation	None

* = statistically significant
± = included isolated acetyl hexapeptide-8 formulation
AH-8 = acetyl hexapeptide-8, cR2 = measure of maximal roughness of skin, cR3 = measure of average roughness of skin F = Female, NA = not applicable, RCT = randomized control trial, O/W = oil-in-water, TEWL = transepidermal water loss, W/W = weight-by-weight

DISCUSSION

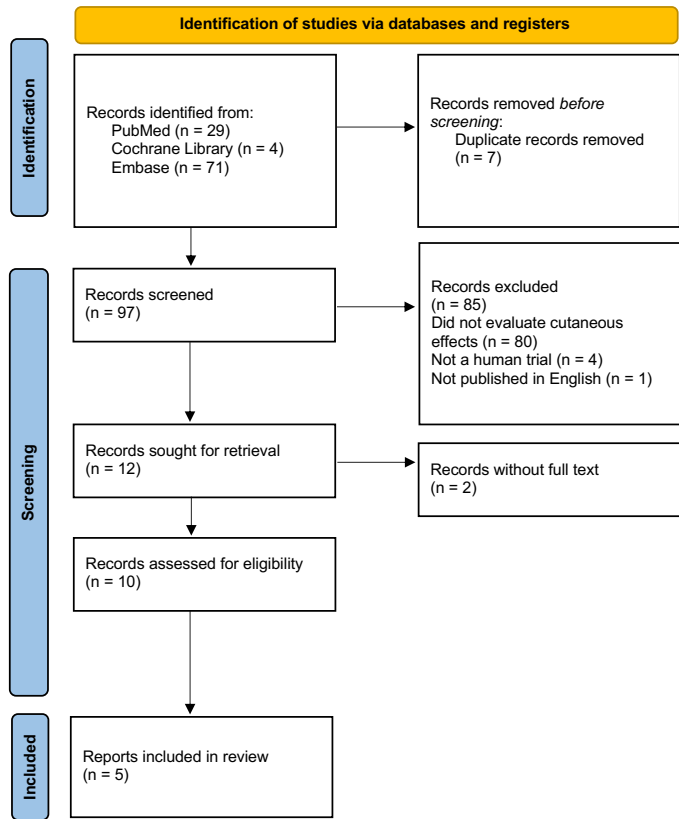
Acetyl hexapeptide-8 is marketed as a milder, non-invasive option for anti-aging treatment because its proposed mechanism of action mimics botulinum toxin. All 10 studies showed improvements in wrinkle appearance with acetyl hexapeptide-8 though statistical significance was inconsistent. Six showed significant improvement in wrinkle parameters.^{4-6,8,11,12} Tadini et al showed significant changes in anisotropy, and Palmieri et al reported significant reductions in scar severity. Studies suggest acetyl hexapeptide-8 may be more effective as an adjunct.⁹⁻¹³ However, only Raikou et al tested acetyl hexapeptide-8 in isolation and combination, making it unclear if improvements are due to synergistic effects or other ingredients.

No standardized acetyl hexapeptide-8 serum formulas were used in these studies, highlighting the need to consider its cutaneous absorption. Kraeling et al analyzed percutaneous penetration of acetyl hexapeptide-8 using hairless guinea pigs and cadaver

human skin.¹⁴ After applying the emulsion of 2 mg/cm² and washing the skin, 99.4% of the metabolite was removed. Only a small proportion reached the epidermis: 0.54% in the stratum corneum and 0.01% in the epidermis, indicating minimal absorption. Acetyl hexapeptide-8's large molecular weight (889 Dalton) and hydrophilic nature likely cause its poor transdermal permeability. Several recent studies have investigated various methods to enhance skin penetration of acetyl hexapeptide-8 and have shown promising results.¹⁵⁻¹⁷

Limitations of this review included study design and an inability to direct comparisons. Study design limitations include small sample sizes, short follow-up, and predominance of female participants (97%). Comparing results was challenging due to varying methodologies and the absence of standardized wrinkle analysis methods. Furthermore, no study directly compared acetyl hexapeptide-8 to botulinum toxin, raising questions about the required concentration for comparable efficacy.

FIGURE 1. PRISMA diagram showing articles identified for inclusion in the review.



CONCLUSION

Current data suggests that acetyl hexapeptide-8 may improve wrinkle appearance, but the significance is unclear due to varying quantification methods. Utilization of acetyl hexapeptide-8 in a multi-ingredient topical shows more consistent and promising results, but formulations vary widely. Compared to botulinum toxin, acetyl hexapeptide-8 has lower potency and toxicity with no serious adverse effects reported. Given the poor intrinsic cutaneous absorption of acetyl hexapeptide-8, further investigation and development of vehicles of application for acetyl hexapeptide-8 are necessary. Larger studies with broader subject populations comparing the effects of acetyl hexapeptide-8 with botulinum toxin using standardized methodology are also needed.

DISCLOSURES

No funding was received for this work. None of the authors disclose conflict of interest related to this work.

REFERENCES

1. Olsson SE, Sreepad B, Lee T, et al. Public interest in acetyl hexapeptide-8: Longitudinal analysis. *JMIR Dermatology*. 2024;7. doi:10.2196/5421.
2. Wang Y, Wang M, Xiao XS, et al. The anti-wrinkle efficacy of Argireline. *J Cosmet Laser Ther*. 2013;15(4):237-241. doi:10.3109/14764172.2013.769273.
3. Grand View Research. *Anti-Aging Market Size & Share Report, 2022-2030*. Grand View Research, Inc. Available from: <https://www.grandviewresearch.com/industry-analysis/anti-aging-market>. Accessed August 18, 2024.
4. Blanes-Mira C, Clemente J, Jodas G, et al. A synthetic hexapeptide (Argireline) with antiwrinkle activity. *Int J Cosmet Sci*. 2002;24(5):303-310. doi:10.1046/j.1467-2494.2002.00153.x.

5. Ruiz Martínez MA, Clares Naveros B, Morales Hernández ME, et al. Evaluation of the anti-wrinkle efficacy of cosmetic formulations with an anti-aging peptide (Argireline®). *Digibug*. 2010;50(4). <http://hdl.handle.net/10481/27392>.
6. Wang Y, Wang M, Xiao S, et al. The anti-wrinkle efficacy of Argireline, a synthetic hexapeptide, in Chinese subjects. *Am J Clin Dermatol*. 2013;14(2):147-153. doi:10.1007/s40257-013-0009-9.
7. Tadini K, Mercurio D, & Campos P. Acetyl hexapeptide-3 in a cosmetic formulation acts on skin mechanical properties-clinical study. *Brazilian Journal of Pharmaceutical Sciences*. 2015;51(4). doi:10.1590/S1984-82502015000400016.
8. An JH, Lee HJ, Yoon MS, Kim DH. Anti-Wrinkle Efficacy of Cross-Linked Hyaluronic Acid-Based Microneedle Patch with Acetyl Hexapeptide-8 and Epidermal Growth Factor on Korean Skin. *Ann Dermatol*. 2019;31(3):263-271. doi:10.5021/ad.2019.31.3.263.
9. Henseler H. Investigating the effects of Argireline in a skin serum containing hyaluronic acids on skin surface wrinkles using the Visia® Complexion Analysis camera system for objective skin analysis. *PubMed*. 2023;12(9). doi:10.3205/jprs000179.
10. Palmieri B, Novello A, V Corazzari, et al. Skin scars and wrinkles temporary camouflage in dermatology and oncoesthetics: Focus on acetyl hexapeptide-8. *Clin Ter*. 2020;171(6). doi:10.7417/ct.2020.2270.
11. Li F, Chen H, Chen D, et al. Clinical evidence of the efficacy and safety of a new multi-peptide anti-aging topical eye serum. *J Cosmet Dermatol*. 2023;22(12):3340-3346.
12. Draelos ZD, Kononov T, Fox T. An open label clinical trial of a peptide treatment serum and supporting regimen designed to improve the appearance of aging facial skin. *J Drugs Dermatol*. 2016;15(9):1100-1106.
13. Raikou V, Varvaresou A, Panderi I, Papageorgiou E. The efficacy study of the combination of tripeptide-10-citrulline and acetyl hexapeptide-3. A prospective, randomized controlled study. *J Cosmet Dermatol*. 2017;16(2):271-278. doi:10.1111/jocd.12314.
14. Kraeling MEK, Zhou W, Wang P, Ogunola OA. In vitro skin penetration of acetyl hexapeptide-8 from a cosmetic formulation. *Cutaneous Ocular Toxicol*. 2014;34(1):46-52. doi:10.3109/15569527.2014.894521.
15. Hou J, Wei W, Geng Z, et al. Developing Plant Exosomes as an Advanced Delivery System for Cosmetic Peptide. *ACS Applied Bio Materials*. 2024;7(5):3050-3060. doi:https://doi.org/10.1021/acsabm.4c00096.
16. Peng, C.-L., Lee, P.-C., Liu, H.-T., & Lai, P.-S. (2024). Advancing transdermal delivery by Zn/Ag-electrode-printed iontophoretic patch with self-generating microcurrents. *Scientia Pharmaceutica*, 92(2), 26. <https://doi.org/10.3390/scipharm9202026>.
17. Lim, S. H., Kathuria, H., Amir, M. H. B., Zhang, X., Duong, H. T. T., Ho, P. C.-L., & Kang, L. (2021). High resolution photopolymer for 3D printing of personalised microneedle for transdermal delivery of anti-wrinkle small peptide. *Journal of Controlled Release: Official Journal of the Controlled Release Society*, 329, 907-918. <https://doi.org/10.1016/j.jconrel.2020.10.021>.

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Readability and Content Characterization of Online Reading Materials for Individuals With Vitiligo

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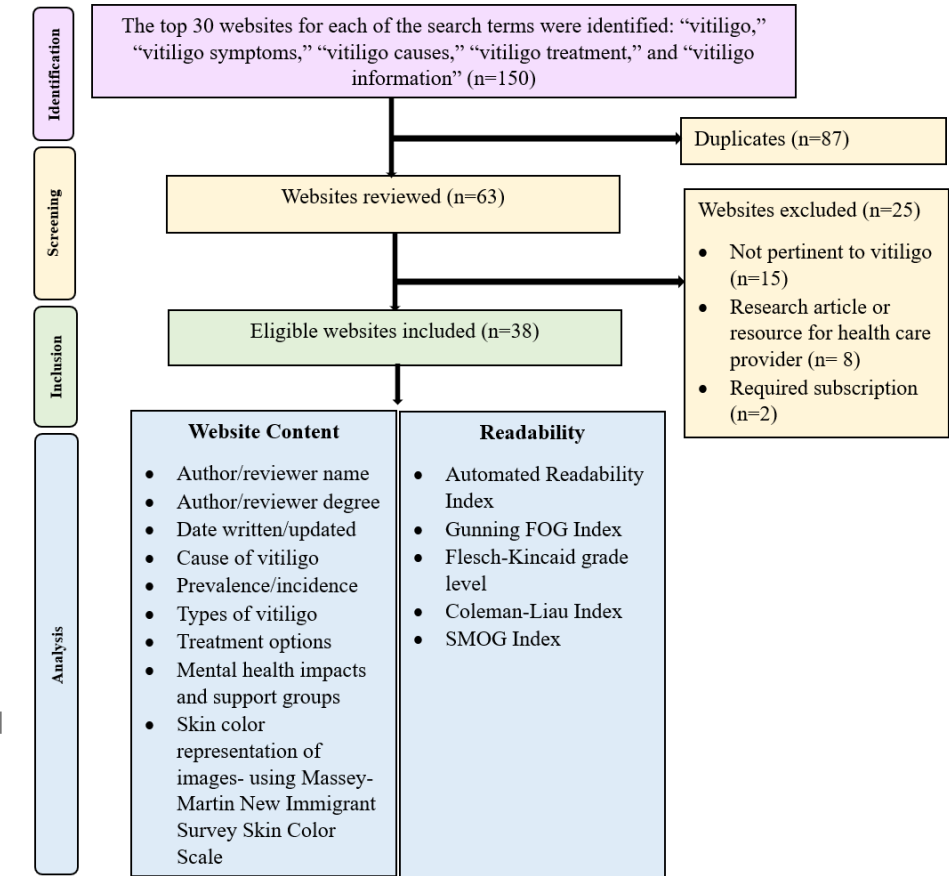
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To the Editor:

Online health resources expand availability of medical information, however, if written at a reading level that is too advanced, may inadvertently lead to confusion or misunderstanding in those with low health literacy.¹ In certain populations, this can exacerbate health disparities.¹ The American Medical Association (AMA) recommends a sixth-grade reading level or below in the creation of patient resources.² The objectives of this study were to determine the readability of online reading materials for vitiligo in the English language and characterize the website content of these resources.

In November 2023, an incognito Google search was performed with the following search terms: “vitiligo,” “vitiligo causes,” “vitiligo symptoms,” “vitiligo treatment,” and “vitiligo information” (Figure 1). The top 30 websites for each search term were screened. Websites requiring a subscription, duplicates, research articles, resources for healthcare providers, and websites not pertinent to vitiligo were excluded.³ The readability of each website was determined using the validated readability scales available on readabilityformulas.com, including the Flesch-Kincaid grade level, Gunning FOG

FIGURE 1. Flow diagram for the selection and assessment of top vitiligo patient education websites on Google.



Index, SMOG Index, Coleman-Liau Index, and the Automated Readability Index. Websites were reviewed for author/reviewer information, date written/updated, website content, and image skin color representation. To rate skin color, the Massey-Martin New Immigrant Survey Skin Color Scale was used. Skin colors 1 to 2 were categorized as light/white, 3 to 5 as medium/brown, and 6 to 10 as dark/black.⁴

Of the 150 websites identified, 38 were eligible. Across the 38 websites, the average reading level was at a tenth-grade level (10.5, range: 8.02-14.9). Less than a third (28.9%, n=11) of websites were written/reviewed by a dermatologist and roughly half (52.6%, n=20) reported the date they were written and/or updated. Of the websites reporting this information, 85.0% (n=17) were written and/or updated within the past two years.

A majority of the websites (97.4%, n=37) mentioned the cause of vitiligo and most (57.9%, n=22) discussed prevalence and/or incidence data. The reporting of vitiligo treatment options varied across websites (Table 1). Several websites described the psychosocial impacts of vitiligo (78.9%, n=30) and vitiligo support groups (71.1%, n=27). Among the 25 websites featuring photographs of individuals with vitiligo, light/white (72.0%, 18/25) and medium/brown (69.0%, 17/25) skin colors were most

TABLE 1.

Website Content and Image Representation Across Online Health Resources for Individuals With Vitiligo	
Website Content (n=38)	Number (%)
Reported name of author/reviewer	13 (34.2%)
Written or reviewed by a dermatologist	11 (28.9%)
Date written/updated reported	20 (52.6%)
Cause of vitiligo reported	37 (97.4%)
Prevalence/incidence reported	22 (57.9%)
Types of vitiligo reported	25 (65.8%)
Mention of mental health impacts	30 (78.9%)
Mention of support groups	27 (71.1%)
Treatment Options	
Phototherapy	34 (89.5%)
Surgical treatment/grafting	30 (78.9%)
Topical steroids	29 (76.3%)
Camouflage	26 (68.4%)
Depigmentation	24 (63.2%)
Topical calcineurin inhibitors	23 (60.5%)
Oral steroids	13 (34.2%)
Ruxotinilob	13 (34.2%)
Vitamins/antioxidants	11 (28.9%)
Skin color representation (n=25)	
Light/white	18/25 (72.0%)
Medium/brown	17/25 (69.0%)
Dark brown/black	12/25 (48.0%)

often represented, whereas dark/black skin colors (48.0%, 12/25) were least represented.

With the expanding role of social media/internet as an information source, this study emphasizes the importance of creating readable, diverse, comprehensive, and where applicable, evidence-based vitiligo reading materials. Similar to a prior study analyzing vitiligo websites in the Arabic language, no websites met the AMA's recommended sixth-grade reading level.⁵ If the readability of content is too advanced, this limits the usability of online health information among individuals with low health literacy.^{1,5} This is especially important considering that low levels of literacy are a prevalent problem in the United States (US), with the US Department of Education estimating that about 54% of adults in the US ages 16 to 74 read at a level below the sixth grade.^{6,7} Further, prior studies have noted certain populations are more vulnerable to experiencing low health literacy.⁸ Some of these groups include racial/ethnic minorities, immigrants, individuals with lower educational attainment, and those speaking a non-English language at home.⁸ Dermatologists, authors, and reviewers of vitiligo reading materials should consider the AMA's grade level recommendations in the creation and dissemination of online educational resources for individuals with vitiligo. In addition, dermatologists have an essential role in directing those with vitiligo to credible and comprehensive online reading materials. Advancements in these areas can promote digital health equity, increasing the usability of educational resources among marginalized communities.

DISCLOSURES

Dr Elbuluk has served as a consultant, advisory board member, and/or speaker for Avita, Incyte, VisualDx, Beiersdorf, Unilever, Eli Lilly, Galderma, Pfizer, La Roche Posay, L'Oreal, McGraw Hill, Dior, Medscape, Abbvie, Takeda, Sanofi. She has received royalties from McGraw-Hill. She has stock options in VisualDx. AMH has no disclosures to report.

REFERENCES

- Rodriguez F, Ngo S, Baird G, et al. Readability of online patient educational materials for coronary artery calcium scans and implications for health disparities. *J Am Heart Assoc.* 2020;9(18):e017372. doi:10.1161/JAHA.120.017372
- Weis BD. Health literacy: a manual for clinicians. American Medical Association Foundation and American Medical Association; 2003. <http://lib.ncfh.org/pdfs/6617.pdf>
- De DR, Seivright J, Yee D, et al. Readability, quality, and timeliness of patient online health resources for urticaria. *J Am Acad Dermatol.* 2022;86(5):1182-1185. doi:10.1016/j.jaad.2021.04.089
- Lamb JE, Stone AX, Davis EM, et al. Visual learning equity: a course auditing system of skin color in preclinical medical education. *Fam Med.* 2023;55(6):375-380. doi:10.22454/FamMed.2023.766642
- Alghanemi L, Sanad SA, Alzahrani FS, et al. The evaluation of the informational content, readability, and quality of online information related to vitiligo in the Arabic Language. *Cureus.* 2022;14(10):e30497.
- Rothwell J. Assessing the Economic Gains of Eradicating Illiteracy Nationally and Regionally in the United States. Barbara Bush Foundation for Family Literacy. September 2020. Accessed June 3, 2024. https://www.barbarabush.org/wp-content/uploads/2020/09/BBFoundation_GainsFromEradicatingIlliteracy_9.8.pdf
- Schmidt E. Reading the Numbers: 130 Million American Adults Have Low Literacy Skills, but Funding Differs Drastically by State. American Public Media. Available from: <https://www.apmresearchlab.org/10xadult-literacy>. Accessed June 3, 2024.
- Health People 2030. Language and Literacy. Office of Disease Prevention and Health Promotion. N.d. Available from: <https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health/literature-summaries/language-and-literacy>. Accessed June 3, 2024.

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Vehicle for Roflumilast
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**The National Mentorship
Match Algorithm:
Mentors Needed**
Surya A. Veerabagu MD



**Patient- and Clinician-
Reported Outcomes for
Tirbanibulin in Actinic
Keratosis in Clinical
Practice Across the
United States (PROAK)**
Todd Schlesinger MD



**Image Analysis of
Xerosis and Atopic
Dermatitis Following
Prebiotic Skincare
Regimen in Ethnically
Diverse Patients**
Hawasatu Dumbuya PhD



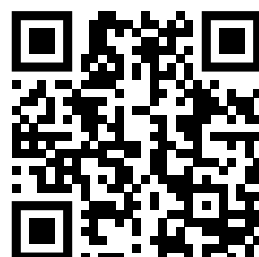
**Efficacy and Tolerance
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Surfactant Technology-
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Exploring the Therapeutic Potential of GLP-1 Agonists in Hidradenitis Suppurativa

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INTRODUCTION

Hidradenitis suppurativa (HS) is a notoriously difficult-to-treat inflammatory skin condition characterized by the presence of deep, painful nodules, abscesses, tracts, and fibrotic scars, often occurring in intertriginous and apocrine gland-rich areas.¹ HS is associated with various comorbid conditions, including polycystic ovarian syndrome (PCOS), metabolic syndrome, and obesity, all of which share a lack of glycemic control.² With the emergence of GLP-1 agonists, and their increased use to achieve glycemic control, exploring their potential advantages for patients with HS is warranted. This letter examines the application of GLP-1 agonists in the treatment of HS to date.

MATERIALS AND METHODS

To identify case reports examining the use of GLP-1 agonists in the treatment of HS, a literature review of PubMed, Web of Science, and Embase using the search terms “hidradenitis suppurativa” and “GLP-1,” was conducted on August 27th, 2024. Two authors (AP and ENM) screened all articles for inclusion and extracted data for the variables in Table 1.

RESULTS

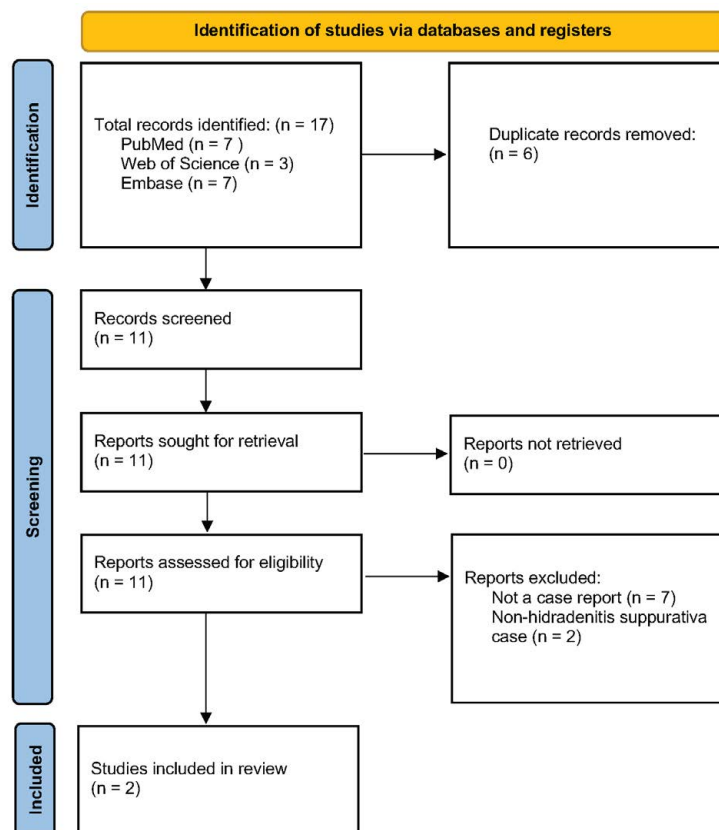
Seventeen articles were identified, with two meeting inclusion criteria following review. For further details, see the PRISMA diagram in Figure 1. Both included articles showed initial weight loss and a reduction of disease severity following treatment with the GLP-1 agonist, Liraglutide (Table 1).^{3,4}

TABLE 1.

Included Case Studies and Their Respective Details				
Case Report	Drug(s) Utilized	Demographic	Treatment Length	Treatment Results
Jennings et al (2017)	Liraglutide (0.6 mg -> titrated to 1.8 mg due to extensive disease)	31-year-old female, concurrent smoker, obesity	8 weeks	After 4 weeks of treatment, the patient had mild residual disease, and their DLQI improved from 24 to 14; after 8 weeks, they had lost 14 pounds
Khandalavala (2017)	Combination of Liraglutide Metformin, Levonorgestrel-ethinyl estradiol, dapsone, and finasteride	19-year-old female, concurrent polycystic ovarian syndrome (PCOS), fatty liver disease, obesity	3 years	Flares decreased in intensity and duration with no instances being reported in the 6 month period between treatment and case report publication. Liver enzymes normalized within one year of treatment, ESR reduced from 120 to 34 mm/hr, and an initial weight loss of 40 pounds

Dermatology Quality Life Index - DLQI: Maximum score of 30, with a larger number indicating a great impairment in quality of life.

FIGURE 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.



DISCUSSION

While the pathogenesis of HS is incompletely understood and likely multifactorial, dysregulation of inflammatory pathways is known to be implicated. Specifically, the upregulation of numerous pro-inflammatory cytokines, including TNF- α , IL-1, IL-17, IL-23, and Th1 and Th17 lymphocytes, have been associated with HS. Liraglutide has been shown to exert its therapeutic effect among psoriasis patients by decreasing IL-17 and TNF- α induced cytokines. As such, Liraglutide may confer benefits to patients with HS in a similar matter.³

Additionally, patients with HS demonstrate high rates of obesity. Adipose tissue in obese patients actively triggers a state of chronic low-grade systemic inflammation. Adipocyte hypertrophy drives the release of adipocytokines (TNF- α , IL-1 β , and IL-6) and other pro-inflammatory mediators.⁵ Body mass index (BMI), as well as increased levels of cytokines, has been associated with worse skin disease severity in psoriasis patients, which makes it likely that these same adipocytokines may contribute to other inflammatory skin diseases like HS.³ The presence of adipose tissue in obese individuals results in the release of pro-inflammatory cytokines. Thus, weight loss likely contributes to decreased pro-inflammatory cytokines associated with inflammatory skin conditions like HS.

CONCLUSION

The interrelation between GLP-1 agonists and the treatment of HS lacks sufficient investigation within the current medical literature. This letter critically assesses all reported cases of GLP-1 agonists in the treatment of HS to date for etiology and clinical characteristics, with the ultimate goal of urging future clinical trials to determine the drug's wide-scale benefits.

DISCLOSURES

All authors have no conflicts of interest to declare.

REFERENCES

1. Ballard K, Shuman VL. Hidradenitis Suppurativa. In: StatPearls. Treasure Island (FL): StatPearls Publishing; April 17, 2023.
2. Tzellos T, Zouboulis CC. Review of comorbidities of hidradenitis suppurativa: implications for daily clinical practice [published correction appears in *Dermatol Ther (Heidelb)*. 2020;10(3):523. doi: 10.1007/s13555-020-00366-y]. *Dermatol Ther (Heidelb)*. 2020;10(1):63-71. doi:10.1007/s13555-020-00354-2
3. Jennings L, Nestor L, Molloy O, et al. The treatment of hidradenitis suppurativa with the glucagon-like peptide-1 agonist liraglutide. *Br J Dermatol*. 2017;177(3):858-859. doi:10.1111/bjd.15233
4. Khandalavala BN. A disease-modifying approach for advanced hidradenitis suppurativa (regimen with metformin, liraglutide, dapson, and finasteride): a case report. *Case Rep Dermatol*. 2017;9(2):70-78. doi:10.1159/000473873
5. Guo Z, Yang Y, Liao Y, et al. Emerging roles of adipose tissue in the pathogenesis of psoriasis and atopic dermatitis in obesity. *JID Innov*. 2021;2(1):100064. doi:10.1016/j.xjidi.2021.100064

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NEWS, VIEWS, AND REVIEWS

Off-Label Management Strategies for Generalized Granuloma Annulare: What's New?

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INTRODUCTION

Granuloma annulare (GA) is a benign, inflammatory granulomatous skin disease with an estimated annualized prevalence of ~0.06% in the United States.¹ The most common subtypes are localized and generalized GA (GGA), which affect about 75% and 15% of patients, respectively.² While localized GA responds well to topical and intralesional corticosteroids, GGA responds poorly to topical therapies and can be challenging to manage, even with systemic treatments. While multiple treatment modalities have been employed in the management of GGA, effective and safe options are still lacking. This review will discuss limitations of traditional therapies and explore emerging treatment modalities for GGA.

Traditional Treatments

Antimalarials, tetracycline antibiotics, and phototherapy have historically been mainstays of GGA management, although varying levels of evidence support their efficacy. In a 2021 claims database study (n=11,608), tetracycline antibiotics (n=820) and hydroxychloroquine (n=268) were the most frequently prescribed systemic therapies in the 6 to 12 months following diagnosis of any GA subtype.¹ Although tetracyclines were prescribed three times more often, evidence supporting their use in GGA is inferior to that of hydroxychloroquine. While one retrospective study found that only 2 of 7 patients responded to oral doxycycline and 0 of 9 responded to oral minocycline, a systematic review (n=35) of hydroxychloroquine for GGA demonstrated that 71.4% of patients experienced partial or complete clearance.³ Of note, however, in a more recent case series (n=26), only 35% of patients experienced partial or complete clearance, suggesting variable efficacy.³ In the aforementioned claims database study, phototherapy was rarely utilized despite being cited as the most well-studied treatment in a review article on GGA's therapeutic options.² The largest retrospective study evaluating psoralen and ultraviolet A (n=33) in GGA found that 66% of patients achieved complete clearance or "good" improvement, though only 32% of patients who achieved clearance remained in remission 1 year post-treatment.⁴ While other phototherapy modalities, such as narrowband ultraviolet B, have also demonstrated similar efficacy rates, phototherapy is limited by logistical constraints.³ Altogether, these data underscore the inadequacy of traditional treatments and the need for more effective GGA management strategies.

Emerging Treatments

Tumor Necrosis Factor-α Inhibitors (TNFis)

TNFis are among the newer treatment classes being employed in the management of GGA. TNF-α has been found at high levels in the skin and serum of patients with GGA.⁵ Further, it plays an active role in both granuloma formation and maintenance, underpinning its utility in GGA management.^{6,7} In a systematic review (n=24) of TNFis for GGA, adalimumab and infliximab exhibited higher efficacy rates than etanercept. The most common dosing regimen for adalimumab (n=16) was 80 mg the first week, followed by 40 mg injections every other week, and 87.5% of patients experienced improvement or complete remission.^{5,8} Seven of the patients treated with adalimumab came from a single case series, in which improvement was appreciated in all patients at the first follow-up visit, occurring at a mean duration of 13.9 ± 9.5 weeks.⁸ Infliximab (n=3) was administered at 5 mg/kg at weeks 0, 2, and 6, then at monthly intervals, and all patients experienced complete remission.⁵ Lastly, etanercept (n=5) was administered at 50 mg twice weekly, resulting in complete resolution in one case and no improvement in the remaining four cases.^{7,9} Etanercept's suboptimal efficacy compared to adalimumab and infliximab is likely due to its inability to bind transmembrane TNF-α and ultimately aid in granuloma destruction.⁷

Across case reports and series, TNFis have demonstrated a favorable safety profile in GGA management. Alopecia and loss of energy have each been reported, however, neither resulted in treatment cessation.⁷ Additionally, while there have been no reports of paradoxical GA exacerbation in GGA patients treated with TNFis, there is some concern for this potential adverse effect due to case reports of TNFis paradoxically inducing GA when used to treat other inflammatory conditions.³

Janus Kinase Inhibitors (JAKis)

JAKis are the newest treatment class being explored in the management of GGA. One of the first studies investigating their efficacy and mechanistic evidence was an open-label clinical trial in which 5 patients with GGA were treated with tofacitinib 5 mg twice daily for 6 months.¹⁰ Before treatment initiation, the investigators identified increased mRNA expression of interferon-γ, oncostatin M,

IL-15, and IL-21 – integral mediators of the JAK-STAT pathway – in GA lesions.¹⁰ Within 1 to 3 months of treatment initiation, all patients experienced improvement, and, after 6 months, 3 patients achieved complete clearance, while 2 experienced partial but significant improvement, further supporting involvement of the JAK-STAT pathway in GA pathogenesis.¹⁰ In another 15-patient case series of tofacitinib 5 mg twice daily, patients exhibited similar results after a mean duration of 4.4 ± 2.1 months, with 11 experiencing complete and 4 experiencing partial responses. In this study, tofacitinib was tapered to 5 mg daily for 1 month before cessation. Only 2 patients experienced lesion recurrence 1 month and 3 months after tofacitinib discontinuation, which resolved with re-administration of tofacitinib 5 mg twice daily for 1 month.¹¹

Upadacitinib has also demonstrated efficacy in GGA treatment at various doses, including 15 mg three times weekly, 15 mg daily, and 30 mg daily. Upadacitinib resulted in complete clearance in most case reports, with one patient experiencing clearance in as little as 8 weeks.¹² Baricitinib has also been effective in a handful of cases when dosed at 2 to 4 mg daily. Finally, abrocitinib, the latest JAKi to be employed in GGA management, has successfully treated two cases at doses of 150 to 200 mg daily.¹²

JAKis have largely been well-tolerated in patients with GGA. However, some adverse effects have been reported, including limited reports of herpes infections and hyperlipidemia.¹² Additionally, in a 3-patient case series of upadacitinib in GGA, therapy was tapered from 30 to 15 mg daily in two patients due to various adverse effects at the higher dose, including generalized weakness, a nonpainful linear lesion in the oral cavity, and respiratory illnesses.¹²

Phosphodiesterase-4 Inhibitors (PDE4is)

PDE4is are another emerging treatment option under investigation for GGA management, with inconsistent results supporting their efficacy. As GA is presumed to be a Th1-type delayed hypersensitivity reaction to unidentified antigens and PDE4 inhibition downregulates Th1 cytokines including TNF- α and interferon- γ , the role of PDE4is in GGA is mechanistically logical.^{3,13} Apremilast's success in treating GGA was first reported in a two-patient case series in which both patients were treated with apremilast 30 mg daily. The first patient achieved significant improvement of all lesions after 3 months of treatment and sustained improvement after 18 months of treatment. The second patient achieved clearance of all chest lesions and improvement of upper extremity lesions after 4 months of treatment.¹³ However, a more recent case series of 8 patients treated with apremilast 30 mg twice daily demonstrated less promising results with only 3 patients experiencing complete clearance, 3 failing to respond, and 1 having a partial response.¹⁴ The last patient initially experienced complete clearance; however, down-titration led to flares and, ultimately, discontinuation. Though its efficacy was variable, apremilast was well-tolerated except for one patient experiencing diarrhea.¹⁴

CONCLUSION

TNFis and JAKis are both promising emerging therapies shown to be effective and safe in GGA management. Although there is still a lack of high-quality, head-to-head trials, both TNFis and JAKis have demonstrated higher rates of efficacy than traditional GGA therapies in the limited existing case series. Notably, while both TNFis and JAKis have demonstrated rapid onset of action in GGA management, JAKis appear to outperform TNFis.¹² Despite their advantages, a major prohibitive factor of TNFis and JAKis is their high cost. Ultimately, while this may prevent them from being used as first-line therapies at this time, both TNFis and JAKis should actively be considered as second-line therapies for GGA.

DISCLOSURE

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REFERENCES

1. Barbieri JS, Rodriguez O, Rosenbach M, Margolis D. Incidence and prevalence of granuloma annulare in the United States. *JAMA Dermatol*. 2021;157(7):824-830.
2. Wang J, Khachemoune A. Granuloma annulare: a focused review of therapeutic options. *Am J Clin Dermatol*. 2018;19(3):333-344.
3. Joshi TP, Duvic M. Granuloma annulare: an updated review of epidemiology, pathogenesis, and treatment options. *Am J Clin Dermatol*. 2022;23(1):37-50.
4. Browne F, Turner D, Goulden V. Psoralen and ultraviolet A in the treatment of granuloma annulare. *Photodermatol Photoimmunol Photomed*. 2011;27(2):81-84.
5. Murdaca G, Colombo BM, Barabino G, et al. Anti-tumor necrosis factor- α treatment with infliximab for disseminated granuloma annulare. *Am J Clin Dermatol*. 2010;11(6):437-439.
6. Ahmed AA, Nordlind K, Schultzberg M, et al. Interleukin-1 alpha- and beta, interleukin-6- and tumour necrosis factor-alpha-like immunoreactivities in chronic granulomatous skin conditions. *Acta Derm Venereol*. 1994;74(6):435-440.
7. Chen A, Truong AK, Worswick S. The role of biologics in the treatment of chronic granuloma annulare. *Int J Dermatol*. 2019;58(5):622-626.
8. Min MS, Lebwohl M. Treatment of recalcitrant granuloma annulare (GA) with adalimumab: A single-center, observational study. *J Am Acad Dermatol*. 2016;74(1):127-133.
9. Shupack J, Siu K. Resolving granuloma annulare with etanercept. *Arch Dermatol*. 2006;142(3):394-395.
10. Wang A, Rahman NT, McGeary MK, et al. Treatment of granuloma annulare and suppression of proinflammatory cytokine activity with tofacitinib. *J Allergy Clin Immunol*. 2021;147(5):1795-1809.
11. Dev A, Keshavamurthy V, Chatterjee D. Therapeutic success of tofacitinib in granuloma annulare: A retrospective case series of 15 patients. *Indian J Dermatol Venereol Leprol*. 2025;91(1):65-70.
12. Heidari S, Omid R, Babaie H, et al. Emerging role of janus kinase inhibitors in treating granuloma annulare: a clinical, narrative review of efficacy and safety. *Int J Dermatol*. Published online ahead of print; Feb. 9, 2025. doi: 10.1111/ijd.17684.
13. Blum S, Altman D. Treatment of generalized granuloma annulare with apremilast: a report of 2 cases. *JAAD Case Rep*. 2019;5(11):976-978.
14. Joshi TP, Tschen J. Apremilast for the treatment of generalized granuloma annulare: a case series of 8 patients. *JAAD Case Rep*. 2023;38:59-60.

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CME/CE*

PIGMENTARY DISORDERS EXCHANGE SYMPOSIUM

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