



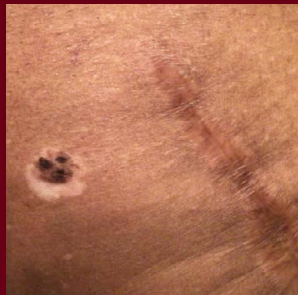
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JOURNAL OF DRUGS IN DERMATOLOGY

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Cutaneous Adverse Events With GLP-1 Agonists

Regulatory Landscape of Regenerative Dermatology Frameworks

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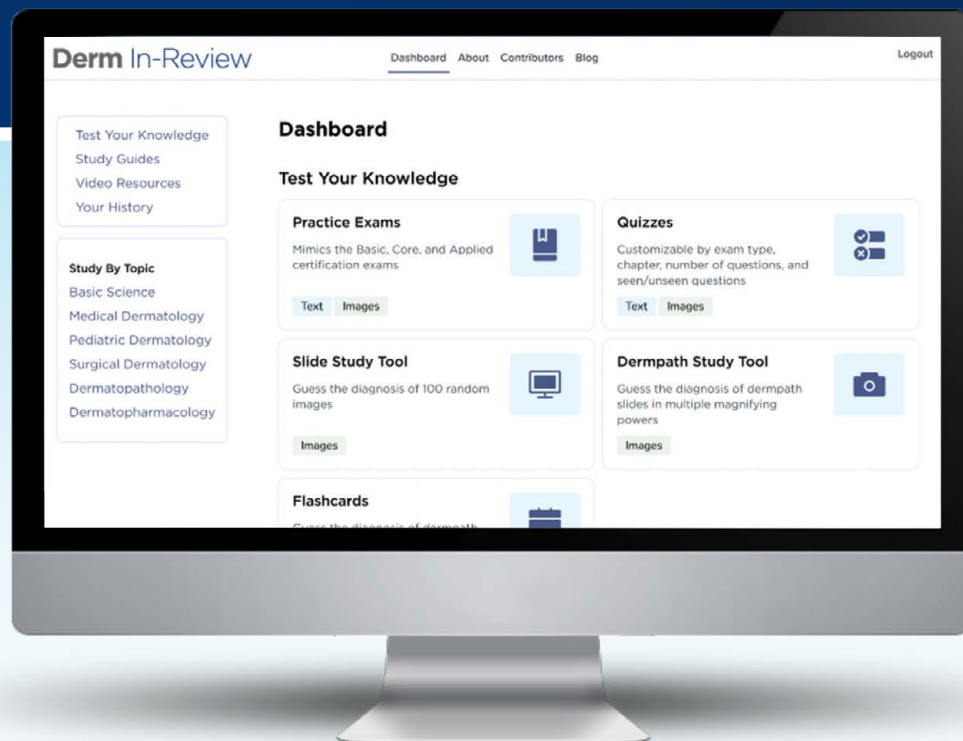


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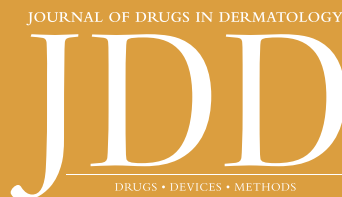
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STEER-OLD STEWARDSHIP: REINING IN AND REINFORCING THE GUARDRAILS ON DERMATOLOGY'S WORKHORSE



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Dr. Alexandra Golant

Corticosteroids have been the effective, accessible, and familiar backbone of dermatologic therapy for decades. But with great power comes great responsibility. In this episode, podcast host Dr. Adam Friedman, Professor and Chair of Dermatology at the George Washington University School of Medicine and Health Sciences, sits down with Dr. Alexandra Golant, Residency Program Director of the Dermatology Residency Program at Mount Sinai and Chair of the newly formed Corticosteroid Stewardship Consortium, to explore how dermatology's most tried and true class of therapeutics is getting a modern era reboot. Together, they unpack what "steroid stewardship" really means, from mitigating misuse and managing patient fears to redefining the role of steroids amid today's expanding therapeutic arsenal of biologics and small molecule inhibitors. This conversation takes a candid look at the balance between efficacy and safety, the evolution of clinical education, and how dermatologists can ensure these invaluable tools continue to serve, not harm, our patients.



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Cutaneous Adverse Events Associated With GLP-1 Receptor Agonists: A FAERS Database Analysis From 2018-2024

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for conditions beyond type 2 diabetes, including psoriasis and hidradenitis suppurativa. Despite this, little is known about their dermatologic safety profiles.

Methods: We analyzed FDA Adverse Event Reporting System (FAERS) data from 2018 to 2024 for semaglutide, liraglutide, exenatide, and dulaglutide. Cutaneous adverse events (AEs) were identified using MedDRA-coded terms: “rash,” “pruritus,” “urticaria,” “alopecia,” and “angioedema.” Frequency and proportional reporting ratios (PRRs) were calculated using dipeptidyl peptidase-4 (DPP-4) inhibitors as a comparator. Logistic regression assessed predictors of cutaneous AEs, with dulaglutide as a reference and sex, age, and GLP-1 RA type as independent variables.

Results: Cutaneous AEs were reported in up to 8.16% of GLP-1 RA cases, more often in females, with a mean patient age of 60. Semaglutide was associated with the highest rate, and dulaglutide the lowest. PRR analysis (0.27; 95% CI: 0.257-0.284) showed these AEs were proportionally less common relative to DPP-4 inhibitor users. Exenatide was associated with increased odds (OR = 5.01, 95% CI: 4.69–5.35), while liraglutide and semaglutide showed decreased odds.

Discussion: Possibly influenced by dosage, immune modulation, and patient perception of efficacy, cutaneous GLP-1RA adverse effects were less frequent than DPP-4 inhibitors, but still warrant clinician awareness. These reactions might impact patient adherence, which highlights the need for further investigation into their mechanisms.

Conclusion: Cutaneous AEs are infrequent but vary by GLP-1 RA. Greater awareness may improve patient counseling as indications expand.

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are a class of medications that have been widely used for the control of Type 2 Diabetes Mellitus (T2DM).¹ A GLP-1 RA stimulates insulin release from the pancreas after glucose is introduced into the body through food or drink. GLP-1 RAs help augment this effect and promote delayed gastric emptying and inhibition of glucagon production in order to prevent blood sugar levels from rising.¹ These medications are now being prescribed by dermatologists for conditions such as hidradenitis suppurativa and psoriasis, not just those experiencing T2DM.² With the rapid rise of off-label use of GLP-1 RAs, understanding the safety profile of these medications has become imperative.

Multiple adverse events from GLP-1 RAs have been documented, most notably nausea, vomiting, and diarrhea³; however, little is known about skin-related side effects. Some studies have mentioned potential safety concerns for cutaneous adverse events such as alopecia, but these types of reactions remain underreported in pharmacological literature and have yet to be studied independently.⁴

Monitoring cutaneous AEs from GLP-1 RAs is important, particularly in the fields of dermatology and primary care. This study uses the FDA Adverse Event Reporting System (FAERS), an information database that contains reports of adverse events from medications that were submitted to the FDA.⁵ The aim of

this study is to identify and describe cutaneous adverse events (AEs) linked to GLP-1 RAs as reported in the FAERS. Additionally, this study uses the FAERS to compare the frequency and types of cutaneous AEs associated with GLP-1 RAs with those reported from dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of antidiabetic medications that shares a similar mechanism to GLP-1 RAs, but that have a distinct pharmacologic profile.

MATERIALS AND METHODS

A cross-sectional analysis was performed using publicly available data from the FDA Adverse Event Reporting System (FAERS) from 2018 to 2024. FAERS contains reports of AEs and medication errors submitted to the FDA and is used to identify harmful events post-marketing. Reported cutaneous AEs associated with the GLP-1 RAs semaglutide, liraglutide, exenatide, and dulaglutide were extracted and analyzed. These were compared to those reported with dipeptidyl peptidase 4 (DPP-4) inhibitors: sitagliptin, saxagliptin, linagliptin, and alogliptin. Prior research has described AEs of GLP-1 RAs, but none has specifically researched cutaneous effects alone.⁶

Data was cleaned and analyzed using Python. Proportional reporting ratios (PRRs) were generated to test whether particular AEs occurred more frequently with a specific medication or medication class. PRR is a well-established signal that a medication or class may be prone to certain AEs and is reliable for identifying drug safety concerns.⁷ The frequency of cutaneous AEs for GLP-1 RAs versus DPP-4 inhibitors was compared. A PRR > 1 indicated a higher reporting frequency for GLP-1 RAs; a 95% confidence interval was constructed to assess the statistical validity of the PRR.

A logistic regression model was then performed to evaluate the likelihood of reporting a cutaneous AE. It models the relationship between multiple predictor variables and a binary outcome.⁸ In this study, the outcome variable was whether a report included a cutaneous AE (1 = cutaneous AE, 0 = other AEs). Predictor variables included age, sex, and specific GLP-1 RA type, with dulaglutide as the reference. Odds ratios (ORs) and 95% CIs were calculated to assess the strength of each

association. An OR > 1 indicated increased odds of a cutaneous AE, while an OR < 1 suggested reduced odds compared to dulaglutide. Confidence intervals helped assess the statistical significance of the ORs. When used properly, ORs were found to be an adequate measurement for the likelihood of an event occurring when compared to another.⁹

The interpretability of log-odds can be difficult, so the conversion of each coefficient to an odds ratio increases the interpretability.⁸ Importantly, the logistic regression and ORs do not provide the absolute probability of a cutaneous AE occurring for each medication, but rather show the relative likelihood compared to dulaglutide.

The Variance Inflation Factor (VIF) was calculated to assess multicollinearity among predictors. Low VIF values (typically <5) indicated minimal multicollinearity, suggesting the predictors were sufficiently independent and the regression coefficients were reliable. Current research has shown that VIF is a suitable test for measuring multicollinearity.¹⁰

RESULTS

The total number of adverse events was 129,330 according to the FAERS database. 7,434, or 5.75% of the total AEs reported were cutaneous. Table 1 details the breakdown of each of the four chosen GLP-1 RA medications by total AE cases, cutaneous only AEs, and mean age:

Dulaglutide had the most total AEs (59,247) but the lowest percentage of cutaneous cases (3.75%), while semaglutide had the highest (8.16%). Liraglutide was linked to the highest mean age for cutaneous AEs (62), and dulaglutide the lowest (58) (Table 1).

To understand the specific cutaneous complaints that made up each reported AE, the top four AEs for each medication were found:

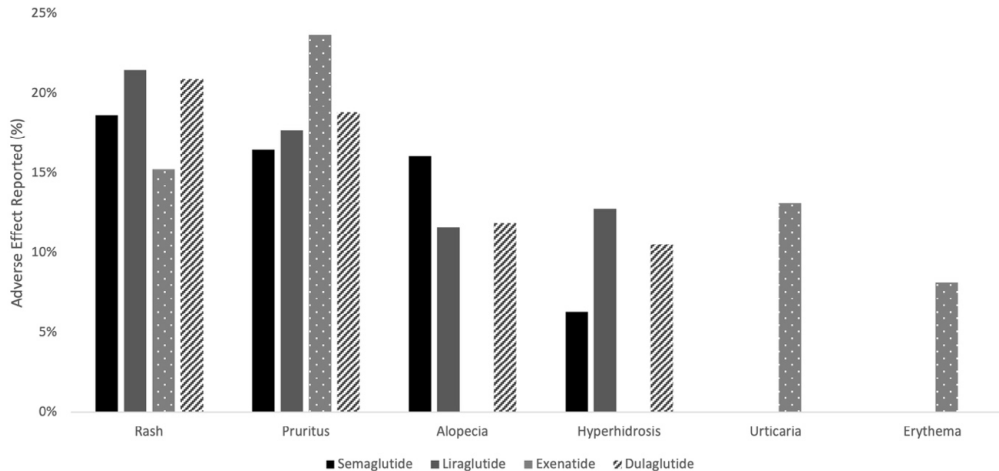
For semaglutide, liraglutide, and dulaglutide, the top cutaneous AEs were rash, pruritus, alopecia, and hyperhidrosis. Users of

TABLE 1.

Adverse Event (AE) Reports From 2018 to 2024 by Medication, Including Total AEs, Cutaneous AEs, Percentage of Cutaneous AEs, and Mean Age for Cutaneous Cases.

Medication	Total AEs	Cutaneous Only AEs	Percentage Cutaneous Only AEs	Mean Age
Semaglutide	40,086	3,271	8.16%	59
Liraglutide	11,378	871	7.66%	62
Exenatide	18,619	1,069	5.74%	60
Dulaglutide	59,247	2,223	3.75%	58
All Four Combined	129,330	7,434	5.75%	60

FIGURE 1. Percentage of cutaneous adverse events (AEs) reported from 2018-2024.



all four medications most commonly reported rash and pruritus, while exenatide users alone reported higher rates of urticaria and erythema than the others (Figure 1).

The Proportional Reporting Ratio (PRR) was calculated to compare cutaneous AE rates between GLP-1 RA and DPP-4 inhibitor users. GLP-1 RA users reported 7,434 cutaneous and 121,896 non-cutaneous AEs; DPP-4 users reported 1,488 and 5,506, respectively. The PRR was 0.270 (95% CI: 0.257–0.284), indicating cutaneous AEs were proportionally less common with GLP-1 RAs than with DPP-4 inhibitors (Table 2).

The PRR was used to compare GLP-1 RAs against DPP-4 inhibitors. The logistic regression was used to compare the GLP-1 RAs against each other to understand which GLP-1 RAs were more likely to report cutaneous AEs:

All six predictor variables were statistically significant at the 1% level. Exenatide was the only variable with a positive coefficient (1.611) and an odds ratio over 1 (OR = 5.008). None of the 95% confidence intervals included 1, confirming significance at the 5% level. Exenatide’s interval included values above 1, while all

TABLE 2.

Proportional Reporting Ratios (95% CI) for GLP-1 Receptor Agonist AEs Compared to DPP-4 Inhibitor AEs, 2018-2024

Proportional Reporting Ratio	0.270
95% Confidence Interval (CI)	CI(95%) = (0.257, 0.284)
GLP-1 RA Cutaneous AEs	7,434
GLP-1 RA Non-Cutaneous AEs	121,896
DPP-4 Cutaneous AEs	1,488
DPP-4 Non-Cutaneous AEs	5,506

RA = receptor agonist; AEs = adverse events.

others were below. VIFs for all predictors except the constant were under 5, indicating no multicollinearity; the constant had a VIF over 10, suggesting potential multicollinearity (Figure 2).

DISCUSSION

Dulaglutide had the highest number of total AEs reported (59,247), but the lowest percentage of cutaneous AEs (3.75%) (Table 1), which may be due to greater prescription rates rather than increased dermatologic risk. Dulaglutide is commonly prescribed due to its once-weekly injection compared to its

FIGURE 2. Logistic regression results for cutaneous adverse events among GLP-1 RA users, including odds ratios and 95% confidence intervals for each predictor.

Predictor	Coefficient (SE)	Odds Ratio	95% CI	VIF
Semaglutide	−0.907*** (0.030)	0.404	[0.381, 0.428]	1.306
Liraglutide	−1.035*** (0.048)	0.355	[0.324, 0.390]	1.205
Exenatide	1.611*** (0.034)	5.008	[4.685, 5.353]	1.201
Patient Age	−0.007*** (0.001)	0.993	[0.991, 0.995]	1.041
Patient Sex	−0.263*** (0.026)	0.769	[0.731, 0.808]	1.026
Constant	−0.482*** (0.061)	0.618	[0.548, 0.697]	24.918

Number of observations: 42,142; Degrees of freedom: 42,136

Pseudo R²: 0.124 Log-Likelihood Ratio p-value: 0.000

*** Significant at 1% level

more frequent counterparts, such as liraglutide and exenatide,¹¹ possibly reducing localized or injection-related reactions. This highlights the need to evaluate not only the quantity of AEs reported, but also the proportion of cutaneous AEs compared to all AEs. Clinicians should consider this when deciding which GLP-1 RA to prescribe to their patients with a history of hypersensitivity or cutaneous conditions.

Out of all AEs reported, cutaneous AEs comprised the highest percentage for semaglutide compared to the other four medications. While hormonal, gastrointestinal, and metabolic AEs might be considered more clinically relevant as they are directly affected by the frequency of injection and medication dosage,¹² cutaneous AEs still made up 8.16% of AEs, warranting caution when prescribing. Possible explanations for cutaneous AEs might be GLP-1 RAs' modulation of inflammatory and immune pathways.¹³ As GLP-1 receptors are expressed on both immune and skin cells, their activation can lead to cytokine suppression, vascular changes, and decreases in barrier function, which may trigger cutaneous reactions in patients who are more easily susceptible.¹⁴

While rash and pruritus were most commonly reported out of all cutaneous AEs for all four medications, urticaria and erythema were reported more frequently for exenatide users (Figure 1). Without knowing the location of the rashes and pruritus on the skin in reference to the site of injection, it is difficult to tell whether the effects could be a product of the medication itself or a combination of other factors. More research should be done on the specific location of these effects. However, rash and pruritus make up the early immune response and may be more easily identifiable by patients and physicians than other less visible cutaneous effects (eg, vasculitis), leading to a higher reporting rate.^{15,16}

Cutaneous AEs were found to be proportionally less common among GLP-1 RA users compared to DPP-4 inhibitors, suggesting no elevated reporting pattern for these events in this population. This finding falls in line with current medical research, which has found GLP-1 RA cutaneous AEs to be uncommon and skin lesions more frequently reported in DPP-4 inhibitor users.¹⁷ Unlike DPP-4, which is an enzyme expressed on immune and skin cells that plays a role in T-cell and cytokine activation, GLP-1 is not directly expressed on skin cells.¹⁸ Thus, there might be more indirect effects on the immune system from GLP-1 RAs.

The logistic regression yielded statistically significant coefficients for all 6 predictors at the 1% level. Exenatide was the only predictor with a positive coefficient of 1.611 and an odds ratio of 5.008, indicating that the odds of a cutaneous AE were 5 times more likely compared to dulaglutide. Moreover, exenatide did not demonstrate multicollinearity with a VIF of 1.201, well under the commonly accepted threshold of 5. Exenatide has

been reported to cause AEs such as increasing the International Normalized Ratio (INR) for patients taking warfarin compared to dulaglutide, but has not been shown to increase cutaneous AEs.¹⁹ Exenatide is injected twice daily or once a week.²⁰ Twice-daily injections could increase skin susceptibility to AEs compared to once-weekly dulaglutide injections. However, the dose within each injection of a given GLP-1 RA varies. Additionally, FAERS did not report whether the patient was using a once-weekly or twice-daily injection.

Semaglutide had a coefficient of -0.907, statistically significant at the 1% level. Furthermore, the odds ratio of 0.404 with a statistically significant confidence interval and a VIF below 5 (1.306) indicated that semaglutide users were 60% less likely to report cutaneous AEs compared to dulaglutide users. Both semaglutide and dulaglutide are once-weekly injections.²¹ Increased cutaneous AEs for these medications have not been widely studied; however, their efficacy has been explored.

Prior medical research has shown that 1.0 mg of semaglutide significantly reduced HbA1c and body weight compared to 3.0 mg and 4.5 mg dulaglutide.²² While not a specifically cutaneous benefit, this finding suggests that semaglutide might offer a psychological benefit, decreasing the reporting rates of AEs in general. Semaglutide users who are satisfied with the efficacy of the medication might report fewer AEs than dulaglutide users who have less idealistic results. This phenomenon, specifically when medication users report fewer AEs due to their perception of an efficacious medication, has been formally recognized in medical research.¹³

Liraglutide exhibited a negative coefficient of -1.035, which was statistically significant at the 1% level. Moreover, the odds ratio of 0.355 was associated with 65% lower odds of a cutaneous AE relative to dulaglutide. This finding was statistically significant as the confidence interval excluded 1, and the VIF was adequate at 1.205—much lower than 5. This finding is peculiar, as liraglutide is a once-daily injection compared to dulaglutide, a once-weekly injection, increasing susceptibility to cutaneous AEs through frequent injection exposure and subsequent hypersensitivity reactions. However, liraglutide has been found to lower HbA1c levels and weight more than dulaglutide.²³ It is possible that the same positive efficacy phenomenon decreases the amount of total AEs reported, lowering the odds ratio of liraglutide compared to dulaglutide.¹³

The coefficients for age and sex were -0.007 and -0.263, respectively. Both coefficients were statistically significant at the 1% level. The odds ratios were 0.993 and 0.769, both having statistically significant confidence intervals and VIFs under 5. Therefore, as patient age increased, fewer cutaneous AEs developed. Literature has contradicted this finding, indicating that older patients traditionally experience more cutaneous AEs

as they age.²⁴ Thus, this finding could be because the mean age for patients with cutaneous AEs was 59.75, an already older population. If the number of young users were to be increased in the sample, the odds ratio may be a different number. Men were reported to have a 23% lower chance of experiencing a cutaneous AE than women, possibly because they have a stronger skin barrier, leading to less transepidermal water loss (TEWL) and a lower pH, enhancing their resilience against environmental damage and infections.²⁵ With more resilient skin, the injections from GLP-1 RAs might not inflict as many cutaneous AEs compared to women.

The pathophysiology underlying cutaneous AEs to GLP-1 RAs is not fully understood but may involve various mechanisms. GLP-1 receptors are not just found in the pancreas, but also on keratinocytes.²⁶ Thus, any activation of GLP-1 receptors could directly activate cells in the epidermis. Additionally, rapid metabolic shifts, such as weight loss and fluctuating insulin or hormone levels, may disrupt the skin barrier by altering the sebaceous glands and lead to a hypersensitivity reaction.²⁷ The cutaneous effects of GLP-1 RAs are multifactorial and warrant further investigation into the specific pathophysiology.

Studying the cutaneous AEs reported from GLP-1 RAs is important because these medications are currently being used beyond diabetes and weight loss. Although cutaneous AEs are considered uncommon in comparison to other organ system AEs, their presence can still affect patients' willingness to take the medications, leading to patient noncompliance. As GLP-1 RA use has increased in recent years, this research plays an important role in highlighting real-world adverse event reporting and can offer physicians insight before prescribing these drugs to patients susceptible to skin conditions. Increased knowledge about cutaneous AEs might lead to better patient counseling and increased awareness in the scientific community. Future research should focus on the pathophysiology and mechanism of GLP-1 interaction with the skin, as well as the incidence of cutaneous AEs amongst a variety of demographics. Using this research when developing and improving these medications may also improve the safety of each medication and patient-centered care.

Currently, limited guidance exists for the treatment of AEs associated with GLP-1 RAs. Systemic corticosteroids have been used for severe injection-site reactions,² and topical corticosteroids such as triamcinolone 0.1% have been reported for morbilliform drug eruptions.²⁸ However, further research is needed on cutaneous AEs from GLP-1 RAs, particularly analyzing the effectiveness of accessible, over-the-counter options such as non-steroidal anti-itch creams, barrier ointments, and moisturizers.

This study is the first to use the FDA Adverse Event Reporting System (FAERS) to analyze cutaneous AEs reported from GLP-1 RAs. The focus on cutaneous events specifically fills a gap in current literature that remains under-characterized. The use of standardized MedDRA terms made the identification and categorization of each cutaneous AE across each drug consistent. Additionally, analyzing a large, nationally representative database with a mixed demographic improves the generalizability of this study to real-world populations. The limitations of this study include that the FAERS database is a passive system and is subject to underreporting. The presence of an AE report does not imply that the selected drug caused that same AE. Prior medical history of each patient is limited, and the database may not capture the entire clinical context of each AE.

CONCLUSION

Cutaneous AEs from GLP-1 RAs are uncommon but notable. They are often underreported in trials. Dermatologists can recognize these patterns as they care for an increasing number of patients who are prescribed these medications in practice, indicating a need for improved monitoring and patient counseling. Future research should be done to determine the underlying mechanisms of GLP-1 RAs leading to cutaneous AEs, prevalence in global populations, and whether more precautions need to be taken when prescribing GLP-1 RAs, particularly for those susceptible to skin reactions.

DISCLOSURES

Marisa Fat BS, Hayden Johnson BA, MQE, and Aaron Farberg MD have no conflicts of interest to disclose.

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Regulatory Landscape of Regenerative Dermatology: Current Frameworks and Future

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ABSTRACT

Background: Regenerative dermatology is an emerging subspecialty that seeks to restore the structure and function of healthy skin. The United States lacks comprehensive regulatory guidance for regenerative therapies. This review provides an overview of available therapies within regenerative dermatology, outlining the pathways for approval.

Methods: Articles on regenerative dermatology in PubMed and guidelines issued by the United States Food and Drug Administration (FDA) were reviewed with emphasis on those published between June 2020 and June 2025, and results were summarized in narrative format.

Results: In the United States, the FDA is the primary regulatory authority responsible for ensuring the safety and efficacy of regenerative biotherapeutics. Classification of a product as a drug, biologic, device, or cosmetic determines the regulatory pathway it must follow.

Discussion: Cosmetics are intended to promote attractiveness without treating or preventing disease and do not require FDA approval prior to marketing, while drugs and biologics undergo a multi-step process to obtain approval: (1) product development, (2) preclinical testing in a laboratory setting, (3) clinical trials involving human subjects, (4) FDA review, and (5) FDA approval. High-risk devices require a Premarket Approval (PMA), while low-to-moderate risk devices have less stringent requirements.

Conclusion: Regenerative dermatology offers significant therapeutic potential. Regulation is governed by the US FDA and varies according to product classification. Clinicians should counsel patients on safety and efficacy data prior to initiating regenerative treatments.

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INTRODUCTION

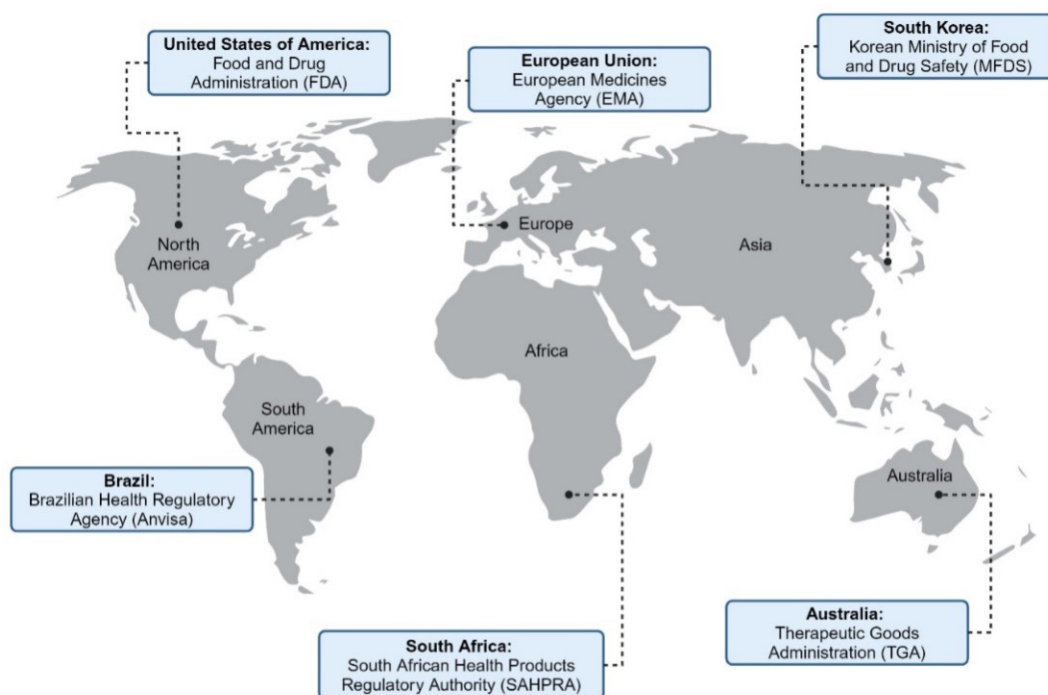
Standards in wellness and aesthetics have evolved over time, yet the desire to preserve youthful skin remains a universal priority shaped by biological and evolutionary factors.¹ Regenerative dermatology is an emerging subspecialty that seeks to restore both the structure and function of healthy skin.² Technological advances have broadened the field beyond primarily stem cell-based treatments to encompass a diverse array of acellular modalities, including extracellular vesicles or exosomes, peptides, and polynucleotides, driving both consumer interest and market expansion.³ Valued at approximately \$30 billion USD globally in 2023, the regenerative medicine market is projected to surpass \$90 billion over the next decade.⁴ As illustrated in Figure 1, regulatory frameworks for regenerative medicine vary significantly across countries. North America accounts for 58% of the global market⁴ and leads in the number of clinical trials in regenerative medicine³; yet the United States currently lacks comprehensive regulatory

guidance for regenerative therapies. This review provides an overview of cellular and acellular therapies within regenerative dermatology and outlines the existing US regulatory pathways for approval of drugs, biologics, and medical devices in this rapidly evolving space.

MATERIALS AND METHODS

Articles on regenerative medicine and dermatology available in PubMed and regulatory guidelines issued by the US Food and Drug Administration (FDA) were synthesized to provide an overview of available therapies and the regulatory framework governing these products in the US Product classification and the nuances in regulatory standards specific to each category are discussed. Priority was given to articles and guidelines published between June 2020 and June 2025, with historical references included where appropriate for context. Results are described in narrative format.

FIGURE 1. Global regulatory agencies for regenerative medicine.



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RESULTS

Understanding Regenerative Dermatology: Cellular and Acellular Therapies

Human skin serves as an epidermal barrier, providing immunologic defense and protection against environmental insults.⁵ Skin aging occurs through both intrinsic and extrinsic mechanisms. Intrinsic aging reflects the physiological, time-dependent decline in skin structure and function, whereas extrinsic aging is driven by environmental factors, such as ultraviolet A (UV-A) radiation, that accelerate the aging process by inducing DNA damage in dermal fibroblasts and other cells responsible for extracellular matrix maintenance.⁶⁻⁸ Over time, this cumulative damage promotes cell cycle arrest, a state known as *cellular senescence*. This is characterized by loss of regenerative capacity and increased inflammatory signaling. Features of aging skin include ECM disorganization, solar elastosis, skin laxity, and the formation of rhytids, among others.⁶⁻⁸ Regenerative dermatology aims to restore skin structural integrity and functional capacity by leveraging the body's endogenous reparative mechanisms.² Regenerative interventions employ bioactive molecules, such as growth factors, cytokines, and signaling proteins, that act as intercellular messengers to stimulate cell proliferation, differentiation, angiogenesis, and other reparative processes, thereby addressing the root causes of aging from within.²

The US FDA defines regenerative therapies as “*cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products*”⁹ Cellular therapies often involve the use of stem cells, which are of significant interest due to their ability to self-renew, differentiate based on tissue origin, and modulate immune responses.² Examples of established clinical applications include hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell (MSC) infusions. HSCT has demonstrated efficacy in treating autoimmune diseases such as systemic sclerosis and epidermolysis bullosa.¹⁰ Autologous adipose-derived stem cells have shown promise in hair restoration, improving graft survival during hair transplantation and increasing hair density in patients with androgenetic alopecia.^{11,12} Outside the United States, regenerative approaches are also being integrated with established dermatologic procedures. For example, conditioned media from adipose MSCs have been combined with fractional CO₂ laser therapy to improve acne scarring in 22 human subjects (Trial registration: JSPH2012-082).¹³ Potential risks associated with allogeneic stem cell therapies have hindered FDA approval for broader clinical use in humans. These risks include immunologic host rejection, host-donor variability,¹⁴ and inconsistent cell yields across donors and anatomical harvest sites.¹⁵ The first FDA-approved stem cell therapy was hematopoietic stem cell transplantation, which was introduced in 1957.^{16,17}

When a product exhibits characteristics that overlap across regulatory categories, the FDA evaluates its primary intended

purpose to determine classification. For example, a product that induces chemical action may still be classified as a device if its principal mode of action is not achieved through that chemical action.²⁸ Soft tissue fillers illustrate this principle well. Although fillers may elicit a chemical response, such as a foreign body reaction, this reaction is an adverse event and not the primary function of the product. Therefore, fillers are regulated as devices rather than drugs.²⁸ In cases where the primary function of the product is to exhibit features of all three categories: biologics, devices, and drugs, the FDA generally classifies it as a biologic.²⁸

DISCUSSION

Regenerative Cosmetics: Understanding the Difference Between FDA Regulation and Approval

Cosmetics are defined by the US FDA as products intended to cleanse, beautify, promote attractiveness, or alter appearance without treating or preventing disease, or altering bodily structure and function.²⁷ Examples include shampoos, hair dyes, makeup, colognes, and facial cleansers.²⁹ Unlike drugs, devices, and biologics, cosmetics do not require FDA approval prior to marketing. Yet, they remain subject to FDA oversight and may be withdrawn from the market if found to pose safety risks.^{27,29} Cosmetic products must also comply with labeling regulations established under the Federal Food, Drug, and Cosmetic (FD&C) Act and the Fair Packaging and Labeling (FP&L) Act,³⁰ frequently informed by the International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and Handbook.³¹

When counseling patients, it is important to clarify the distinction between FDA regulation and FDA approval. While all cosmetics are regulated by the FDA, stating that a product is “FDA regulated” is misleading to consumers.^{27,29} Such language

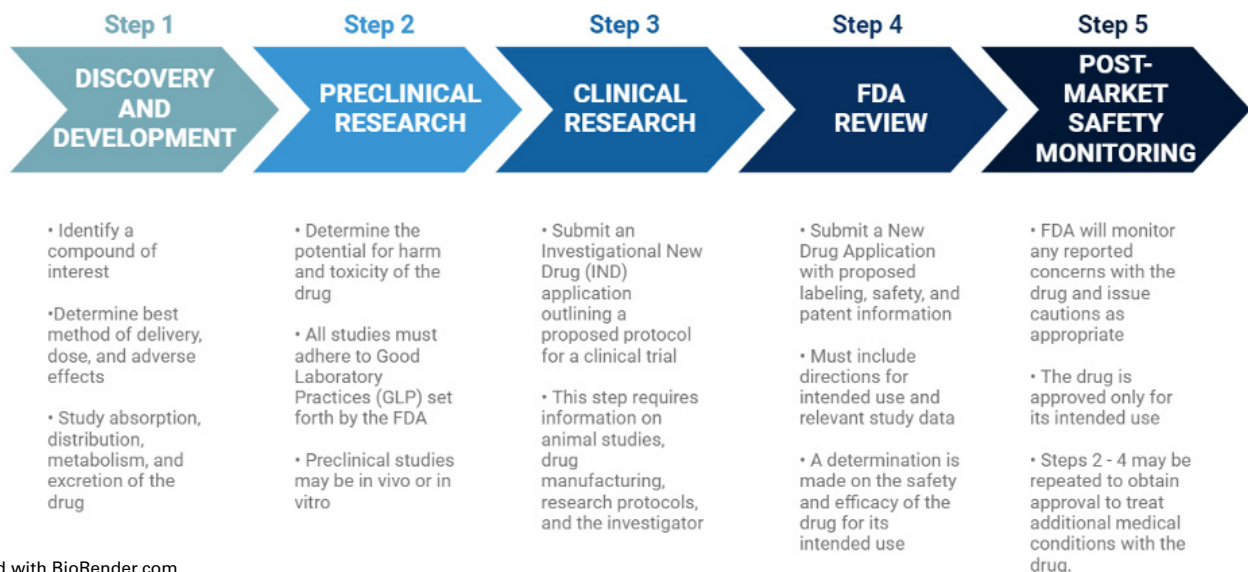
may incorrectly imply that the product has completed FDA evaluation and approval, potentially instilling an unwarranted sense of legitimacy.^{27,29} At present, the FDA does not approve cosmetic products.²⁹ An exception to this rule is for cosmetic products with color additives (other than coal-tar hair dye), which do require FDA premarket approval.²⁹

Regenerative Drugs and Biologics: Process for Approval

Regenerative drugs and biologics must undergo a structured, multi-step process to obtain FDA approval: (1) product development, (2) preclinical testing in a laboratory setting, (3) clinical trials involving human subjects, (4) FDA review, and (5) FDA approval (Figure 3).³² FDA approval signifies that the product’s quality has been validated and that its demonstrated benefits outweigh any potential risks when used as intended.²⁹ Regulatory oversight is divided between the FDA’s Center for Biologics Evaluation and Research (CBER) for biologics and the Center for Drug Evaluation and Research (CDER) for drugs.

Following development in the laboratory, investigators must submit an investigational new drug (IND) application to the FDA before administering the investigational drug or biologic to human subjects.³³ The IND allows the FDA to assess whether the proposed clinical trial poses an acceptable level of risk to participants. In urgent situations, such as when a patient who requires treatment does not meet the eligibility criteria for an existing study, or when time does not permit a standard IND submission, an Emergency Use IND may be requested. Emergency Use INDs are reserved for life-threatening conditions where no satisfactory standard treatment exists, and immediate intervention is medically necessary.³⁴

FIGURE 3. Key Steps to FDA Approval for Regenerative Drugs and Biologics in the United States.³²



Prior to approval, the FDA conducts lot release testing, a quality control process designed to assess product quality, consistency, and batch-to-batch variability.²⁹ Acellular therapies present challenges, particularly in the standardization of manufacturing processes. Isolating and characterizing extracellular vesicles (EVs) or exosomes based on their bioactive components is complex due to substantial variability in source material, molecular composition, and functional activity. Existing techniques for quantification are primarily based on total protein content or particle number, metrics that do not reliably reflect functional potency.¹⁸

Given the manufacturing complexities of regenerative therapies and the stringent requirements for FDA approval under biologic or drug pathways, many regenerative products in the US are currently marketed exclusively for cosmetic purposes. For instance, polynucleotides are commonly formulated as cosmetic ingredients and promoted for aesthetic benefits rather than for the treatment of specific medical conditions.^{27,35} To qualify for drug approval, clinical studies must demonstrate that polynucleotides are both safe and effective for the treatment or mitigation of a specific medical condition.³⁶ Until such evidence is submitted and approval is granted, polynucleotides may be included in cosmetic formulations; however, they cannot be listed as 'active ingredients,' a designation reserved for components that have demonstrated therapeutic effects at specific concentrations.²⁷

Regenerative Medicine Advanced Therapy Designation (RMAT)

The 21st Century Cures Act, enacted in December 2016, was designed to bring innovations to patients efficiently,³⁷ and as part of this legislation, the US FDA established the Regenerative Medicine Advanced Therapy (RMAT) designation to accelerate the review of therapies that target serious or life-threatening conditions. Made concurrently with the IND submission, the request for RMAT designation allows integration of real-world evidence and patient-centered clinical outcomes into the product evaluation and approval process.⁹ As of June 2024, ten therapies have received RMAT designation,³⁸ including StrataGraft (Mallinckrodt Pharmaceuticals), which utilizes allogeneic human keratinocytes and fibroblasts to stimulate dermal regeneration in patients with thermal burns.³⁹

Regenerative Devices: Process for Approval

There are currently more than 6,000 medical devices regulated by the FDA,⁴⁰ with oversight provided by the CDRH through a risk-based, tiered regulatory framework.²⁹ Devices classified by the FDA as high-risk require a Premarket Approval (PMA) request, a process comparable to the NDA used for drugs and biologics.⁴¹ In contrast, devices deemed low-to-moderate risk are subject to less stringent requirements. In cases where a legally marketed predicate device is available, applicants may simply submit a Premarket Notification [510(k)] to the FDA.⁴¹

Submitting a 510(k) requires evidence that the new device has the same intended use as the predicate and utilizes either similar technology or different technology in a way that does not introduce new safety or effectiveness concerns.⁴² For low-to-moderate risk devices without a legally marketed predicate, a De Novo Classification Request must be submitted to evaluate the safety and efficacy of the device.⁴¹

When a device is intended for the treatment of a rare disease, it can be challenging to generate sufficient data to support traditional regulatory approval. In these instances, the FDA allows an investigator to file a Humanitarian Device Exemption (HDE), which allows for marketing of the device based on reasonable assurance of safety, while waiving the requirement to demonstrate effectiveness under the FD&C Act.⁴³ To qualify for an HDE, the device must be intended to treat a rare disease, defined by the FDA as affecting fewer than 8,000 people annually in the United States.⁴³

Examples of approved regenerative devices include Poly-L-lactic acid (PLLA) by the trade name Sculptra,⁴⁴ as an implant to restore midfacial volume loss and treat lipoatrophy in persons with human immunodeficiency virus (HIV).⁴⁵ It is important to note that FDA approval for soft tissue fillers is anatomically specific and only cleared for use in designated regions. Use outside of approved indications constitutes off-label treatment, which is permissible when guided by clinical judgment, patient-specific considerations, and informed patient consent.^{46,47} To increase clinical use and healthcare provider confidence, manufacturers may pursue supplemental FDA approvals for additional anatomic areas.

Lasers are classified by the US FDA as medical devices, due to their action in inducing controlled dermal injury that stimulates collagen production and skin remodeling. Their clinical use has expanded significantly, with a reported 483% increase in laser procedures performed between 2000 and 2020.⁴⁸ Given their capacity to alter skin structure, lasers require FDA pre-market approval. Following approval, the FDA also mandates ongoing manufacturing and maintenance requirements for lasers.⁴⁹ However, the FDA does not regulate operator training or procedural protocols for laser devices.⁴⁹

Combination Products

Technological advances have enabled the development of combination products that incorporate features of drugs, devices, and biologics, thereby blurring the regulatory boundaries between the CBER, CDER, and CDRH.⁵⁰ Examples include pre-filled vaccine syringes and microneedling cartridges preloaded with growth factors, both of which integrate biologic or drug components within a medical device.⁵¹ Combination products pose unique regulatory challenges as each component type, drug, biologic, and device has distinct approval and post-

market requirements. To address these complexities, the FDA implemented an Inter-Center Agreement between CBER and CDRH, allowing devices related to blood and cellular products to be regulated under CBER rather than CDRH.⁵² As regenerative medicine continues to evolve and novel products emerge, the FDA retains the authority to reclassify products and reassign regulatory oversight across its centers.⁵³

CONCLUSION

Regenerative medicine is a rapidly expanding field that offers significant potential in both medical and aesthetic dermatology. In the United States, regulation of regenerative dermatologic therapies is highly complex and requires a nuanced understanding of each product’s mechanism of action and its implications for skin structure and function. Regulatory oversight, governed by the US FDA, varies according to product classification as a cosmetic, drug, device, or biologic, each of which follows distinct approval pathways. As the field advances, ensuring patient safety remains paramount. Clinicians must provide thorough counseling based on available safety and efficacy data to support informed decision-making by patients prior to initiating regenerative treatments.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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A Randomized, Controlled, Split-Face, Double-Blind Study Comparing Topical Malassezin to Hydroquinone 4% for Melasma

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ABSTRACT

Background: Previous studies have documented the capacity of malassezin to brighten the skin. It represents a novel agent for the treatment of hyperpigmentation.

Objective: To compare the efficacy and safety of a topical 0.75% malassezin formulation to 4% hydroquinone, the gold standard for treating melasma.

Methods: A randomized, controlled, split-face, double-blind study was conducted in 20 adult female subjects with symmetrical mild-to-moderate melasma. Subjects were randomized 1:1 to determine the allotted side of the face treated twice per day with malassezin or hydroquinone for 12 weeks. Treatment efficacy was evaluated by measuring brightening effects, global improvement, split-face Melasma Area Severity Index (hemi-MASI) scores, colorimetry measurements, and photography.

Results: Twenty subjects completed the study. Compared to baseline, both malassezin and hydroquinone-treated facial areas showed significant efficacy at 12 weeks in brightening (1.85 and 1.95, $P=0.027$ and 0.008); global improvement (2.2 and 2.3, $P=0.004$ and 0.001); and hemi-MASI reduction (2.49 and 2.33; $P<0.001$ and $P<0.001$), respectively. However, there were no statistically significant differences when comparing the malassezin-treated side to the hydroquinone-treated side at each visit. Side effects in both groups were mild throughout the study.

Conclusion: These findings suggest that malassezin shows comparable efficacy to the gold standard, hydroquinone. Our results further support malassezin as a promising new treatment for patients with melasma.

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INTRODUCTION

Melasma is a chronic condition characterized by often symmetrical areas of hyperpigmentation affecting the cheeks, nose, chin, and forehead. Genetics, hormonal influences, ultraviolet, and visible light exposure are significant contributing factors for melasma.¹⁻³ It is most common in individuals with Fitzpatrick skin type III-V. Current data suggest that melasma represents a phenotype of photodamage.³ The negative impact on quality of life can be substantial, as affected individuals frequently experience low self-esteem and depression.^{4,5} Despite advancements in dermatological treatments, melasma remains therapeutically challenging due to its complex pathophysiology and universal relapses to available therapies.^{2,3}

The current therapeutic landscape for melasma involves a multimodal approach.^{6,7} Photoprotective agents, antioxidants, chemical exfoliants, and resurfacing procedures are often combined to achieve optimal results. Skin-lightening agents, such as hydroquinone, kojic acid, azelaic acid, vitamin C, and retinoids, are commonly used in clinical practice.^{6,8} Hydroquinone, in particular, has been considered the gold standard for treating melasma.^{9,10} However, these agents are not universally effective. Long-term use of hydroquinone can lead to adverse effects, including skin irritation, rebound hyperpigmentation, and ochronosis in rare cases.¹⁰ These limitations underscore the pressing need for new, safe, and efficacious topical therapies to address the global burden of facial hyperpigmentation.

Emerging research in the development of novel dermatological treatments has highlighted the potential role of the *Malassezia* species, a genus of lipophilic fungi.¹¹ *Malassezia* species are predominant commensal fungal organisms, constituting 50-80% of the human skin mycobiome.¹² These lipophilic yeasts are thought to play a role in the pathogenesis of skin diseases, including tinea versicolor, seborrheic dermatitis, and atopic dermatitis.^{13,14} They produce a range of biologically active indole compounds, including malassezin, a natural indole derived from *Malassezia furfur*.¹⁵ Malassezin is a ligand for the aryl hydrocarbon receptor (AhR), triggering signaling pathways that influence melanocyte activity and melanin production.^{16,17} Our preliminary in vitro and ex vivo investigations have documented the ability of malassezin to suppress melanogenesis and decrease skin pigmentation.¹⁸ We also conducted a proof-of-concept study evaluating malassezin, which demonstrated substantial skin-brightening effects at 14 weeks with good tolerability, further suggesting its potential as a novel therapeutic modality for hyperpigmentation.¹⁹ In addition, histopathological features of treated patients revealed a decrease in melanin and loss of melanocyte dendritic activity, which recovered 8 weeks following treatment.²⁰

This study was designed to further evaluate malassezin's efficacy and safety in treating facial melasma. A randomized, controlled, split-face, double-blind study was conducted, which compared a 0.75% topical malassezin formulation to 4% hydroquinone, the benchmark treatment for hyperpigmentation.

MATERIALS AND METHODS

Study Design

A randomized, controlled, split-face, double-blind study was conducted at the Vitiligo and Pigmentation Institute of Southern California in accordance with good clinical practice. Subjects provided written informed consent before study procedures were performed. The protocol, informed consent form, and patient information were approved by Advarra IRB, Columbia, MD. The study design involved subjects with facial melasma who underwent treatment for 12 weeks.

Study Participants

Enrollment included 20 female subjects aged 20 to 65 years with symmetrical mild-to-moderate melasma of the face who met the specific inclusion and exclusion criteria. Key inclusion criteria included subjects in good general health with Fitzpatrick skin types II to VI. Subjects who used topical lighteners, retinoids, or any other agents impacting pigmentation for at least six weeks prior to study enrollment were excluded. Subjects with skin type I, unwilling to wear sunscreen, and pregnant females were excluded.

Randomization

Investigational site staff randomly assigned the blinded treatment product to each side of the face, with subjects

maintaining the same treatment per side throughout the study. The principal investigator, staff, and subjects were blinded to treatment allocation, which was only known to the sponsor through product codes until study completion. Subjects were randomized 1:1 to determine the side of the face receiving malassezin or hydroquinone.

Treatment Protocol

Subjects were randomized to apply malassezin to one side of the face and hydroquinone to the contralateral side. Each side of the face received 0.25 mL of the assigned product, applied twice daily. Assessments occurred at baseline, 2, 4, 8, and 12 weeks. The morning application was followed by SPF 50 sheer zinc sunscreen, and all subjects used Cetaphil cleanser twice daily.

Efficacy and Safety Assessments

Subjects were evaluated at baseline and weeks 2, 4, 8, and 12. Clinical skin assessments included skin brightening on a 5-point scale (0-no difference, 1-slight brightening, 2-mild brightening, 3-moderate brightening, and 4-significant brightening). Global improvement was assessed using a 5-point scale (0-none, 1-minimal, 2-mild, 3-moderate, and 4-marked improvement) and the split-face Melasma Severity Index Score (hemi-MASI)²¹ was performed at each visit.

Photographs were taken using the Visia-CR system (Canfield) at baseline and follow-up visits. Images included frontal (0°) and profile views (±45°) under controlled lighting. Colorimetry measurements using the Mexameter MX 18 (Courage Khazaka electronic GmbH, Köln, Germany) were taken from the same involved and uninvolved areas of the face at baseline and weeks 2, 4, 8, and 12. Adverse events were recorded at each study visit. Subjects were examined for erythema, edema, dryness/scaling, pruritus, or other adverse changes.

Statistical Analysis

The study used R for statistical evaluations comparing malassezin with hydroquinone. Parametric and nonparametric analyses, including Mann-Whitney U and chi-square tests, determined statistical significance (≤ 0.05). The primary outcome compared the brightening effects of 0.75% malassezin to 4% hydroquinone to improve melasma. Primary outcome measures comparing both sides included brightening scales, global improvement, and hemi-MASI assessments.²¹ Secondary outcome measures included differences in the tolerability of malassezin compared to hydroquinone.

RESULTS

Subject Demographics

Twenty female subjects were enrolled, ranging in age from 43 to 65 years (Table 1). The mean age was 55.9 (SD 7.46). 25% of patients were skin type III and 75% were skin types IV and V. All subjects completed the trial. Eleven (55%) subjects had mild involvement. Nine (45%) subjects had moderate disease.

TABLE 1.

Subject Disposition and Baseline Characteristics	
Characteristics	N = 20
Mean age, y (range)	55.9 (43-65)
Sex, female, n(%)	20 (100)
Race and ethnic subgroup, n (%)	
Asian	8 (40)
Black or African American	7 (35)
Hispanic	5 (25)
Fitzpatrick skin type, n(%)	
III	5 (25)
IV	11 (55)
V	4 (20)
Melasma Severity	
Mild	11(55)
Moderate	9 (45)

Demographic data for the baseline characteristics of 20 female participants. The mean age and range were 55.9 and 43–65, respectively. 40% of participants were Asian, 35% were African American, and 25% were Hispanic. Study participants were Fitzpatrick III–V.

Efficacy

Compared to baseline, facial areas treated with malassezin and hydroquinone (Table 2) showed a significant improvement at 12 weeks in brightening (1.85 and 1.95, $P=0.027$ and $P=0.008$); global improvement (2.2 and 2.3, $P=0.004$ and 0.001); and hemi-MASI reduction (2.49 and 2.33, $P<0.001$ and $P<0.001$), respectively. However, there were no statistically significant differences when comparing the malassezin-treated side to the hydroquinone-treated side (Table 3). Side effects in both groups were mild throughout the study. Colorimetry (Melanin Index) revealed a greater reduction from baseline at 12 weeks for hydroquinone 4% compared to malassezin (0.15 vs 0.07, $P=0.04$).

Figures I and II compare facial areas treated with malassezin and the contralateral areas treated with hydroquinone. Both areas at 12 weeks demonstrated brightening of the hyperpigmented patches. No subjects demonstrated worsening or darkening of affected areas.

TABLE 2.

Observed Global Improvement, Brightening Effect, and hemi-MASI Score					
	HQ (SD)	P-value of HQ	SM (SD)	P-value of SM	P-value (HQ vs SM)
Global Improvement					
Week 2	0.7 (0.80)	--	0.65 (0.93)	--	0.804
Week 4	1.2 (1.00)	0.217	1.35 (1.04)	0.140	0.379
Week 8	2.15 (1.22)	0.004*	2.1 (1.16)	0.009*	0.666
Week 12	2.3 (1.26)	0.001*	2.2 (1.15)	0.004*	0.494
Brightening Effect					
Week 2	0.55 (0.83)	--	0.55 (0.95)	--	1
Week 4	0.9 (0.97)	0.505	1.1 (1.02)	0.160	0.297
Week 8	1.9 (1.45)	0.014*	1.8 (1.24)	0.017*	0.428
Week 12	1.95 (1.47)	0.008*	1.85 (1.23)	0.027*	0.428
hemi-MASI Score					
Baseline	4.22 (1.14)	--	4.21 (1.13)	--	NA
Week 4	3.90 (0.87)	0.162	3.81 (0.98)	0.196	0.640
Week 8	2.74 (0.82)	< 0.001*	2.96 (0.96)	< 0.001*	0.493
Week 12	2.33 (0.80)	< 0.001*	2.49 (0.86)	< 0.001*	0.491

Compared to baseline, both malassezin and hydroquinone-treated facial areas showed significant efficacy at 12 weeks in brightening (1.85 and 1.95, $P=0.027$ and 0.008); global improvement (2.2 and 2.3, $P=0.004$ and 0.001); and hemi-MASI reduction (2.49 and 2.33, $P<0.001$ and $P<0.001$), respectively. However, there were no statistically significant differences when comparing the malassezin-treated side to the hydroquinone-treated side.

FIGURE 1. Comparison of 0.75% malassezin (SM) and 4% hydroquinone (HQ) at baseline and 12 weeks. Clinical images of a 57-year-old Asian female with Fitzpatrick skin type IV show improvement in melasma for both treatment sides. (A) left cheek treated with SM at baseline, (B) left cheek at 12 weeks, (C) right cheek treated with HQ at baseline, and (D) right cheek at 12 weeks.



FIGURE 2. Comparison of 0.75% malassezin (SM) and 4% hydroquinone (HQ) at baseline and 12 weeks. Clinical images of a 49-year-old Hispanic female with Fitzpatrick skin type IV show improvement in melasma for both treatment sides. (A) right cheek treated with SM at baseline, (B) right cheek at 12 weeks, (C) left cheek treated with HQ at baseline, and (D) left cheek at 12 weeks



Tolerability

Malassezin was well-tolerated throughout the study with minimal to mild erythema, dryness/scaling, and skin peeling in 1 of 20 subjects (5%). Hydroquinone showed slightly higher rates, with erythema and dryness/scaling in 2 of 20 subjects (10%), and skin peeling in 1 subject (5%). No edema was reported with either treatment. No subjects discontinued due to side effects.

DISCUSSION

Malassezin is a natural AHR agonist produced by *Malassezia furfur*.¹⁷ Studies suggest it may undergo intracellular transformation to indole (3, 2-b) carbazole (ICZ) like metabolites which are the highly active agonists of AHR. The AHR receptor is a ligand-activated transcription factor regulating genes involved in immune regulation, stem cell maintenance, wound healing, and cellular differentiation.²² Investigations of chemically synthesized malassezin tested negative in both genotoxicity and phototoxicity assessments.¹⁸ When tested in the MelanoDerm™ model, malassezin demonstrated reductions in melanin, which compared favorably to kojic acid, a naturally occurring hydrophilic fungal product that reduces hyperpigmentation by inhibiting free tyrosinase.¹⁸ Ex vivo studies confirmed that malassezin is a powerful antioxidant and was not a direct tyrosinase inhibitor.¹⁸ Our previous studies documented the novel in-vivo skin brightening effects of malassezin in a series of patients with melasma and photodamage. Biopsies of patients showed a decrease in melanin and loss of melanocyte dendricity, with recovery 8 weeks post-treatment.^{19,20} Malassezin was well-tolerated throughout the study with minimal side effects.

The current randomized split-face investigation compared the efficacy and safety of twice-daily malassezin to twice-daily hydroquinone 4%.^{9,10} In some previous studies of melasma comparing hydroquinone to the marketed formulation, hydroquinone was applied once a day.^{23,24} Hence, our study was a more rigorous comparison. The results of this investigation showed significant changes in brightening, global improvement, and reduction in hemi-MASI scores evident bilaterally at 4, 8, and 12 weeks. However, there were no statistically significant differences observed when comparing efficacy outcomes between the 2 sides. However, melanin index (colorimetry) assessments had significantly greater reduction with hydroquinone. These findings support malassezin showing overall efficacy comparable to hydroquinone. Tolerability assessments demonstrated that both malassezin and hydroquinone were well tolerated throughout the study.

An advantage of the randomized, split-face protocol was its ability to address exposomal influences (sun-exposure, inflammation, lifestyle), which could impact study outcomes.²⁵ In addition, 75% of our patients were skin types IV and V. Such individuals may have a more therapeutically challenging disease. Responses were comparable in skin types III, IV, and V. Limitations of the

study were a small sample size and the potential to deviate from protocol instruction in the use of products (ie, applying products to the incorrect side). To address this possibility, instructions and product use were reviewed at each visit, and containers were weighed.

CONCLUSION

There is indeed an ongoing need for efficacious and safe lightening agents for melasma. The results of this investigation document encouraging results when using the novel agent malassezin for the treatment of melasma. Our findings support comparable efficacy to hydroquinone 4%. These results further support the need for larger clinical trials assessing the efficacy of malassezin in subjects with melasma.

DISCLOSURES

Dr Grimes has served as a clinical investigator and/or consultant for Galderma, Clinuvel, L'Oreal, Johnson & Johnson, LaserOptek, Versicolor Technology, Merck, DermBiont, VYNE Therapeutics, RAPT Therapeutics, Incyte, Pfizer, AbbVie/Allergan, SkinBetterScience, and Medscape; stock options for Versicolor Technologies LLC. She serves on the Board of Directors for Clinuvel and Global Vitiligo Foundation. Drs Oparaugo, Tatarinova, and Ms. Dias have no disclosures to declare. Dr McCraw is a consultant, investigator, and stockholder of Versicolor Technologies LLC and is the founder of Skin Science Advisors LLC.

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Sunless Tanners in Dermatology: A Review of Ingredients, Efficacy, and Safety Profiles

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ABSTRACT

Background: Sunless tanners offer a safer alternative to ultraviolet (UV)-based tanning but may cause adverse skin reactions, including irritant and allergic contact dermatitis. This study examines the composition, efficacy, safety, and reported side effects of commonly used sunless tanning products.

Methods: The top 50 sunless tanners on Amazon's Best Sellers list (March 2025) were reviewed. After excluding bundles, applicators, and non-self-tanning cosmetics, 37 products were included. Ingredient lists were analyzed, and customer reviews were screened for reports of skin reactions using predefined keywords.

Results: All products contained dihydroxyacetone (DHA), 38% included erythrulose, 11% contained melanin, and 5% included tyrosine derivatives. Only one product (3%) also contained sunscreen. On average, 1.96% of customer reviews mentioned skin reactions.

Discussion: DHA remains the predominant active ingredient, with erythrulose, melanin, and tyrosine derivatives used less frequently. Emerging or less common agents such as troxerutin, melanotan, and melanoidins raise safety and regulatory concerns. Reported adverse effects include contact dermatitis and pigmentary changes, which may complicate dermatologic assessments.

Conclusion: While sunless tanners provide a UV-free tanning option, dermatologists should educate patients on ingredient safety, potential adverse effects, and proper application techniques. Given their minimal UV protection, patients should be advised to continue regular sunscreen use.

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INTRODUCTION

Sunless tanners offer an alternative to traditional tanning methods that involve exposure to ultraviolet (UV) radiation. Dermatologists have long advised patients to avoid excess exposure to UV radiation due to its well-documented association with an increased risk of skin cancer and photoaging.¹ Yet, many patients still desire to have a darkened or tanned complexion. To meet this demand, a variety of products commonly referred to as sunless or self-tanners have been developed to darken the skin without the harmful effects of UV radiation. According to a Market Research Report by Fortune Business Insights, the sunless tanner market was valued at 1.04 billion United States Dollars (USD) in 2022 and is expected to grow to 1.7 billion USD by 2030.² While sunless tanners are generally considered safer than UV-based tanning, they are not without risks, including allergic and irritant contact dermatitis, among other dermatologic conditions.^{3,4}

In this article, we aim to provide dermatologists with practical, up-to-date information to better counsel patients seeking sunless tanning options. To inform our review, we analyzed ingredient lists and consumer-reported reactions from top-selling sunless tanning products on Amazon.com to identify which ingredients patients are most likely to encounter. We then examined the mechanisms of action, efficacy, and adverse

effects of both widely used and emerging tanning agents, along with best practices for optimizing cosmetic outcomes and minimizing skin-related complications.

MATERIALS AND METHODS

To better understand which sunless tanning ingredients patients are most likely to encounter, we conducted an ingredient and review analysis of the top-selling sunless tanning products on Amazon.com as of March 2025.⁵ Amazon's Best Sellers list was used as a proxy for consumer popularity and product usage patterns. A total of 50 products were screened, with 13 excluded as bundles, applicators, or non-self-tanning cosmetics. For each included product, ingredient lists and customer reviews were collected and analyzed. Ingredient lists were examined for self-tanning agents previously reported as commonly used in sunless tanners, as described by Martini.⁶ Customer reviews were screened for mention of skin reactions using the keywords: "allergic," "allergy," "hives," "rash," and "reaction." Reviews containing these terms were subsequently assessed to ensure proper context.

RESULTS

Of the products analyzed, all (n=37) contained dihydroxyacetone (DHA), 38% (n=14) contained erythrulose, 11% (n=4) contained melanin, and 5% (n=2) contained tyrosine/tyrosine derivative.

TABLE 1.

Ingredient List and Customer Review Analysis of Best-Selling Sunless Tanning Products						
Amazon Best Sellers List Ranking	Brand	Product Name	Ingredients	Number of Consumer Reviews	Number of Reported Skin Reaction Reviews*	% of Reported Consumer Skin Reactions*
1	Bondi Sands	SelfTanning Foam	Dihydroxyacetone	5883	91	1.55%
2	Beauty by Earth	SelfTannerTanning Lotion	Dihydroxyacetone	8640	380	4.40%
3	Beauty by Earth	SelfTannerTanning Drops	Dihydroxyacetone, Erythrulose, N-Acetyl-L-Tyrosine	1727	43	2.49%
4	b.tan	Ultra Dark SelfTanner Mousse	Dihydroxyacetone, Melanin	8035	149	1.85%
5	Jergens	Natural Glow	Dihydroxyacetone	3548	94	2.65%
6	b.tan	Violet SelfTanner	Dihydroxyacetone	2878	47	1.63%
7	Coco & Eve	Sunny Honey Bali Bronzing SelfTanner Mousse	Dihydroxyacetone, Erythrulose	2452	60	2.45%
8	b.tan	Clear SelfTan Gel	Dihydroxyacetone	1798	13	0.72%
9	Beauty by Earth	SelfTanner Mousse	Dihydroxyacetone	2005	65	3.24%
10	Jergens	Natural Glow Instant Sun Body Mousse	Dihydroxyacetone, Erythrulose	3848	46	1.20%
13	Coco & Eve	Antioxidant FaceTanning Micromist	Dihydroxyacetone, Erythrulose	562	56	9.96%
14	St.Tropez	SelfTan Purity Face Mist	Dihydroxyacetone	939	24	2.56%
15	Jergens	Natural Glow Wet Skin Moisturizer	Dihydroxyacetone, Erythrulose	1616	38	2.35%
17	St.Tropez	SelfTan Express Mousse	Dihydroxyacetone, Melanin	2580	47	1.82%
18	L'Oreal Paris	Sublime Bronze SelfTanning Towelettes	Dihydroxyacetone	1434	10	0.70%
19	Isle of Paradise	SelfTanning Drops	Dihydroxyacetone, Erythrulose	1261	26	2.06%
20	LovingTan	2 HR Express Mousse - Dark	Dihydroxyacetone, Erythrulose	742	9	1.21%
22	Peta Jane	MediumTanning Mousse	Dihydroxyacetone	312	2	0.64%
24	LovingTan	Deluxe Bronzing Mousse	Dihydroxyacetone, Erythrulose	748	14	1.87%
25	L'Oreal Paris	Sublime Bronze SelfTanning Facial Drops	Dihydroxyacetone	977	12	1.23%
26	L'Oreal Paris	Sublime Bronze SelfTanning Mist	Dihydroxyacetone	1202	11	0.92%
27	St.Tropez	SelfTan Classic Bronzer Mousse Foam	Dihydroxyacetone	3736	140	3.75%
29	St. Moriz	Professional Instant SelfTanning Mousse	Dihydroxyacetone	2515	23	0.91%
30	Bondi Sands	1-Hour Express SelfTanning Foam	Dihydroxyacetone, Erythrulose	317	0	0.00%
31	Peta Jane	Tanning Mist	Dihydroxyacetone, Erythrulose	115	4	3.48%
33	Body Drench	QuickTan Instant SelfTanner	Dihydroxyacetone, Erythrulose	1557	16	1.03%
34	L'Oreal Paris	Sublime BronzeTinted SelfTanning Lotion	Dihydroxyacetone	1595	29	1.82%
35	+Lux Unfiltered	Self-Tanning Cream	Dihydroxyacetone	329	5	1.52%
36	SkinnyTan	Body Glow	Dihydroxyacetone	343	6	1.75%
37	LovingTan	2 HR Express Mousse - Medium	Dihydroxyacetone, Erythrulose	382	5	1.31%
39	Norvell	Premium SunlessTanning Solution-Venetian	Dihydroxyacetone	817	5	0.61%
40	TAN-LUXE	The GradualTan Lotion	Dihydroxyacetone, Erythrulose, Melanin	363	8	2.20%
45	The Sicilian	Double Dark Bronzing Blend	Dihydroxyacetone, Melanin, Methylsilanol Acetyltyrosine, Oleoyl Tyrosine	790	6	0.76%
47	Ten Physics	True Color SunlessTanner	Dihydroxyacetone	3408	29	0.85%
48	L'Oreal Paris	Sublime Bronze SelfTanning Water Mousse	Dihydroxyacetone	1010	15	1.49%
49	+Lux Unfiltered	N 12 Bronzing Face Drops	Dihydroxyacetone, Erythrulose	207	5	2.42%
50	Norvell	Venetian Sunless SelfTanner Mousse	Dihydroxyacetone	729	7	0.96%
Average				1930	42	1.96%

*Search terms for reported reactions included: allergic, allergy, hives, rash, and reaction

Only one (3%) of the products also included a sunscreen component. On average, products had 1930 customer reviews, with 1.96% of reviews reporting skin reactions (Table 1).

DISCUSSION

Our analysis clearly demonstrates that DHA is the most common ingredient in sunless tanners, with erythrulose, melanin, and tyrosine/tyrosine derivatives being less frequently used. The following discussion examines the mechanisms of action, efficacy, and adverse effects of these agents, as well as other notable tanning agents, including troxerutin, melanotan, and melanoidins. This list includes agents that, while not necessarily present in the top 50 Amazon bestsellers, are important for dermatologists to be familiar with when advising patients on safe and effective methods to achieve a tanned appearance while minimizing UV exposure (Table 2). Additionally, we discuss best practices for optimizing cosmetic outcomes when using sunless tanners.

Dihydroxyacetone

Dihydroxyacetone (DHA) is a three-carbon sugar that reacts with amino acids such as glycine, alanine, leucine, and valine in a non-enzymatic glycation process known as the Maillard reaction. This reaction results in the formation of brown-colored

complexes within the stratum corneum, producing a tanned appearance.⁷ DHA is approved by the United States Food and Drug Administration (FDA) for topical use in creams and lotions as a sunless tanner. However, its use in tanning booths and airbrush applications is not FDA-approved due to the potential for exposure to non-skin surfaces, including the eyes and mucous membranes.⁸

Clinical research has explored both the photoprotective effects and safety profile of DHA. One study compared DHA alone to DHA combined with naphthoquinone in a population of minimally pigmented patients over two consecutive years. During the first year, patients applied a DHA solution nightly, while in the second year, they applied DHA, waited 15 minutes, and subsequently applied naphthoquinone. The combined application provided a sun protection factor (SPF) of 18, whereas DHA alone provided an SPF of 3–4.^{9,10} Concerns regarding potential carcinogenic activity have been raised due to the formation of free radicals during the Maillard reaction. However, this risk is thought to be negligible, as the free radicals are confined to the nonviable keratin layer.⁹ Another clinical trial assessed the potential interference of DHA with vitiligo treatment when used as camouflage. The study found that DHA improved patient quality of life without adversely affecting vitiligo.¹¹

TABLE 2.

Sunless Tanning Ingredients: Mechanisms, Efficacy, Safety, and Potential Adverse Effects						
Ingredient	Mechanism of Action	Route of Administration	Efficacy	Safety Profile	Possible Side Effects	SPF
Dihydroxyacetone (DHA)	Maillard reaction forms a brown-colored complex in the stratum corneum	Topical Creams, Lotions, and Sprays	Most efficacious and contained in 100% of top-purchased sunless tanning products on Amazon.	FDA approval for skin. No FDA approval for spray due to absorption through mucous membranes.	chromonychia, contact dermatitis, pseudochromhidrosis, xanthotrichia	3 - 4
Erythrulose	Maillard reaction forms a brown-colored complex in the stratum corneum	Topical Creams, Lotions, and Sprays	Great outcomes when used in conjunction with DHA to create a more even, longer-lasting tan.	No FDA regulation as a cosmetic. Considered safe.	Possible skin, eye, and respiratory irritation in strong concentrations.	--
Troxerutin	Antioxidant	Topical Creams, Lotions, and Gels	Poor tanning efficacy and works adjunctively as an antioxidant	Approved as an oral drug in several countries.	Possible cardiac toxicity at extremely high doses far above what is found in topicals.	--
Tyrosine and Derivatives	Precursor to melanin. Involved in the rate-limiting step	Topical Creams, Lotions, and Sprays. Oral Pill Form	Unlikely to be of benefit in producing tanned skin.	Not FDA approved. FDA warns against oral tyrosine supplementation.	No established side effects, as studies on long-term supplementation are limited.	--
Melanotan	Alpha-melanocyte-stimulating hormone analog	Subcutaneous injection, oral pill, and nasal spray	Shown to have an increased half-life and is 100-fold more effective in tanning than native alpha-melanocyte stimulating hormone.	Not FDA approved. Heavily warned against by the FDA and various other international health agencies.	Renal infarction, systemic toxicity, rhabdomyolysis, priapism, melanoma, and eruptive nevi and lentiginosis.	--
Melanin	No known reaction with the skin. Simply used as a colorant	Topical Creams, Lotions, and Sprays	Unlikely to be of benefit in producing tanned skin aside from providing a superficial coloration tint.	The FDA has no information regarding melanin being used in tanning agents.	No established side effects.	1.5-2
Melanoidins	End product of Maillard reaction. As a stand-alone ingredient, it acts as a coloring agent	Topical Creams, Lotions, and Sprays	As a stand-alone ingredient, it is unlikely to be of benefit in producing tanned skin aside from providing a superficial coloration tint.	The FDA has no information regarding melanoidins being used in tanning agents.	No established side effects.	--

Although DHA is generally considered safe for external use, adverse events have been reported. Case reports describe reactions such as orange chromonychia, contact dermatitis, pseudochromhidrosis, and xanthotrichia.^{3,4,12,13} The incidence of these adverse effects has not been well characterized. Additionally, DHA use has been associated with alterations in the appearance of pigmented lesions. One study suggested that DHA can cause follicular pigmentation, which may resemble lentigo maligna under dermoscopy, potentially leading to unnecessary biopsies.¹⁴ Another report indicated that DHA-induced changes in pigmented lesions could raise suspicion for melanoma if a history of sunless tanning is not elicited.¹⁵

Erythrulose

Erythrulose is a keto-sugar that functions similarly to DHA, participating in the Maillard reaction to produce a dark pigment within the stratum corneum.¹⁶ However, erythrulose alone does not produce the same intensity of pigmentation as DHA. When combined with DHA, erythrulose has been shown to enhance tanning outcomes by creating a more homogenous, natural-looking, and longer-lasting tan due to improved pigment distribution within the stratum corneum.⁶ It is suggested that this combination also results in a more natural tone compared to DHA alone.

Although erythrulose is generally considered safe for cosmetic use, it is classified as a potential skin, eye, and respiratory irritant.¹⁷ It is important to note that erythrulose is a cosmetic ingredient and is not regulated as a drug by the United States FDA. As of now, DHA remains the only sunless tanning agent formally approved by the FDA for use as a sunless tanner.¹⁸

Troloxerutin

Troloxerutin is a flavonoid that does not impart color to the skin but serves as an adjunct ingredient in sunless tanning products due to its antioxidant and anti-inflammatory properties.¹⁹ When combined with dihydroxyacetone (DHA), troloxerutin has been reported to enhance the quality and longevity of the tan, contributing to a softer skin texture and a more uniform complexion.⁶ Although troloxerutin shows potential benefits in improving the appearance and feel of sunless tans, data on its efficacy, specifically as a sunless tanning additive, remains limited. Beyond its cosmetic applications, troloxerutin has shown promise in improving chronic venous insufficiency.²⁰

Research has also explored the photoprotective effects of troloxerutin. An in vitro study using HaCaT keratinocyte cells evaluated its ability to protect against UVB-induced damage.²¹ The study determined that troloxerutin exhibited low toxicity at concentrations up to 20 μ M. Pre-treatment of cells with 0–10 μ M of troloxerutin prior to exposure to 50 mJ/cm² of UVB radiation demonstrated protective effects, including improved cell viability, reduced cell death, attenuation of UVB-induced

growth arrest, preservation of cell migration capacity, and enhanced DNA repair activity. While no specific sun protection factor (SPF) rating has been established, these findings suggest that troloxerutin may offer photoprotective properties. Further investigation by the same research group indicated that these protective effects may be mediated by the modulation of microRNA expression.²²

Tyrosine and Tyrosine Derivatives

The inclusion of tyrosine in self-tanning products is based on its role as a precursor in melanin biosynthesis. Melanogenesis begins with the enzymatic conversion of L-tyrosine to L-DOPA by tyrosine hydroxylase, a rate-limiting step in melanin production.²³ The rationale behind adding tyrosine to topical self-tanners is that an increased supply of this precursor might enhance melanin synthesis.²⁴ However, no clinical or biochemical evidence currently supports the efficacy of topical tyrosine in enhancing tanning outcomes.

Under normal physiological conditions, the conversion of L-tyrosine to L-DOPA is believed to operate near saturation, suggesting that excess tyrosine would not significantly influence melanogenesis.²⁵ Despite this, tyrosine supplements continue to be marketed for enhancing sunless tanning, although no studies substantiate their efficacy. Moreover, the United States FDA has classified these supplements as potentially harmful due to the lack of safety data.²⁴

Currently, no established adverse effects are associated with tyrosine supplementation. However, isolated reports have described potential adverse effects, such as altered saccadic eye movements in patients with schizophrenia following tyrosine intake.²⁵ Long-term safety data on tyrosine supplementation remain limited, warranting further investigation.

Melanotan

Melanotan-I (MT-I) and Melanotan-II (MT-II) are synthetic analogs of α -melanocyte-stimulating hormone (α -MSH), a peptide that regulates skin pigmentation through melanocortin receptor activation on melanocytes.²⁶ MT-I and MT-II exhibit increased stability and potency compared to endogenous α -MSH, with studies suggesting they are approximately 100-fold more effective at inducing melanogenesis, leading to excess melanin pigment production.²⁷

MT-I and MT-II are readily available for illicit purchase online, often in injectable, oral, or nasal spray formulations.²⁸ Due to concerns over their safety, the FDA and international health agencies have issued warnings regarding their unregulated production and potential adverse effects.²⁹ Reported complications, though rare, include renal infarction, systemic toxicity, rhabdomyolysis, priapism, melanoma, eruptive nevi, and lentiginosis.^{30–35} MT-II is frequently associated with amplified side effects in comparison

to MT-I, as its high lipophilicity enables it to cross the blood-brain barrier.²⁸

The cosmetic effects of MT-I and MT-II may also interfere with dermatologic assessment, as artificially induced pigmentation can obscure the evaluation of pigmented lesions. One study suggested that sunless tanning induced by these peptides could complicate melanoma detection if a history of use is not obtained.³⁶

The original formulation of Melanotan-I is now being referred to as afamelanotide by the pharmaceutical industry as they seek to distance themselves from the illicitly sold compounds claiming to be Melanotan.²⁸ Afamelanotide has been extensively studied for the treatment of erythropoietic protoporphyria (EPP). Being administered as a rice-sized, bioabsorbable, subcutaneous implant, afamelanotide has been shown to be effective at reducing the number of phototoxic reactions, increasing the duration of pain-free time after sun exposure, and increasing the quality of life in patients with EPP.²⁸ Unlike its illicit counterparts, afamelanotide is FDA-approved for preventing phototoxicity in adult EPP patients.³⁷

Melanin

Melanin is a naturally occurring pigment synthesized in response to UV radiation as part of the skin's photoprotective mechanism, conveying an SPF of 1.5-2.^{23,38} Increased production of melanin leads to the tanning of skin pigment. The inclusion of melanin in self-tanning products is aimed at increasing said melanin concentration, thus leading to a tanning of the skin. Topical application of melanin has demonstrated significant darkening of pigment and ultimate UV protection in "redhaired" Mc1r-deficient mice.³⁹ However, topical application of melanin to human skin has not demonstrated these same findings. It is proposed that the increased protection of the human epidermis does not allow penetration of topical melanin, as was seen in mice.

Recent research has explored small-molecule inhibition of salt-inducible kinases (SIK) as a novel approach to stimulating melanogenesis.³⁹ SIK inhibition has been shown to upregulate the melanocyte-inducing transcription factor (MITF), which regulates key pigment enzymes. Specifically, the SIK inhibitors YKL-06-061 and YKL-06-062 increased MITF expression and promoted melanosome transfer in human skin explants. While these inhibitors have not yet been tested for topical self-tanning applications, their ability to enhance melanin production suggests a potential role in improving the efficacy of topical melanin formulations. Theoretically, combining SIK inhibitors with topical melanin could enhance melanin deposition within the epidermis, overcoming current limitations and leading to more effective pigmentation. However, further studies are needed to evaluate the safety, efficacy, and potential oncogenic risks associated with MITF modulation.

Melanin is also commonly used as a pigment in cosmetic and food industries, reinforcing its potential role in self-tanning formulations.⁴⁰ Notably, the FDA has not provided specific guidance on the use of melanin as an ingredient in self-tanners.

Melanoidins

Melanoidins are brown polymeric pigments formed through the Maillard reaction, which also contributes to the pigmentation effects of DHA and erythrulose.⁹ These pigments accumulate within the stratum corneum, imparting a temporary tanned appearance that fades with corneocyte desquamation.⁷⁹

Despite their superficial similarity to melanin, melanoidins are structurally and functionally distinct.⁹ Melanin is synthesized within melanocytes and deposited in the basal epidermis, whereas melanoidins are exogenous pigments that remain confined to the stratum corneum. Furthermore, unlike melanin, melanoidins do not confer significant UV protection.⁹

Melanoidins are widely used as coloring agents in the food and cosmetic industries.⁴¹⁻⁴⁴ When applied topically, they are generally well tolerated, with no reported toxicity.⁶ However, no studies have specifically evaluated their long-term effects in self-tanning products.⁴⁵ Additionally, the FDA has not issued formal guidance on melanoidins in cosmetic formulations.

Cosmetic Considerations in Sunless Tanners

While sunless tanners effectively darken the skin, they have notable cosmetic limitations. Increased pigmentation can occur in areas with a thicker stratum corneum, such as the palms, soles, elbows, knees, and ankles, often leading to uneven or exaggerated coloration. Streaking may also occur if the product is applied unevenly or inadequately blended.⁴⁶

To optimize cosmetic outcomes, best practices have been developed for proper skin preparation before application.⁴⁶ Best practices include cleansing, exfoliating, and thoroughly drying the skin to ensure an even distribution of the tanning agent. Application should be sparing in areas of thickened stratum corneum to prevent excessive darkening. To avoid unintended staining of the palms and knuckles, patients are advised to wash their hands immediately after application or use an applicator glove for more controlled distribution.

CONCLUSION

Sunless tanners provide a popular alternative to traditional tanning through UV exposure, offering a safer option for individuals seeking a darker complexion. While DHA remains the primary active ingredient, the inclusion of additional ingredients can influence both the efficacy and final tone, leading to a wide range of outcomes across different formulations.¹⁶ Given the variation in individual preferences, determining an "optimal" sunless tanning formulation remains challenging.

Dermatologists play a key role in educating patients about sunless tanners, including their ingredients, potential risks, and best practices for safe and effective use. Recognizing the potential impact of these products on pigmented lesions is particularly important, as they may alter lesion appearance and raise concerns for malignancy. Awareness of patient use can help distinguish benign changes from true pathology, reducing unnecessary interventions.

Patients should be informed of potential side effects, such as contact dermatitis, and advised to discontinue use if adverse reactions occur.^{3,4} Importantly, sunless tanners provide minimal UV protection, necessitating continued sunscreen use to prevent UV-induced skin damage.

Ultimately, sunless tanners remain a safe and effective option for achieving a tanned appearance without UV exposure. By guiding patients in their use, dermatologists can help optimize cosmetic results while minimizing risks and promoting overall skin health and safety.

DISCLOSURES

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Evaluation of an Advanced, Multimodal Skin Tone Correcting Serum in Participants With Mild-to-Severe Dyschromia and Hyperpigmentation

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ABSTRACT

Background: A new multimodal skin tone correcting serum formulated with *b.r.y.t.e.r.* (brown, red, and yellow tones with enhanced resurfacing) technology (EV-I) targets brown, red, and yellow dyschromia and acts through 5 pathways of melanin synthesis to reduce pigmentation, resurface and exfoliate skin, and improve overall skin tone.

Methods: A single-center, open-label, 12-week trial enrolled females with mild-to-severe dyschromia/hyperpigmentation. EV-I was applied twice daily for 12 weeks, with a subset of participants also applying a double-conjugated retinoid/AHA cream (AHARet) nightly. Pigmentation was graded using the Melasma Area and Severity Index (MASI) scale at baseline and at weeks 2, 4, 8, and 12. Skin dullness and texture were assessed using a 6-point grading scale. Erythema and dryness/flaking were assessed using a 4-point grading scale. Participant satisfaction and adverse events (AEs) were collected over 12 weeks.

Results: Sixty-five participants were enrolled (EV-I, n=40; EV-I/AHARet, n=25) with a mean age of 53 years; 78% of participants had Fitzpatrick skin types (FST) I-III, 22% were FST IV-VI. The majority of participants presented with moderate-to-severe dyschromia/hyperpigmentation. Significant percent improvements from baseline were demonstrated based on MASI scores at 12 weeks (EV-I, 42%, EV-I/AHARet, 47% [all, $P<.0001$]). Significant improvements from baseline were demonstrated in the appearance of skin texture (EV-I, 46%; EV-I/AHARet, 59% [all, $P<.0001$]) and dullness (EV-I, 47%; EV-I/AHARet, 59% [all, $P<.0001$]) at 12 weeks. No increases in erythema or dryness/flaking were observed.

Conclusions: A new multimodal skin tone correcting serum demonstrated significant improvements in MASI scores and in the appearance of skin texture and dullness. Significant improvements were also achieved in participants using both the skin tone correcting serum and double-conjugated retinoid/AHA cream. Participants reported high levels of satisfaction over 12 weeks.

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INTRODUCTION

Melanin provides pigmentation to skin, hair, and eyes and protects epidermal cells by absorbing harmful ultraviolet (UV) rays. Hyperpigmentation results from excess, cumulative melanin triggered by extrinsic aggressors such as UV radiation and pollution, and intrinsic factors including genetics, hormonal fluctuations, and imbalances that induce oxidative stress.¹⁻³

Melanogenesis is a complex biochemical process that involves multiple pathways.⁴ Among the primary cell signaling pathways that influence skin pigmentation are melanocyte activation, melanosome formation, melanin synthesis, and melanin transfer and removal.⁴ Melanocyte activation and formation can be triggered by UV exposure, pregnancy, other hormonal fluctuations, inflammation, and aging. Sun exposure causes the body to increase production of melanin to defend against

UV rays, increasing skin pigmentation. UV radiation produces free radicals, which, along with UV light, activate biological mechanisms that impact melanocytes.⁵ In the presence of tyrosinase, a key enzymatic regulator of melanin production,⁶ the amino acid L-tyrosine is converted to dopaquinone (DOPA), which is then transformed into either eumelanin (black-brown pigmented melanin) or pheomelanin (yellow-red pigmented melanin).^{4,5}

Multiple modalities or agents are often required to manage hyperpigmentation sufficiently, and strategies always include routine, daily use of sunscreen and sun-protective measures. In an effort to address the multiple pathways involved in the development of melanin, recommended regimens often include the adjunctive use of several topical prescription and/or nonprescription products, including hydroquinone (HQ), retinoids, alpha-hydroxy acids (AHAs), and antioxidants.⁷⁻¹³

Prescription HQ has been the standard treatment for hyperpigmentation due to its ability to inhibit tyrosinase and reduce the conversion of DOPA to melanin.^{14,15} However, due to its association with adverse events such as erythema, irritant or allergic contact dermatitis, and, in rare cases, ochronosis, use is limited to 3- to 4-month cycles, and its use is banned in some countries.¹⁶

A non-hydroquinone skin tone correcting formulation comprising *b.r.y.t.* (brown, red, yellow tones) technology was developed to address 4 core pathways of pigmentation – melanocyte activation, melanosome formation, melanin synthesis, and melanin transfer.¹⁷ The formulation was designed to interrupt the pigment cascade, correct redness and sallowness, and improve skin texture.^{17,18} Results from an initial clinical study in 52 participants who used this topical serum twice-daily demonstrated significant mean percent reductions from baseline in the appearance of dyschromia/hyperpigmentation after 12 weeks (-31%; $P<.0001$) based on a 6-point grading scale (0=None to 5=Severe), with a subset of participants combining use with a double-conjugated retinoid/alpha hydroxy acid cream (AHARet; PM only) demonstrating a 44% reduction ($P<.0001$) in the appearance of dyschromia/hyperpigmentation from baseline after 12 weeks.¹⁷

A new, advanced multimodal skin tone correcting serum formulated with *b.r.y.t.e.r.* technology (brown, red and yellow tones with enhanced resurfacing) has been developed to uniformly improve the appearance of photodamaged skin by addressing persistent hyperpigmentation, redness, and yellow, sallowness-looking skin with the incorporation of additional ingredients such as tranexamic acid, phenylethyl resorcinol, allyl pyrroloquinoline quinone (PQQ; antioxidant), acetyl glycyl beta-alanine (peptide), and a blend of alpha hydroxy acids (AHAs) comprising glycolic, lactic, and citric acids. This new formulation (EV-I) targets 5 key pathways of pigmentation: (1) melanocyte and (2) tyrosinase stimulation, (3) melanosome maturation, (4) melanosome transport, and (5) melanin removal or surface reduction.¹⁸ The current study described herein evaluated the effectiveness and tolerability of this new, multimodal skin tone correcting serum in participants with mild-to-severe dyschromia/hyperpigmentation.

MATERIALS AND METHODS

This single-center, open-label trial was conducted under Institutional Review Board approval (Allendale Institutional Review Board, CT) in conjunction with Good Clinical Practice (cGCP) guidelines. A board-certified dermatologist recruited and enrolled healthy females, all of whom signed written informed consents prior to study participation.

The 12-week study enrolled female participants, aged 30 to 65 years, with mild (2) to severe (4) dyschromia/hyperpigmentation

according to a 6-point grading scale (0=None to 5=Very Severe). Participants were deemed eligible for inclusion following a 2-week washout of alpha hydroxy acids (AHAs), beta hydroxy acids (BHAs), antioxidants, peptides, or nonprescription topical retinoids, and a 4-week washout of prescription topical products including tretinoin, hydroquinone, retinoids, corticosteroids, or medications for rosacea. Participants with severe lines/wrinkles, skin laxity, melasma, post-inflammatory hyperpigmentation (PIH), or scarring (acne or surgical) were excluded from study participation, as were participants with active or a history of atopic dermatitis or psoriasis, keloid scarring, or lupus erythematosus, or who were planning to become pregnant, were pregnant, or lactating. All participants were required to minimize UV exposure, apply the provided sunscreen daily, and wear sun-protective clothing.

Participants were instructed to apply the study product (EV-I) twice daily for 12 weeks (AM/PM) after cleansing their face, followed by a moisturizer (AM/PM) and sunscreen (AM). A subset of participants ($n=25$) also applied AHARet nightly for 12 weeks after applying EV-I.

All investigator assessments occurred at baseline and at weeks 2, 4, 8, and 12. Investigator evaluation of pigmentation was assessed using the Melasma Area and Severity Index (MASI) scale in which each area of involvement is assigned a numeric value of 0 (No Involvement) to 6 (90%-100% Involvement), resulting in a total MASI score range of 0 to 48.¹⁹ The investigator also assessed skin dullness and texture/roughness using a 6-point grading scale (0=None to 5=Very Severe), and erythema and dryness/flaking using a 4-point grading scale (0=None to 3=Severe). In addition, participants completed self-assessment questionnaires at weeks 2, 4, 8, and 12. Adverse events (AEs) were collected throughout the study period.

RESULTS

Demographics

Sixty-five (65) participants were enrolled and completed the study. Participants were randomized to 2 groups, EV-I ($n=40$) and EV-I/AHARet ($n=25$, Table 1). Both groups were similar, with a mean age of 53 years, and the majority of females presented with moderate dyschromia/hyperpigmentation. Among the participants in the EV-I group, 93% were non-Hispanic, and 70% were Caucasian; 77% were FST I-III, 23% were FST IV-V. Similarly, 96% of participants in the EV-I/AHARet group were non-Hispanic, 76% were Caucasian, 80% were FST I-III, and 20% were FST IV-VI.

Efficacy

Significant mean percent reductions from baseline were demonstrated in MASI scores at 12 weeks in the EV-I group (-42%; $P<.0001$; Figure 1) and in the combination use group (EV-I/AHARet, -47%; $P<.0001$; Figure 2). A post-hoc analysis

TABLE 1.

Baseline Demographics				
Baseline Demographics	EV-I (n=40)		EV-I/AHARet (n=25)	
Mean Age (Range)	53 yrs (34 – 64)		53 yrs (38 – 65)	
Race	African American: 23%		African American: 20%	
	Caucasian: 70%		Caucasian: 76%	
	Other: 7%		Other: 4%	
Ethnicity	Hispanic: 7%		Hispanic: 4%	
	Non-Hispanic: 93%		Non-Hispanic: 96%	
Fitzpatrick Skin Type	FST I: 27%	FST IV: 3%	FST I: 20%	FST IV: 4%
	FST II: 45%	FST V: 20%	FST II: 56%	FST V: 12%
	FST III: 5%	FST VI: 0%	FST III: 4%	FST VI: 4%
Severity (Dyschromia)	Mild: 23%		Mild: 16%	
	Moderate: 70%		Moderate: 80%	
	Severe: 8%		Severe: 4%	

conducted in participants with FST IV-V (n=9) in the EV-I group demonstrated a 48% reduction from baseline in MASI scores at week 8 and a 68% reduction from baseline in MASI scores at week 12 (all, $P<.05$) with no observable increase in PIH. Participants in this group presented with either mild or moderate dyschromia/hyperpigmentation at baseline.

Significant mean improvements from baseline were demonstrated in both groups in the appearance of skin texture/roughness (EV-I, 46%; EV-I/AHARet, 59%) and skin dullness (EV-I, 47%; EV-I/AHARet, 59%) at 12 weeks (all, $P<.0001$; Figures 3, 4). No increases in erythema or dryness/flaking were observed in either group (Figures 5-8).

Participant Satisfaction

Participant satisfaction was high in both groups throughout the study, with most reporting that their skin tone was more even-looking (EV-I, 95%; EV-I/AHARet, 88%), looked brighter (EV-I,

98%; EV-I/AHARet, 96%), and the overall appearance of their skin improved (EV-I, 95%; EV-I/AHARet, 96%) at week 12.

At 4 weeks, 93% of participants in the EV-I group reported that their skin tone was more even-looking, 98% reported their skin looked brighter, and 93% reported the overall appearance of their skin improved. Ninety percent (90%) of participants reported that the brown/dark spots or patches on their skin were lighter in appearance after 12 weeks.

Ninety-two percent (92%) of participants in the EV-I/AHARet group reported that their dark spots were lighter in appearance and their skin tone looked more even and smoother at week 4. After 12 weeks, 96% of participants reported that their skin appeared brighter, less dull, and less discolored, 88% reported that the brown/dark spots or patches on their skin were lighter in appearance, and 100% reported feeling more confident in the appearance of their skin.

FIGURE 1. Mean percent reduction in MASI (EV-I Group, n=40).

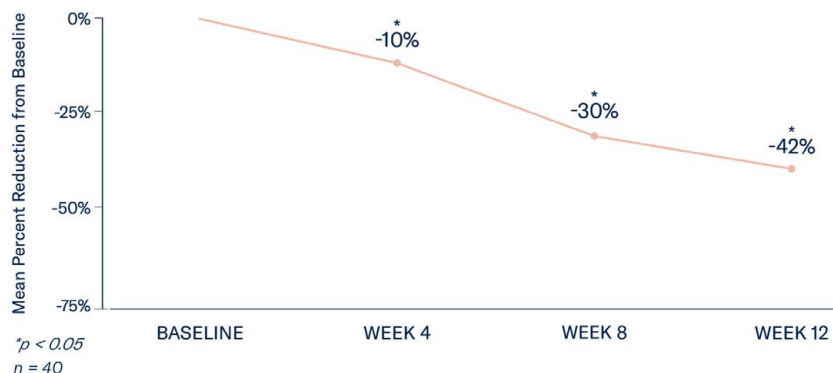


FIGURE 2. Mean percent reduction in MASI (EV-I/AHARet Group, n=25).

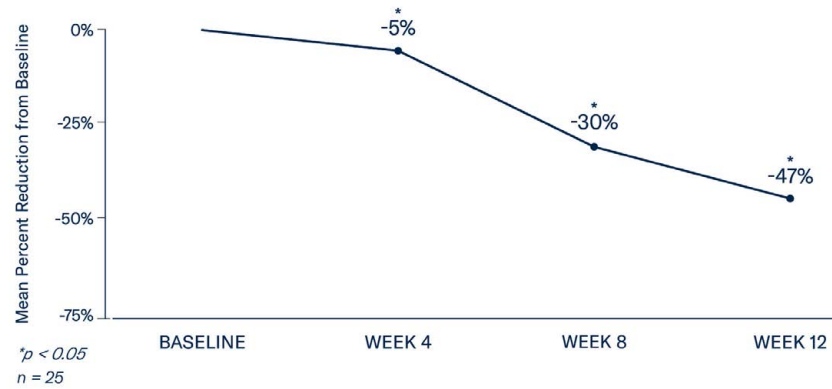


FIGURE 3. Mean percent improvement in the appearance of skin texture and skin dullness (EV-I Group, n=40).

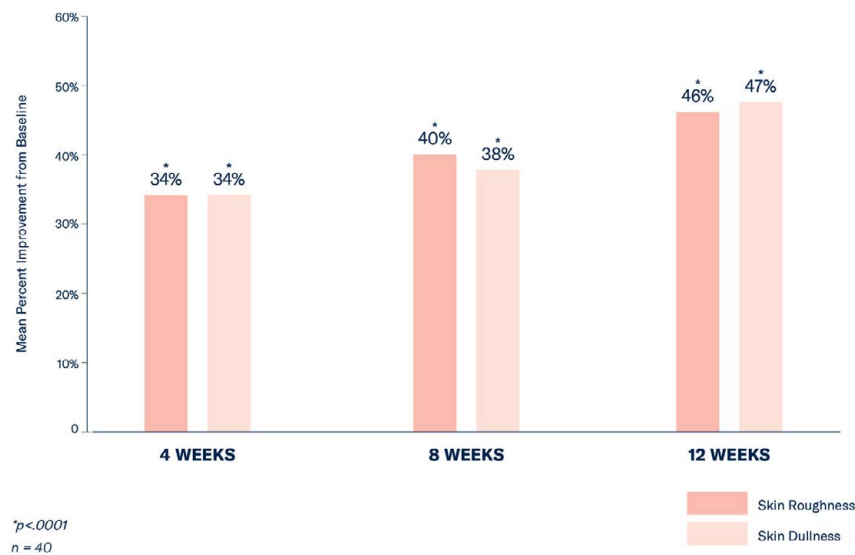


FIGURE 4. Mean percent improvement in the appearance of skin texture and skin dullness (EV-I/AHARet Group, n=25).

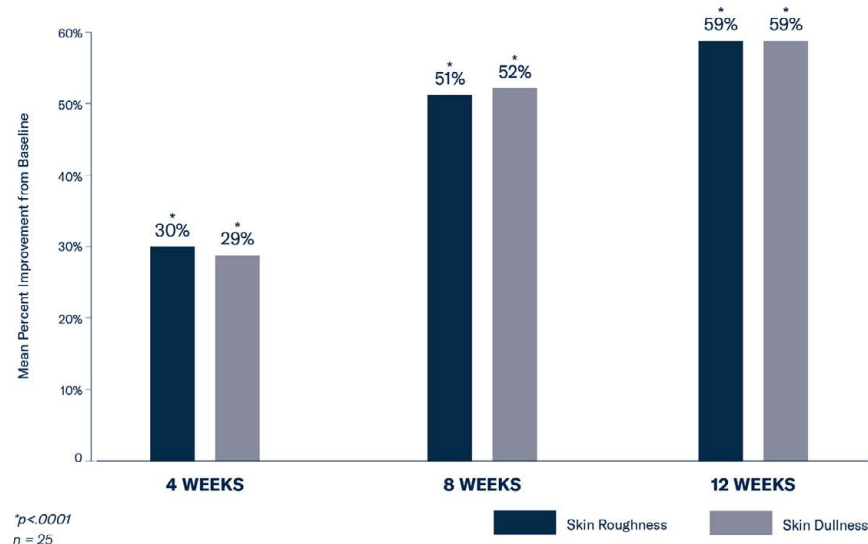


FIGURE 5. Visible improvements demonstrated after 12 weeks (EV-I Group).



*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

FIGURE 6. Visible improvements demonstrated after 12 weeks (EV-I Group).



*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

FIGURE 7. Visible improvements demonstrated after 12 weeks (EV-/AHARet Group).



*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

FIGURE 8. Visible improvements demonstrated after 12 weeks (EV-/AHARet Group).



*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

DISCUSSION

The complex nature of melanogenesis and the diverse underlying etiologies make hyperpigmentation challenging to manage.²⁰ Treatment regimens often include the use of multiple topical agents, some of which may be irritating to the skin, impeding adherence, and influencing suboptimal outcomes.^{13,21} In addition, treatment regimens involving multiple products can be costly and cumbersome for patients to manage, highlighting the need for tolerable, efficacious, and streamlined regimens to facilitate adherence and optimize results.

It is imperative that treatment strategies integrate sun-protective measures to minimize the consequences of sun exposure. In addition, numerous nonprescription topical ingredients have been shown to afford unique benefits in improving the

appearance of hyperpigmented skin. The key ingredients in the formulation used in this study were selected owing to their specific benefits in addressing the 5 pathways of pigmentation (Table 2).^{20,25-47} To facilitate a uniform, brighter skin tone, the active ingredients in EV-I help minimize the appearance of skin discoloration, brown patches and spots, and red, yellow, sallowness, and dull skin often caused by photodamage.

A subset of participants also applied AHARet cream in the evening. The intent of the study design was to ascertain incremental benefits associated with the combination use of the skin tone correcting serum and a double-conjugated retinoid/ AHA cream. The unique structure of the AHARet molecule enables the gradual release of a retinoid and lactic acid to minimize irritation. Other ingredients contained in AHARet

TABLE 2.

Key Ingredients		
Category	Ingredient	Properties
b.r.y.t.e.r. Technology	Acetyl glycyl beta-alanine	Peptide that interferes with production and transport of melanosomes. ²⁵
	Aminopropyl ascorbyl phosphate	Water-soluble, stabilized form of vitamin C that inhibits tyrosinase. ^{20,26}
	AHA Blend (glycolic, lactic and citric acids)	Helps accelerate cell turnover and exfoliates surface pigmentation.
	Alpha-arbutin	Tyrosinase inhibitor that diminishes the appearance of unwanted pigmentation. ²⁷
	Glycyrrhiza glabra root extract/ licorice root extract	Isoflavone comprised of glabrinin that inhibits melanogenesis and brightens skin. ^{26,28}
	Niacinamide	Vitamin B3 derivative; protects the skin barrier, decreases hyperpigmentation, redness, and inflammation (PIH) by inhibiting melanosome transfer from melanocytes to keratinocytes. ²⁹⁻³¹
	Pancratium maritimum extract (sea daffodil)	Inhibits melanin synthesis and transfer, minimizing dark spots and evening skin tone appearance. ³²
	Phenylethyl resorcinol	Tyrosinase inhibitor derived from Scotch pine bark, known for its skin brightening properties. ³³
	Tranexamic acid (TXA)	Inhibits binding of plasminogen to keratinocytes and reduces the activity of melanocytes, inhibiting tyrosinase activity. Inhibits production of the inflammatory mediators, arachidonic acid and prostaglandin, which trigger melanogenesis. Improves barrier function permeability. ^{34,35}
	Ziziphus spina-christi leaf extract	Extract with antimicrobial properties and benefits. Reduces visible effects of glycation including skin yellowing and dullness. ^{36, 37}
Additional Ingredients	Blend of aloe, buddleja officinalis flower extract, ergothioneine, grape flower cell extract, and phloretin	A blend of botanical ingredients and extracts with known inflammatory and free radical protection properties. ³⁸⁻⁴⁰
	Topical Allyl pyrroloquinoline quinone (TAP)	A redox cofactor shown to have protective effects against free radical damage in mitochondria; supports creation of mitochondrial energy necessary for renewal and repair processes of skin. ⁴¹⁻⁴⁵
	Superoxide Dismutase	Neutralizes superoxide radicals to mitigate oxidative damage. ^{46,47}
	Arginine	Amino acid that enhances antioxidant actions, stimulates collagenesis, protects the skin barrier and facilitates hydration. ⁴¹
	Hydrolyzed sodium hyaluronate	Provides antioxidant support and hydration. ⁴²

include glycolic acid, niacinamide, ceramides, and peptides, all of which work together to support cellular turnover, hydration, and exfoliation.⁴⁸ The effectiveness and tolerability of AHARet applied each night has been studied alone and in combination with antioxidants and other products in a variety of skin types in participants with photodamaged skin, and has been shown to facilitate significant improvements in lines and wrinkles, skin texture, and skin tone, with mild, transient adverse events reported.^{49,50}

In the current study, twice-daily application of EV-I, along with the use of sunscreen and a moisturizer, led to early and significant reductions from baseline in MASI scores, with significant reductions occurring among participants with darker skin tones. A post-hoc analysis in participants with FST IV–V noted a 68% significant reduction in hyperpigmentation based on the MASI scale at 12 weeks following twice-daily application of EV-I alone, with a noticeable decrease in PIH. Further, recognizing that UV damage and other extrinsic and intrinsic factors affect skin quality, this study demonstrated that use of EV-I alone or in combination with AHARet led to significant improvements

in skin texture/roughness and dullness at 12 weeks without causing erythema or flaking. These beneficial results led the majority of participants to report being highly satisfied with the overall appearance of their skin after 12 weeks of use.

Due to the open-label nature of this study, a limitation of this study was the lack of a control comparison and a smaller sample size. The study was conducted during the Spring months in the southern part of the United States. While participants were provided with a mineral SPF50 sunscreen and were instructed and continually reminded to use the sunscreen along with other sun-protective measures, it is reasonable to assume that participants had encountered incremental exposures to UV, making this study representative of a real-world experience.

CONCLUSION

Twice-daily use of a multimodal skin tone correcting serum formulated with *b.r.y.t.e.r.* technology that targets key pathways involved in melanin production demonstrated significant reductions from baseline in MASI scores in participants with mild-to-severe dyschromia/hyperpigmentation after 12 weeks.

Significant reductions in MASI scores were demonstrated as early as week 4. A subset of participants with FST IV-V demonstrated significant reductions in dyschromia/hyperpigmentation at weeks 8 and 12. When combined with the use of a double-conjugated retinoid/AHA cream in the evening, additional and significant reductions from baseline were demonstrated in MASI scores in a subset of participants at week 4. Significant improvements in the appearance of skin texture and dullness occurred in both groups at 12 weeks. No increases in dryness/flaking or erythema were observed throughout the study. More than 90% of participants in both groups reported more even looking and brighter skin tone, and improvements in the overall appearance of their skin as early as week 4.

DISCLOSURES

Dr Draelos was a study investigator, and Ms Nelson was an employee of skinbetter science. This study was sponsored by skinbetter science, a Dermatological Beauty Brand of L'Oréal USA, Inc.

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Prospective Single-Site Open-label Study Assessing Safety and Efficacy of Poly-L-Lactic Acid for Temple Volume Loss

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ABSTRACT

Background: Poly-L-lactic acid (PLLA) is an injectable biostimulatory filler used for restoring facial fat volume loss.

Objective: To evaluate the safety and efficacy of injectable PLLA injections for volume loss in the temples using dual plane injections. Assessments included live ratings and ratings of standardized pictures and ultrasound imaging at weeks 4, 8, 12, and 16 by a trained evaluator.

Results: At the 8-week follow-up, there was a statistically significant increase in temporal volume and improvement in skin elasticity in PLLA-treated subjects. Treatment was well-tolerated with minimal self-resolving adverse effects. Ultrasound imaging confirmed that the injection plane was free of vasculature, posing no safety risk.

Conclusion: Repeated PLLA treatments in the temporal region elicited a global improvement in facial shape, particularly the mid and upper face region. The temple hollowness and facial laxity improved over time with no safety sequelae.

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INTRODUCTION

The aging process is complex, influenced by a dynamic interplay of external (lifestyle and environment) and internal (genetics) factors. Changes such as bone resorption, fat pad depletion, muscle atrophy, and changes in skin tone, color, and texture transform a youthful appearance into one characterized by aging-related changes.¹ Notably, volume loss in the temples is an early sign of aging, which contributes to the lowering of the eyelid and eyebrow, skin laxity in the periorbital and cheek areas, and changes to the overall shape of the face.^{2,3} Currently, the use of injectable soft tissue fillers and neurotoxins for correcting facial changes associated with aging is the cornerstone for restoring soft tissue loss in aesthetic medicine. Together with energy-based devices and a consistent skincare regimen, patients can achieve natural, long-lasting facial rejuvenation, reverse the signs of aging without the need for surgery, associated downtime, or significant health risks.⁴

While some fillers like hyaluronic acid provide instant volumization at the injection site, they gradually degrade over time and require future injections for volume maintenance. In contrast, poly-L-lactic acid (PLLA) fillers are biostimulatory; they activate resident fibroblasts to produce autologous collagen over time, leading to a more natural and long-lasting effect. The mechanism through which PLLA stimulates neocollagenesis is by triggering a foreign body reaction to the injected material,

succeeded by a cellular inflammatory response which leads to the formation of vascularized, connective tissue.^{5,6} PLLA is then hydrolyzed into lactate, converted to pyruvate, and oxidized into carbon dioxide.^{7,8} While the inflammatory response subsides in 6 months, the extracellular matrix production continues, leading to a gradual increase in dermal thickness that may last up to 2 years in some patients.^{5,9}

PLLA was first approved as Sculptra® in 2004 by the Food and Drug Administration (FDA) for the treatment of HIV-associated lipoatrophy, and later as Sculptra® Aesthetic in 2009 for the correction of shallow to deep nasolabial folds and other facial wrinkles in healthy patients.^{10,11} It is distinguished as the only FDA-approved PLLA facial injectable that stimulates the skin's own collagen production to smooth facial wrinkles. Common side effects include localized swelling, tenderness, redness, itching, and bruising, which typically resolve within 1-7 days. Occurrence of nodules and papules several months after injection has also been reported, but can be prevented with appropriate product dilution, injection depth, and post-injection massage.¹²⁻¹⁵

Given the benefits and low risk associated with Sculptra, the objective of this study was to evaluate the effectiveness of PLLA injections in the temple area for restoring temporal and midface volume through dual plane injections.

MATERIALS AND METHODS

Patients

All subjects provided written informed consent prior to receiving any study-related procedures. Eligible subjects were healthy males and females (over 25 years of age, Fitzpatrick photo skin types I-IV), with temporal hollows with a volume deficit of grade 2 to 4 on the Galderma Temple Volume Deficit Scale. Moreover, subjects agreed not to have any other procedures that affect facial wrinkles (eg, filler, botulinum toxin, radiofrequency, laser, IPL, and ultrasound) or skin quality (microdermabrasion, peels, acne treatments, etc.) for the duration of the study. Negative urine pregnancy test results were required for women with childbearing potential before enrollment. Previous therapy with botulinum toxin, fillers within 12 months of the baseline visit, or treatment with poly-L-lactic acid in the face at any time precluded women from participation. Intake of any NSAIDs (aspirin, ibuprofen, etc.) within 7 days and acetaminophen 24 hours before treatment makes the subject ineligible to participate. Subjects with dermatologic conditions, including acne, rosacea, eczema, psoriasis, actinic keratosis, severe sun damage, scars, or a history of keloids were also excluded from the study.

Study Design

This was a prospective, single-site, open-label study conducted in accordance with the principles of the Declaration of Helsinki, current GCP guidelines, and IRB approval. The safety and efficacy of injectable Poly-L-Lactic Acid (Sculptra Aesthetic) for volume loss in the temples using dual plane injections were assessed in this study. Eligible subjects received 3 treatments, four weeks apart, with poly-L-lactic acid in the temples. After the treatments, subjects returned to the research site 4 weeks and 8 weeks post last treatment for follow-up visits.

Treatment

Twenty-four hours prior to injection, 8 mL of sterile water was added to up to 2 PLLA vials. Immediately prior to the injections, an additional 1 mL of 1% lidocaine was added for a final dilution of the PLLA. Injections were carried out in a dual plane technique initially into the supraperiosteal region and then subsequently in the deep dermis using a 26-G needle (1.0 inches) at a 30–40° entry angle. Aspiration was performed before Injection. Product was injected with approximately 50% in the deep plane (supraperiosteal) and 50% in the superficial plane (deep dermis), adjusted based on individual anatomy. To ensure even product distribution and prevent nodule formation, the injected area was massaged after every 2 to 3 injections and longer at the end of treatment. Patients were instructed to massage the injected areas for 5 minutes, 5 times per day, for 5 days following the procedure. The follow-up phase consisted of visits at 4 weeks and 8 weeks after the last treatment. Standardized photographs and ultrasound images (Doppler, sonographic, 3D) were taken by a trained evaluator at baseline, week 4, 8, 12, and 16. The primary endpoint was defined as at least one degree of improvement in

the temporal area volume using the Galderma Temple Volume Deficit Scale and GAIS at the last follow-up as compared with baseline. Secondary endpoints were defined as improvement of facial skin laxity, as at least 1 point of improvement in the facial area (mid and lower face, including cheek and jawline) using the 10-point facial laxity rating scale from baseline throughout week 16.

Assessments

Temporal volume loss

The assessment of temporal volume loss was performed at baseline through week 16 using the Galderma Temple Volume Deficit Scale. Half-grades were not allowed. During visits when study injections were performed, the assessment was performed prior to the injection. No reference to previous visits was made when performing this evaluation.

Facial Laxity Rating Scale

The assessment of facial skin quality was performed at baseline through week 16 using the Facial Laxity Rating Scale (FLRS) 10-point scale (0 = no laxity, 10 = severe laxity). The evaluation was performed for each subject by the same evaluating investigator after the subject performed a self-assessment. Half-grades were not allowed. During visits when study injections were performed, the assessments were performed prior to the injection.

Global Aesthetic Improvement Scale (Investigator and Subject)

The treating investigator completed the live assessment by circling the number on the scale that corresponded to the description that best fit the current description of overall change in aesthetic appearance at each visit post baseline.

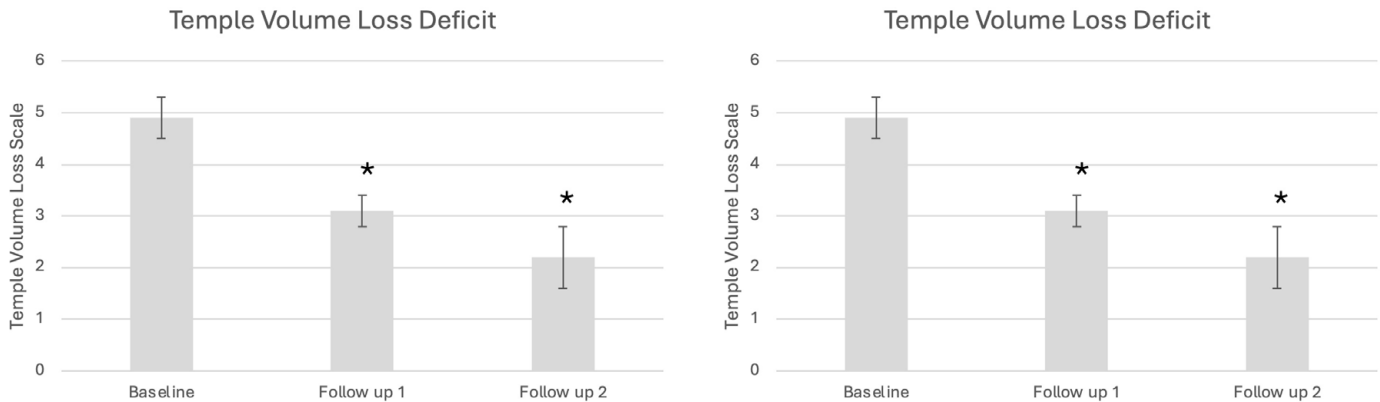
Standardized Photography and Ultrasound

Standardized photographs were taken at 0°, 45°, and 315° angles using the Canfield PRIMOSCR camera system (Canfield Imaging Systems, Fairfield). Subjects were not allowed to wear any makeup except mascara. Subjects wore a black headband and a black cape. Jewelry, including earrings and facial piercings, were removed for photos. Ultrasound images were taken (sonographic, Doppler, and 3D) to ensure the injection field is free of vascularity. The standardized photography was conducted for all subjects at baseline through week 16. During visits when study injections were performed, the standardized photography was performed prior to the injection. Ultrasound (US) imaging system (14-MHz B and M-mode operation, Lumify, Philips) was utilized to visualize the injection site structures.

Safety

Adverse events were monitored and recorded throughout the study. Patients were asked to report product-related adverse events.

FIGURE 1. Change in volume loss deficit (A) and facial laxity (B) at 4 and 8 weeks following 3 treatments with PLLA. Asterisk (*) signifies statistical significance, $P<0.05$.



Statistical Analysis

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

RESULTS

Of the 23 patients enrolled in the study, 20 patients completed the study. The mean age was 58 years old and all but one patient were female. Patients who received treatment with PLLA exhibited a substantial decrease in temple volume loss at the first and second follow-up assessments compared to baseline measurements. Notably, at the second follow-up evaluation, the reduction in temple volume loss deficit exceeded 2 points, indicating a significant improvement (Figure 1A; $P=0.03$ at 2nd follow-up). Evaluation of skin laxity showed that patients

treated with PLLA had a 2–4-point significant decrease in facial laxity at the first two follow-up visits (Figure 1B; $P=0.02$ at 2nd follow-up). Investigator GAIS assessments showed that patients treated with PLLA had a slight improvement in GAIS (score, 1.5) at the first follow-up visit and a moderate improvement at the 2nd follow-up visit (score, 2.2), though the change between the 2 follow-ups was not significant. Representative images of patients are shown in Figures 2 and 3. All patients were very satisfied with their overall appearance at 8 weeks post-3rd PLLA treatment.

Safety

Although the temple is generally considered a safe zone, ultrasound imaging was included to confirm vascular anatomy and avoid high-risk injection sites. No adverse events related to the treatment were reported. The safety profile of PLLA was similar to that reported in the literature, with mild self-resolving side effects occurring in a few patients. All adverse effects were injection-related (bruising, erythema) that resolved without sequelae within two weeks after treatment. There were no

FIGURE 2. Representative clinical photographs of a 56-year-old subject before (A) and after (B) 8 weeks of 3 PLLA treatments. Reduction of pore size, increased radiance, and smoother, more even tone are noted post-PLLA treatment.



FIGURE 3. Representative clinical photographs of a 46-year-old subject before (A) and after (B) 8 weeks of 3 PLLA treatments. Aside from temporal volumization, brow lift, and midface reshaping are observed post-PLLA treatment.

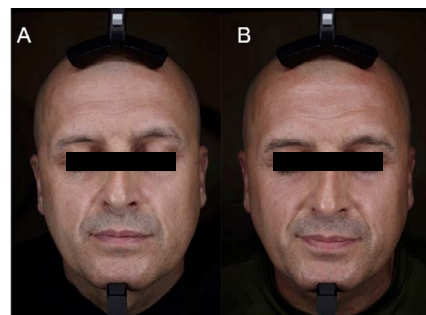
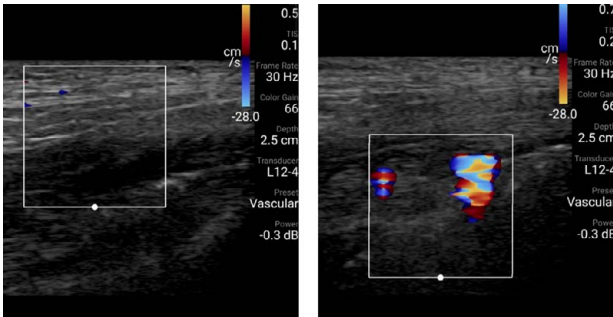


FIGURE 4. Ultrasound analysis (volumetric and Doppler) showing that the field of injection is clear of vascularity pre-injection (left) and the depot of PLLA is visible post-injection (right).



reports of post-inflammatory pigmentation following bruising. Ultrasound imaging using sonogram and Doppler to assess vascular structures in the field of injection showed no evidence of vascularity that would pose a safety issue during and after the deposition of PLLA (Figure 4).

DISCUSSION

This study demonstrates the efficacy of repeated, dual-plane injections of PLLA in improving the appearance of the temple area, facial skin laxity, and overall aesthetic appearance. Significant improvements were observed 8 weeks following treatment, with no treatment-related adverse events reported, highlighting the effectiveness and safety of PLLA for restoring facial volume loss. As temple volumization is an underutilized yet impactful aspect of facial rejuvenation, the results demonstrated strong effectiveness and safety, underscoring the importance of this approach in achieving a harmonious and natural rejuvenation outcome.

One of the key findings of the study was the global improvement in restoring the facial shape, particularly in the mid and upper face region, after patients underwent PLLA injections in the temporal area. The temple hollowness and facial laxity, which often contribute to an aged appearance, showed significant improvement over time, leading to a more youthful and rejuvenated look. Previous findings have demonstrated an effect of PLLA in improving skin quality, and the results of our study showing a global improvement following PLLA treatment may be attributed to its biostimulatory properties. Exploratory analysis with ultrasound showed that the dermal layers underwent remodeling following PLLA treatment, highlighting the additional attributes of PLLA aside from volumization.

Patient satisfaction was high across all participants, indicating that the procedure effectively met their aesthetic goals. The treatment was well tolerated, with only transient numbness or pain in the injection area reported as potential side effects, which were minimal to nonexistent, further highlighting the

safety and comfort associated with the procedure. To ensure optimal safety, ultrasound imaging was employed to identify safe injection zones, minimizing the risk of vascular events and ensuring that the injections were performed in appropriate areas. The ultrasound analysis confirmed that the injection points were located in safe zones, further validating the safety and efficacy of the procedure.

The injections were carried out using a dual-plane technique, a method that involves initially targeting the supraperiosteal region and subsequently the deep dermis. This approach is crucial as the temporal region comprises distinct layers, including the skin, subcutaneous tissues, superficial and deep temporal fascia, temporalis muscle, and the temporal bone. Additionally, the superficial temporal artery, particularly its frontal branch and zygomatico-orbital artery, holds significance in this area, necessitating careful consideration during the injection process.

Limitations of the study include the small sample size, relatively short follow-up, and completion at a single site. These factors may affect the generalizability of our findings. Additionally, future studies could explore the long-term outcomes of PLLA treatments in the temple area.

CONCLUSION

The results presented herein demonstrate that repeated treatments of PLLA resulted in notable improvements in temple volume, facial laxity, as well as overall aesthetic appearance. Our findings not only support the continued use of PLLA for addressing temple hollowness and facial laxity but also highlight its role as an effective, non-surgical option for achieving panfacial rejuvenation and restoring facial balance. While the temporal region is often overlooked in facial rejuvenation procedures, this study highlights its vital role in achieving a harmonious and natural rejuvenation outcome. By addressing this area through PLLA injections, practitioners can effectively restore volume and contour, leading to a more youthful and refreshed appearance.

DISCLOSURES

NSS received research support and serves on advisory boards for Galderma. SA, AS, ZE, JG have no conflicts of interest to disclose.

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Clinical Evaluation of a Thiamidol-Based Regimen With SPF Compared With SPF Alone for Facial Hyperpigmentation

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ABSTRACT

Background: Hyperpigmentation disorders are common skin concerns that negatively impact patient quality of life and self-perception. Hyperpigmentation results from the overproduction of melanin via a multi-step process with a rate-limiting step catalyzed by tyrosinase. Thiamidol, an effective human tyrosinase inhibitor, has recently been shown to reduce visible signs of hyperpigmentation and could provide additional benefits when combined with the standard of care treatment for hyperpigmentation: photoprotection, specifically sunscreens with sun protection factor (SPF).

Methods: A randomized study was performed with 95 subjects (n=47, Thiamidol regimen; n=48, standard SPF 30 lotion) aged 18–65 clinically presenting with facial hyperpigmentation (measured by colorimeter and individual typology angle [ITA°]) to assess the efficacy of the Thiamidol-containing regimen (Day Lotion with SPF 30 and Serum applied in the morning, Night Cream and Serum applied in the evening) compared with a standard SPF 30 lotion for 12 weeks, followed by a 6-week regression phase.

Results: Facial hyperpigmentation, measured by skin lightness, ITA° values, radiance, and shine, was significantly reduced relative to baseline for both groups as early as week 2, and significantly reduced for patients receiving the Thiamidol-containing regimen vs the standard SPF 30 lotion at weeks 8 and 12.

Discussion: This study demonstrates that while SPF alone can reduce the visible signs of hyperpigmentation, the addition of Thiamidol to a daily skin care regimen confers additional, durable benefits with regard to skin lightness, radiance, and shine.

Conclusion: These data support the integration of Thiamidol-containing formulations into existing skin regimens for individuals with facial hyperpigmentation.

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INTRODUCTION

Pigmentary disorders (particularly melasma, postinflammatory hyperpigmentation, and solar lentigines) are among the most common skin disorders, impacting patient quality of life, perception by others, and even self-perception.^{1,2} Hyperpigmentation results from excess production of melanin induced by dysregulation of a multi-step synthesis process that converts tyrosine to L-DOPA via tyrosinase activity, eventually producing eumelanin and pheomelanin, which are deposited at the dermal and epidermal layers of skin.³

Excess melanin production may be initiated in response to skin injury, inflammation, certain medications, and sun exposure.⁴ Melanin confers skin pigmentation and affords some protection to the skin from ultraviolet radiation.⁵ Prolonged sun exposure stimulates melanogenesis, which generates superoxide and hydrogen peroxide, reactive oxygen species that can cause DNA damage and trigger inflammation, further upregulating melanogenesis.^{6,7} Additionally, in patients with inflammatory skin conditions, the levels of antioxidants, which neutralize

reactive oxygen species, can be lower than in patients with healthy skin.⁸ As a result of the impact of prolonged sun exposure on excess melanin production, a fundamental aspect of hyperpigmentation management is the use of photoprotection (eg, photoprotective clothing, sunglasses, and topical application of sunscreen) to prevent worsening appearance of hyperpigmentation.⁹ Specifically, the use of broad-spectrum sunscreens with SPF is recommended as the standard of care for arresting hyperpigmentation, particularly sunscreens that provide visible light protection using iron oxide and/or neutralize reactive oxygen species using antioxidants.¹⁰⁻¹² Common active treatments for hyperpigmentation (treatments that seek to reverse hyperpigmentation rather than just prevent further hyperpigmentation) include hydroquinone (often considered the most effective ingredient for hyperpigmentation), retinoids, kojic acid, chemical peels, laser therapy, and oral tranexamic acid, which have demonstrated some efficacy, but carry the risk of adverse effects and may not be as accessible as over-the-counter products due to price or the need for a doctor's visit or a prescription.⁹

Recently, isobutylamido thiazolyl resorcinol (Thiamidol) was identified as the most effective human tyrosinase inhibitor out of >50,000 screened compounds, with an affinity for human tyrosinase orders of magnitude better than common anti-hyperpigmentation ingredients such as hydroquinone and kojic acid (Thiamidol IC_{50} =1.1 μ mol/L; hydroquinone IC_{50} >4000 μ mol/L; kojic acid IC_{50} =500 μ mol/L).¹³ This high affinity makes Thiamidol a suitable ingredient for over-the-counter anti-hyperpigmentation skin care products, particularly in combination with SPF. The objective of this study was to evaluate the efficacy of a Thiamidol-containing regimen (Day Lotion with SPF 30 and Serum applied in the morning, Night Cream and Serum applied in the evening) at reducing the visible signs of hyperpigmentation compared with a vehicle control that includes the same ingredients as the Day Lotion with SPF 30 minus Thiamidol, thus allowing for evaluation of Thiamidol with SPF or SPF alone.

MATERIALS AND METHODS

Study Design

This randomized clinical study was conducted between August 2024 and January 2025 in a study center (Dermico, Broomall, PA). Subjects were assessed at baseline, weeks 2, 4, 8, and 12 of the 12-week treatment phase, and again at week 18 after a 6-week regression phase. The study was conducted following International Conference on Harmonization Good Clinical Practice guidelines, and in accordance with the Declaration of Helsinki. Prior to study initiation, the protocol, informed consent form, and product information were submitted and approved by the Sterling Investigational Review Board. Subject anonymity in the study documentation was maintained by coded entry.

Population and Treatment

Eligible subjects were aged 18–65 with Fitzpatrick Skin Types (FST) I–VI and individual typology angles (ITA°) ranging from +65° to -31° and with an ITA° difference of >5 ITA units on their facial skin between an area of interest and surrounding skin sites, as determined at the pre-study visit. Subjects must have been able to read, understand, and sign the Informed Consent Form, and been willing and able to follow the study requirements. Subjects were asked to discontinue the use of any topical products on their face and avoid sun exposure exceeding 15 minutes (including tanning) from 3 days prior to the study start and through the completion of the 12-week treatment period. Additionally, prior to the first 2 visits, activities that would raise body temperature or induce sweating were not allowed in the 2 hours before their visits. Facial cleansers without brightening or medical properties were permitted. The use of antiinflammatory medications, including topical corticosteroids, or antihistamines was not allowed in the 48-hour period before visits.

Subjects received either the Thiamidol-based regimen (Day Lotion with SPF 30 and Serum applied in the morning, Night

Cream and Serum applied in the evening) or a standard SPF 30 lotion (applied 1–4 times daily as needed) for 12 weeks, followed by a 6-week regression phase. The standard SPF 30 lotion had the same formulation as the Day Lotion with SPF 30, but with no Thiamidol; neither the Day Lotion with SPF 30 nor the standard SPF 30 lotion contained visible light filters.

Assessments

The primary outcome of the study was the evaluation of the hyperpigmentation-reducing effect of the Thiamidol-regimen or standard SPF 30 lotion through skin pigmentation measurements (L^* mean and ITA°), radiance, and shine at baseline, week 2, week 4, week 8, week 12, and after a 6-week regression (week 18). Briefly, Visible, cross-polarized (X-Pol), parallel-polarized (P-Pol) and UV fluorescence clinical images were acquired for each time point using a Visia-CR system (Canfield, Parsippany, NJ). X-Pol and P-Pol images were used to quantify skin tone, shine, and radiance. A standardized region of interest from each facial image was translated pixel by pixel from the native RGB values into the $L^*a^*b^*$ color space, then analyzed in terms of their image histogram parameters. Individual Topology Angle (ITA) was calculated from L^* and b^* values using the equation $ITA = [\arctan(L^*-50)/b^*] * 180/\pi$. The mean of the L^* value and ITA value were used to represent skin lightening, while a partial least squares regression model was employed to quantify perceived shine and radiance as a balance of skin surface and subsurface reflection components.^{14,15}

Statistical Analysis

Statistical analyses of efficacy variables were based on the full analysis set consisting of all randomized subjects having completed the study without any major protocol deviation. Statistical significance amongst and between groups was determined using the Wilcoxon signed-rank test using the Statistical Analysis System (SAS Institute, Cary, NC) software package.

RESULTS

Study Demographics

A total of 95 subjects with facial hyperpigmentation enrolled between August 2024 and January 2025 and were randomized to receive either a Thiamidol-containing regimen (n =47) or a standard SPF 30 lotion (n =48). Demographics were well balanced between treatment groups (Table 1).

Skin Pigmentation Efficacy

The skin lightening efficacy of the Thiamidol regimen and standard SPF 30 lotion was assessed using L^* mean and ITA°. Subjects receiving the Thiamidol regimen had a greater change from baseline in L^* mean than did patients receiving standard SPF 30 lotion, with significant changes between the treatment groups at weeks 8 and 12 (P <0.05); both treatment groups experienced significant changes from baseline starting at week

TABLE 1.

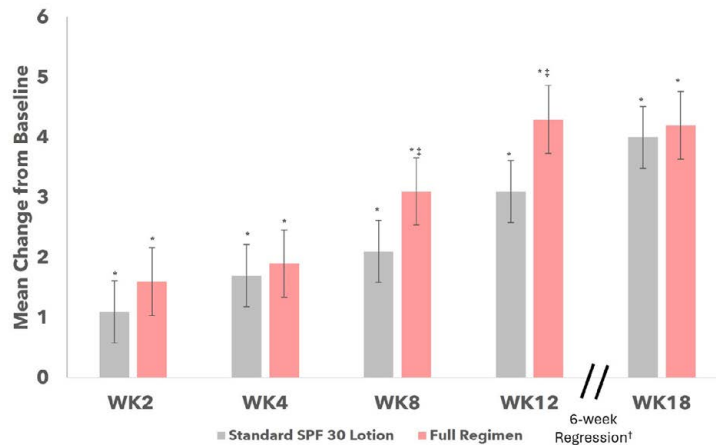
Study Demographics		
Characteristic	Thiamidol Regimen Group (n=47)	Standard SPF 30 Lotion Group (n=48)
Sex, n (%)		
Female	47 (100)	44 (91.7)
Male	0 (0)	4 (8.3)
Age, years (SD)	50.15 (11.48)	53.40 (9.92)
Phototype, n (%)		
FST I	3 (6.4)	1 (2.1)
FST II	13 (27.7)	13 (27.1)
FST III	14 (29.8)	17 (35.4)
FST IV	2 (4.3)	4 (8.3)
FST V	12 (25.5)	12 (25.0)
FST VI	3 (6.4)	1 (2.1)

2 and through week 18 ($P<0.05$; Figure 1). Similarly, subjects receiving the Thiamidol regimen had statistically significant improvements from baseline in ITA° compared with subjects receiving the standard SPF 30 lotion at weeks 2, 8, and 12 ($P<0.05$), while both treatment groups again had significantly improved ITA° compared with baseline from week 2 and through week 18 ($P<0.05$; Figure 2).

Radiance and Shine Efficacy

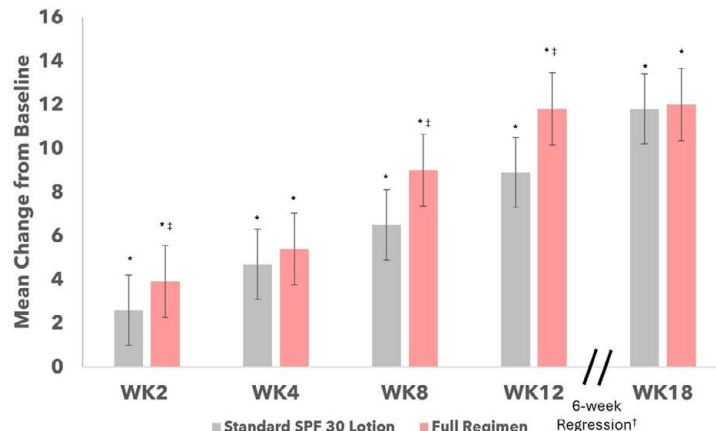
While skin lightening remains an effective measure of anti-hyperpigmentation, radiance and shine, which confer the appearance of brighter, even-toned, and youthful skin have become objective assessments in their own right.^{14,15} For both radiance and shine, subjects receiving the Thiamidol regimen had significant improvements compared with subjects receiving the standard SPF 30 lotion at weeks 8 and 12 ($P<0.05$); both treatment groups experienced significant improvements compared with baseline at all time points ($P<0.05$; Figures 3 and 4).

FIGURE 1. L* mean following treatment with Thiamidol-formulated full product regimen (serum, day lotion, and night cream) or standard SPF 30 lotion compared with baseline.



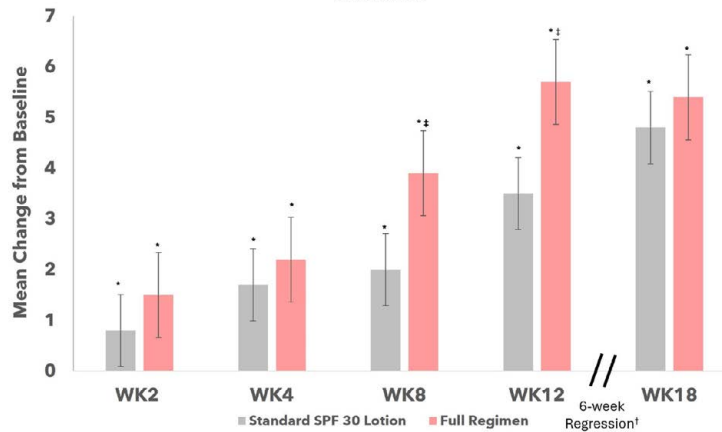
Significant difference between treatment groups and baseline as indicated (* $P<0.05$). Significant difference between full regimen and standard SPF 30 lotion as indicated († $P<0.05$).
†Subjects did not use any Thiamidol-containing products during the regression phase.

FIGURE 2. Mean Individual Typology Angle (ITA°) following treatment with Thiamidol-formulated full product regimen or standard SPF 30 lotion compared with baseline.



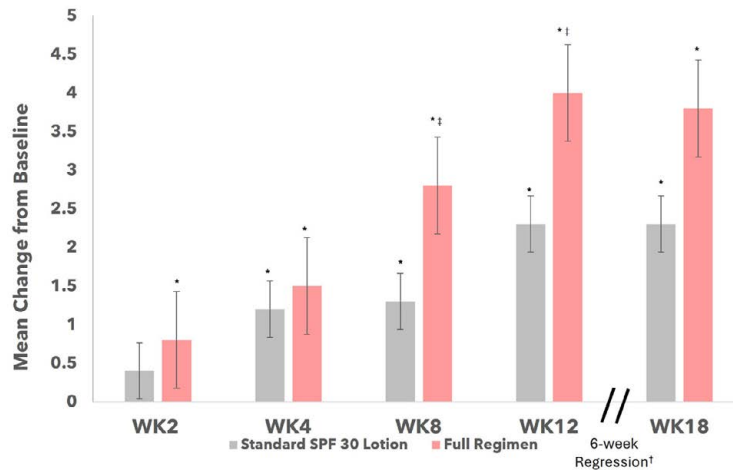
Significant difference between treatment groups and baseline as indicated (* $P<0.05$). Significant difference between full regimen and standard SPF 30 lotion as indicated († $P<0.05$).
†Subjects did not use any Thiamidol-containing products during the regression phase.

FIGURE 3. Mean radiance measured following treatment with Thiamidol-formulated full product regimen or standard SPF 30 lotion compared with baseline.



Significant difference between treatment groups and baseline as indicated (* $P < 0.05$). Significant difference between full regimen and standard SPF 30 lotion as indicated ($\dagger P < 0.05$). [†]Subjects did not use any Thiamidol-containing products during the regression phase.

FIGURE 4. Mean shine measured following treatment with Thiamidol-formulated full product regimen or standard SPF 30 lotion compared with baseline



Significant difference between treatment groups and baseline as indicated (* $P < 0.05$). Significant difference between full regimen and standard SPF 30 lotion as indicated ($\dagger P < 0.05$). [†]Subjects did not use any Thiamidol-containing products during the regression phase.

Clinical Photography

In addition to objective measurements of skin lightening, radiance, and shine, subjects receiving the Thiamidol regimen (Figure 5A-B) had reductions in the visible appearance of hyperpigmentation, as did subjects receiving the standard SPF 30 lotion (Figure 5C-D) in clinical photographs taken at baseline and at week 12. Importantly, the use of the Thiamidol-containing regimen lightened hyperpigmented skin, without whitening the surrounding, unaffected skin. The generally lighter appearance of the subjects' skin tones in the week 12 photographs may be due to the combination of limited sun exposure (protocol-mandated limit of 15 minutes of sun exposure at a time) and subject compliance with sunscreen application during the study period. Photograph lighting and exposure were consistent across timepoints.

DISCUSSION

The standard of care treatment for facial hyperpigmentation is consistent application of broad-spectrum sunscreen with SPF. In this study, the efficacy of skin care regimens utilizing sunscreen with SPF in the visible reduction of facial hyperpigmentation was demonstrated, with both treatment groups experiencing significant improvements in skin lightness, radiance, and shine compared with baseline. The use of the Thiamidol-containing skin care regimen consisting of the Day Lotion with SPF 30 and Serum applied in the morning and Night Cream and Serum applied in the evening, conferred additional benefits to skin lightness, radiance, and shine compared with SPF sunscreen alone. Notably, both the regimen and standard SPF 30 lotion treatment groups retained statistically significant improvements in skin lightness, radiance, and shine compared with baseline

In conclusion, while photoprotection via sunscreens with SPF alone can reduce the visible signs of hyperpigmentation, the addition of Thiamidol to a daily skin care regimen utilizing SPF can confer additional benefits, particularly skin lightness, radiance, and shine. These data support the integration of Thiamidol-containing formulations into the dermatologist's armamentarium and existing skin care regimens for individuals with facial hyperpigmentation.

DISCLOSURES

ST has served as an investigator for Allergan Aesthetics, Concert Pharmaceuticals, Croma-Pharm GmbH, Lilly, and Pfizer; as a consultant for Arcutis, Armis, Avita Medical, Beiersdorf, Biorez Inc, BMS, Cara Therapeutics, Dior, EPI Health, Estee Lauder, Evolus Inc, Galderma, GloGetter, HugelAmerica, Incyte, Johnson & Johnson, L'Oreal, Lilly, Medscape, Pfizer, Piction Health, Sanofi, Scientis US, UCB, Vichy Laboratories; as a speaker for Beiersdorf, Catalyst Medical Education, CME Outfitters, DermSquared, HMP Global, LearnSkin, Medscape, and MJH Lifesciences; and as an editorial board member for Archives in Dermatologic Research, Cutis, and Practical Dermatology. She has also received royalties from McGraw-Hill. PEG has served as an investigator and/or consultant for Allergan, BOD Clinuvel, Clinuvel, Incyte, Johnson & Johnson, L'Oreal, Merck, Pfizer, SkinBetterScience, and Versicolor Technologies.

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Racial and Ethnic Disparities in Access to Advanced Therapies for Atopic Dermatitis in the United States

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ABSTRACT

Background: Atopic dermatitis (AD) disproportionately affects diverse patient populations, and complex factors influence access to treatment among different racial and ethnic groups.

Objective: This study aimed to assess racial and ethnic differences in AD severity and access to treatment in clinical practice.

Methods: The study included patients aged 6 and older with AD enrolled in TARGET-DERM AD, an observational, longitudinal study utilizing electronic medical records from 43 academic and community centers across the United States.

Results: The analysis included 1,928 participants: 577 children (30%) and 1,351 adults (70%), with 42% identifying as Non-White. Non-Hispanic (NH) Asian participants exhibited the highest percentage of moderate-to-severe AD at 63%, followed by NH-Black (61%), Hispanic (49%), and NH-White (48%) participants. Over half (56%) of NH-Asian patients reported comorbid asthma. NH-Black and Hispanic individuals were less likely to receive advanced systemic therapies compared to NH-White individuals, with odds ratios of 0.71 and 0.66, respectively, both statistically significant ($P < 0.01$).

Conclusion: Despite having moderate-to-severe AD, NH-Black and Hispanic patients had significantly lower odds of receiving advanced systemic therapy compared to NH-White patients, highlighting potential disparities in access to advanced treatments for AD.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, systemic disease that impacts individuals of all ages, races, and ethnicities worldwide. It is strongly influenced by genetic, socioeconomic, and environmental factors and is associated with an increased risk of multiple comorbidities, including allergic and autoimmune conditions.¹ Despite growing interest and understanding of AD, evidence suggests that there are racial and ethnic differences in prevalence, disease severity, and treatment patterns in the United States. However, data on the distribution of comorbidities among racial and ethnic groups and their impact on management and treatment remain limited.² Additionally, non-white patients and those with comorbidities are underrepresented in clinical trials for advanced systemic therapies for AD.^{3,4}

Systemic therapies play a significant role in the management of moderate-to-severe AD, particularly when topical treatments are insufficient or impractical.⁵ Conventional systemic therapies

include systemic corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine. Advanced systemic therapies, including injectable biologics and oral Janus Kinase inhibitors, are now approved and strongly recommended by the American Academy of Dermatology (AAD) guidelines for the management of AD.⁵

The objective of this study was to compare participant characteristics, disease severity and impact, comorbidities, and treatment type across racial and ethnic groups. Additionally, we sought to evaluate whether race/ethnicity was an independent predictor of advanced systemic therapy use.

MATERIALS AND METHODS

This cohort study assessed treatment patterns within the TARGET-DERM AD registry and compared enrollment characteristics across established racial and ethnic categories. The registry comprises an ongoing, IRB-approved, multi-center, observational cohort of patients diagnosed with AD

(NCT03661866).⁶ Upon enrollment, patients consent to grant access to up to three years of their prior electronic health records (EHRs) and have the option to consent to completing patient-reported outcomes and providing biosamples. Health care providers document clinician-reported outcomes both at the time of enrollment and during subsequent visits.

Patients, Groupings, and Subsets

TARGET-DERM AD was launched on January 19th, 2019, and patients who were at least 6 years of age and enrolled through August 22nd, 2022, were eligible for inclusion in this analysis. Participants were categorized into one of the following racial/ethnic groups: Hispanic, Non-Hispanic (NH)-American Indian or Alaskan Native (NH-AIAN), NH-Asian/Pacific Islander (NH-API), NH-Black, NH-White, or some other race (SOR), based on the same classification system used by the US census.⁷ The primary source was the patient's medical record; if this information was unavailable, data from a supplemental questionnaire were used.

Measures and Variables

Site staff and physicians recorded demographic characteristics, disease severity and impact, comorbidities, and treatment type at registry enrollment.

Disease severity was assessed using validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD), total body surface area (BSA), and vIGA-AD x BSA (VxB), Patient Oriented Eczema Measure (POEM), and Patient-Oriented SCORing of Atopic Dermatitis (PO-SCORAD). Additional patient-reported outcome measures included: Children's Dermatology Life Quality Index (cdLQI), Dermatology Life Quality Index (DLQI), Numeric Rating Scale – Pain (NRS-Pain), Numeric Rating Scale – Sleep (NRS-Sleep), Patient Reported Outcome Measurement Information System (PROMIS) ItchMood and Sleep [adult], PROMIS Itch Questionnaire Child (PIQ-C), PROMIS Depression, PROMIS Pediatric Depressive Symptoms, PROMIS Anxiety, and Work Productivity and Activity Impairment (WPAI) questionnaire. Comorbidity data were collected from both the EHR and the supplemental patient questionnaire. Natural language processing was used to identify historical comorbid diagnoses from the EHR. PRO-consenting patients completed a supplemental questionnaire which asked if a patient has a prior diagnosis of comorbidities (attention-deficit or attention-deficit hyperactivity disorder, ADD/ADHD, Asthma, Anxiety, Cancer, Conjunctivitis, Depression, Diabetes, Hay Fever, High cholesterol, Hypertension, Obesity, Skin infections, Rheumatoid arthritis, Urticaria).

Medications

A comprehensive review of all AD-related medications recorded in the historical patient records over the past three years, up to and including the registry enrollment date (April 22, 2022), was conducted (Table 4). The records were assessed for prior use of topical calcineurin inhibitors (pimecrolimus

and tacrolimus), topical corticosteroids (alclometasone, betamethasone, clobetasol, desonide, desoximetasone, fluocinolone, fluocinonide, flurandrenolide, fluticasone, halobetasol, mometasone, and triamcinolone), and topical phosphodiesterase-4 inhibitors (crisaborole). Systemic treatments were defined as those administered orally, via subcutaneous injection, intravenously, or by phototherapy. Specifically, conventional systemic immunosuppressive therapies included methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, and/or phototherapy. Oral phosphodiesterase-4 inhibitors were apremilast and roflumilast. For this study, the advanced systemic therapy (AST) specifically considered was dupilumab. The choice to focus solely on dupilumab as the advanced therapy is due to its approval in 2017. Other ASTs, such as tralokinumab, upadacitinib, and abrocitinib, received FDA approval in close proximity to the analysis cutoff date (in December 2021 and January 2022, respectively) and consequently had limited utilization data available within the timeframe of this study.

Statistical Analysis

Demographic characteristics, disease severity and impact at enrollment, comorbidities at enrollment, and types of AD treatment were compared across racial and ethnic groups. For continuous variables, mean and median averages, standard deviation, range counts, minimum and maximum values, along with interquartile ranges were calculated. The Kruskal-Wallis test was used to compare groups. For categorical variables, frequencies and their corresponding percentages were calculated, and the Chi-square test or Fisher's Exact test were used to compare groups. The threshold of statistical significance was set at P -values < 0.05 .

Ordinal logistic regression models were utilized to assess the association between racial/ethnic group (NH-Black, NH-API, Hispanic, and NH-White as reference) and advanced systemic therapy use at or prior to baseline, adjusting for participant characteristics by racial and ethnicity group (age, sex, geographic location, site type, insurance status; Table 1) and AD severity at baseline (vIGA-AD, BSA, and VxB; Table 2). Comorbidity data collected by questionnaire were considered in the analysis and included asthma, anxiety, depression, hypertension, infections, cancer, conjunctivitis, ADHD, hay fever, obesity, diabetes, high cholesterol, RA, and urticaria.

Rotated principal factor analysis addressed multicollinearity between vIGA-AD and BSA. Data management, descriptive statistics, and modeling were performed using SAS 9.4 (SAS Institute, Cary, NC), while R-Studio v. 1.4.1106 (2009-2021 RStudio, PBC) was used to create forest plots.

RESULTS

This cohort included 2,028 AD participants aged 6 years or older who were enrolled in the TARGET-DERM AD registry as of

TABLE 1.

Participant Characteristics by Racial/Ethnic Group							
Summary	NH-White (N=1118)	NH-Black (N=251)	NH-Asian or Pacific Islander (N=271)	Hispanic (N=288)	All (N=1928)	P-value	American Indian or Alaska Native (N=12)
Age							
Mean (SD)	39 (22)	31 (20)	29 (16)	24 (18)	34 (21)	<.0001	24 (14)
Median (n)	36 (1118)	25 (251)	25 (271)	17 (288)	29 (1928)		25 (12)
Q1 - Q3 (IQR)	19-59 (40)	12-47 (35)	16-39 (23)	11-32 (21)	16-53 (37)		14-28 (15)
Age Category, n (%)							
N	1118	251	271	288	1928	<.0001	12
Children ¹	253 (22.6%)	100 (39.8%)	75 (27.7%)	149(51.7%)	577 (29.9%)		5 (41.7%)
Adult ²	865 (77.4%)	151 (60.2%)	196 (72.3%)	139 (48.3%)	1351 (70.1%)		7 (58.3%)
Sex, n (%)							
n	1112	250	268	286	1916	0.0723	12
Female	637 (57.3%)	162 (64.8%)	146 (54.5%)	173 (60.5%)	1118 (58.4%)		5 (41.7%)
Male	475 (42.7%)	88 (35.2%)	122 (45.5%)	13 (39.5%)	798 (41.6%)		7 (58.3%)
Not Available	6 (1.0%)	1 (0.0%)	3 (1.0%)	2 (1.0%)	12 (1.0%)		0 (0.0%)
US Region, n (%)							
n	1109	249	267	288	1913	<.0001	12
Midwest	268 (24.2%)	45 (18.1%)	40 (15.0%)	118 (41.0%)	471 (24.6%)		2 (16.7%)
Northeast	535 (48.2%)	100 (40.2%)	139 (52.1%)	81 (28.1%)	855 (44.7%)		6 (50.0%)
Southeast	108 (9.7%)	83 (33.3%)	3 (1.1%)	25 (8.7%)	219 (11.4%)		1 (8.3%)
Southwest	110 (9.9%)	7 (2.8%)	6 (2.2%)	12 (4.2%)	135 (7.1%)		0 (0.0%)
West	88 (7.9%)	14 (5.6%)	79 (29.6%)	52 (18.1%)	233 (12.2%)		3 (25.0%)
Site Type, n (%)							
n	1118	251	271	288	1928	<.0001	12
Academic	429 (38.4%)	150 (59.8%)	80 (29.5%)	112 (38.9%)	771 (40.0%)		4 (33.3%)
Community	689 (61.6%)	101 (40.2%)	191 (70.5%)	176 (61.1%)	1157 (60.0%)		8 (66.7%)
Insurance, n (%)							
Medicaid	73 (6.5%)	68 (27.1%)	26 (9.6%)	133 (46.2%)	300 (15.6%)	<.0001	5 (41.7%)
Medicare	114 (10.2%)	16 (6.4%)	5 (1.8%)	11 (3.8%)	146 (7.6%)		0 (0.0%)
Other ³	24 (2.1%)	13 (5.2%)	2 (0.7%)	18 (6.3%)	57 (3.0%)		1 (8.3%)
Private	778 (69.6%)	108 (43.0%)	222 (81.9%)	102 (35.4%)	1210 (62.8%)		5 (41.7%)
Uninsured ⁴	129 (11.5%)	46 (18.3%)	16 (5.9%)	24 (8.3%)	215 (11.2%)		1 (8.3%)

¹Age (6-17) are considered as children

²Age (18+) are considered as adults

³The private insurance category includes participants with private commercial insurance and those with “other” insurance. The majority of these patients have Tricare (a military and veteran insurance.)

⁴The uninsured insurance category includes participants with unknown insurance.

TABLE 2.

Atopic Dermatitis Severity at Enrollment by Racial/Ethnic Group							
Summary	NH-White (N=1118)	NH-Black (N=251)	NH-Asian or Pacific Islander (N=271)	Hispanic (N=288)	All (N=1928)	P-value	American Indian or Alaska Native (N=12)
vIGA-AD at enrollment, n (%)							
n	1107	248	270	286	1911		12
Clear	110 (9.9%)	16 (6.5%)	11 (4.1%)	19 (6.6%)	156 (8.2%)	<.0001	0 (0.0%)
Almost clear	177 (16.0%)	23 (9.3%)	18 (6.7%)	43 (15.0%)	261 (13.7%)		1 (8.3%)
Mild	292 (26.4%)	57 (23.0%)	72 (26.7%)	83 (29.0%)	504 (26.4%)		3 (25.0%)
Moderate	402 (36.3%)	101 (40.7%)	117 (43.3%)	106 (37.1%)	726 (38.0%)		8 (66.7%)
Severe	126 (11.4%)	51 (20.6%)	52 (19.3%)	35 (12.2%)	264 (13.8%)		0 (0.0%)
BSA							
Mean (SD)	13 (19)	21 (24)	16 (21)	16 (22)	15 (21)		19 (17)
Median (n)	5 (1028)	12 (231)	7 (232)	6 (265)	5 (1756)	<.0001	18 (10)
Q1 - Q3 (IQR)	2 - 16 (14)	3 - 30 (27)	3 - 20 (17)	3 - 20 (17)	2 - 20 (18)		5 - 22 (17)
BSA sensitivity analysis, n (%)							
n	1028	231	232	265	1756		10
<=10%	672 (65.4%)	115 (49.8%)	144 (62.1%)	165 (62.3%)	1096 (62.4%)	0.0002	3 (30.0%)
>10%	356 (34.6%)	116 (50.2%)	88 (37.9%)	100 (37.7%)	660 (37.6%)		7 (70.0%)
POEM Category, n (%)							
n	798	149	171	172	1290		6
Clear or almost clear	145 (18.2%)	22 (14.8%)	28 (16.4%)	27 (15.7%)	222 (17.2%)	0.9423	0 (0.0%)
Mild	181 (22.7%)	35 (23.5%)	47 (27.5%)	41 (23.8%)	304 (23.6%)		0 (0.0%)
Moderate	299 (37.5%)	60 (40.3%)	62 (36.3%)	66 (38.4%)	487 (37.8%)		4 (66.7%)
Severe	134 (16.8%)	25 (16.8%)	28 (16.4%)	26 (15.1%)	213 (16.5%)		2 (33.3%)
Very severe	39 (4.9%)	7 (4.7%)	6 (3.5%)	12 (7.0%)	64 (5.0%)		0 (0.0%)
Total PO-SCORAD Score							
Mean (SD)	34 (20)	37 (21)	34 (18)	35 (21)	34 (20)		45 (22)
Median (n)	31 (752)	33 (137)	31 (162)	33 (152)	31 (1203)	0.4217	48 (6)
Q1 - Q3 (IQR)	19 - 46 (27)	21 - 48 (27)	20 - 45 (25)	17 - 48 (31)	19 - 46 (27)		24 - 67 (43)
Children's DLQI ¹							
n	175	61	44	84	364		2
No effect at all	51 (29.1%)	23 (37.7%)	10 (22.7%)	16 (19.0%)	100 (27.5%)	0.4334	1 (50.0%)
Small effect	57 (32.6%)	20 (32.8%)	11 (25.0%)	26 (31.0%)	114 (31.3%)		0 (0.0%)
Moderate effect	36 (20.6%)	9 (14.8%)	12 (27.3%)	23 (27.4%)	80 (22.0%)		0 (0.0%)
Very large effect	28 (16.0%)	7 (11.5%)	9 (20.5%)	16 (19.0%)	60 (16.5%)		1 (50.0%)
Extremely large effect	3 (1.7%)	2 (3.3%)	2 (4.5%)	3 (3.6%)	10 (2.7%)		0 (0.0%)
DLQI ²							
n	578	82	123	81	864		3
No effect at all	138 (23.9%)	15 (18.3%)	26 (21.1%)	20 (24.7%)	199 (23.0%)	0.2767	0 (0.0%)
Small effect	190 (32.9%)	26 (31.7%)	32 (26.0%)	19 (23.5%)	267 (30.9%)		1 (33.3%)
Moderate effect	138 (23.9%)	16 (19.5%)	30 (24.4%)	20 (24.7%)	204 (23.6%)		0 (0.0%)
Very large effect	87 (15.1%)	18 (22.0%)	28 (22.8%)	15 (18.5%)	148 (17.1%)		2 (66.7%)
Extremely large effect	25 (4.3%)	7 (8.5%)	7 (5.7%)	7 (8.6%)	46 (5.3%)		0 (0.0%)

¹CDLQI scoring: no effect at all (0-1 points), small effect (2-6 points), moderate effect (7-12 points), very large effect (13-18), extremely large effect (19-30 points)

²DLQI scoring: no effect at all (0-1 points), small effect (2-5 points), moderate effect (6-10 points), very large effect (11-20), extremely large effect (21-30 points)

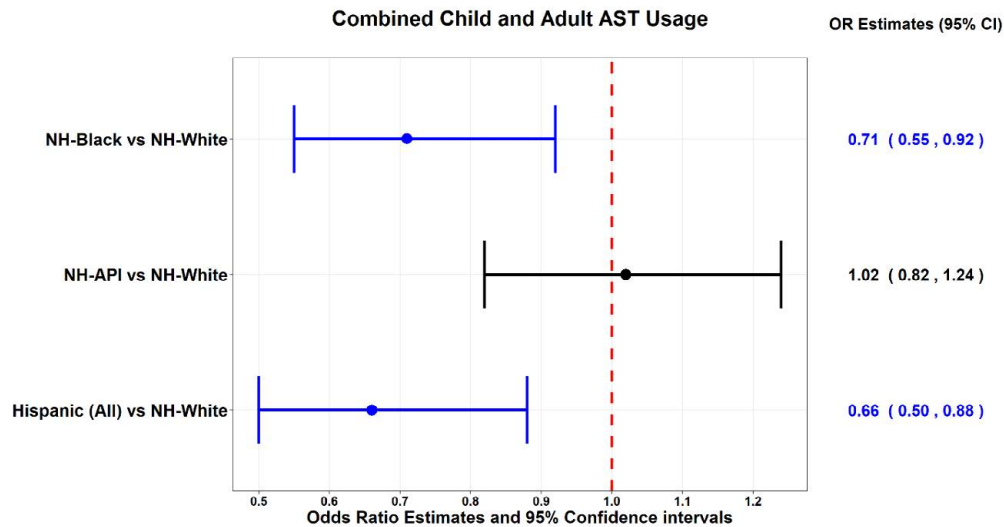
TABLE 3.

Comorbidities by Racial/Ethnic Group							
Summary	Race				All (N=1928)	P-value	American Indian or Alaska Native (N=12)
	NH-White (N=1118)	NH-Black (N=251)	NH-Asian or Pacific Islander (N=271)	Hispanic (N=288)			
Mean (SD)	2.33 (1.95)	2.12 (1.85)	1.53 (1.54)	1.51 (1.67)	2.07 (1.88)		1.42 (1.93)
Median (n)	2.00 (1118)	2.00 (251)	1.00 (271)	1.00 (288)	2.00 (1928)	<.0001	1.00 (12)
Q1 - Q3 (IQR)	1.00 - 4.00 (3.00)	1.00 - 3.00 (2.00)	0.00 - 2.00 (2.00)	0.00 - 2.00 (2.00)	1.00 - 3.00 (2.00)		0.50 - 1.00 (0.50)
Comorbidities, n (%)							
ADD/ADHD	4 (0.4%)	1 (0.4%)	2 (0.7%)	2 (0.7%)	9 (0.5%)	0.7865	0 (0.0%)
Asthma	558 (49.9%)	151 (60.2%)	152 (56.1%)	113 (39.2%)	974 (50.5%)	<.0001	6 (50.0%)
Anxiety	196 (17.5%)	20 (8.0%)	13 (4.8%)	15 (5.2%)	244 (12.7%)	<.0001	0 (0.0%)
Cancer	109 (9.7%)	19 (7.6%)	13 (4.8%)	11 (3.8%)	152 (7.9%)	0.0014	1 (8.3%)
Conjunctivitis	235 (21.0%)	41 (16.3%)	45 (16.6%)	49 (17.0%)	370 (19.2%)	0.1230	2 (16.7%)
Depression	199 (17.8%)	25 (10.0%)	15 (5.5%)	18 (6.3%)	257 (13.3%)	<.0001	1 (8.3%)
Diabetes	56 (5.0%)	17 (6.8%)	12 (4.4%)	15 (5.2%)	100 (5.2%)	0.6430	0 (0.0%)
Hay Fever	288 (25.8%)	59 (23.5%)	39 (14.4%)	59 (20.5%)	445 (23.1%)	0.0007	2 (16.7%)
Hypercholesterolemia	83 (7.4%)	10 (4.0%)	11 (4.1%)	8 (2.8%)	112 (5.8%)	0.0042	0 (0.0%)
Hypertension	204 (18.2%)	35 (13.9%)	25 (9.2%)	23 (8.0%)	287 (14.9%)	<.0001	0 (0.0%)
Obesity	62 (5.5%)	16 (6.4%)	8 (3.0%)	7 (2.4%)	93 (4.8%)	0.0413	0 (0.0%)
Skin Infections	315 (28.2%)	72 (28.7%)	45 (16.6%)	74 (25.7%)	506 (26.2%)	0.0011	3 (25.0%)
Rheumatoid Arthritis	40 (3.6%)	6 (2.4%)	2 (0.7%)	5 (1.7%)	53 (2.7%)	0.0422	0 (0.0%)
Urticaria	259 (23.2%)	61 (24.3%)	32 (11.8%)	37 (12.8%)	389 (20.2%)	<.0001	2 (16.7%)

TABLE 4.

Atopic Dermatitis-Related Treatment Use by Racial/Ethnic Group (up to April 22, 2022)							
Summary	Race				All (N=1928)	P-value	American Indian or Alaska Native (N=12)
	NH-White (N=1118)	NH-Black (N=251)	NH-Asian or Pacific Islander (N=271)	Hispanic (N=288)			
Conventional Systemic Therapies, n (%)							
Any	240 (21.5%)	54 (21.5%)	58 (21.4%)	57 (19.8%)	409 (21.2%)	0.9381	6 (50.0%)
Methotrexate	49 (4.4%)	9 (3.6%)	7 (2.6%)	7 (2.4%)	72 (3.7%)	0.2979	1 (8.3%)
Cyclosporine	31 (2.8%)	6 (2.4%)	8 (3.0%)	10 (3.5%)	55 (2.9%)	0.8901	0 (0.0%)
Mycophenolate mofetil	7 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.4%)	0.1655	0 (0.0%)
Azathioprine	3 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	4 (0.2%)	0.6694	0 (0.0%)
Systemic corticosteroids	168 (15.0%)	41 (16.3%)	46 (17.0%)	45 (15.6%)	300 (15.6%)	0.8567	3 (25.0%)
Phototherapy	30 (2.7%)	3 (1.2%)	4 (1.5%)	6 (2.1%)	43 (2.2%)	0.3886	3 (25.0%)
Advanced Systemic Therapies, n (%)							
Dupilumab	311 (27.8%)	49 (19.5%)	68 (25.1%)	48 (16.7%)	476 (24.7%)	0.0002	2 (16.7%)
Topical Therapies, n (%)							
Topical calcineurin inhibitors, topical corticosteroids, and/ or topical phosphodiesterase inhibitors	558 (49.9%)	114 (45.4%)	122 (45.0%)	137 (47.6%)	931 (48.3%)	0.3583	8 (66.7%)

FIGURE 1. Adjusted odds ratios of a participants’ likelihood of being treated with advanced systemic therapy (AST).



April 22, 2022. Of these, 88 participants (4%) were excluded due to missing race-ethnicity information. Among the remaining 1,940 participants, 40% were from academic sites, all affiliated with major tertiary care centers (Table 1). The community sites involved were all secondary care centers, such as dermatology or allergy referral sites.

Most participants identified as Non-Hispanic (NH) White (58%), followed by Hispanic (15%), NH-Asian/Pacific Islander (NH-API, 14%), NH-Black (13%), and Alaskan or American Indian (AIAN, less than 1%). Due to the small sample size (N=12) for AIAN participants, analysis was limited to descriptive statistics as it was insufficient for statistical inference.

The final dataset included 577 children aged 6-17 years (30%) and 1,351 adults aged 18 and above (70%). While most participants were from the United States, 82 were from Canada (4.3%, representing 3 sites).

Descriptive Statistics

Across all race-ethnicity categories, most patients were female, and the median age was 29 years (Table 1). NH-API and NH-White individuals had the greatest proportions of private insurance (82% and 70%, respectively), and were most likely to be enrolled in community practices (71% and 62%, respectively), as compared to the other racial/ethnic groups.

At enrollment, NH-API and NH-Black participants had the highest proportion of moderate-to-severe disease as assessed by clinicians (vIGA-AD, 63% and 61%, respectively). NH-Black participants had the highest median total BSA score of 12 (Table 2). There were no differences across racial/ethnic categories among the patient-reported outcomes of severity and impact (POEM, PO-SCORAD, DLQI, NRS-Pain, NRS-Sleep, PROMIS-Itch mood and sleep, PROMIS-Itch Scratching Behavior, PROMIS Depression, PROMIS Anxiety, and WPAl.

Regarding comorbidities, NH-White participants demonstrated the highest prevalence in 8 comorbidities: Anxiety, cancer, conjunctivitis, depression, hay fever, hypercholesterolemia, hypertension, and rheumatoid arthritis (Table 3). Over 51% of all patients had comorbid asthma, with the highest proportion among NH-Black participants (60%). No significant differences were found in the prevalence of ADHD/ADD, conjunctivitis, or diabetes. NH-White patients reported the highest proportion of cancer cases (9.7%, $P<0.05$).

Utilization of conventional topical and systemic treatments was similar across all racial and ethnic groups (Table 4). While the use of advanced topical therapies was also comparable, advanced systemic therapy (AST) usage varied by racial/ethnic group (Table 4): Hispanic subjects had the lowest proportion of dupilumab utilization at 17%, followed by NH-Black at 19%, NH-API at 25.1%, and NH-White at 25% ($P<0.001$).

The final list of comorbidities with meaningful associations, identified via backward selection, included anxiety, depression, cancer, and obesity. After adjusting for sex, age, region, treatment site type, insurance category, comorbidities (anxiety, depression, cancer, and obesity), and disease severity (vIGA and BSA), NH-Black and Hispanic patients were less likely than NH-White subjects to be treated with ASTs, with odds ratios of 0.71 and 0.66, CIs 0.55-0.92 and 0.55-0.88, respectively (Figure 1). Additionally, differences were also observed within insurance type: private insurance was associated with a greater likelihood of AST treatment, with private insurance participants having 71% greater odds of receiving AST treatment relative to uninsured participants ($P=0.036$).

DISCUSSION

Our study underscores the racial and ethnic differences in the burden and treatment of AD among a large and diverse cohort of children and adults treated at US community and academic

centers. After adjusting for confounding factors, NH-White participants were significantly more likely to receive advanced systemic therapies than NH-Black and Hispanic participants. Socioeconomic factors likely influence access to advanced treatments; this aligns with previous studies demonstrating a racial and ethnic disparity in accessing newly approved and standard-of-care medical therapies in dermatology.⁸ Our findings may underestimate racial and ethnic differences in disease severity because many clinician-assessed severity ratings rely on clinical signs (eg, erythema, xerosis, pruritus, and lichenification), some of which may be more challenging to assess in darker skin and therefore may result in underestimation of AD severity in patients with darker skin tone.⁹

While the TARGET-DERM AD cohort is diverse, it was not designed to be a representative US sample, and selection bias may be present. The largest proportion of TARGET-DERM AD sites are located in the Northeast (50.0%), followed by the West (25.0%) and the Midwest (16.7%). A common bias in real-world cross-sectional registry studies is that key patient subgroups might choose not to participate. Since January 1st, 2021, TARGET-DERM AD enrollment has focused on patients with either moderate-to-severe AD or having been exposed to at least one advanced systemic therapy, likely resulting in an elevated proportion of patients receiving systemic therapy compared to the general population. Furthermore, we did not evaluate the temporal relationship between disease severity and advanced systemic therapy; prospective data will help clarify this issue. Despite adjusting for insurance status in our models, residual confounding may exist, as newer advanced therapies may vary across insurance plans.

In conclusion, the cohort study offers valuable real-world data on underrepresented racial and ethnic groups often overlooked in clinical trials. Despite all participants having moderate-to-severe disease severity, NH-Black and Hispanic subjects were less likely to receive advanced systemic therapy than NH-White patients. The lower use of advanced systemic therapies in NH-Black and Hispanic patients, despite similarities in comorbidity burden, disease severity, and quality of life, indicates other social and environmental factors that may contribute to this disparity, warranting further investigation. Addressing these factors will be essential in improving outcomes for all patients with AD.

DISCLOSURES

KA is a consulting member for Target RWE and reports consulting/advising fees from Amgen, Apogee, Astria, Incyte Derm, Medidata, Nektar Therapeutics, and Sanofi; and research funding from Pfizer and Cosmestique International SNC to her University. LWL has received research funding from AbbVie, Amgen, Amryt Pharma, among others, and honoraria or fees from several companies, including Amryt Pharma, and Novartis. AG, BMC, RG, and CO are full-time employees of AbbVie Inc.

and may hold its stock and/or stock options. AGM and BS have no conflicts of interest or financial relations to disclose. JC is a speaker for companies such as AbbVie, Amgen, and Regeneron. KDK, BM, JMC, and ADP are employees of TARGET RWE and may hold stock and/or stock options. JS has received honoraria as a consultant and/or advisory board member for numerous companies, including AbbVie, Alamar, Aldena, Amgen, AOBiome, Arcutis, Arena, Asana, BiomX, Biosion, Bodewell, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Dermavant, Dermira, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Menlo, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sanofi-Genzyme, Shaperon, Union, and UpToDate. He is a speaker for AbbVie, Eli Lilly, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme, and his institution has received grants from Galderma, Incyte, and Pfizer.

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Combined Use of Relabotulinum Toxin A and NASHA Gel Skinbooster for Rejuvenation of the Upper Third of the Face

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ABSTRACT

Background: Aging of the upper third of the face is characterized by dynamic forehead wrinkles and volume loss in the temporal region, resulting in a fatigued and aged appearance. Addressing both muscle hyperactivity and soft tissue atrophy is essential for effective rejuvenation.

Objective: To evaluate a combined injectable treatment protocol using Relabotulinum Toxin A for frontalis muscle modulation and NASHA™-based gel skinbooster for temporal skin quality enhancement.

Methods: Patients received intramuscular injections of Relabotulinum Toxin A targeting the frontalis muscle, followed by three monthly sessions of NASHA gel skinbooster injected subcutaneously into the temporal region using a blunt cannula technique. Dosages and injection points were individualized based on detailed anatomical and functional assessments.

Results: Preliminary clinical evaluations indicate that the protocol is minimally invasive and well-tolerated, producing progressive aesthetic improvements lasting beyond six months. Patients reported enhanced skin tone, elasticity, hydration, and a natural-looking lift of the eyebrow tail. Improvements in psychological well-being and patient satisfaction were also observed.

Conclusion: This combined neuromodulation and skin quality improvement approach provides a comprehensive and synergistic strategy for upper facial rejuvenation. The ready-to-use liquid formulation of Relabotulinum Toxin A allows for precise application, rapid onset of results within 24–48 hours, and sustained improvement of forehead dynamic wrinkles for up to six months. The collagen-stimulating properties of NASHA gel deliver natural, long-lasting enhancement of the temporal region, contributing to high levels of patient satisfaction.

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INTRODUCTION

Rejuvenation of the upper third of the face is integral to achieving comprehensive facial aesthetic restoration. Prominent age-related changes in this region include dynamic rhytides secondary to repetitive frontalis muscle activity, as well as progressive soft tissue atrophy and volume depletion in the temporal fossa. These anatomical alterations contribute to the characteristic skeletonization of the temples and deepening of horizontal forehead lines, resulting in a fatigued and senescent appearance. Addressing these anatomical changes is critical for restoring a youthful and balanced upper facial contour.

Targeted relaxation of facial expression muscles with botulinum toxin A remains a first-line treatment for reducing the appearance of dynamic rhytides in the upper face. By limiting repetitive muscle movement, it smooths the forehead and produces a more relaxed, youthful expression.

Skin degeneration in the temple region results from a combination of photoaging and chronological aging. It is characterized by sagging, loss of tone and elasticity, increased roughness, reduced hydration, and diminished radiance. Additionally, subcutaneous fat loss in this region contributes to temporal hollowing and lowering of the lateral eyebrow tail.

The use of NASHA™ gel (20 mg/mL), a non-animal stabilized hyaluronic acid-based gel, as a skin booster offers an effective strategy for improving these signs of aging by enhancing skin quality, restoring tone and elasticity, delivering deep hydration, and imparting a natural radiance.¹⁻³ Importantly, NASHA gel has been shown histologically to induce neocollagenesis, stimulating long-term biosynthesis of new collagen and improving dermal structure.² The rheological properties of NASHA gel allow for correction of temporal hollowing, improving contour and skin quality, such as softness and plumpness, without creating excessive fullness, contour irregularities, or nodularity.

A treatment protocol combining these two approaches, neuromodulation with botulinum toxin A and skin quality enhancement with NASHA gel skinbooster, provides a harmonized strategy for upper facial rejuvenation. By targeting both muscle activity and soft tissue quality, this dual-modality approach addresses the primary anatomical and functional contributors to upper face aging.

Anatomy

The frontalis muscle is the only true elevator of the upper third of the face. Anatomically, it originates from the galea aponeurotica and inserts into the dermis of the eyebrows. Its fibers begin deep at the level of the scalp and progressively become more superficial as they descend, terminating within the dermal layers of the supraorbital region.

Although it is the sole muscle of the forehead, the frontalis exhibits interconnections with adjacent muscles: medially, it interdigitates with the corrugator supercilii at the middle third of the eyebrow; laterally, it interfaces with both the orbicularis oculi and the superficial lateral fibers of the corrugator. It is anatomically positioned superficial to the corrugator and deep to the orbicularis oculi in the upper periorbital region.

Dynamic anatomical evaluation reveals that the frontalis functions in an accordion fashion. The upper portion of the muscle exerts a downward pull on the hairline, while the lower fibers elevate the eyebrows. Structurally, the superior segment of the frontalis remains deep—originating at the galea—and begins to superficialize as it descends toward the midline, particularly along the anatomical landmark known as the Cotofana C-line. The lower portion of the muscle lies in a more superficial plane as it approaches its dermal insertion, facilitating its role in eyebrow elevation.

At the midline, there is a convergence of muscle fibers from the two functional subdivisions of the frontalis muscle, which move in opposing directions. The superior portion, when contracted, exerts a downward pull on the scalp and hairline. In contrast, the inferior portion, through its superficial insertion into the dermis above the eyebrows, contracts to elevate the

brows. This functional duality highlights the importance of understanding the layered anatomy of the frontalis for precise aesthetic intervention.

The temporal fossa is anatomically bounded by distinct landmarks: the superior temporal line anteriorly and superiorly, the frontal process of the zygomatic bone antero-inferiorly, and the zygomatic arch inferiorly. At the level of the superior temporal line, the temple transitions into the forehead, while inferiorly, at the zygomatic arch, it blends into the midface. The temporal hairline follows a variable, oblique course across this region, contributing to its aesthetic complexity.

From superficial to deep, the anatomical layers of the temporal fossa include: the skin, subcutaneous tissue, superficial temporal fascia, deep temporal fascia, and the temporalis muscle beneath. This multilayered anatomy must be carefully considered in aesthetic procedures to ensure safe and effective filler placement while minimizing the risk of vascular or structural complications.⁵

MATERIALS AND METHODS

The protocol utilizes Relabotulinum Toxin A (Relfydess™, 100 units/mL; Ipsen Pharma) to modulate frontalis muscle activity, followed by the application of a non-animal stabilized hyaluronic acid (NASHA) gel (Restylane® Skinboosters™ Vital Lidocaine, 20 mg/mL; Q-Med AB/Galderma, Uppsala, Sweden) to reduce temporal hollow and improve skin quality in the temporal.

Subjects Eligibility

Ten healthy female patients, aged 42 to 57 years, presenting with forehead hypertonicity and mild temporal hollowing, were selected to undergo treatment with this combined approach. Inclusion criteria comprised mild to severe horizontal forehead lines graded on the FAS 4-point scale for dynamic wrinkles (ref. Nikolis A et al, Clinical, Cosmetic and Investigational Dermatology, 2024) and a temporal hollow score of 1 on the Galderma Temple Volume Deficit Scale (GTVDS), as assessed by the treating physician at baseline.^{5,6}

Since NASHA™ Skinbooster works to improve and restore skin quality and provides only a plumping effect, patients with moderate to severe temporal hollowing who might require volumizing fillers were excluded from the protocol. Additionally, patients were required to have no prior cosmetic treatments in the temporal area. Medical histories and concomitant medications that could interfere with the study protocol were negative. All patients provided signed, dated informed consent. Assessments were conducted at baseline (T0), after 2 and 7 days (T1 and T2), and at 3 and 6 months (T3 and T4). Evaluations included clinical grading of forehead wrinkle severity, skin quality, temple hollowness, and digital photography (Nikon D5300 DSLR, 18-140 mm lens).

The FAS Facial Assessment Scale, based on a 4-point grading system (0 = none; 1 = mild; 2 = moderate; 3 = severe), was used to grade static and dynamic wrinkles and temple skin quality. The GTVDS rated the severity of temporal hollowing from none (0) to severe (3).

Temple treatment was limited to patients with mild hollowing (score 1), as graded on the Galderma Temple Volume Deficit Scale (range: 0 = none to 3 = severe). Patients with moderate (score 2) or severe (score 3) temporal hollowing were excluded, as these cases typically require volumizing fillers for adequate correction. NASHA Skinbooster is intended primarily to improve skin quality and provide a subtle plumping effect, rather than to restore significant volume.

TREATMENT AND PROCEDURE

The treatment begins with the administration of Relabotulinum Toxin A in the upper face, delivered intramuscularly.

Successful outcomes require a thorough pre-treatment clinical evaluation, both at rest (static) and during facial expression (dynamic). This assessment helps identify individual patterns of muscle contraction and guides precise and personalized treatment planning. In addition to clinical evaluation, a detailed understanding of the static and functional anatomy of each muscle is essential. Knowledge of underlying soft tissue and skeletal structures, from superficial to deep planes, is critical to accurately place injection point to avoid anatomically high-risk zones. Because facial anatomy and muscle activity vary significantly among individuals, dynamic examination – such as asking the patient to smile, frown, to assume an angry expression, raise the eyebrows (like surprised face) - should be performed from both frontal and lateral views. The personalized approach ensures effective, natural-looking, and safe outcomes when using botulinum toxin for upper facial rejuvenation. The primary muscles targeted in this region include the corrugator supercilii, procerus, orbicularis oculi, and frontalis. Dosage is individualized based on each patient's muscle anatomy and functional characteristics to effectively modulate frontalis muscle activity and reduce dynamic wrinkles.

Treatment of the Frontalis Muscle

Based on the anatomical and functional considerations outlined above, the therapeutic strategy for treating frontalis muscle hypertonicity and horizontal forehead wrinkles with botulinum toxin must be carefully tailored. Injection sites should correspond to the distinct upper and lower functional of the frontalis muscle.

Injections targeting the upper portion of the frontalis muscle should be administered deeply and intramuscularly, typically at a higher dosage to counteract the muscle's downward pull on the scalp and hairline. This deeper placement and increased dosing address the muscle's role in lowering the hairline.

Relabotulinum Toxin A is a ready-to-use solution formulated using PEARL™ Technology. It is designed to preserve the potency and native conformation of the core toxin molecule.⁷⁻⁸ This process maintains the structure and activity of the light chain keeping the toxin in a liquid state and natural conformation without requiring stabilization in a powder form.

Based on these properties, the therapeutic approach targets the frontalis muscle with botulinum toxin to correct hypertonicity and reduce horizontal forehead wrinkles.

The number of injection points in the upper frontalis region generally ranges from three to four per side arranged in an alternating pattern to avoid creating horizontal bands of muscle relaxation that could lead to undesirable eyebrow ptosis or asymmetry. Dosage for this area is typically 4-5 units (0.04-0.05 mL) per injection point

Conversely, injections in the lower frontalis muscle should be delivered more superficially—either subcutaneously or intradermally—and at a reduced dosage. This approach preserves and supports the muscle's lifting action on the eyebrows. The number of injection points in the lower region varies from two to three per side, arranged in either a horizontal or alternating line. Dosage for this area is typically 2 units (0.02 mL) per injection point.

The total amount of Relabotulinum Toxin A used for forehead rejuvenation generally ranges between 32 and 52 units (0.32–0.52 mL). Dosage is individualized based on each patient's muscle anatomy and functional characteristics to effectively modulate frontalis muscle activity and reduce dynamic wrinkles.

Treatment of the Temple

After completing treatment with botulinum toxin, temple rejuvenation can be performed using a NASHA gel skinbooster, with the objective of reducing temporal hollowing, enhancing skin quality, and improving tissue hydration.

Injections were administered using a 25-gauge x 50-mm blunt-tip, ultra-thin-wall, flexible nanocannula (Feel Tech Co, Seoul, South Korea). The entry point for cannula insertion was created using a 21-gauge needle and positioned near the temporal hairline at the superior temporal line, where the temple transitions to the forehead.

The NASHA Skinbooster is equipped with an on/off smart-click system to control gel delivery. When injected with a cannula, the system is turned off, allowing the injector to manually control the volume administered. Injections were performed in a linear pattern, extending from the entry point toward the temple and the tail of the eyebrow.

The injected volume was 0.5 mL per side. Following treatment, no visible or palpable lumps were observed. Minor bruising may occur but typically resolves within a few days. Patients were advised to avoid sun exposure for approximately 1 week following the procedure.

The treatment was repeated monthly for up to 3 sessions. Aesthetic improvements were observed progressively. Long-lasting results were noted over time, with maintenance sessions recommended every 6 months.

Treatment Schedule

The final treatment protocol is scheduled as follows: the initial session involves administration of Relabotulinum Toxin A to the forehead. Fifteen days later, the first NASHA™ gel Skinbooster session is performed, injecting 0.5 mL per side. Subsequent NASHA™ gel sessions are conducted monthly, with the second and third treatments each involving 0.5 mL per side, completing a total of three Skinbooster sessions.

Clinical Outcomes

Representative outcomes are illustrated in two patients. Patient 1 (Figure 1A–G) received 40 units of Relabotulinum Toxin A to the frontalis and demonstrated visible smoothing of forehead lines with preserved natural expression at 7 days.

Patient 2 (Figure 2A–D) received 40 units of Relabotulinum Toxin A to the frontalis followed by three monthly sessions of NASHA™ gel skinbooster (0.5 mL per side), with progressive reduction of forehead lines, restoration of temporal contour, and improved skin quality through 6 months.

RESULTS

Treatment of the temporal area with NASHA™ Skinbooster progressively improved skin firmness, elasticity, and hydration across all 10 patients, resulting in a subtle plumping effect that reduced the appearance of hollowing and contributed to a visible lift of the lateral eyebrow tail. At the conclusion of three monthly treatment sessions, temporal hollowing was graded 0 bilaterally in all subjects, based on the Galderma Temple Volume Deficit Scale (GTVDS).

The aesthetic effect of Relabotulinum Toxin A on horizontal forehead lines was observed within 24–48 hours post-injection and persisted for up to 6 months, consistent with Phase 3 clinical data for glabellar and periocular treatments, where sustained efficacy was noted in up to 75% of patients.^{9–11}

Detailed quantitative data assessing wrinkle severity, skin elasticity, hydration levels, and volumetric changes in the treated areas are currently being analyzed. Patient-reported outcome measures (PROMs) on satisfaction and psychological impact are also under evaluation.

FIGURE 1A–G. Treatment of the frontalis muscle with Relabotulinum Toxin A (40 units, 0.40 mL) in patient 1. **Panel A:** Pre-treatment (T0) overview of injection distribution to frontalis (40 U), corrugators (40 U), procerus (10 U), and periocular muscles (60 U). **Panel B:** Injection mapping of frontalis muscle showing deep (blue, 4 U) and superficial (light blue, 2 U) points, individualized based on muscle contraction pattern. **Panels C–E:** Static view comparison at T0 and T2 (7 days), demonstrating visible smoothing of forehead lines. **Panels F–G:** Dynamic view comparison at T0 and T2 (7 days), showing effective reduction in forehead muscle activity with natural expression preserved.



FIGURE 2-5. Patient 2, full treatment: Relabotulinum Toxin A, 40 Units / 0.40 ml, combined with 3 sessions of Restylane Vital, total 3 ml at 20 mg/ml. Progressive improvements in forehead line reduction, temporal contour restoration, and skin quality were noted.



Baseline photograph before any treatment.

2 days post-treatment:
• 40 units (0.40 ml) Relfydese injected in the forehead

7 days post-treatment:
• 40 units (0.40 ml) Relfydese injected in the forehead
• 1 ml Restylane Vital (20mg/ml), 0.5 ml per side

3 months post-treatment:
• 40 units (0.40 ml) Relfydese injected in the forehead
• 3 ml Restylane Vital (20mg/ml) total 0.5 ml per side per session
• 3 sessions completed

6 months post-treatment, no touch-ups performed



Baseline photograph before any treatment.

2 days post-treatment:
• 40 units (0.40 ml) Relfydese injected in the forehead

7 days post-treatment:
• 40 units (0.40 ml) Relfydese injected in the forehead
• 1 ml Restylane Vital (20mg/ml), 0.5 ml per side

3 months post-treatment:
• 40 units (0.40 ml) Relfydese injected in the forehead
• 3 ml Restylane Vital (20mg/ml) total 0.5 ml per side per session
• 3 sessions completed

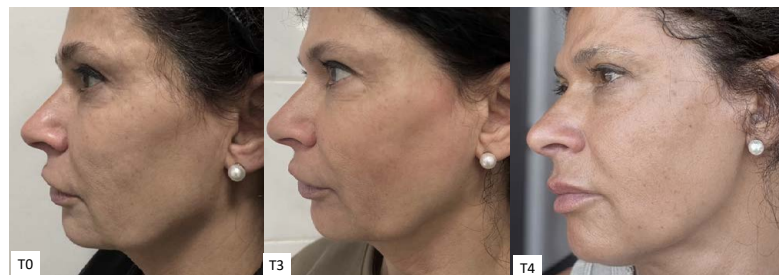
6 months post-treatment, no touch-ups performed



Full treatment: 40 units (0.40 ml) Relfydese to the forehead and 3 ml Restylane Vital (20mg/ml) over 3 sessions.

3-month follow-up: Repeat of 40 units Relfydese and 3 ml Restylane Vital (0.5 ml/side/session; 3 sessions).

6-month follow-up: No additional treatment.



Full treatment: 40 units (0.40 ml) Relfydese to the forehead and 3 ml Restylane Vital (20mg/ml) over 3 sessions.

3-month follow-up: Repeat of 40 units Relfydese and 3 ml Restylane Vital (0.5 ml/side/session; 3 sessions).

6-month follow-up: No additional treatment.

Patient 2, full treatment: Relabotulinum Toxin A, 40 Units / 0.40 ml, combined with 3 sessions of Restylane Vital, total 3 ml at 20 mg/ml.

T = Time point during treatment follow-up.

TABLE 1.

Treatment Schedule and Follow-Up Timeline	
T0	Relabotulinum Toxin A (32–52 units, 0.32-0.52 mL) to frontalis
T1	Follow-up check-up (2 days post-treatment)
T2	Follow-up (7 days post-treatment) + Start NASHA™ Skinboosters: 3 sessions (0.5 mL each side at 0, 1, and 2 months)
T3	Follow-up check-up (3 months)
T4	Final follow-up check-up (6 months)

DISCUSSION

Forehead and temple rejuvenation using injectable treatments represents a highly effective therapeutic approach that prioritizes patient comfort and satisfaction. This minimally invasive protocol is associated with minimal downtime, offering patients a convenient and well-tolerated treatment experience. Preliminary observations suggest that the protocol yields progressive, and long-lasting aesthetic improvements.

Additionally, patients frequently report improvements in psychological well-being and self-perception following treatment.

CONCLUSION

Relabotulinum Toxin A is highly regarded not only for its precision, efficacy, and rapid onset of action but also for its formulation free of animal- or human-derived components. This aspect, combined with its production in an environmentally sustainable facility, appeals to patients who prioritize both clinical outcomes and ethical considerations in their treatment choices.

The use of NASHA™ gel at a concentration of 20 mg/mL as a skinbooster provides a robust strategy to enhance skin quality in the temporal region. It effectively restores skin tone, improves elasticity, and replenishes the natural hollow of the temple, contributing to elevation of the lateral eyebrow tail. Additionally, its hydrating properties impart a subtle yet noticeable radiance to the skin.

When used in combination, these treatments exert a synergistic effect, resulting in a harmonious, natural, and rejuvenated appearance of the upper third of the face. In our clinical experience, the aesthetic improvements are durable, typically lasting beyond six months, underscoring the protocol’s efficacy and patient satisfaction.

DISCLOSURES

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Topical Efinaconazole 10% for Onychomycosis: Pooled Phase 3 Analysis in White, Black, and Asian Participants

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ABSTRACT

Background: Topical efinaconazole 10% solution has demonstrated efficacy and safety in two phase 3 trials of onychomycosis. As clinical data for onychomycosis treatments are limited in patients with skin of color, this post hoc analysis evaluated efinaconazole in participants categorized by race.

Methods: Data were pooled from 2 multicenter, double-blind, phase 3 trials (NCT01007708, NCT01008033). Participants aged 18 to 70 years with mild-to-moderate distal lateral subungual onychomycosis in ≥1 great toenail were randomized (3:1) to once-daily efinaconazole or vehicle for 48 weeks. Efficacy endpoints at week 52 included rates of mycologic cure (MC; negative potassium hydroxide examination + negative fungal culture), complete cure (0% clinical involvement + MC), complete/almost complete cure (≤5% clinical involvement + MC), and clinical efficacy (<10% clinical involvement). Adverse events (AEs) were assessed.

Results: Participants (n=1655) were categorized by self-reported race: White (n=1251), Asian (n=269), or Black (n=98). At week 52, more efinaconazole- vs vehicle-treated participants achieved complete cure (White, 14.7% vs 2.0%; Asian, 27.5% vs 13.0%; Black, 12.9% vs 7.1%), complete/almost complete cure (22.8% vs 4.6%; 35.5% vs 18.8%; 25.7% vs 7.1%), and clinical efficacy (31.2% vs 8.6%; 46.0% vs 23.2%; 31.4% vs 21.4%). Mycologic cure rates were also higher with efinaconazole (range: 53.4%–61.4%) vs vehicle (10.7%–30.4%). Most treatment-emergent AEs with efinaconazole were mild/moderate, with low discontinuation rates (<6%).

Conclusions: Topical efinaconazole 10% showed favorable efficacy/safety in White, Asian, and Black participants with mild-to-moderate onychomycosis. Results were generally consistent with the overall phase 3 populations and position efinaconazole as an efficacious treatment for patients, regardless of race.

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INTRODUCTION

Onychomycosis, a chronic fungal infection of the nail plate or bed, affects up to 14% of individuals in North America and is the most commonly diagnosed nail disorder in the United States.^{1,2} Onychomycosis can cause toenail deformity, discomfort, and pain; interfere with daily living activities; act as a risk factor for other infections, including lower-extremity cellulitis; exacerbate foot problems from other illnesses, such as diabetes; and negatively affect quality of life and well-being.²⁻⁵

Although it is a common infection, prevalence data regarding onychomycosis in patients with skin of color (SoC) are lacking.⁶ The US National Ambulatory Medical Care Survey showed that patients with healthcare visits and a diagnosis of onychomycosis in the years 1993-2010 were 84.6% White, 7.6% Black, and 1.9% Asian.⁶ Another retrospective study found that while Black and Hispanic patients in the US comprised a smaller proportion of the patient population with onychomycosis (19.6% and 16.0%, respectively, vs 44.9% White), their risk of onychomycosis was greater than White patients (Black and Hispanic odds ratios

[95% CI]: 1.29 [1.23-1.36] and 1.24 [1.17-1.31], respectively).⁷ In addition, most published clinical trials of onychomycosis treatments do not report the distribution of race/ethnicity of study participants, which can make it difficult to generalize efficacy and safety results to patients with SoC. A systematic review of 182 onychomycosis clinical trials conducted between 1988 and 2020 showed that only 32 (17.5%) reported the race/ethnicity of the study population, and only 1 (0.5%) trial reported treatment outcomes by race.⁸

It has been suggested that topical efinaconazole 10% solution could be beneficial as a first-line therapy for most patients with onychomycosis, alone or in combination with an oral antifungal.¹ Two-phase 3 randomized controlled trials have shown that once-daily efinaconazole is safe and effective in participants with mild to moderate toenail onychomycosis.⁹ Efinaconazole differs from other topical treatments because of its relatively low keratin binding affinity¹⁰ and its greater transungual penetration compared with topical ciclopirox 8% or tavaborole 5%.¹¹ Here, we report efficacy and safety findings from a pooled analysis of the pivotal phase 3 trials of topical efinaconazole in White, Asian, and Black adults with mild to moderate toenail onychomycosis.

MATERIALS AND METHODS

Study Design and Participants

Two multicenter, randomized, double-blind, vehicle-controlled, parallel-group phase 3 trials of the efficacy and safety of efinaconazole (NCT01008033 and NCT01007708) were pooled for this analysis. The methods of these trials have been previously published.⁹ In brief, eligible participants were male or female of any race, 18-70 years of age, and had a confirmed diagnosis of distal lateral subungual onychomycosis involving ≥ 1 great toenail that was mild to moderate in severity, with a positive potassium hydroxide (KOH) examination of the target toenail. Participants were randomized 3:1 to once-daily application of efinaconazole 10% solution (Jublia®; Ortho Dermatologics, Bridgewater, New Jersey) or vehicle treatment for 48 weeks, with a follow-up visit at week 52.

Investigational sites were located in the US, Canada, and Japan. The trials were performed in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided informed consent.

Assessments

Efficacy was evaluated by visual examination of clinical involvement, KOH examination, and mycological culture of samples taken from the target toenail at weeks 12, 24, 36, 48, and 52. The primary efficacy endpoint was complete cure (defined as no clinical involvement of the target toenail plus mycologic cure [negative KOH examination and negative fungal culture of the target toenail]) at week 52.

Secondary efficacy endpoints included complete or almost complete cure ($\leq 5\%$ of the affected target toenail plus mycologic cure), mycologic cure, unaffected new toenail growth (change from baseline in unaffected target toenail measurement), and clinical efficacy ($< 10\%$ clinical involvement of the target toenail) at week 52. The onychomycosis quality of life questionnaire (OnyCOE-tTM), which consists of 33 items,¹² was administered at baseline and at weeks 24 and 52. As this survey has not been validated in languages other than English, it was only given to participants whose primary language was English.

Adverse events (AEs) were evaluated at baseline and at all postbaseline visits. AEs were classified using the Medical Dictionary for Regulatory Activities, version 12.1.

Statistical Analyses

The intent-to-treat (ITT) population included all randomized participants who were dispensed the study drug. The safety population included all participants who were randomized to treatment, received ≥ 1 confirmed application of the study drug, and had ≥ 1 postbaseline assessment. Participants were categorized by self-reported race: White, Black or African American (herein referred to as Black), or Asian. Differences between treatment groups were analyzed using Cochran-Mantel-Haenszel test stratified by analysis center for all efficacy outcomes. In order to adjust for multiplicity, secondary endpoints were analyzed in a sequential manner. Unaffected new nail growth was tested for significance for active vs vehicle only if the complete or almost complete cure rate was statistically significant. Mycologic cure rate was tested for significance for active vs vehicle only if both complete or almost complete cure rate and unaffected new nail growth were statistically significant. The last observation carried forward method was employed to impute missing efficacy data.

Statistical analyses were performed using SAS® (SAS Institute; Cary, North Carolina). Safety data, treatment compliance (defined as not missing > 14 cumulative doses in the 28 days leading up to week 48, not missing $> 20\%$ of the total number of expected doses during treatment and not missing ≥ 28 consecutive doses during treatment), and quality of life (QoL) data were summarized using descriptive statistics. All OnyCOE-t QoL questionnaire items were transformed to a 0 to 100 scale, with higher scores indicating improvements in QoL.

RESULTS

Participant Baseline Demographics and Characteristics

The pooled ITT population included a total of 1618 participants, of whom 1251 (77.3%) were White, 269 (16.6%) were Asian, and 98 (6.1%) were Black. Most participants were male and not Hispanic or Latino, and the average age was approximately 50 years (Table 1). Baseline clinical characteristics were generally similar across the 3 subgroups and treatment groups;

TABLE 1.

Demographic and Baseline Characteristics by Participant Race (ITT Population, Pooled)						
	White		Asian		Black	
	Efinaconazole 10% (n=947)	Vehicle (n=304)	Efinaconazole 10% (n=200)	Vehicle (n=69)	Efinaconazole 10% (n=70)	Vehicle (n=28)
Age, mean (range), y	51.3 (18.0-71.0)	50.9 (18.0-70.0)	55.4 (20.0-70.0)	54.9 (27.0-70.0)	46.3 (24.0-68.0)	49.7 (23.0-65.0)
Male, n (%)	752 (79.4)	246 (80.9)	134 (67.0)	43 (62.3)	51 (72.9)	23 (82.1)
Not Hispanic or Latino, n (%)	767 (81.0)	238 (78.3)	200 (100)	69 (100)	66 (94.3)	26 (92.9)
Affected toenail, mean (range), %	36.7 (20.0-60.0)	36.9 (20.0-50.0)	35.6 (20.0-50.0)	37.2 (20.0-50.0)	35.1 (20.0-50.0)	32.0 (20.0-50.0)
Affected nontarget toenails, mean (range), n	2.8 (0-5.0)	2.9 (0-5.0)	2.4 (0-5.0)	2.4 (0-5.0)	3.3 (0-5.0)	2.9 (0-5.0)
Treatment compliance, n (%) ^a	823 (91.2) ^b	246 (88.2) ^b	186 (93.0)	67 (97.1)	59 (95.2) ^b	22 (81.5) ^b

^aDefined as not missing >14 cumulative doses in the 28 days leading up to week 48, not missing >20% of the total number of expected doses during treatment, and not missing ≥28 consecutive doses during treatment.

^bDosing compliance was unknown for some participants (efinaconazole, vehicle: White n=45, n=25; Black n=8, n=1).

ITT, intent to treat.

approximately one-third of the target toenail was affected, and the mean number of affected nontarget toenails was approximately 3. Treatment compliance with efinaconazole was >90% in all subgroups (Table 1).

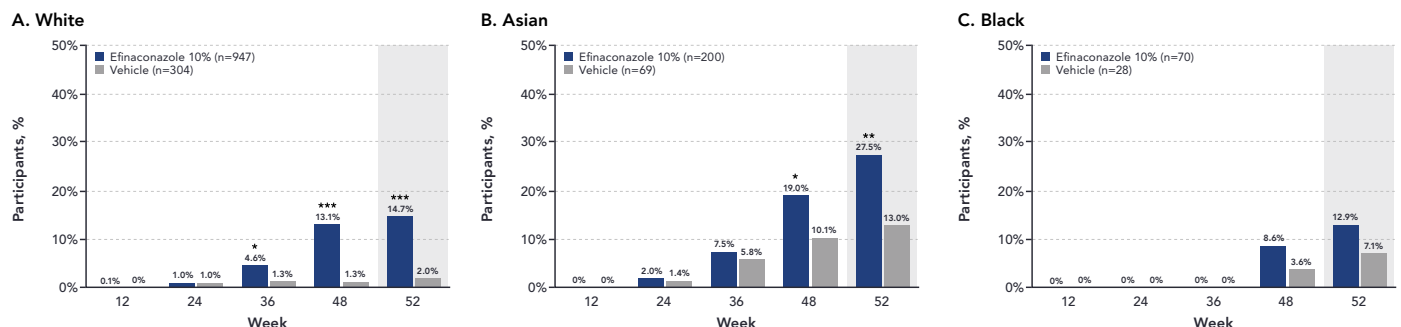
Efficacy

At week 52, complete cure rates with efinaconazole were significantly greater than vehicle in White (14.7% vs 2.0%; $P<0.001$) and Asian participants (27.5% vs 13.0%; $P<0.01$; Figure 1A and B) and numerically greater in Black participants, though this difference did not reach statistical significance (12.9% vs 7.1%; Figure 1C). Statistical separation of efinaconazole from vehicle occurred as early as week 36 in the White subgroup and week 48 for the Asian subgroup; numeric but not statistically significant differences occurred as early as week 48 in Black participants.

A significantly greater percentage of White and Asian participants achieved complete or almost complete cure with efinaconazole vs vehicle at week 52 (White: 22.8% vs 4.6%, $P<0.001$; Asian: 35.5% vs 18.8%, $P<0.01$; Figure 2A and B). Significant improvements were observed as early as weeks 24 and 48 for the White and Asian subgroups, respectively ($P<0.05$, both). Numerically, but not significantly, more efinaconazole-treated Black participants achieved complete or almost complete cure vs vehicle at weeks 24 to 52 (25.7% vs 7.1%; Figure 2C).

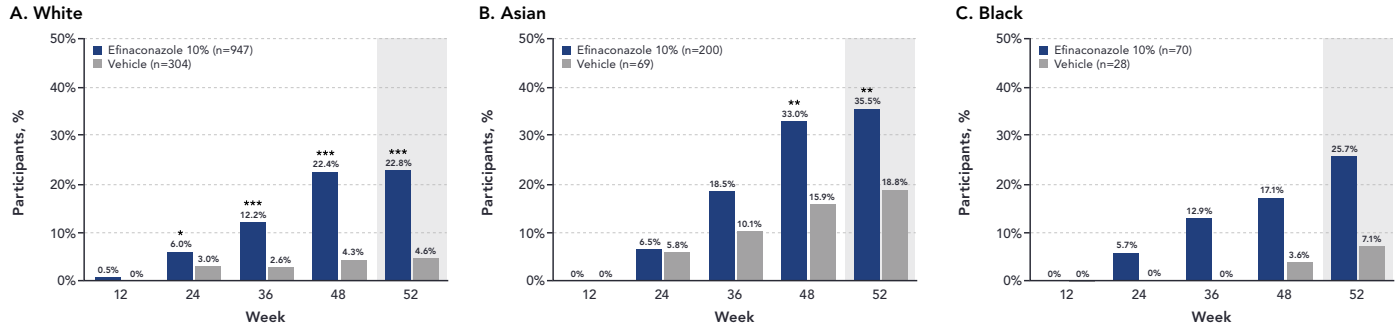
Efinaconazole-treated participants had significantly greater unaffected new nail growth than vehicle-treated participants starting at week 24 for White participants and week 48 for Asian participants ($P<0.001$, all; Figure 3A and B), with numerically greater new nail growth in Black participants observed as early as week 24 (significance was not tested per sequential analysis [see Methods]; Figure 3C).

FIGURE 1. Complete cure by participant race (ITT population, pooled).^a



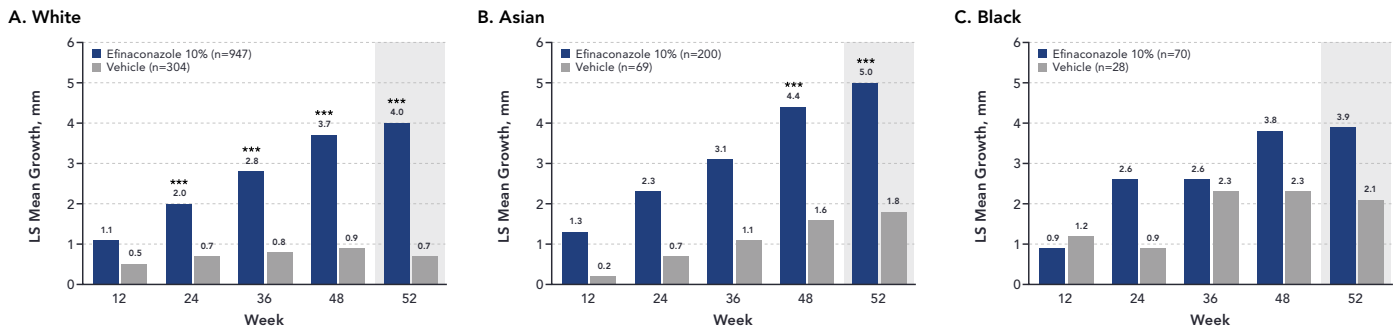
* $P<0.05$, ** $P<0.01$, *** $P<0.001$ vs vehicle. ^aComplete cure was defined as no clinical involvement of the target nail (ie, the nail was completely clear) in addition to mycologic cure. Complete cure rates at week 52 with efinaconazole in the overall phase 3 populations were 17.8% and 15.2%.³ ITT, intent to treat.

FIGURE 2. Complete or almost complete cure by participant race (ITT population, pooled).^a



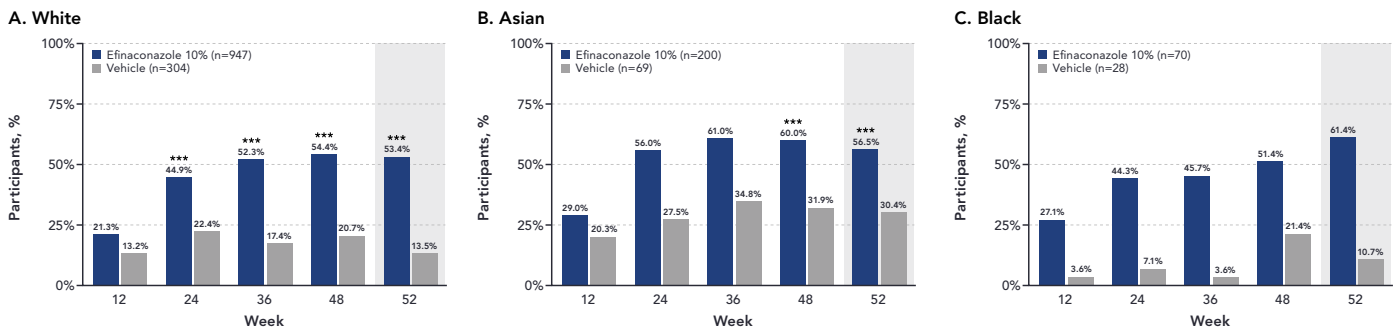
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs vehicle. ^aComplete or almost complete cure was defined as $\leq 5\%$ affected target nail area in addition to mycologic cure. Complete/almost complete cure rates at week 52 with efinaconazole in the overall phase 3 populations were 26.4% and 23.4%.[§] ITT, intent to treat.

FIGURE 3. Unaffected new nail growth by participant race (ITT population, pooled).



*** $P < 0.001$ vs vehicle. Interpretation of results was performed in a sequential manner to adjust for multiplicity. Unaffected new toenail growth was tested for statistical significance (active vs vehicle) only if the complete or almost complete cure rate (shown in Figure 2) was statistically significant. Mean unaffected new toenail growth rates at week 52 with efinaconazole in the overall phase 3 populations were 5.0 mm and 3.8 mm.[§] ITT, intent to treat.

FIGURE 4. Mycologic cure by participant race (ITT population, pooled).^a



*** $P < 0.001$ vs vehicle.

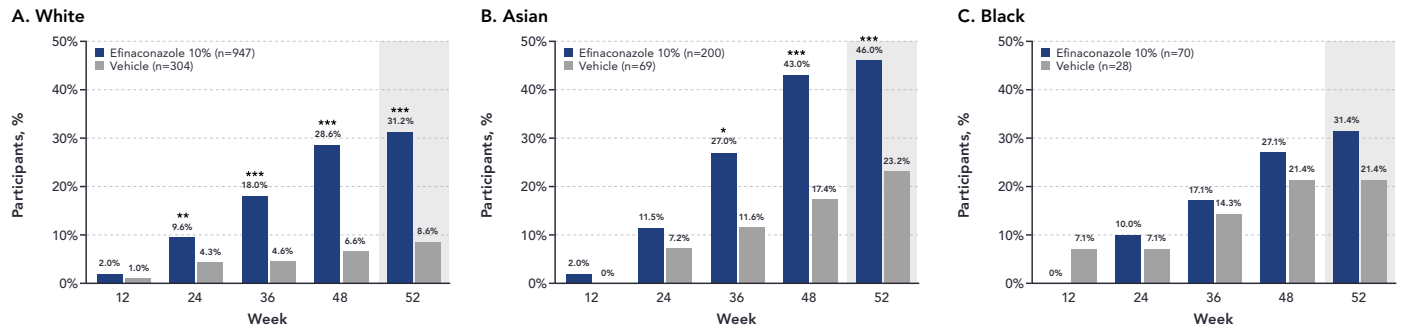
^aMycologic cure was defined as a negative potassium hydroxide examination and a negative fungal culture of the target nail specimen. Interpretation of results was performed in a sequential manner to adjust for multiplicity. Mycologic cure rate was tested for statistical significance (active vs vehicle) only if both the complete or almost complete cure rate (shown in Figure 2) and unaffected new toenail growth (shown in Figure 3) were statistically significant. Mycologic cure rates at week 52 with efinaconazole in the overall phase 3 populations were 55.2% and 53.4%.[§] ITT, intent to treat.

At week 52, over half of efinaconazole-treated participants in each group achieved mycologic cure vs less than one-third with vehicle (53.4%-61.4% vs 10.7%-30.4%; Figure 4A-C); this difference reached statistical significance in the White and Asian subgroups ($P<0.001$, both), with numeric improvements in the Black subgroup (significance was not tested per sequential analysis [see Methods]). Mycologic cure with efinaconazole was significant as early as week 24 for White participants ($P<0.001$) and week 48 for Asian participants ($P<0.001$); numeric differences vs vehicle were observed as early as week 12 for all participants.

Significantly more White and Asian participants treated with efinaconazole achieved clinical efficacy compared with vehicle at week 52 (31.2% and 46.0% vs 8.6% and 23.2%, respectively; $P<0.001$, both), with significant improvements occurring as early as weeks 24 and 36 in the White and Asian subgroups, respectively (Figure 5A and B). Improvements were numerically but not statistically greater in Black efinaconazole-treated vs vehicle-treated participants starting at week 24 (31.4% vs 21.4%; Figure 5C).

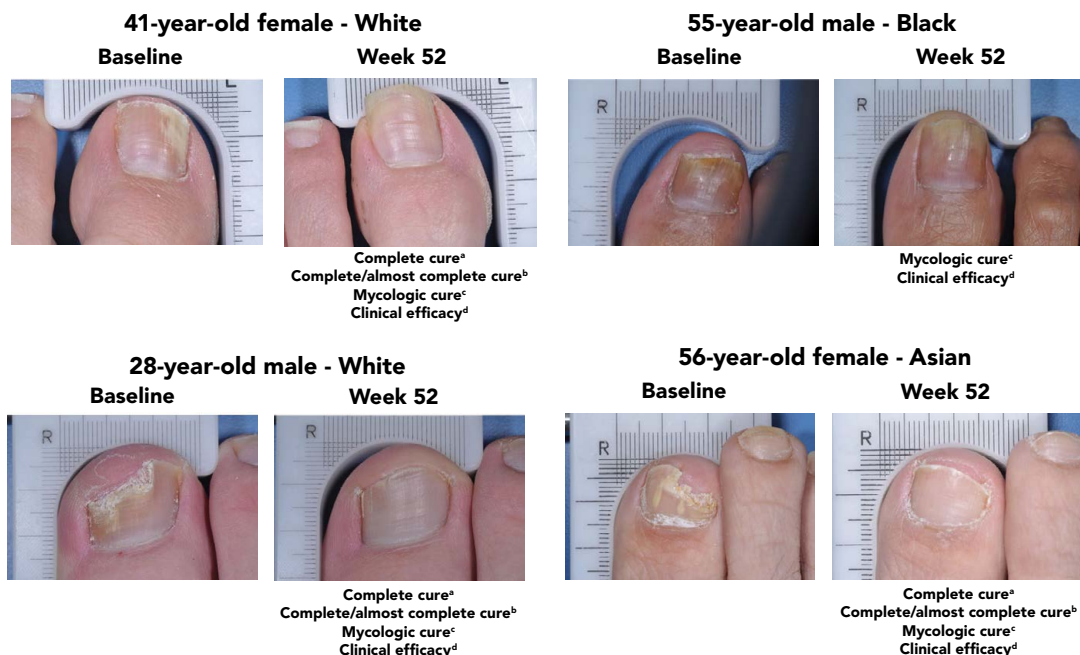
Representative photographs of improvements in affected toenails treated with efinaconazole are shown in Figure 6.

FIGURE 5. Clinical efficacy by participant race (ITT population, pooled).^a



* $P<0.05$, ** $P<0.01$, *** $P\leq 0.001$ vs vehicle. ^aClinical efficacy was defined as $<10\%$ of the affected target nail area. Clinical efficacy rates at week 52 with efinaconazole in the overall phase 3 populations were 35.7% and 31.0%.³ ITT, intent to treat.

FIGURE 6. Representative photographs from participants treated with efinaconazole 10% for 48 weeks.



Individual results may vary. Photographic Images® 2025, courtesy of Ortho Dermatologics Study Investigators. ^aDefined as no clinical involvement of the target toenail and mycologic cure (negative potassium hydroxide [KOH] examination and negative fungal culture) of the target toenail sample. ^bDefined as $\leq 5\%$ clinical involvement and mycologic cure of the target toenail sample. ^cDefined as a negative KOH examination and a negative fungal culture of the target toenail sample. ^dDefined as $<10\%$ clinical involvement of the affected target nail area.

Quality of Life

The mean change from baseline in all OnyCOE-t scale scores at week 52 was greater (indicating improvement) with efinaconazole in the White and Black subgroups vs vehicle (Table 2). Improvements were observed in 2 of 7 domains (symptom frequency and treatment satisfaction) for the efinaconazole-treated Asian subgroup.

Safety

Slightly more participants experienced treatment-emergent AEs (TEAEs) through week 52 with efinaconazole compared with vehicle in the White (65.7% vs 58.6%) and Black subgroups (54.3% vs 46.4%), whereas TEAEs with vehicle were greater in the Asian subgroup (65.5% vs 69.6%; Table 3). Treatment-related TEAE rates with efinaconazole were relatively low and similar across

TABLE 2.

Change from Baseline to Week 52 in OnyCOE-t™ Quality of Life Questionnaire ^a by Participant Race (ITT Population, Pooled) ^b						
	White		Asian		Black	
	Efinaconazole 10% (n=947)	Vehicle (n=304)	Efinaconazole 10% (n=200)	Vehicle (n=69)	Efinaconazole 10% (n=70)	Vehicle (n=28)
Symptom frequency						
n	715	221	16	10	56	22
mean (SD)	26.6 (23.6)	15.6 (25.6)	17.0 (29.1)	15.8 (20.6)	30.8 (26.0)	21.5 (28.8)
Symptom bothersomeness						
n	539	178	11	9	47	18
mean (SD)	17.6 (22.5)	11.0 (24.7)	3.4 (32.5)	5.3 (19.2)	25.5 (27.7)	11.7 (30.8)
Physical activity problems						
n	716	221	16	10	56	22
mean (SD)	16.8 (26.8)	10.2 (25.5)	8.3 (17.5)	21.9 (17.8)	31.3 (29.6)	16.2 (29.6)
Appearance problems						
n	716	221	16	10	56	22
mean (SD)	22.2 (24.1)	13.6 (25.1)	15.1 (26.0)	24.2 (24.7)	29.4 (29.9)	17.6 (27.5)
Overall problem						
n	716	221	16	10	56	22
mean (SD)	27.7 (32.7)	14.6 (31.3)	12.5 (31.9)	50.0 (28.3)	38.7 (39.6)	21.2 (41.8)
Stigma						
n	714	220	16	10	56	22
mean (SD)	9.0 (20.9)	3.5 (18.0)	5.6 (33.0)	8.9 (17.1)	11.4 (25.6)	9.1 (33.3)
Treatment satisfaction						
n	719	222	16	10	56	22
mean (SD)	71.2 (31.9)	39.5 (34.8)	64.1 (34.0)	58.3 (34.7)	80.8 (24.2)	53.4 (37.3)

Quality of life data were summarized using descriptive statistics. ^aThis questionnaire has not been validated in languages other than English and was not provided to participants for whom English was not their primary language; some investigative sites were located in Japan, and thus, not all Asian participants received the questionnaire. ^bHigher mean changes indicate greater improvement. ITT, intent to treat.

TABLE 3.

Treatment-Emergent Adverse Events Through Week 52 by Participant Race (Safety Population, Pooled)						
	White		Asian		Black	
	Efinaconazole 10% (n=939)	Vehicle (n=302)	Efinaconazole 10% (n=200)	Vehicle (n=69)	Efinaconazole 10% (n=70)	Vehicle (n=28)
Reporting any TEAE, n (%)	617 (65.7)	177 (58.6)	131 (65.5)	48 (69.6)	38 (54.3)	13 (46.4)
Treatment-related TEAEs, n (%)	52 (5.5)	12 (4.0)	17 (8.5)	1 (1.4)	6 (8.6)	0
Discontinued drug or study due to AE, n (%)	20 (2.1)	1 (0.3)	11 (5.5)	0	0	0
Number of AEs	1700	504	313	99	76	20
Mild, no. (%)	986 (58.0)	289 (57.3)	59 (18.8)	18 (18.2)	50 (65.8)	13 (65.0)
Moderate, no. (%)	639 (37.6)	204 (40.5)	247 (78.9)	81 (81.8)	19 (25.0)	6 (30.0)
Severe, no. (%)	75 (4.4)	11 (2.2)	7 (2.2)	0	7 (9.2)	1 (5.0)
Most common treatment-related TEAEs, ^a n (%)						
AS dermatitis	10 (1.1)	0	15 (7.5)	0	1 (1.4)	0

^aReported in ≥3% of participants in any treatment group. AE, adverse event; AS, application site; TEAE, treatment-emergent adverse event.

subgroups (5.5%-8.6%). Most TEAEs were mild to moderate in severity, and discontinuations due to AEs were <6% across subgroups. The most common ($\geq 3\%$ of participants) treatment-related TEAE with efinaconazole in any racial subgroup was dermatitis at the application site.

DISCUSSION

Overall, a greater percentage of White, Asian, and Black participants with mild to moderate toenail onychomycosis achieved complete, complete or almost complete, or mycologic cure with efinaconazole 10% topical solution vs vehicle at week 52. Furthermore, efinaconazole demonstrated a favorable safety profile in all analyzed subgroups with low rates of treatment-related TEAEs and discontinuations due to AEs. These findings are consistent with those from the pivotal phase 3 trials of efinaconazole⁹ as well as other post hoc analyses demonstrating its efficacy and safety in diverse patient subgroups based on age, sex, ethnicity, disease severity, and concurrent tinea pedis or diabetes.¹³⁻¹⁸

Few US clinical trials of onychomycosis treatments have reported outcomes by race, with a systematic review identifying only 1 study.⁸ This study of the efficacy of topical ciclopirox 8% lacquer with debridement or debridement alone in patients with onychomycosis also examined patient variables that could affect the likelihood of achieving cure (eg, age, gender, race, and ethnicity).¹⁹ While Black participants were observed to be statistically more likely to achieve mycologic cure than White participants, the overall population was small (N=55), and the number of participants categorized as Black or White was not reported.

To our knowledge, there are no other published US clinical trials data on onychomycosis treatments that specifically examined Black or Asian race. While it is estimated that more than half of the US population will identify as having SoC by 2044,²⁰ there is inadequate representation of patients with SoC during training for clinicians, as well as a lack of reporting of treatment outcomes for patients with SoC in dermatologic and other clinical trials.⁸ For example, in published onychomycosis clinical trial articles that provided patient images with Fitzpatrick skin type, most images were I-II (59.7%; typically considered not SoC) with only 22.1% III-IV and 5.4% V-VI (typically considered SoC)^{8,21}; however, Fitzpatrick skin types were not originally designed to determine race or ethnicity, but rather the propensity to burn when exposed to ultraviolet light.²¹ A standardized classification system for skin color has not been adopted.

Another issue is that patients with SoC may be less likely to see a dermatologist²² and may be undertreated for common dermatologic conditions when they do.²³ Recent analyses of underrepresented patients with onychomycosis in the US National Institutes of Health "All of Us" research program confirmed these racial disparities in real-world clinical practice.

Black and Hispanic patients not only have higher odds of onychomycosis than White patients but also are significantly less likely than White patients to receive diagnostic testing or prescription topical/oral treatments other than fluconazole.^{7,24} These analyses did not include Asian patients.

Onychomycosis can negatively affect QoL and well-being.^{3,4} In the present analyses, the greater improvements in QoL at week 52 with efinaconazole vs vehicle were similar in Black and White participants and were consistent with the improvements observed in the overall phase 3 populations.²⁵ Unfortunately, similar assessments in Asian participants were not possible due to the low number of responses. This likely resulted from the lack of validation of the OnyCOE-t in languages other than English¹²; many of the Asian participants from the present trials were recruited from sites in Japan and did not speak English as their primary language.

Once-daily efinaconazole was not only efficacious but also safe in White, Asian, and Black participants with onychomycosis. Treatment-related TEAE rates with efinaconazole were <9% across all 3 groups. Most TEAEs were mild to moderate in severity, and discontinuations due to AEs were also low (<6%) across the subgroups. The proportion of severe AEs with efinaconazole was slightly higher in the Black participants (9.2%) vs the White (4.4%) and Asian (2.2%) participants; this may be due to the smaller number of Black participants. In a pooled analysis by ethnicity of the 2 efinaconazole phase 3 trials, AE rates in Hispanic efinaconazole-treated participants were similar to those of the White, Black, and Asian efinaconazole-treated participants in the present studies (Hispanic, 65.3% vs 54.3%-65.7%).¹⁵ AEs were also generally mild to moderate in severity, with similarly low rates of discontinuations due to AEs (Hispanic, 1.6% vs 0%-5.5%). Overall, the safety profile in the present analyses and that of the post hoc analysis by ethnicity¹⁵ are generally in line with the overall phase 3 populations,⁹ demonstrating that efinaconazole is safe and tolerable in racially and ethnically diverse patients with onychomycosis.

Limitations of this pooled post hoc analysis include limited generalizability owing to the exclusion of participants with severe disease and the small number of participants who self-identified as Black. Further, nail pigmentation in patients with SoC may affect the visual evaluation of treatment outcomes. Treatment adherence may also be higher in clinical trials compared with real-world settings. Finally, these studies were not statistically powered for subgroup analyses.

CONCLUSION

In conclusion, this pooled post hoc analysis showed that topical efinaconazole 10% solution for onychomycosis treatment is efficacious, safe, and generally well tolerated among White, Asian, and Black participants, with results generally in line with those of the overall phase 3 populations.⁹ These results add to

previous post hoc analyses, demonstrating that efinaconazole can be used in a variety of patient populations, including racially and ethnically diverse patients with onychomycosis.

DISCLOSURES

Shari R. Lipner has served as a consultant for Moberg Pharmaceuticals and BelleTorus Corporation. Aditya K. Gupta has served as a consultant, speaker, and investigator for Ortho Dermatologics. Tracey C. Vlahovic has served as an investigator and speaker for Ortho Dermatologics. Ted Rosen has nothing to disclose. Boni Elewski has provided clinical research support (research funding to University) for AbbVie, Anaptys-Bio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, LEO Pharma, Lilly, Merck, Menlo, Novartis, Pfizer, Regeneron, Sun Pharma, Ortho Dermatologics, and Vanda; and served as a consultant (received honorarium) from Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, LEO Pharma, Lilly, Menlo, Novartis, Pfizer, Sun Pharma, Ortho Dermatologics, and Verrica. Su Yong Choi and Eric Guenin are employees of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Linda Stein Gold has served as an investigator/consultant or speaker for AbbVie, Arcutis, Dermavant, Incyte, Lilly, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sun Pharma, and UCB.

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A Novel Topical Agent for the Management of Hyperpigmentation, Including Melasma and Age Spots

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ABSTRACT

Background/Objectives: Melasma and age spots are among the most persistent and difficult-to-treat forms of hyperpigmentation. While traditional therapies offer some clinical efficacy, they often carry risks of irritation and rebound pigmentation. This study aims to evaluate the therapeutic potential and user tolerability of nanodiamond-zinc oxide (ND-ZnO)-containing skin preparations in improving hyperpigmentation conditions through 11 individual case series and 32 user-reported outcomes.

Methods: We analyzed 11 real-world case studies involving daily usage of ND-ZnO-containing cream and serum over a period of 4 to 12 weeks. Participants varied in age, ethnicity, and Fitzpatrick skin type (FST). Cases were selected based on adherence, diversity of presentation, and completeness of photographic and evaluative documentation.

Results: All 11 case participants demonstrated visible improvements in hyperpigmentation, with varying degrees of reduction in melasma and age spots. Among 32 questionnaire respondents, 90.63% reported a visible reduction in hyperpigmentation, 96.9% noted brighter and more even skin tone, and 93.75% observed improved radiance. All participants tolerated the treatment well, with 100% non-irritation confirmed by two separate Human Repeat Insult Patch Test (HRIPT) studies.

Conclusions: ND-ZnO-containing skin preparations offer a well-tolerated and effective alternative to conventional treatments for melasma and age spots. Their multi-action approach, which combines UV protection, reactive oxygen species (ROS) scavenging, and enhanced delivery of actives, supports both prevention and repair of pigmentation. These findings suggest ND-ZnO formulations may serve as a safer and more compliant option for long-term hyperpigmentation management.

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INTRODUCTION

Melasma is a chronic hyperpigmentation disorder that affects approximately 1% of the general population and up to 1 in 2.5 people in high-risk groups and poses a major therapeutic challenge for dermatologists. This disorder appears as dark brown or gray-brown patches symmetrically on the face, especially on the cheeks, forehead, nose, and upper lip. Melasma has a multifactorial etiology including a combination of genetic predisposition, hormonal factors, ultraviolet radiation, skin phototype, and different environmental factors.¹⁻³

Genetic predisposition is a major cause of melasma: 48% to 64% of affected individuals reported a family history. Melasma is more common among women due to hormonal factors. Previous studies have also shown that taking oral contraceptives increases the chance of melasma due to drastic hormonal

shifts.² Pregnancy has also been proven to be a major cause. Between 15% and 50% of pregnant women are reported to be affected by melasma. Beyond intrinsic factors, sun exposure is a major external trigger. Ultraviolet (UV) radiation and even visible light at 415 nm from sun exposure have been identified as major triggers inducing reactive oxygen species and melanin production.

Age spots, also known as solar lentigines or liver spots, are another common type of hyperpigmentation. These flat, tan, brown, or black growths usually appear on parts of the skin that are most exposed to the sun (face, hands, shoulders, and arms). Age spots are the result of cumulative sun exposure over time, leading to the production of excess melanin in localized patches. Age spots are different from melasma in their cause, appearance, distribution, demographic prevalence,

and persistence. They're more common in older adults and those with fair skin, and tend to be more stable, usually not fading without treatment. Treating hyperpigmentation remains a challenge. The most common treatment option for hyperpigmentation is combination topical therapies, in which multiple ingredients are used together to achieve the highest efficacy.

Recent discoveries in the function of nanodiamond-zinc oxide (ND-ZnO) in topical therapies demonstrate its potential as a novel molecule that offers a dual-action approach to managing hyperpigmentation, including melasma, providing both preventive and reparative benefits.⁴ Both melasma and age spots can be triggered by prolonged UV exposure, and ND-ZnO has demonstrated 5-times higher absorbance in the UVA range than traditional zinc oxide, making it one of the most potent UV blockers, effectively mitigating photodamage and delaying the progression of age-related pigmentation.⁵⁻⁷ Beyond UV protection, ND-ZnO exhibits anti-inflammatory and reactive oxygen species-scavenging properties, counteracting the oxidative stress that fuels melasma development.⁸ The incorporation of a ND-ZnO's core-shell structure also allows for deeper interaction of active ingredients with pigment deposits to facilitate pigmentation breakdown. Using ND-ZnO in a combined topical therapy not only prevents further hyperpigmentation but also actively repairs existing damage by mitigating inflammation and impairing melanin build-up.⁹

In this paper, we evaluate the therapeutic benefits of ND-ZnO in topical treatments for hyperpigmentation. We present our findings in 11 real-world cases: In cases 1 to 7, we evaluate an ND-ZnO-containing cream, Dynamic Age Defense (DAD), which has been shown to reduce hyperpigmentation in participants as early as 4 weeks after consistent use. In cases 8 to 11, we expand upon this analysis by evaluating the synergistic therapeutic effects of DAD with a Bioadaptive Stress Repair (BSR) serum that contains ND-ZnO. Both DAD and BSR significantly reduced hyperpigmentation in the participants, demonstrating the promising benefits of ND-ZnO in real-world hyperpigmentation treatments. Moreover, based on results from 2 separate Human Repeat Insult Patch Tests (HRIPT), ND-ZnO skin preparations were confirmed to be 100% non-irritating, supporting their classification as gentle formulations and reinforcing their potential as a safer and more accessible option for long-term hyperpigmentation management.

MATERIALS AND METHODS

An expert panel selected 11 real-world cases to illustrate the impact of ND-ZnO-containing skincare formulations among patients of different ages and with diverse skin types and treatment goals. These cases represent a variety of Fitzpatrick skin types (FST), ensuring inclusivity across different phototypes. Participants were selected based on predefined inclusion and

exclusion criteria to ensure consistency across the case series. Inclusion criteria required the presence of aging-related skin concerns, including hyperpigmentation such as melasma or age spots. Exclusion criteria eliminated individuals with medical or dermatologic conditions that could confound the assessment of skin response, as well as those unable to comply with the study protocol. The cases presented were selected based on adherence, diversity of presentation, and completeness of photographic and evaluative documentation.

The first 7 cases (cases 1-7) involved participants using ND-ZnO-containing cream once daily, while the last 4 cases (cases 8-11) involved participants using ND-ZnO-containing serum twice daily, with ND-ZnO-containing cream applied on top of the serum once daily in the morning. All participants received clear written instructions on product use and maintained daily logs to ensure compliance. All participants were advised to avoid excessive sun exposure and to avoid using other skincare products while using the ND-ZnO skin preparations.

Dermatological evaluations and digital imaging analyses were performed on each participant at baseline and weeks 4, 8, or 12 to assess and document the changes in skin tone, pigmentation, texture, and hydration. Questionnaires were used to obtain self-assessments of their experience with the product, as well as its efficacy and tolerability. The results demonstrate the utility and the clinical benefit of ND-ZnO-containing skin preparations in protective and corrective skin care based on improvement in skin clarity, pigmentation, and skin health.

RESULTS

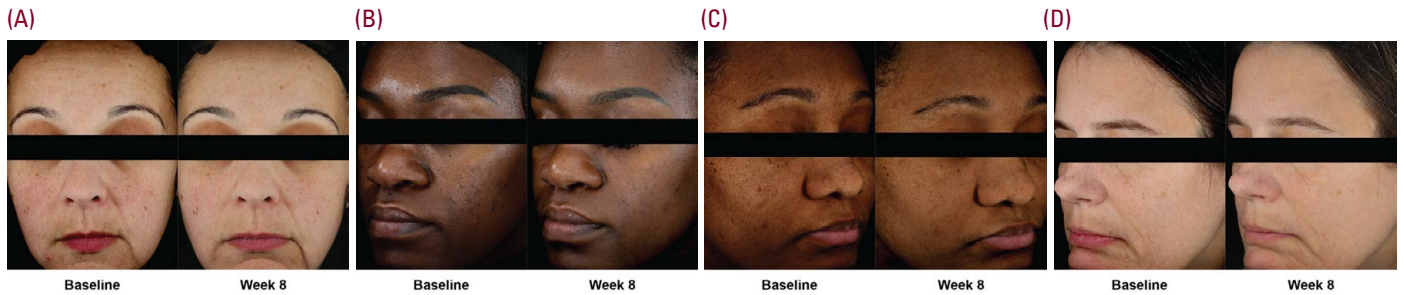
We evaluated the effects of once-daily topical application of Pavise Dynamic Age Defense (DAD) and Pavise Bioadaptive Stress Repair (BSR) serum combined with DAD cream across a diverse cohort of participants with varying ages, skin types, and clinical presentations. Results were assessed through expert grading, participant self-reporting, and digital imaging.

Case Evaluations for DAD Monotherapy

Case 1

A 42-year-old female with FST II presented with age-related hyperpigmentation, early signs of photoaging, and dullness unresponsive to general moisturizers. She was particularly concerned about pigmentation above the upper lip—commonly referred to as a “melasma mustache.” By week 4 of daily DAD application, she reported improved hydration, reduced dry patches, and a brighter complexion. At week 8, pigmentation—including the melasma mustache—had visibly faded, her fine lines appeared softened, and the skin looked more plump and luminous (Figure 1A). The improvement was attributed to both photoprotection from the ND-ZnO and stimulation of reparative pathways.

FIGURE 1. Clinical photographs of cases 1 to 4 demonstrate facial improvements after 8 weeks of once-daily use of Pavise Dynamic Age Defense (DAD). (A) Case 1: 42-year-old female at baseline and after 8 weeks. (B) Case 2: 33-year-old female at baseline and after 8 weeks. (C) Case 3: 40-year-old female at baseline and after 8 weeks. (D) Case 4: 38-year-old female at baseline and after 8 weeks.



Case 2

A 33-year-old female with FST VI presented with stubborn dark spots, post-inflammatory hyperpigmentation (PIH), and reactive skin with a history of sensitivity to hydroquinone. Within 4 weeks of daily DAD use, she reported fewer signs of irritation and early fading of pigmentation. By week 8, the reduction in PIH was marked, especially in previously inflamed areas. She also experienced smoother skin texture and a transition from oily to balanced skin in the forehead region, suggesting improved skin barrier function and regulated sebum production (Figure 1B).

Case 3

Another participant, a 40-year-old female with FST V, reported melasma and diffuse hyperpigmentation concentrated on the cheeks and jawline. These concerns were likely exacerbated by hormonal fluctuations and were unresponsive to over-the-counter brightening products. After 4 weeks of DAD use, she noticed improved tone and a subtle reduction in dark spots. By week 8, digital imaging confirmed ongoing pigment fading and improved skin uniformity (Figure 1C). The participant also reported reduced skin sensitivity, possibly due to mitigation of oxidative stress.

Case 4

A 38-year-old female with FST III and dry, sensitive skin reported pregnancy-related melasma affecting her cheeks, jawline, and upper lip. She was seeking a gentle treatment that would not

trigger further dryness or irritation. After 4 weeks of DAD use, melasma lesions appeared lighter and her skin tone more even. By week 8, digital analysis showed a significant reduction in both superficial and deeper pigment layers (Figure 1D). The pigmentation on her upper lip also improved noticeably, leading to a more uniform appearance.

Case 5

A male participant in his 60s with FST II had longstanding sun exposure that led to visible age spots, uneven texture, and pigment clustering along the sides of his face. After 4 weeks of daily DAD application, he reported smoother skin and subtle fading of dark patches. By week 8, imaging confirmed a significant reduction in pigmentation on the cheeks and jawline, and his skin appeared brighter and better hydrated overall

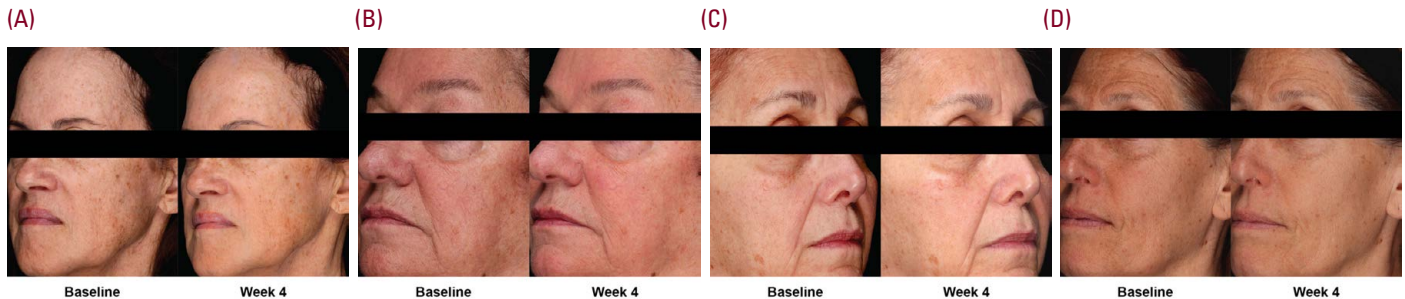
Case 6

A female in her early 30s with FST III presented with mild but progressive hyperpigmentation from intermittent sun exposure without consistent photoprotection. She reported scattered dark spots on the cheeks and uneven skin tone. By week 4 of daily DAD use, her skin felt smoother and brighter. At week 8, the pigmentation had visibly faded, particularly in the sun-exposed regions, and her overall tone appeared more even and radiant (Figure 2B).

FIGURE 2. Cases 5 to 7 demonstrate facial improvements after 8 weeks of once-daily use of Pavise Dynamic Age Defense (DAD). (A) Case 5: Male in his 60s with Fitzpatrick Skin Type II presenting with age spots and sun-induced pigmentation. Week 8 image shows visibly reduced pigmentation on the cheeks and improved skin tone. (B) Case 6: Female in her early 30s with Fitzpatrick Skin Type III and mild sun-induced hyperpigmentation. Week 8 image shows enhanced clarity and brightness, with noticeable fading of scattered dark spots. (C) Case 7: Female in her 30s with Fitzpatrick Skin Type III and diffuse hyperpigmentation. Week 8 image demonstrates improved skin texture and reduced blotchiness, with a visibly more even skin tone following 12 weeks of DAD use.



FIGURE 3. Clinical photographs of Cases 8 to 11 at baseline and after 4 weeks of twice-daily use of Pavise Bioadaptive Stress Repair (BSR) serum combined with once-daily application of Pavise Dynamic Age Defense (DAD). (A) Case 8: 56-year-old female with Fitzpatrick Skin Type III and sun-induced freckles and pigmentation. Week 8 image shows visibly lighter freckles, improved skin clarity, and a smoother texture. (B) Case 9: 63-year-old female with Fitzpatrick Skin Type III and age-related hyperpigmentation and fine lines. Week 4 image demonstrates reduced dark spots, softened lines, and a brighter overall complexion. (C) Case 10: 61-year-old female with Fitzpatrick Skin Type II and photoaging concerns. After 4 weeks, age spots and pigmentation were visibly reduced, with improved firmness and hydration. (D) Case 11: 49-year-old female with Fitzpatrick Skin Type III and combination skin. Week 4 photo shows a more even skin tone, reduced redness, and faded pigmentation with no visible irritation.



Case 7

Another female participant in her 30s, also FST III, had diffuse hyperpigmentation and mild post-inflammatory pigmentation from prolonged sun exposure. After trying multiple over-the-counter brightening products with little success, she began daily DAD application. At week 12, there was a clear reduction in blotchiness and pigmentation irregularities. Her skin texture also improved, with fewer rough patches and a more even, luminous tone (Figure 2C).

Case Evaluations for BSR + DAD Combination Therapy

Case 8

A 56-year-old female with FST III and a history of chronic sun exposure presented with persistent hyperpigmentation, sun-induced freckles, and coarse texture. She was particularly concerned about dark spots on her forehead and cheeks and sought a regimen that could address both pigmentation and skin dullness. She followed a twice-daily application of the ND-ZnO-containing serum, layered with DAD cream in the morning and a moisturizer at night. By week 4, she noted a visible brightening effect and smoother skin texture. Freckles on the forehead appeared lighter, and her complexion looked less dull (Figure 3A). Imaging confirmed improvements in both pigmentation intensity and textural refinement.

Case 9

A 63-year-old female with FST III and normal skin sought treatment for progressive age spots, fine lines, and a lack of radiance. Despite consistent use of anti-aging creams, she continued to experience visible hyperpigmentation and early skin laxity. She applied the ND-ZnO-containing serum twice daily, followed by DAD cream each morning. After 4 weeks, she reported increased hydration, a brighter skin tone, and fading of pigmentation, especially on her cheeks and forehead.

Dermatologist assessment noted softened fine lines and early improvements in texture. The participant reported a marked enhancement in radiance and skin smoothness, with a restored, healthier-looking complexion (Figure 3B).

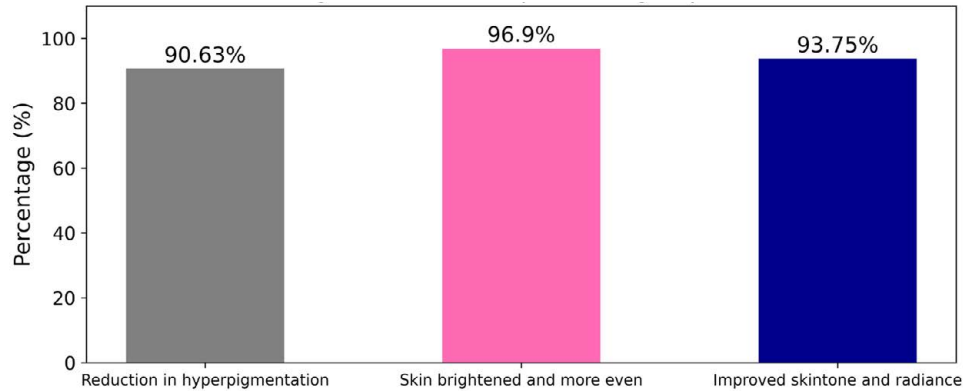
Case 10

A 61-year-old female with FST II and combination skin presented with concerns about photoaging, including prominent dark spots, sagging, and fine lines, especially around the mouth and cheeks. She had observed a steady worsening of hyperpigmentation over time and wanted to improve firmness and tone. Following a regimen of ND-ZnO serum twice daily, combined with DAD cream in the morning and a hydrating moisturizer at night, she noted softer skin and less prominent pigmentation. Her age spots had significantly faded, and the skin appeared firmer and more luminous. The combined regimen improved elasticity and hydration while visibly reducing pigmentation, offering a multifaceted anti-aging benefit (Figure 3C).

Case 11

A 49-year-old female with FST III and combination skin reported uneven tone, blotchiness, and mild roughness, as well as past difficulty with tolerating depigmenting agents. She sought a regimen that would improve skin clarity without irritation. She used the ND-ZnO serum twice daily, in the morning with DAD cream and in the evening with a separate moisturizer. By week 4, she noted a more even tone and less redness, with pronounced improvement in pigment uniformity across the cheeks and jawline. She also reported her skin felt more balanced, with reduced oiliness in the T-zone and improved hydration elsewhere. Her skin appeared smoother, more radiant, and healthier overall, highlighting the regimen's effectiveness in both pigment correction and barrier restoration (Figure 3D).

FIGURE 4. Percentage of patients experiencing improvements in skin conditions (n = 32).



DISCUSSION

Evaluation of the Results

These 11 real-world cases demonstrated the effectiveness of ND-ZnO-containing skin preparations in treating hyperpigmentation conditions such as melasma and age spots, which are often challenging to manage. All participants in the reported case series experienced varying degrees of improvement. The diversity in the participants' ethnicities, ages, and FSTs suggests that these findings are broadly applicable. Furthermore, ND-ZnO skin preparations are specifically formulated for sensitive skin, making them a suitable option for individuals who may not tolerate harsher depigmenting treatments. Most participants reported that the ND-ZnO-containing skin preparations felt soothing and were easier to incorporate into their routine compared to other hyperpigmentation treatments they had previously used (Figure 4).

In a post-use questionnaire assessing participant experience and self-perceived efficacy across a cohort of 32 independent participants, 90.63% of participants reported a visible reduction in hyperpigmentation, stating that ND-ZnO skin preparations had "visibly reduced the look of hyperpigmentation and dark spots." Additionally, 96.9% of participants noted that their skin appeared brighter and more even-toned, while 93.75% observed improvements in overall skin tone and radiance after consistent use for 4, 8, or 12 weeks (Figure 12). These findings underscore the potential of ND-ZnO-containing formulations as an effective, well-tolerated alternative for individuals seeking to improve hyperpigmentation with a gentler, non-irritating approach.

Moreover, previous research efforts have demonstrated that most melasma treatments, such as hydroquinone, retinoids, and other depigmenting agents, take at least 8 to 12 weeks to show meaningful improvement.¹⁰ This is because it takes time for skin cells to turn over, for existing melanocyte activity to downregulate, and for pigmentation to gradually fade. Hence, melasma treatments are most effective with regular, long-term

use. Based on these findings, it can be expected that ND-ZnO-containing skin preparations, when used continuously, would further reduce hyperpigmentation beyond the 8-week mark. Participants using ND-ZnO-containing formulations should be encouraged to maintain continuous use over multiple weeks to fully experience the benefits in reducing melasma and age spots.

A few mechanisms may account for these improvements. Previous research shows that UVR exposure is a significant contributor to the development of hyperpigmentation. ND-ZnO is a potent UV filter that not only provides comprehensive UVA and UVB protection but also protects skin from further photodamage. The ND-ZnO-containing skin preparations operate by blocking UV light, preventing activation of melanocytes and preventing further pigmentation from occurring or even worsening.

Exposure to UV light, oxidative stress, and inflammation are also critical factors in the pathogenesis of hyperpigmentation. ND-ZnO inhibits the formation of reactive oxygen species (ROS), which can reduce inflammation and subsequently decrease pigment formation. ND-ZnO also regulates the activity of melanocytes responsible for melanin production, and excessive melanin secretion has been linked to repeated rounds of inflammatory insults, which can be avoided with ND-ZnO administration.

Previous papers have also shown that ND-ZnO increases the percutaneous penetration of active compounds such as niacinamide.⁴ Its deeper penetration into the skin allows it to break down pigment, leading to improved skin tone and long-term pigmentation care. A plausible hypothesis is that, with a combined topical therapy of ND-ZnO and niacinamide, niacinamide can reach the basal layers of the epidermis where melanin is produced, and hence lead to more effective and prolonged depigmentation.

Limitations

The combined effect of these observations supports the potential of ND-ZnO-containing formulations as a promising approach for hyperpigmentation management. While the findings are encouraging, a few limitations should be noted. As a case series, this study did not include a randomized control group, and outcomes were not assessed under blinded conditions. Additionally, because improvements in hyperpigmentation typically continue to develop beyond 8 to 12 weeks of treatment, the duration of observation in some cases may not fully capture the long-term benefits of the ND-ZnO-containing skincare. Future studies with larger cohorts, controlled comparisons, and longer follow-up periods would be valuable to further substantiate and expand upon these initial findings.

CONCLUSION

In this paper, we presented 11 cases demonstrating the effectiveness of ND-ZnO-containing skin preparations in reducing hyperpigmentation with continuous use over 4 to 12 weeks. This real-world case series confirmed that consistent application of ND-ZnO-containing formulations leads to visible improvements in skin evenness and a reduction in dark spots. In the week 8 questionnaire, 96.9% of users reported that ND-ZnO-containing products felt gentle and non-irritating with daily use. Unlike conventional treatments such as hydroquinone, which are known to cause irritation, rebound pigmentation, and long-term skin sensitivity, ND-ZnO provides a milder, well-tolerated alternative. By combining photoprotection, ROS scavenging, and enhanced pigment correction, ND-ZnO addresses multiple pathways involved in hyperpigmentation, making it an effective option for individuals seeking sustained improvement without the adverse effects associated with traditional therapies.

Beyond its role in reducing hyperpigmentation, ND-ZnO offers a safe and versatile approach to melasma management. Its ability to block UVA exposure, mitigate oxidative stress, and enhance the penetration of active ingredients supports its efficacy as a multi-functional treatment. Unlike chemical depigmenting agents that focus solely on melanin inhibition, ND-ZnO simultaneously prevents further pigmentation and facilitates the repair of existing damage. This dual mechanism underscores its potential for long-term skin health, making it a promising choice for individuals looking for a gentle, non-invasive solution to hyperpigmentation. Future research could further explore its synergy with other mild brightening agents to refine treatment protocols and maximize therapeutic benefits.

DISCLOSURES

XDZ, CT and XB are employees of B.A.I. Biosciences owns the development and commercialization of ND-ZnO, its formulation, and the use thereof.

Funding: This research was funded by B.A.I. Biosciences.

Ethical Statement: This case series was conducted in accordance with the Declaration of Helsinki and followed ethical guidelines for cosmetic research. The case series was assessed under cosmetic safety regulations, and ethical review and approval were waived for this study due to and determined to pose no more than minimal risk to participants.

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Characterizing Safety Outcomes of a Dermal Filler: Injection Site and Timing Insights from the Maude Database

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ABSTRACT

Background: Juvéderm Volbella distinguishes itself for being the only hyaluronic acid filler with dual FDA approval for perioral and infraorbital regions. Its Vycross technology formulation and use in high-risk vascular areas necessitate a comprehensive real-world safety analysis to inform clinical practice.

Objective: To evaluate and categorize adverse events associated with Juvéderm Volbella injections using the Manufacturer and User Facility Device Experience (MAUDE) database, focusing on injection sites and the number of treated areas.

Methods and Materials: Adverse event reports from January 2020 to January 2024 were reviewed and graded using standardized criteria. Events were grouped by injection site, number of anatomical areas injected, and time of symptom onset. Statistical analyses included chi-square and Kruskal-Wallis tests.

Results: Among 315 patients, dermatologic and vascular events predominated, with higher vascular complication rates following perioral injections. Severe adverse events (CTCAE >2) occurred at a median of 75 days postinjection versus 51 days for moderate events. Perioral injections required antibiotics in 53.3% of severe cases versus 28.6% of mild cases ($P=0.0003$).

Conclusion: Perioral Volbella injections demonstrate increased vascular complication risks requiring modified clinical protocols: extended follow-up schedules (2–3 months versus standard 2 weeks), enhanced informed consent, and site-specific risk stratification. These findings provide immediate, actionable evidence for improving patient safety through evidence-based practice modifications.

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INTRODUCTION

The number of aesthetic procedures performed has risen sharply in recent years, increasing 14% from 2019 through 2022. This change is primarily due to a 23% increase in non-surgical aesthetic procedures over the same period. Among non-surgical aesthetic procedures, dermal fillers contribute 14% of the total revenue.¹ With the increasing demand for dermal fillers and the large financial implications, many companies have sought to introduce new products. Juvéderm Volbella XC represents a critical case study for evidence-based safety analysis due to several unique characteristics that distinguish it from other hyaluronic acid fillers. First, it is the only FDA-approved filler with dual-site indication for both perioral (2016) and infraorbital (2021) regions, enabling direct comparison of site-specific adverse event profiles within a single product formulation.²⁻⁴ Second, its proprietary Vycross technology creates distinct cross-linking density and particle size characteristics that may influence adverse event patterns compared to conventional hyaluronic acid fillers.^{5,6} Third, its approved use in anatomically delicate, highly vascularized regions where serious complications like vascular occlusion can cause permanent tissue damage makes understanding its safety profile clinically relevant.⁷ Previous

clinical trials demonstrated promising aesthetic outcomes but identified site-specific differences in adverse event rates, with perioral injections showing higher complication frequencies than infraorbital procedures.^{8,9} However, controlled trial conditions may not reflect real-world usage patterns, injection techniques, or patient populations, necessitating comprehensive postmarket analysis. The Manufacturer and User Facility Device Experience (MAUDE) database provides the largest available dataset for analyzing real-world adverse events, though systematic analysis using standardized severity grading has been limited.¹⁰ This study addresses these gaps by providing the first comprehensive analysis of Volbella adverse events using Common Terminology Criteria for Adverse Events (CTCAE) grading,¹¹ enabling standardized severity assessment and clinical correlation. We hypothesize that perioral injections will demonstrate higher rates of vascular complications due to regional vascular density, and that adverse event timing patterns will inform evidence-based follow-up protocols. These findings will directly inform practice by: (1) establishing site-specific complication rates for enhanced informed consent, (2) defining evidence-based follow-up schedules based on adverse event timing, and (3) providing risk stratification frameworks for clinical decision-making.

MATERIALS AND METHODS

The MAUDE database was queried for reports on adverse events related to Juvéderm Volbella. “UNK Volbella” was used as the search term. Reports were gathered from January 1, 2020, through January 24, 2024, to gain a representative sample of reports on this product, as we aimed to collect a sample from recent years. Duplicate and case series reports, since their contents did not have enough clarity to evaluate each report among the many reports that were described, were excluded.

Each event description was categorized into different sections based on Common Terminology Criteria for Adverse Events (CTCAE) grading (1 = Patient experiences mild or asymptomatic symptoms with no intervention indicated, 2 = Patient experiences moderate symptoms with minimal or noninvasive intervention, 3 = Patient experiences severe but not life threatening symptoms, hospitalization indicated, 4 = Patient experiences life threatening symptoms, urgent intervention required, and 5 = Patient experiences death related to adverse events). The highest graded adverse events experienced by each patient were grouped into fourteen event types. The location of injection sites, timing of event, prescribed antibiotics, steroids, antihistamines, and anti-inflammatories were recorded. Clavien Dindo grading¹² (1 = Any deviation from normal postoperative procedure without the use of any antibiotics or surgical treatment, 2 = Any deviation from the normal postoperative procedure with the use of antibiotics, 3 = Intervention requiring various degrees and is sub-classified into intervention performed under local anesthesia or interventions requiring general or epidural anesthesia, 4 = Complication threatening life of patients requiring intensive care unit support, further sub-classified into single organ dysfunction or multi-organ dysfunction, and 5 = Death of the patient) was also used as a supplement to CTCAE grading to further categorize the severity of adverse events.

CTCAE and Clavien Dindo grades, as well as CTCAE main adverse event types, were reviewed and evaluated by at least two reviewers (EDA, MMS, DY). If there was a disagreement between two reviewers on a report’s adverse event category, then the categorization was determined by the third reviewer. Injection sites were grouped as follows: lips, marionette lines, and immediate surrounding areas were classified as “perioral”; jaw, chin, and mandible were classified as “mandibular area”; nasolabial folds and nose were grouped with “nose”; cheeks were grouped under “zygomatic region”; the glabella and temple were both included within the “forehead group”; and the “orbital area” included tear trough, infraorbital and all periorbital injections. These classifications were made to better stratify the relevant anatomy into more comprehensive groups to determine the impact of the injection site on adverse events. Finally, the timing of adverse events refers to the number of days following an injection during which the main adverse event began.

Data Analysis

Chi-square tests were used to compare categorical variables. Independent sample t-tests were used for continuous variables, except when Levene’s test was significant, in which Welch’s t-tests were used. CTCAE and Clavien-Dindo scores from both raters were averaged together to assign a single score to each patient’s main adverse outcome. Injection location combinations with at least 10 patients were stratified by category of adverse event. Kruskal-Wallis tests compared patients based on the number of distinct anatomic injections and injury severity as defined by CTCAE scoring and timing of adverse events. The Kruskal-Wallis test also compared CTCAE scores and timing of adverse events to determine the relationship between severity and timing of symptom onset. The Kruskal-Wallis test was selected, given both the ordinal nature of CTCAE scoring and the highly skewed days to adverse events. All statistical analyses were conducted using SPSS (Version 29.0.0.0). *P*-values <0.05 were considered statistically significant. Categorical variables were reported with counts and percentage frequency, and continuous variables were reported as mean ± standard deviation. Values assessed using Kruskal-Wallis tests were presented as median and interquartile range (IQR). CTCAE Grade 2 was used as the threshold for clinically significant toxicity because it represents moderate events that often necessitate intervention and impact patient care. While Grades 3 and 4 reflect more severe toxicity, they are comparatively rare and may not provide sufficient power for robust statistical analysis. Therefore, a cutoff of 2 or greater CTCAE grades was used to balance clinical relevance with analytic feasibility.

RESULTS

The MAUDE database search resulted in 315 patients experiencing at least one reported adverse event following Juvéderm Volbella injection. The characteristics of the complications and reported treatments are summarized in Table 1. Overall, most (82.5%) of the reported adverse events did not have an identified device or use problem. Grading for Clavien-Dindo was consistent with CTCAE grading, as patients with a CTCAE score of greater than two had significantly higher Clavien-Dindo scores (1.8 ± 0.3 versus 1.5 ± 0.4 , $P < 0.0001$). Adverse events began on average 115.9 ± 178.2 days after injection. Antibiotics were the most prescribed medication, which was prescribed more commonly for patients with CTCAE scores greater than two (53.3% versus 28.6%, $P = 0.0003$). Steroids were the next most frequent prescription (11.7%), which were also prescribed more frequently in the group with more severe adverse events, although these results were not statistically significant (18.3% vs 10.2%, $P = 0.078$).

Figure 1 demonstrates the variation between the rater-assigned main adverse event and the MAUDE database-assigned event. The most apparent differences were that the MAUDE database had assigned a greater number of vascular and respiratory tract-related adverse events. In contrast, dermatologic conditions

TABLE 1.

Overview of Patients With Adverse Events Following UNK Volbella Injection				
	Total (N = 315)	CTCAE ≤ 2 (N = 255)	CTCAE > 2 (N = 60)	P-Value
Device Problem [Count (%)]				
Adverse Event Without Identified Device or Use Problem	260 (82.5)	210 (82.4)	50 (83.3)	0.98
Improper or Incorrect Procedure or Method	44 (14.0)	36 (14.1)	8 (13.3)	
Off-Label Use	11 (3.5)	9 (3.5)	2 (3.3)	
Clavien-Dindo Classification Score [Mean (SD)]	1.5 (0.4)	1.5 (0.4)	1.8 (0.3)	<0.0001
Time of Adverse Event after Injection (Days) [Mean (SD)]	115.9 (178.2)	101.5 (147.4)	159.1 (247.4)	0.11
Unknown Time of Adverse Event [Count (%)]	102 (32.4)	95 (37.3)	7 (11.7)	<0.0001
Treated with Antibiotic [Count (%)]	105 (33.3)	73 (28.6)	32 (53.3)	0.0003
Treated with Steroid [Count (%)]	37 (11.7)	26 (10.2)	11 (18.3)	0.078
Treated with Antihistamine [Count (%)]	7 (2.2)	3 (1.2)	4 (6.7)	0.0094
Treated with Anti-Inflammatory [Count (%)]	14 (4.4)	11 (4.3)	3 (5.0)	0.82

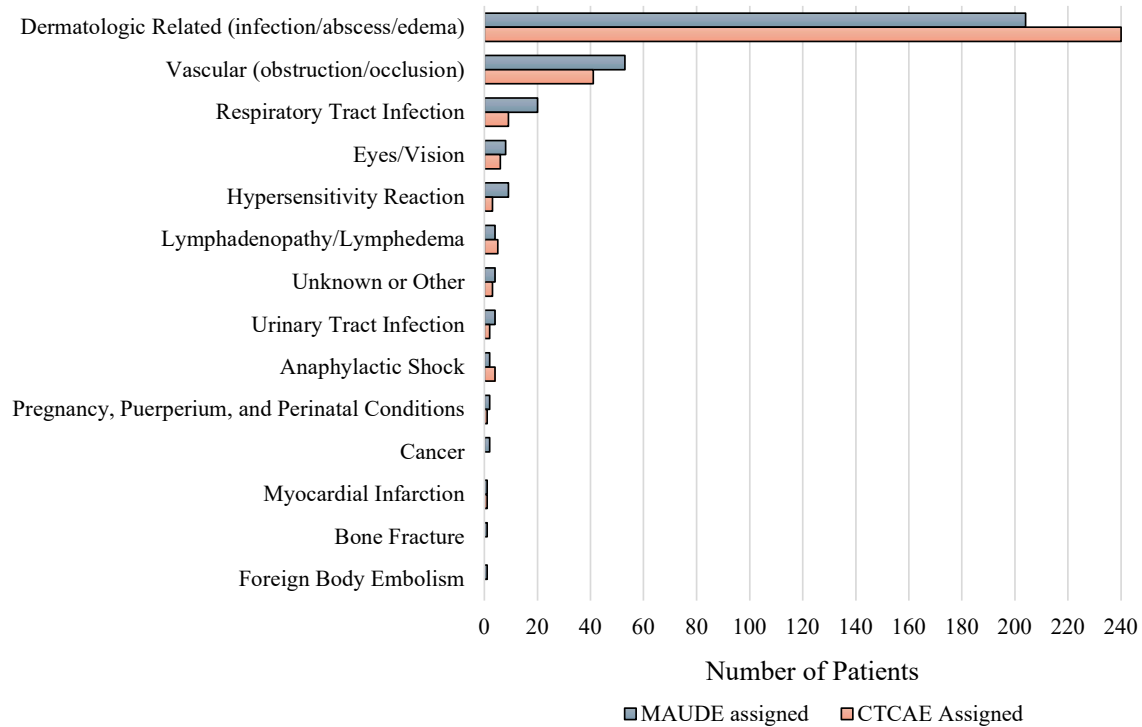
were more commonly deemed to be the main adverse event based on CTCAE scoring. Receiving perioral injections without other locations was the most common (N=99). The most frequent combination was perioral with mandibular (N=16). Across all the most frequent injection site combinations, dermatologic-related adverse events were most common. Those receiving perioral injections (both perioral alone and in combination with another site) had more instances and a greater proportion of vascular-related adverse events Table 2.

Figure 2A suggests that the number of injection sites did not seem to lead to more severe adverse events. Patients with a minimum of one (N=198) through the maximum of five (N=8) distinct injection sites all had a median CTCAE score of two. Considering the variability (demonstrated by interquartile range) of CTCAE scores, patients with four injection sites had the greatest CTCAE scores (median = 2.0, IQR: 1.8, 2.5), but this was not significantly greater than patients receiving injections into one, two, three, or five anatomic sites (P=0.20). Furthermore, as shown in

TABLE 2.

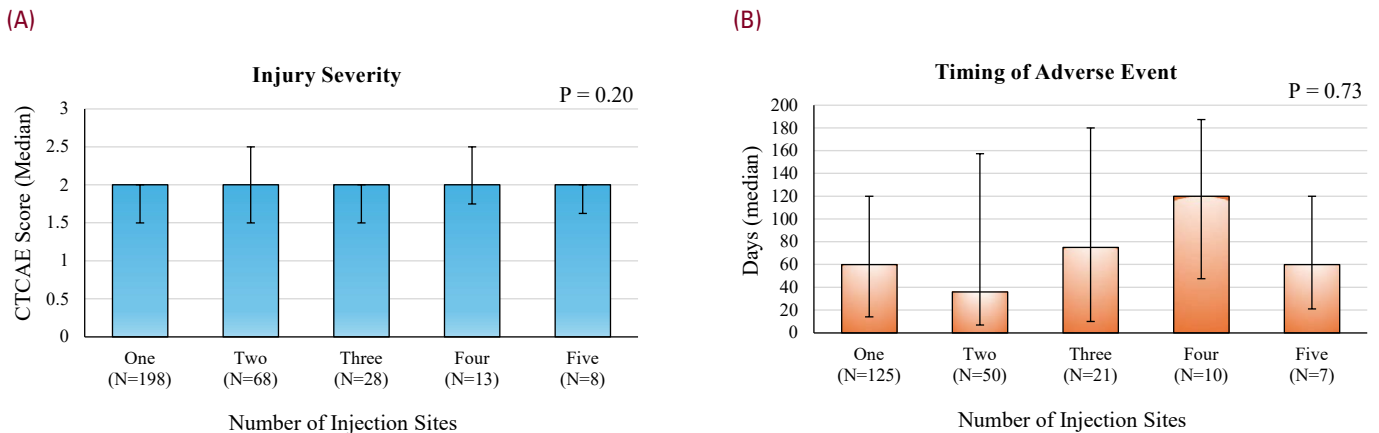
Common Injection Patterns and Complication Category							
Counts	Perioral (N=99)	Unknown (N=43)	Periorbital (N=35)	Perioral + Mandibular (N=16)	Perioral + Nose (N=12)	Perioral + Zygomatic (N=11)	Nose + Periorbital (N=10)
Dermatologic Related (infection/abscess/edema)	80	34	27	13	9	11	6
Vascular (obstruction/occlusion)	15	3	1	3	2	0	1
Respiratory Tract Infection	2	1	1	0	0	0	1
Eyes/Vision	0	0	1	0	0	0	1
Hypersensitivity Reaction	0	0	3	0	0	0	0
Lymphadenopathy/Lymphedema	1	1	1	0	0	0	0
Unknown or Other	0	0	0	0	0	0	1
Urinary Tract Infection	0	1	1	0	0	0	0
Anaphylactic Shock	1	1	0	0	1	0	0
Pregnancy, Puerperium, and Perinatal Conditions	0	1	0	0	0	0	0
Cancer	0	0	0	0	0	0	0
Myocardial Infarction	0	1	0	0	0	0	0
Bone Fracture	0	0	0	0	0	0	0
Foreign Body Embolism	0	0	0	0	0	0	0

FIGURE 1. Adverse events by category.



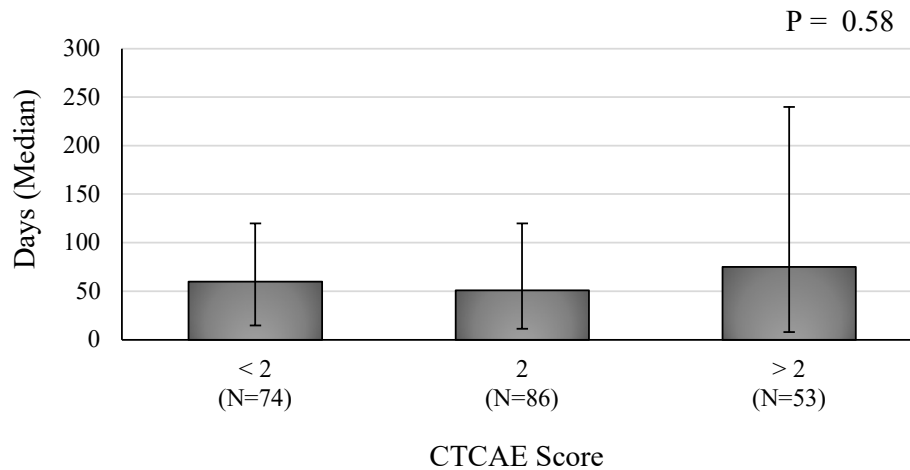
Events were categorized by the MAUDE database and by authors using CTCAE criteria.
MAUDE: Manufacturer and User Facility Device Experience CTCAE: Common Terminology Criteria for Adverse Events

FIGURE 2. Number of injection sites and resulting (A) injury severity and (B) timing of adverse event.



Values are presented as medians, and error bars denote the interquartile range. Not all patients had a reported time of onset.
Kruskal-Wallis tests were used to calculate P-values.

FIGURE 3. Injury severity and number of days to onset.



Values are presented as medians, and error bars denote the interquartile range. Not all patients included in the study had a reported time of onset. Kruskal-Wallis tests were used to calculate P-values. CTCAE = Common Terminology Criteria for Adverse Events

Figure 2B, four injection sites also had the greatest time to adverse event occurrence (median = 120.0 days, IQR: 47.5, 187.5). However, this too was not significantly different from patients receiving injections into a different number of anatomic sites ($P=0.73$). There was also no statistically significant difference in the severity of an adverse event and the time of onset. However, CTCAE scores greater than two seemingly had a slower time to onset (median = 75.0 days, IQR: 14.8, 240.0) compared to CTCAE scores of two (median = 51.0, IQR: 11.5, 120.0) and lower than two (median = 60.0, IQR: 14.8, 120.0; Figure 3).

DISCUSSION

The goal of this study was to describe and establish the clinical significance of the adverse events associated with Juvéderm Volbella dermal filler injections reported in the MAUDE database. The use of the CTCAE scoring system provided an in-depth view of adverse events associated with Juvéderm Volbella dermal filler injections. The present study analyzed the implications of various factors. These factors included the number of injection sites, the timing of adverse events, and their implications for the severity of adverse events. This analysis provides actionable data on both the risks of receiving the Juvéderm Volbella dermal filler injection in general, as well as how the choice of where to inject and how many locations to inject affects the probability and severity of adverse outcomes.

Within the MAUDE database, most of the reports were related to the intrinsic characteristics of the FDA-approved Juvéderm Volbella formulation as opposed to device malfunction or off-label product use. In a previous study, Benham et al¹³

demonstrated underreporting of surgical staplers and clip device malfunctions in the MAUDE database, which can explain the discrepancies between device malfunctions and product adverse event reports.¹³ The generalizability of these findings to dermal injection fillers is unknown. Regardless, it is worth considering that the likely number of injection-related adverse events is much higher than what was found in the MAUDE database, considering the growing literature and warnings from health policymakers^{14,15} on this matter. This is likely to be especially true for adverse events due to off-label use, as there may be increased hesitation to report these outcomes.

Intuitive concordance existed between Clavien-Dindo scores and CTCAE grades. This agreement represents how increased adverse event severity contributes to stepwise increases in interventions in patient care. This study found that antibiotics are being used more than steroids or other anti-inflammatory medications. The high use of antibiotics is likely due to the high number of skin infection-like symptoms reported. Finally, adverse events that did not include their timing of postinjection symptoms had many more instances of less severe outcomes. This trend may be a consequence of less vigilant reporting because less severe adverse events may be assumed to be less important.

Among the most common adverse effects, the majority were dermatological, and some were vascular, like the trends seen in a previous study related to hyaluronic acid injections. Figure 1 shows that the MAUDE assigned main adverse events were mostly congruent with the adverse events assigned by this

study's graders. However, the present study differs from the previous study¹⁶ which had far more reports that were specific to the cheeks (zygomatic region) as opposed to lips (perioral region). It is hypothesized that the perioral flora or concentration of vasculature may be a contributor to more infectious and occlusive adverse events that were seen in our study.

Interestingly, this study provides some insight into the number of injection sites and their relationship to the severity of adverse events and their timing. Figure 2A depicts that there is no difference between CTCAE grades and the number of injection sites, which likely shows the limitations of using CTCAE scoring as a metric for severity due to the ordinal scale being too narrow to showcase the nuances between each report. On the contrary, Figures 2B and 3 were more useful because they provided insight into follow-up appointment timing for physicians following dermal filler injections. Although there was large variability between the number of injection sites and timing of adverse events, this study prompts users to follow up with their clinicians long-term, up to 8 months following their injections, to screen for and diagnose any adverse events that occur. This is especially important for catching adverse events with CTCAE scores greater than 2.

Based on our findings, several critical modifications to current practice standards are warranted. Firstly, given that severe adverse events occur at a median of 75 days postinjection, current industry standard 2-week follow-up schedules are inadequate. We recommend mandatory follow-up appointments at 2-3 months post-injection, particularly for perioral procedures, with patient education about potential delayed complications extending to 8 months. Secondly, Perioral injections require enhanced pre-procedural evaluation, including vascular anatomy assessment and bleeding disorder screening. Patients should receive specific counseling about increased vascular complication risks compared to other injection sites. Thirdly, informed consent documentation should include site-specific complication rates derived from this real-world data, delayed adverse event onset patterns, and the potential need for antibiotic intervention in severe cases. Finally, the significantly higher antibiotic usage in severe cases (53.3% vs 28.6%) suggests clinicians should maintain lower thresholds for antimicrobial therapy in high-risk patients or when inflammatory complications develop.

Limitations of this study include the voluntary submission of MAUDE report sampling bias, which may not represent the true number of adverse events seen in practice. In addition, as stated previously, the ordinal scoring criteria of CTCAE proved difficult to assess since it may not have addressed the nuances of adverse events, which would be needed to discern whether more or fewer injection sites cause severe adverse reactions.

In addition, it is impossible to identify the demographics or comorbidities of the patient population who experienced adverse reactions, which can confound the severity of adverse events. Future research should prioritize prospective clinical studies rather than retrospective database analyses to more accurately assess the effects of dermal filler injections in real-world settings.

This study highlighted how the reporting of adverse events by the MAUDE database likely does not capture the true associated adverse events. Furthermore, while more detailed prospective studies are needed to determine how location and number of injection sites impact outcomes, we found preliminary evidence that perioral injections have higher rates of vascular complications. Lastly, this study provides strong evidence that long-term follow-up is necessary in patients receiving Juvéderm Volbella injection to monitor for adverse outcomes, specifically because the more severe outcomes may present at a later time.

CONCLUSION

This comprehensive analysis of Volbella adverse events using standardized CTCAE grading provides evidence-based support for immediate clinical practice modifications. The significantly higher antibiotic requirements in severe cases (53.3% vs 28.6%) and delayed onset patterns for serious complications (median 75 days) demonstrate that current follow-up protocols are inadequate for optimal patient safety. Perioral injections carry demonstrably higher vascular complication risks, necessitating enhanced informed consent and risk stratification protocols. The finding that severe adverse events characteristically present months after treatment directly contradicts current 2-week follow-up standards and manufacturer guidelines.

These real-world findings provide immediate, actionable evidence for modifying clinical practice to improve patient safety: extending follow-up protocols from 2 weeks to 2-3 months, implementing site-specific risk stratification, and enhancing informed consent with evidence-based complication rates. While prospective validation studies remain important, this MAUDE analysis offers the most comprehensive real-world safety data currently available for Volbella, enabling evidence-based practice improvements immediately.

The clinical significance of these findings extends beyond Volbella to inform broader dermal filler safety practices, particularly the critical importance of extended postprocedural monitoring and site-specific risk assessment in aesthetic medicine.

DISCLOSURES

The authors declare no conflicts of interest.

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Astragalus membranaceus Extract as a Botanical Ingredient for Pigmentary and Anti-Aging Skincare: A Systematic Review

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ABSTRACT

Background: Skin aging results from intrinsic and extrinsic factors, including oxidative stress, ultraviolet (UV) radiation, and declining cellular functions. These factors lead to visible changes like rhytids, pigmentation, and loss of elasticity. Meanwhile, interest in plant-based skincare ingredients for skin aging has been increasing.

Objective: This systematic review investigates the anti-aging potential of *Astragalus membranaceus*, a botanical plant. The authors focused on its active components and their roles in dermal protection, antioxidant, anti-inflammatory, anti-aging properties, and telomere elongation.

Methods: A comprehensive PubMed search from 2015 to 2025 per PRISMA guidelines identified clinical and experimental studies assessing the anti-aging effects of *Astragalus membranaceus*.

Results: Bioactive compounds, including astragaloside IV, cycloastragenol, flavonoids, and polysaccharides, showed photoprotective effects, including reactive oxygen species (ROS) reduction, inflammatory signaling inhibition, mitochondrial preservation, and promotion of collagen synthesis. Elongation of telomeres under oxidative stress was also demonstrated with Astragaloside IV. Clinical trials showed improvements in skin hydration, tone, and wrinkle reduction.

Conclusion: *Astragalus membranaceus* offers promise as a botanical anti-aging agent. Its effects on collagen, oxidative defense, and telomere preservation support its potential use in cosmeceuticals. However, further randomized trials are needed to confirm long-term efficacy and safety.

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INTRODUCTION

Skin aging is an inevitable biological process, regardless of skin type. This natural progression of dermal senescence is influenced by intrinsic and extrinsic factors, where intrinsic aging refers to the skin's natural physiological decline characterized by a reduction in elasticity and collagen, skin thinning, and dryness.¹ Extrinsic aging is mediated through environmental stressors like ultraviolet (UV) radiation, pollution, and lifestyle factors such as smoking and inadequate nutrition.¹ This dual mechanism accelerates skin aging, leading to visible changes such as deep wrinkles, uneven skin tone, and loss of skin firmness.^{1,2}

The demand for cosmetic strategies to mitigate these changes has grown in popularity, with more individuals seeking solutions to maintain a youthful appearance.¹ Among the various approaches to skin rejuvenation, natural plant-based agents, such as those derived from *Astragalus membranaceus*, have garnered attention due to their perceived safety and holistic benefits.³

Astragalus membranaceus (Figure 1) has been a cornerstone of traditional Chinese medicine for over 2 millennia, and it is recognized for its wide-ranging therapeutic properties, including skin anti-aging.⁴ The root of *Astragalus membranaceus* is rich in bioactive compounds such as polysaccharides, flavonoids, and saponins.^{5,6} These herbal compounds have been shown to be effective in mitigating skin aging through mechanisms of enhanced antioxidant and anti-inflammatory activity, collagen preservation, and UV protection.^{6,7} These properties not only address visible signs of aging but also support the skin's structural integrity and resilience. Furthermore, astragaloside IV is a powerful astragalus-based triterpenoid saponin that can elongate telomeres, a key marker of cellular aging and a promising target for developing anti-aging interventions.¹ By elucidating *Astragalus membranaceus's* molecular mechanisms, this herb can provide natural and effective solutions for skin aging.

FIGURE 1. Drawing of *Astragalus membranaceus* created by primary author (SJ).



MATERIALS AND METHODS

Literature Search and Study Selection

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as illustrated in Figure 2. A thorough search of the PubMed database was performed using keywords such as “*Astragalus membranaceus*,” “Huangqi,” “*Astragali radix*,” “Astragaloside IV,” “Cycloastragenol,” “skin vitality,” “anti-aging,” “photoaging,” “wrinkles,” “pigmentation,” and “dermal rejuvenation.” The search was restricted to English-language publications from January 2015 to January 2025. Two reviewers (SJ and LP) independently assessed the titles and abstracts of clinical trials, case reports, cohort studies, and in vitro studies focusing on *Astragalus membranaceus* and its active compounds in dermatological and cosmetic contexts. Studies unrelated to dermatology or cosmetics were excluded. Full-text reviews were conducted for selected articles, and reference lists of included studies were manually reviewed to identify any additional relevant sources.

Data Extraction and Analysis

Data from the selected studies were extracted using a standardized form that captured details such as study design, subject, sample size, intervention, outcomes, and study limitations. The studies were then evaluated using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence. Results were synthesized and categorized according to their relevance to hair regrowth applications.

RESULTS

Collagen is a structural protein in the skin that plays a pivotal role in maintaining dermal strength, elasticity, and overall integrity.³ Degradation of type 1 collagen is a primary driver of visible skin aging, especially under chronic exposure to ultraviolet (UV) radiation.³ Exposure to UV light reduces type I collagen levels by downregulating type I procollagen synthesis and upregulating enzymes like matrix metalloproteinase-1 (MMP-1), which promote collagen breakdown.²

Protective Mechanisms Against UV Damage

Astragaloside IV (AS-IV), a key saponin component of *Astragalus membranaceus*, has been shown to prevent UV-induced type I collagen degradation by activating the transforming growth factor- β (TGF- β)/Smad signaling pathway and inhibiting MMP-1 expression.² Activation of this pathway supports the skin's ability to repair and rebuild its structural matrix after UV-induced damage.

Promotion of Collagen Synthesis and Prevention of Degradation
Further research suggested that AS-IV promotes type I collagen synthesis through multiple mechanisms beyond TGF- β /Smad activation. In UVB-irradiated dermal fibroblasts, AS-IV restored collagen I levels by enhancing autophagy, which helped remove damaged cellular components and encouraged type 1 collagen turnover to support recovery.⁸ AS-IV also suppressed the extracellular signal-regulated kinase (ERK) and p38 branches of the MAPK signaling pathway, both of which are known to drive collagen degradation following UV exposure.⁹

Reduction of Reactive Oxygen Species and Proinflammatory Cytokines

UV radiation induces the formation of reactive oxygen species (ROS), which trigger oxidative stress, DNA damage, and inflammation in skin cells. This oxidative environment accelerates cellular aging and activates proinflammatory pathways that contribute to the breakdown of skin structure and function. In keratinocytes, AS-IV conferred protection by suppressing the TLR4/NF- κ B inflammatory pathway, resulting in decreased ROS and proinflammatory cytokines such as inducible Nitrous Oxide Synthase and Cyclooxygenase-2 (COX-2) after UVB exposure.⁹

Cycloastragenol (CAG) is a triterpenoid saponin from *Astragalus membranaceus*.¹³ As a natural derivative of AS-IV, it also exhibits strong photoprotective effects by reducing ROS and the expression of matrix metalloproteinases to prevent collagen breakdown.¹⁴ CAG targets MMP-1, MMP-9, and MMP-13 while enhancing collagen I levels in UVB-exposed fibroblasts and keratinocytes.^{14,15} These effects are particularly important because while CAG reduces ROS, it also boosts antioxidant activity to protect the extracellular matrix and preserve collagen integrity.¹⁴ CAG also increases hyaluronic acid and skin hydration factors such as filaggrin and serine palmitoyltransferase (SPT).¹⁴ These effects reinforce the skin's physical barrier, making it more resistant to UV-induced damage and oxidative stress.¹⁵ As a result, CAG contributes to moisture protection and improves skin resilience while slowing the onset of premature photoaging.

Clinical Evidence Supporting Astragalus-Based Anti-Aging Formulations

A 12-week open-label clinical trial evaluating a multi-ingredient anti-aging moisturizer containing *Astragalus membranaceus* root extract demonstrated significant improvements in the visual appearance and vitality of facial skin.¹⁶ The astragalus-based agent was used twice daily by 37 women aged between 35 and 60, and 100% of participants showed an overall improvement in skin quality by week 12.¹⁶ Specifically, there was a 25.1% average improvement in fine lines, 16.9% in wrinkles, 26.4% in visual roughness, and 19.0% in skin tone evenness related to hyperpigmentation, highlighting the moisturizer's broad efficacy in enhancing skin texture and tone.¹⁶ Although this study is limited by the absence of a comparative control group and the presence of other active ingredients, its findings

suggest that Astragalus-based agents may protect against UV-induced molecular damage and improve facial skin quality.

In another open-label clinical trial, participants applied a cream containing AS-IV (2 mg/mL) and hyaluronic acid (HA) versus a control group with HA only, twice daily for 4 weeks.¹ In an in vitro study, treatment with AS-IV protected telomeres under oxidative stress. After 4 weeks, cells treated with AS-IV showed significantly longer median telomere length (9002 bp vs 8541 bp), and fewer critically short telomeres (<3 Kbp: 9.5% vs 11.5%) compared to the control group.¹ These results were further supported by subjective evaluations, with 90% of participants reporting improved skin brightness, 95% noting enhanced moisturization, and 70% observing a reduction in the visibility of wrinkles based on self-assessment questionnaires.¹

TABLE 1.

Summary of Included Studies					
Author (Year)	Study Design (Level of Evidence)	Subject	Intervention (Agent / Dose / Frequency)	Outcomes	Study Limitations
Alt et al ¹ (2022)	Open-label clinical trial (LOE 2)	20 Females (40–70 years)	Face cream containing astragaloside IV (2 mg/mL) and hyaluronic acid applied twice daily for 28 days	Improved skin hydration (+16%), firmness (+15%), and wrinkle depth (–8%)	Short duration; small sample size; limited generalizability
Chen et al ² (2015)	In vitro study (LOE 5)	Human skin fibroblasts	Topical application of Astragaloside IV in various concentrations followed by UVA irradiation	Inhibition of collagen degradation; reduced MMP-1 expression; improved TGF-β/Smad signaling; increased type I procollagen	Lacks in vivo validation; undefined long-term effects
Wen et al ⁸ (2018)	In vitro study (LOE 5)	Rat dermal fibroblasts	6 exposures of UVB at 4mJ/cm ² followed by treatment with astragaloside standards (0–100 µg/mL)	↓ UVB-induced Col1 degradation, ROS, and senescence; inhibited ERK/p38; enhanced Col1 levels via autophagy activation	Lacks in vivo validation; minimal effects in non-photoaged cells
Wang et al ⁹ (2022)	In vitro study (LOE 5)	HaCaT keratinocytes	Pretreated with AS-IV (10–150 µM) for 2 hours; UVB (50 mJ/cm ²) exposure for 45 mins – 2 hrs	AS-IV 50 µM increased viability and SOD; reduced ROS, apoptosis, and inflammatory cytokines; suppressed TLR4/NF-κB signaling; reversed by NAC	Lacks long-term data and in vivo validation; mutated cell survival not explored
Li et al ¹² (2020)	In vitro study (LOE 5)	HaCaT keratinocytes	<i>Astragalus membranaceus</i> polysaccharide (AP): 50–600 µg/mL, with UVA (30 J/cm ²) exposure	AP 200 µg/mL increased viability, reduced ROS, and restored mitochondrial membrane potential	Upper-dose not optimized; mitochondrial mechanisms not verified in vivo
Yang et al ¹⁴ (2023)	In vitro study (LOE 5)	Human skin fibroblasts and HaCaT keratinocytes	UVB (100 mJ/cm ²) irradiation then treated with Cycloastragenol (CAG) 0.5–2 µM and N- acetyl L-cysteine (NAC) 3 mM x 12 hrs	CAG reduced MMPs, ROS, and H ₂ O ₂ ; restored collagen I; enhanced skin hydration factors	Lacks in vivo validation and long term effects
Herndon et al ¹⁶ (2015)	Open-label non-randomized clinical trial (LOE 3)	37 Females (35 – 60 years)	Application of astragalus root extract-infused moisturizer twice daily x 12 weeks	Average improvement: 25.1% fine lines, 16.9% wrinkles, 26.4% roughness, 19.0% tone	No control group or blinding; small sample size
Tsao et al ¹⁷ (2017)	In vitro study (LOE 5)	Murine B16F10 melanoma cells	100 ng/ml of AP for 24 hours and 50 µM of a selective inhibitor of ERK x 1 hr	AP dose-dependently reduced melanin and tyrosinase; phosphorylated ERK but not p38	Lacks in vivo validation; ERK-dependent effects may vary by cell type
Liu et al ¹⁹ (2020)	In vitro study (LOE 5)	Human epidermal melanocytes from foreskin	Treated with AS-IV (0 – 100 µM) or 8-methoxypsoralen 100µM x 24 hr	AS-IV increased melanin and tyrosinase expression; activated Aryl hydrocarbon receptor (AhR) and AKT/GSK-3β/β-catenin pathway;	Lacks in vivo validation; inhibition of AhR or downstream targets reduced AS-IV effects

Melanin Regulation

In addition to improving facial texture and tone, *Astragalus membranaceus* may support a more even complexion by influencing melanin production.⁶ For example, a polysaccharide-rich extract of *Astragalus membranaceus* reduced melanin content in melanocyte cells by downregulating melanocyte-inducing transcription factor (MITF) and tyrosinase via activation of the extracellular signal-regulated kinase (ERK) signaling pathway.¹⁷ Similarly, the pharmacological analysis identified bioactive compounds in astragalus, such as wogonin and baicalein, which may target core pigmentation-related genes like Prostaglandin-endoperoxide synthase 2 (PTGS2) and STAT1(signal transducer and activator of transcription 1), suggesting a broader role in managing pigment-related disorders like vitiligo.¹⁸

While studies mentioned above showed anti-melanogenic activity, AS-IV has demonstrated the opposite effect under certain conditions, enhancing melanin production via activation of the Aryl hydrocarbon receptor(AhR)-dependent AKT (protein kinase B)/GSK-3 β (Glycogen Synthase Kinase-3 β)/ β -catenin signaling pathway in normal melanocytes.¹⁹

These differing effects suggest that Astragalus's impact on skin pigmentation may depend on the specific extract, formulation, and cellular context. Nonetheless, its ability to modulate pigmentation pathways has potential value in cosmetic dermatology, whether for brightening or evening skin tone.

CONCLUSION

The studies included in this systematic review support *Astragalus membranaceus* and its main constituents, such as cycloastragenol, flavonoids, astragalus polysaccharides, and astragaloside IV, as potential antiaging agents with photoprotective and skin-rejuvenating effects (Table 1).

At the cellular level, they lower ROS, suppress inflammatory signaling cascades like TLR4/NF- κ B, and preserve mitochondrial function by balancing ATP synthesis and membrane potential. Additionally, by blocking MMPs, triggering TGF- β /Smad signaling, and modulating autophagy and oxidative stress pathways, these bioactive substances help protect type I collagen, reinforcing the skin's structural integrity and slowing photoaging.

Though limited in scale, clinical trials provided evidence of visible improvements in wrinkle depth, elasticity, tone, and overall skin quality. Enhancements in skin hydration and barrier function were also seen.

Our review highlights the therapeutic promise of *Astragalus membranaceus* in cosmetic and dermatologic applications, particularly for preventing photoaging and skin pigmentation.

As consumer interest in plant-based skincare grows, *Astragalus* could play an innovative role. Further studies, including randomized controlled clinical trials, are necessary to confirm its long-term efficacy and safety.

DISCLOSURES

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Photodistributed Hyperpigmentation Associated With COVID-19 Vaccination

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ABSTRACT

Background: Although drugs are a common cause of hyperpigmentation, the pathogenesis is unclear and varies based on the offending agent. Classic medications associated with hyperpigmentation secondary to increased melanin deposition include tetracyclines, prostaglandins, nicotine, and antimalarial medications. We report the case of a 70-year-old female who developed photodistributed hyperpigmentation due to increased melanin deposition following COVID-19 vaccination.

Case Report: A 70-year-old female presented with a one-year history of diffuse blue-grey hyperpigmentation in a photodistributed pattern. Eight months prior to onset, she received her third COVID-19 booster vaccine. The patient had never undergone therapy with medications classically implicated in the condition. A punch biopsy of the left cheek demonstrated brown pigment deposition with both superficial perivascular and deep focal interstitial and perivascular distribution. Fontana-Masson stain positivity in the setting of Prussian blue negativity was suggestive of increased melanin pigment deposition as the cause of her hyperpigmentation. Extensive laboratory workup was unremarkable.

Discussion: While the COVID-19 vaccine has been associated with a variety of cutaneous reactions, there is little evidence describing drug-induced hyperpigmentation after vaccination. Although we cannot definitively establish a causal relationship between the patient's COVID-19 vaccination and the development of her photoinduced hyperpigmentation, an in-office literature review suggested the correlation of these two events. The timing of the vaccine relative to the onset of pigmentary changes and the absence of other identifiable metabolic triggers elevate COVID-19 vaccination as a plausible offending agent. This report is intended to raise awareness of a rare but cosmetically disfiguring potential complication of COVID-19 vaccination.

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INTRODUCTION

Up to twenty percent of all cases of acquired hyperpigmentation are postulated to be drug-induced. The incidence and pathogenesis of drug-induced hyperpigmentation are unclear and vary based on the offending medication.¹ Mechanisms postulated in the literature include drug-induced formation of special pigments, iron deposition through leakage of damaged dermal vessels, drug-induced melanin deposition, and the accumulation of the inciting medication with subsequent pigmentation secondary to chemical reaction induced by sun exposure.¹

Classic medications associated with hyperpigmentation secondary to increased melanin deposition include tetracyclines, prostaglandins, phenothiazines, nicotine, amiodarone, cytotoxic agents, and antimalarial medications.^{1,2} Many cutaneous reactions (including urticarial eruptions, eczematous dermatides, and papulovesicular eruptions) have been associated with COVID-19 vaccination. We report the unique case of a 70-year-old female who developed photodistributed hyperpigmentation following COVID-19 vaccination.

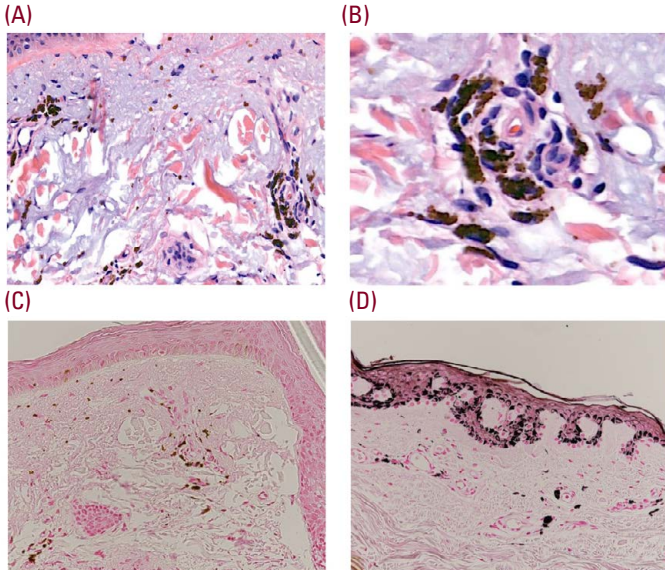
CASE REPORT

A 70-year-old female presented to our clinic with a one-year history of diffuse blue-grey hyperpigmentation in a photodistributed pattern on the face, hands, and dorsal forearms (Figure 1).

FIGURE 1. Blue-grey dyspigmentation on sun-exposed skin.



FIGURE 2. Hematoxylin-eosin- superficial perivascular inflammation with pigment deposition, medium (A) and high (B) power. Pigment stained positive for Perls (iron) (C) and Fontana-Masson (melanin) in the superficial and mid-dermis (D).



Eight months prior to the onset of her hyperpigmentation, she received a third COVID-19 booster vaccine. The patient had never undergone therapy with amiodarone, tetracyclines (including minocycline), antimalarials, kratom, or gold. For several years prior to presentation, her only prescription medications included levothyroxine, lisinopril, and aspirin. She also took various vitamins and supplements (including vitamin D3, vitamin K2, biotin, vitamin E, grape seed, red wine, pine bark, bilberry, and citrus bioflavonoid complex). Prior to evaluation, the patient had undergone a skin biopsy of the dorsal hand, which was simply suggestive of postinflammatory hyperpigmentation (PIH). However, as her clinical presentation was at odds with her prior pathologic diagnosis, a repeat punch biopsy was performed on the left cheek. This demonstrated brown pigment deposition with both superficial perivascular and deep focal interstitial and perivascular distribution. Fontana-Masson stain positivity in the setting of Prussian blue negativity was suggestive of melanin-like pigment deposition (Figure 2). Extensive laboratory workup, including antinuclear antibody screen, complete blood count, complete metabolic panel, serum cortisol, and adrenocorticotrophic studies, was unremarkable and unrevealing. She was referred for pico-laser treatment.

DISCUSSION

Although the patient regularly took numerous medications, vitamins, and herbal supplements, none have been associated with hyperpigmentation secondary to increased melanin deposition. Additionally, she had remained on a consistent medication regimen for years without alteration. However, as her blue-grey hyperpigmentation developed eight months following administration, COVID-19 vaccination remains a temporally plausible offending agent.

Lu et al report the case of a 27-year-old female who, one week following COVID-19 vaccination, developed dark brown macules and papules on the chest, which subsequently generalized and persisted for approximately one year.³ This case differs in that the hyperpigmentation was not in a photodistributed pattern. Similar to our case, however, it was associated with melanin-like deposition. Pathology from repeat biopsy performed on our patient demonstrated findings consistent with increased melanin-like deposition, or at least exogenous pigment deposition from a medication with melanin-like chemical properties, to allow for Fontana-Masson positivity.

The two most common COVID-19 vaccines in the United States utilize modified messenger RNA (mRNA) to encode the SARS-CoV-2 spike protein with the intent of inducing an immune or inflammatory reaction.⁴ The numerous cutaneous reactions associated with the COVID-19 vaccine may be secondary to a type IV or immune complex-mediated hypersensitivity reaction, with the antigen being the spike glycoprotein (or another substance in the vaccine). In individuals with a genetic predisposition, the vaccine may also enhance the immune system, triggering the development of inflammatory disorders such as psoriasis.⁴

COVID-19 vaccination has been associated with new-onset and worsening vitiligo, suggesting a possible immune-mediated cutaneous reaction.⁵ Similar to drug-induced pigmentary changes, it is also possible that vaccination leads to an inflammatory response, yielding either increased melanin production or substances that result in pigmentation with sun exposure.

Although we cannot definitively establish a causal relationship between the patient's COVID-19 vaccination and the development of her photoinduced hyperpigmentation, the timing of the vaccine relative to the onset of pigmentary changes and the absence of other identifiable metabolic triggers elevate COVID-19 vaccination as a plausible offending agent. This report is intended to raise awareness of a rare but cosmetically disfiguring potential complication of COVID-19 vaccination.

DISCLOSURES

The authors have no conflicts of interest to declare.

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Halo Seborrheic Keratosis in a Patient of Color With Vitiligo

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ABSTRACT

A 73-year-old woman with Fitzpatrick skin type V presented with a long-standing brownish-black, three-tone macule on the right anterior thigh that developed a sharply demarcated depigmented halo. She also exhibited depigmented patches on the buttocks, hands, and feet consistent with vitiligo. Horizontal excision with histopathology confirmed seborrheic keratosis (SK) without atypia. This case highlights that the halo phenomenon can occur in non-melanocytic lesions, including SK,¹ a presentation that may mimic melanoma and complicate diagnosis in richly pigmented skin.^{2,3} We review halo SK, discuss dermoscopic–pathologic features that distinguish it from melanoma and adult-onset halo nevus, and summarize evidence-based therapies for coexisting vitiligo, including topical ruxolitinib 1.5% cream and narrowband UVB (NB-UVB).^{4,5}

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INTRODUCTION

Practice Points

- Depigmented halos are not restricted to melanocytic lesions; SK can rarely display a halo and may clinically resemble melanoma.^{1,2}
- Dermoscopy of seborrheic keratosis is characterized by features such as milia-like cysts, comedo-like openings, a cerebriform sulcus–gyrus pattern, moth-eaten borders with irregular peripheral indentations, and sharp demarcation.² However, melanoma clues include blue-black/blue-white structures and an atypical network. Recognition of these patterns guides biopsy decisions.^{2,6}
- In skin of color, overlapping dermoscopic findings (eg, clonal SK vs pigmented basal cell carcinoma) create diagnostic pitfalls, underscoring the need for biopsy when uncertain.³
- For vitiligo, phase 3 and randomized evidence support topical ruxolitinib cream and NB-UVB, with both modalities applicable to patients with richly pigmented skin.^{4,5}

CASE PRESENTATION

A 73-year-old woman with Fitzpatrick skin type V presented for progressive hypopigmentation. Depigmented patches began on the buttocks three years earlier, with later involvement of hands and feet. She also reported a stable, brownish-black, three-tone macule on the right anterior thigh present for nearly two decades, but within the past year, it developed an enlarging depigmented ring.

On examination, there was an 8–10 mm smooth, brownish-black, three-tone macule on the right anterior thigh that was encircled by a sharply bordered depigmented halo. Additional well-demarcated depigmented macules and patches were observed on the buttocks, hands, and feet.

A horizontal excision under local anesthesia was performed. Histopathology demonstrated classic SK morphology without atypia or malignancy, confirming a benign SK with a halo phenomenon.

The patient was reassured. Vitiligo management was discussed, including photoprotection, topical calcineurin inhibitors, NB-UVB phototherapy, and topical ruxolitinib 1.5% cream applied twice daily.^{4,5}

FIGURE 1. Clinical image of the right anterior thigh showing waxy, medium-brown macule with a sharply demarcated depigmented halo in a patient with Fitzpatrick Skin Type V skin and concurrent vitiligo.



Differential Diagnosis

The differential diagnosis for a haloed papule in an adult is broad. A halo nevus is most often seen in children and adolescents, but when it develops later in life, it warrants careful evaluation, given the reported risk of associated melanoma within one year of diagnosis.⁴ Melanoma itself may also resemble seborrheic keratosis, and in such cases, dermoscopy is critical because features such as an atypical pigment network or blue-black and blue-white structures favor melanoma, whereas seborrheic keratosis more commonly displays milia-like cysts, comedo-like openings, and cerebriform ridges.^{2,6} Rare cases of halo eczema have also been documented around seborrheic keratoses, producing an inflammatory halo without true regression.⁷ In patients with richly pigmented skin, additional diagnostic challenges exist, as clonal seborrheic keratosis can mimic pigmented basal cell carcinoma under dermoscopy, reinforcing the need for histopathologic confirmation.³

DISCUSSION

The halo phenomenon, usually linked to melanocytic lesions, has also been documented in non-melanocytic growths such as SK, albeit rarely.¹ Dermoscopy is indispensable: benign SK hallmarks (milia-like cysts, comedo-like openings, cerebriform fissuring) contrast sharply with melanoma clues (blue-white/blue-black areas, atypical network).^{2,6} Where findings are equivocal, a biopsy provides a definitive diagnosis.²

For vitiligo management, topical ruxolitinib cream demonstrated significant repigmentation in phase 3 trials,⁴ while NB-UVB remains a cornerstone therapy, with RCT data supporting its use alone or combined with topical corticosteroids for localized disease.⁵ These therapies are effective across skin types, though counseling must address expectations and psychosocial burden, particularly in patients with darker skin.

This case underscores that halo SK, though rare, should be considered in the differential diagnosis for haloed pigmented lesions in adults. Awareness of this presentation, especially in patients with skin of color, is essential to avoid unnecessary excision while ensuring melanoma is not overlooked.

DISCLOSURES

Written consent for publication of de-identified case details and images was obtained. IRB approval was not required for this single-patient, de-identified report. The authors have no relevant disclosures to declare.

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Private Insurance Coverage for Botulinum Toxin for Primary Axillary Hyperhidrosis: A Cross-Sectional Analysis

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INTRODUCTION

Axillary hyperhidrosis is a chronic dermatological condition characterized by excessive underarm sweating, often interfering with daily activities.¹ It is relatively common, with a prevalence of nearly 5.75%.¹ Despite substantial impacts on quality of life, the exact pathogenesis remains unclear. Treatment strategies primarily focus on reducing excessive sweating, commonly including topical agents, oral pharmacotherapy, and botulinum toxin in the axillary region.² Botulinum toxin selectively targets neurotransmitters in sebaceous glands to prevent the transmission of signals that induce sweat production.^{2,3} Although these neurotoxins have been proven to decrease sweating, insurance coverage varies, and the out-of-pocket expenses are typically high.^{1,2} To date, no studies have evaluated private insurance coverage of botulinum toxin in the treatment of primary axillary hyperhidrosis in the United States. Thus, our objective is to analyze the most up-to-date insurance coverage for botulinum toxin treatment for primary axillary hyperhidrosis among the largest private insurers in each US state.

The largest private insurers were identified using the National Association of Insurance Commissioners' yearly Accident and Health Market Share Report of 2024. Insurers were selected based on total earned premiums and market share percentage. Subsequently, insurers' online medical coverage policies were searched for prior authorization requirements, and injection timing was documented. Results are listed in Table 1.

Of the 50 states, a total of 40 identified private insurers with publicly available coverage guidelines for botulinum toxin use in treating primary axillary hyperhidrosis. States without publicly available coverage information included the following: Illinois Health Service Corporation, Mississippi Blue Cross Blue Shield, Montana Health Service Corporation, New Mexico Health

Service Corporation, Oklahoma Health Service Corporation, Oregon Cambia, Texas Health Service Corporation, Utah InterMountain Healthcare, Vermont Blue Cross Blue Shield, and Washington Kaiser. All private insurers with publicly available guidelines explicitly list primary axillary hyperhidrosis as a criterion for medically necessary botulinum toxin. The majority of policies listed coverage for all formulations of botulinum toxin type A, including Botox (onabotulinumtoxinA), Daxxify (daxibotulinumtoxinA), Dysport (abobotulinumtoxinA), and Xeomin (incobotulinumtoxinA). Additionally, all required prior authorization with evidence of failed topical or oral medications (eg, topical aluminum chloride, anticholinergics, etc.). The mean number of covered sessions per year was 3.9 sessions.

Our results indicate that all private insurers cover botulinum toxin for primary axillary hyperhidrosis after failed treatment with standard topical or oral agents, reinforcing evidence of its safety and efficacy.¹ Despite this, the cost of illness for the disease remains high, with botulinum toxin accounting for the highest percentage of out-of-pocket costs.² Financial barriers may include high copayments and deductibles, as well as the need for repeat treatments to achieve desired outcomes. Moreover, certain toxins may be more costly than others (eg, Botox, Daxxify, Dysport, etc.). Increasing patient education on insurance coverage policies and alternative financial assistance programs may aid in reducing the financial burden of disease and improving long-term outcomes.

Our study has several limitations—namely, only the largest private insurers per state were analyzed, limiting the generalizability of our results. Future research should investigate coverage variability among smaller insurers, as well as Medicaid and Medicare policies.

TABLE 1.
State-by-State Coverage for Botox for Primary Axillary Hyperhidrosis Among the Largest Private Insurers

State	Top Private Insurer	Market Share	Coverage Per Private Insurer	Max Injections Covered	Notes
Alabama	BCBS	86%	Yes	4 sessions/year	Requires failed topical treatments
Alaska	Premera Blue Cross	46%	Yes	N/A	Requires failed topical treatments
Arizona	United Healthcare	28%	Yes	4 sessions/year	Requires failed topical treatments
Arkansas	BCBS	45%	Yes	4 sessions/year	Requires failed topical or oral treatments
California	Kaiser	37%	N/A	N/A	N/A
Colorado	United Healthcare	24%	Yes	4 sessions/year	Requires failed topical treatments
Connecticut	Elevance Health	37%	Yes	4 sessions/year	Requires failed topical or oral treatments
Delaware	Highmark	56%	Yes	N/A	Requires failed topical treatments
District of Columbia	BCBS	22%	Yes	N/A	Requires failed topical and oral treatments
Florida	BCBS	36%	Yes	4 sessions/year	Requires failed topical or oral treatments
Georgia	Elevance Health	33%	Yes	4 sessions/year	Requires failed topical or oral treatments
Hawaii	Hawaii Medical Service Association	63%	Yes	N/A	Requires failed topical treatments
Idaho	Blue Cross of Idaho	42%	Yes	3 sessions/year	Requires failed topical treatments
Illinois	Health Care Service Corporation	53%	Yes	N/A	N/A
Indiana	Elevance Health	56%	Yes	4 sessions/year	Requires failed topical or oral treatments
Iowa	Wellmark	47%	Yes	N/A	Requires failed topical or oral treatments
Kansas	BCBS	45%	Yes	N/A	Requires failed topical treatments
Kentucky	Elevance Health	67%	Yes	4 sessions/year	Requires failed topical or oral treatments
Louisiana	BCBS	66%	Yes	N/A	Requires failed topical treatments
Maine	Elevance Health	43%	Yes	4 sessions/year	Requires failed topical or oral treatments
Maryland	CareFirst	43%	Yes	N/A	Requires failed topical and oral treatments
Massachusetts	BCBS	35%	Yes	N/A	Requires failed topical treatments
Michigan	BCBS	67%	Yes	N/A	Requires failed topical or oral treatments
Minnesota	BCBS	38%	Yes	4 sessions/year	Requires failed topical treatments
Mississippi	BCBS	50%	Yes	N/A	N/A
Missouri	Elevance Health	29%	Yes	4 sessions/year	Requires failed topical or oral treatments
Montana	Health Care Service Corporation	50%	Yes	N/A	N/A
Nebraska	BCBS	45%	Yes	N/A	N/A
Nevada	United Healthcare	36%	Yes	4 sessions/year	Requires failed topical treatments
New Hampshire	Elevance Health	48%	Yes	4 sessions/year	Requires failed topical or oral treatments
New Jersey	Horizon	39%	Yes	N/A	Requires failed topical treatments
New Mexico	Health Care Service Corporation	48%	N/A	N/A	N/A
New York	United Healthcare	26%	Yes	4 sessions/year	Requires failed topical treatments
North Carolina	BCBS	48%	Yes	4 sessions/year	Requires failed topical treatment
North Dakota	BCBS	48%	Yes	4 sessions/year	Requires failed topical treatment
Ohio	Elevance Health	31%	Yes	4 sessions/year	Requires failed topical or oral treatments
Oklahoma	Health Care Service Corporation	57%	N/A	N/A	N/A
Oregon	Cambia	21%	N/A	N/A	N/A
Pennsylvania	Highmark	31%	Yes	4 sessions/year	Requires failed topical treatment
Rhode Island	BCBS	42%	Yes	N/A	Requires failed topical treatment
South Carolina	BCBS	59%	Yes	N/A	Requires failed topical treatment
South Dakota	Avera Health	33%	Yes	N/A	N/A
Tennessee	BCBS	42%	Yes	4 sessions/year	Requires failed topical treatment
Texas	Health Care Service Corporation	44%	N/A	N/A	N/A
Utah	Intermountain Healthcare	46%	N/A	N/A	N/A
Vermont	BCBS	57%	Yes	N/A	N/A
Virginia	Elevance Health	43%	Yes	4 sessions/year	Requires failed topical or oral treatments
Washington	Kaiser	21%	N/A	N/A	N/A
West Virginia	Highmark	52%	Yes	N/A	Requires failed topical treatments
Wisconsin	United Healthcare	27%	Yes	4 sessions/year	Requires failed topical treatments
Wyoming	Cigna	40%	Yes	4 sessions/year	Requires failed topical treatments

BCBS: Blue Cross Blue Shield
Source: <https://content.naic.org/sites/default/files/publication-msr-hb-accident-health.pdf>

DISCLOSURES

The authors have no financial or non-financial interests to disclose.

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illuminating LiDAR Use in Dermatologic Surgery: A Pilot Survey Exploring New Dimensions in Procedural Care

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INTRODUCTION

Photography is essential in dermatology for longitudinal comparisons and referrals. While advancements in cameras and mobile phones/tablets have increased technology accessibility, these modalities are limited to two-dimensional (2D) imaging.¹ Current advanced imaging technologies are often costly/impractical for most dermatology practices.²⁻⁴ Light/laser-imaging detection and ranging (LiDAR) measures the time taken for emitted infrared light to return to a sensor to create virtual, high-resolution, proportional three-dimensional (3D) models.⁵ Studies suggest LiDAR could be a cost-effective clinical tool.⁵ This study assesses the perceptions and feasibility of LiDAR compared to conventional photography for pre-operative dermatology assessments.

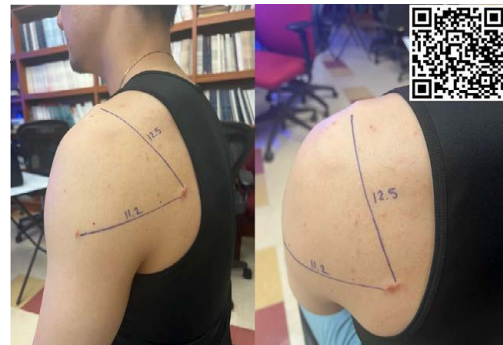
MATERIALS AND METHODS

The IRB-approved survey was distributed electronically via the American College of Mohs Surgeons (ACMS) to US-based Mohs surgeons, fellows, and residents. The 18-item survey gathered information on practice setting, experience, pre-operative assessment protocols, and photography device usage. Participants evaluated a vignette using both a still photo (Figure 1A) and a LiDAR model (Figure 1B), rating the ease of use and likelihood of incorporating LiDAR in practice on a 5-point Likert scale (1=very difficult to 5=very easy). Data were analyzed via chi-square or Mann-Whitney U-test with post-hoc Holm-Bonferroni test, with $P<.05$ denoting significance.

RESULTS

Final analysis included 37 participants (Table 1) with 59.4% having over 10 years of independent practice, and 45.9% in group dermatology private practice settings. Tablets were the most used photo capture device ($n=25$; 67.5%; Table 1) with the Apple iPad being the most used tablet ($n=24$; 96%; Table 1). Whether referrals were accompanied by documentation was significantly associated with referral source (e.g., dermatologists vs non-dermatologists vs non-physician clinician, $P<.001$; Figure 2). If

FIGURE 1. Hypertrophic scar. Pre-operative still photographs and a QR code to an interactive three-dimensional LiDAR of our mock patient were provided to survey participants.



referrals included documentation, they most commonly were clinical photographs without triangulations/markings among dermatologists ($n=18$; 48.5%) and non-physician clinicians ($n=13$; 35.1%; Figure 2). For non-dermatologist physicians, anatomical diagrams or patient charts with written descriptions or triangulations were more commonly provided ($n=12$; 32.4%, Figure 2).

Although majority (69.4%) of participants were unfamiliar with LiDAR and its availability on smart devices (91.9%; Table 1), participants reported similar interpretation ease between photographs ($\bar{x}=4.75$) and LiDAR ($\bar{x}=4.63$; Table 2). While LiDAR was rated easy to use among those unfamiliar with the technology ($\bar{x}=4.63$; Table 1), participants were generally less inclined to adopt it into clinical workflow ($\bar{x}=2.00$ - 2.71 ; Table 2). Dermatologists in academic/government/ university settings were more likely to consider using LiDAR for pre-operative planning ($\bar{x}=3.67$) and patient and resident education ($\bar{x}=3.67$) and in their surgical practice as a whole ($\bar{x}=3.67$) compared to their colleagues, which were both significant with Bonferroni's Correction ($P=0.04$; Table 2).

TABLE 1.

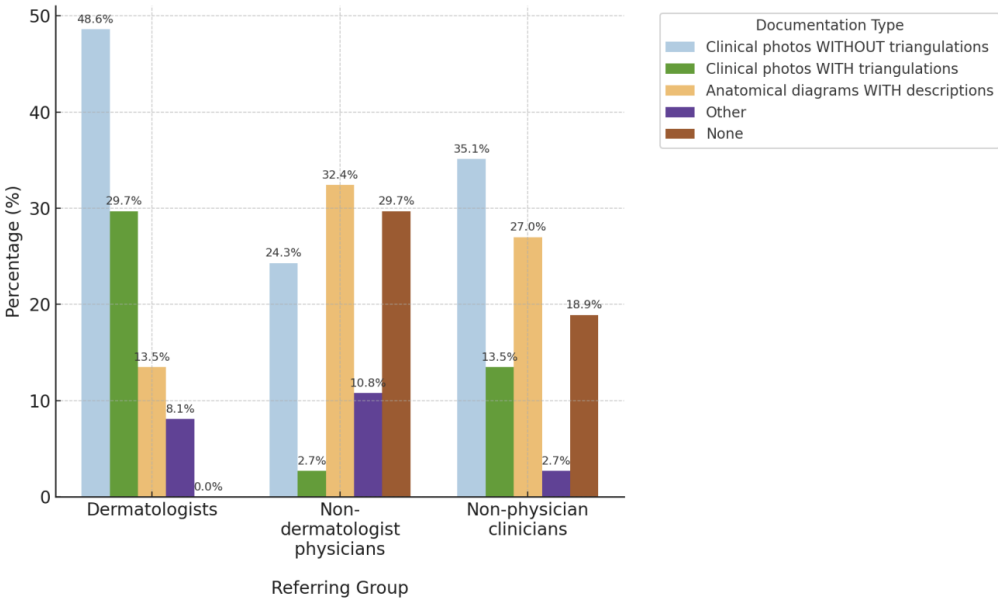
Demographics Of Survey Respondents, Types of Smart Devices Used, Knowledge of LiDAR	
Demographics of survey respondents	Count (%) N=37
Gender	
Male	18 (48.6)
Female	18 (48.6)
No answer	1 (2.7)
Years in Practice	
Current Resident/ Fellow	2 (5.4)
1-10 years	13 (35.1)
11-20 years	11 (29.7)
21-30 years	7 (18.9)
≥31 years	4 (10.8)
Practice Setting	
Solo private practice	5 (21.6)
Dermatology group private practice	17 (45.9)
Multi-specialty group private practice	6 (16.2)
Academic / Government/ University	8 (21.6)
Hospital Based	1 (2.7)
Approximate # of Mohs/dermatologic surgery cases performed per year	
1-500	10 (27)
500-1000	12 (32.4)
1000-1500	9 (24.3)
>1500	10 (27.0)
None	1 (2.7)
Prior to day-of-surgery, do you have a separate visit for preoperative evaluation?	
Yes	8 (21.6)
No	29 (78.4)
Type of smart devices	
Type of device primarily used for still photography in practice:	
Tablet	25 (67.5)
Camera (i.e. point-and-shoot)	7 (18.9)
Smartphone	5 (13.5)
Brand of device used	
Smartphone (n=5)	
Apple iPhone	5 (100%)
Tablet (n=25)	
Apple tablet	24 (96%)
Microsoft Surface Pro	1 (4%)
Knowledge of LIDAR	
Prior to taking this survey, were you aware of...	
LiDAR technology?	
Yes	13 (35.1)
No	24 (64.9)
LiDAR technology being available on smart devices?	
Yes	3 (8.1)
No	34 (91.9)

TABLE 2.

Crosstabulation of LiDAR Awareness and Average Likert Rating for Ease of Use of Photography vs LiDAR and Likelihood to Integrate LiDAR.									
		Mean Rating for Ease of Use of ...		Mean Rating of Likelihood to Incorporate LiDAR for:					
		Photography	LiDAR	Preoperative Planning	Biopsy Site Identification	Wound Checks	Patient/Resident Education	Surgical Approach Planning	Surgical Practice as a whole
Aware of LiDAR before?	No	4.75	4.63	2.42	2.71	2.00	2.29	2.00	2.46
	Yes	4.69	4.77	3.15	3.38	2.54	3.23	2.54	3.31
	MW	1	1	0.51	0.40	1	0.22	1	0.19
Practice Setting	Academic/Hospital	4.67	4.78	3.67	3.67	3.11	3.67	3.11	3.67
	Private§	4.75	4.63	2.36	2.71	1.89	2.29	1.89	2.46
	MW	1	1	0.04*	0.12	0.17	0.04*	0.21	0.04*
Years of Experience	<10 years	4.53	4.47	2.40	2.80	1.93	2.60	1.87	2.53
	>10 years	4.86	4.81	2.86	3.05	2.36	2.64	2.41	2.91
	MW	1	1	1	1	1	1	1	1

Likert scale rating of 1=very difficult to 5=very easy. MW – Mann-Whitney U with Bonferroni correction (*= P<0.05). § = multispecialty, solo, or group.

FIGURE 2. Type of documentation received with referral.



CONCLUSION

Our study found significant gaps in referral documentation, especially from non-dermatology sources. Although most surveyed dermatologists were unfamiliar with LiDAR technology, many recognized its potential in pre-operative assessments. This survey suggests that LiDAR could enhance dermatologic care by democratizing access to 3D imaging. Although participants unfamiliar with LiDAR reported being less likely to utilize it, increased awareness and familiarity with LiDAR may address knowledge gaps regarding practical dermatologic applications. Limitations include a small sample size and response bias; however, the sample was diverse in practice experience/setting.

Additionally, the study assessed LiDAR’s user-friendliness with only one item, so further research is needed to thoroughly evaluate its ease of use.

LiDAR offers an accessible way to integrate 3D imaging into dermatology. LiDAR may provide an affordable alternative to costly commercially available 3D-imaging devices, especially given the near ubiquitous (clinical-)adoption of handheld devices. Future studies should explore LiDAR’s utility across diverse dermatological domains and clinical settings to lower costs, improve patient outcomes, and increase healthcare access.

DISCLOSURES

JWM serves as a Digital Health Fellow for Doximity, Inc. JWM and DMS serve as Clinical Advisors for Berman Medical, Inc. YN, MDM, and RMC have no disclosures.

IRB approval status: Reviewed and exempt (approved) by SUNY Downstate IRB & Privacy Board; approval FWA#:00003624 · IORG#:0000064

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Updated Insights From an Expanded Survey on Monopolar Radiofrequency Treatment

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INTRODUCTION

Thermage® FLX is an advanced, non-invasive monopolar radiofrequency (RF) device used in aesthetic dermatology to address skin laxity and signs of aging. Building on the success of earlier Thermage models, it delivers RF energy to stimulate collagen production, enhancing skin firmness and texture.^{1,2} The FLX model represents the latest advancement in the Thermage platform, offering faster treatment times, improved precision, and greater patient comfort. It uses a single RF electrode in a monopolar configuration to deliver controlled heat into the dermis, creating thermal injury that triggers the body's natural wound-healing response and collagen regeneration.^{3,5}

Following our previous investigations,^{6,9} the 2024 survey provides updated insights into expert perceptions of Thermage FLX regarding its efficacy, complications, and usage patterns. This cross-sectional survey was conducted across eight countries in the Asia-Pacific region.

MATERIALS AND METHODS

A 29-item questionnaire on Thermage FLX was distributed to physicians across the Asia-Pacific region who had at least one year of experience using the device. Participants were recruited from attendees of the 2024 annual Thermage user meetings in their respective countries. Eligible physicians were invited to complete an online survey. All questions were multiple-choice, with the option to select multiple responses. The study was approved by the Institutional Review Board (IRB) of Incheon St. Mary's Hospital, The Catholic University of Korea (IRB number: OC25QISI0019).

A total of 204 physicians participated (90 from Korea and 114 from Taiwan, China [including Hong Kong], Thailand, Vietnam, Singapore, Malaysia, and Australia). The respondents had an average of 7.8 years (range: 1–23) of experience with Thermage and 3.2 years (range: 1–6) with Thermage FLX (Figure 1). The questionnaire addressed three main areas: (a) perceived effectiveness, (b) complications encountered, and (c) practice patterns. Compared to prior surveys, this edition included expanded questions on EyeThermage and physicians' personal use of the FLX platform.

RESULTS AND DISCUSSION

Consistent with our 2020 survey 9, individuals in their 40s remained the most frequently identified ideal candidates for Thermage FLX using the total tip. Skin thickness, in conjunction with age-related changes (e.g., laxity, wrinkling), continued to be the key predictor of treatment response. In addition to tightening, the total tip was reported effective for improving pores (80.9%), rosacea (30.4%), and acne (28.9%) as reported in previous studies (Figure 2A).⁶⁻¹³

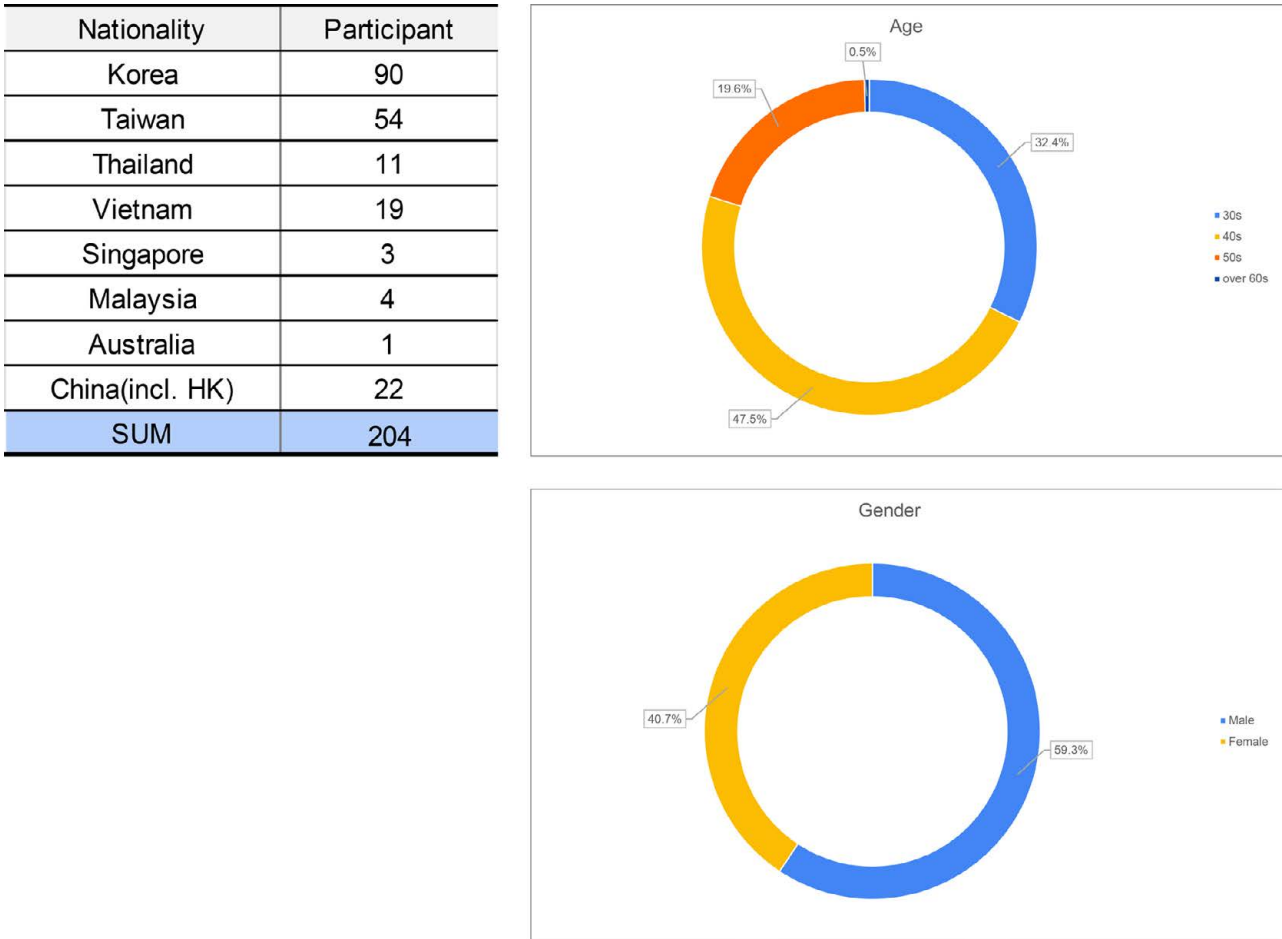
The 2024 survey indicated an improved non-responder rate compared to 2011,⁶ with 69.1% of physicians reporting fewer than 20% non-responders. However, 30.9% still experienced higher non-responder rates, underscoring the need to manage patient expectations, which are often heightened due to online media. Physicians emphasized the importance of counseling and suggested adjusting treatment parameters or combining Thermage with injectables to improve results.¹⁴ Notably, 75.5% reported performing both treatments on the same day, with 93.5% starting with RF (Figure 2A).

The Thermage EyeTip, a specialized tool for non-invasive eyelid rejuvenation, has become a popular choice due to its ability to tighten upper eyelids with no downtime.^{15,16} As the only treatment option for upper eyelid tightening with no downtime, EyeThermage has gained significant popularity. As with the total tip, individuals in their 40s were considered ideal candidates. Thin periorbital skin was cited as a predictor of successful outcomes. EyeThermage was frequently paired with injectables (80.6%), and in 94.6% of such cases, physicians treated the eye area first when crow's feet were present (Figure 2B).

Topical EMLA (2.5% lidocaine/2.5% prilocaine) remained the preferred anesthetic (Figure 3A), while ~30% of respondents reported using sedation. With growing concern over propofol-related risks, nitrous oxide ("laughing gas") is increasingly used as a safer alternative that maintains patient communication during treatment.¹⁴

The preferred treatment interval for the total tip was one year (67.2%), followed by 6–11 months (31.9%) (Figure 3A). The 600 REP 4 cm² and 900 REP 4 cm² tips were similarly popular

FIGURE 1. Characteristics of the 204 physicians who participated in the 2024 Thermage FLX survey.



overall (53.9% and 50.5%, respectively). However, regional preferences differed: Korean dermatologists overwhelmingly favored the 600 REP tip (97.8%), while 86% of physicians in other countries used the 900 REP tip. This may reflect differing clinical practices—Korean dermatologists personally perform treatments and adjust energy settings for precision.

Regarding Eye Thermage, 76% of respondents used both the total and eye tips in combination, 13.7% alternated, and 10.3% used only the eye tip. Yearly intervals were most common (58.3%), followed by 6–11 months (35.8%) and <6 months (3.9%). The 450 REP 0.25 cm² tip was preferred over the 225 REP version (81.7% vs 18.3%) (Figure 3B).

Compared to 2020,⁹ treatment settings were generally higher in 2024. Preferred levels were: 3–3.5 (cheeks, 56.4%), 2–2.5 (forehead, 56.4%), 1–1.5 (neck, 50%), and 3–3.5 (eyelids, 42.6%) (Figure 3C). Korean dermatologists tend to use lower energy settings compared to those in other countries. For example, for the cheeks, 56.7% of Korean dermatologists chose 2–2.5,

while 58.8% of physicians in other countries chose 3–3.5. Some even used levels above 4 for various areas, but we recommend conservative settings, especially for the neck, to minimize complications.¹⁷

The most-commonly reported complications were erythema, edema, and vesicles, followed by post-inflammatory hyperpigmentation, fat atrophy, and scarring.^{17,18} With the eye tip, additional complications included eye dryness, corneal erosion, and blurred vision (Figure 4).

Regarding physicians’ self-treatment experience, 76.5% had undergone total tip treatment and 35.3% had received Eye Thermage (Figure 5A–B). The most used tips were the 900 REP 4cm² tip (outside Korea), 600 REP 4cm² tip (in Korea), and 450 REP 0.25cm² eye tip. Most self-treatments occur annually. Interestingly, 17.3% (total tip) and 38.9% (eye tip) underwent treatment without pain control.¹⁵ Despite experiencing some side effects (18.6% and 8.3%, respectively), physician satisfaction was high: 94.8% for total tip and 81.9% for eye tip.

FIGURE 2A. Perceived effectiveness of the Thermage FLX total tip.

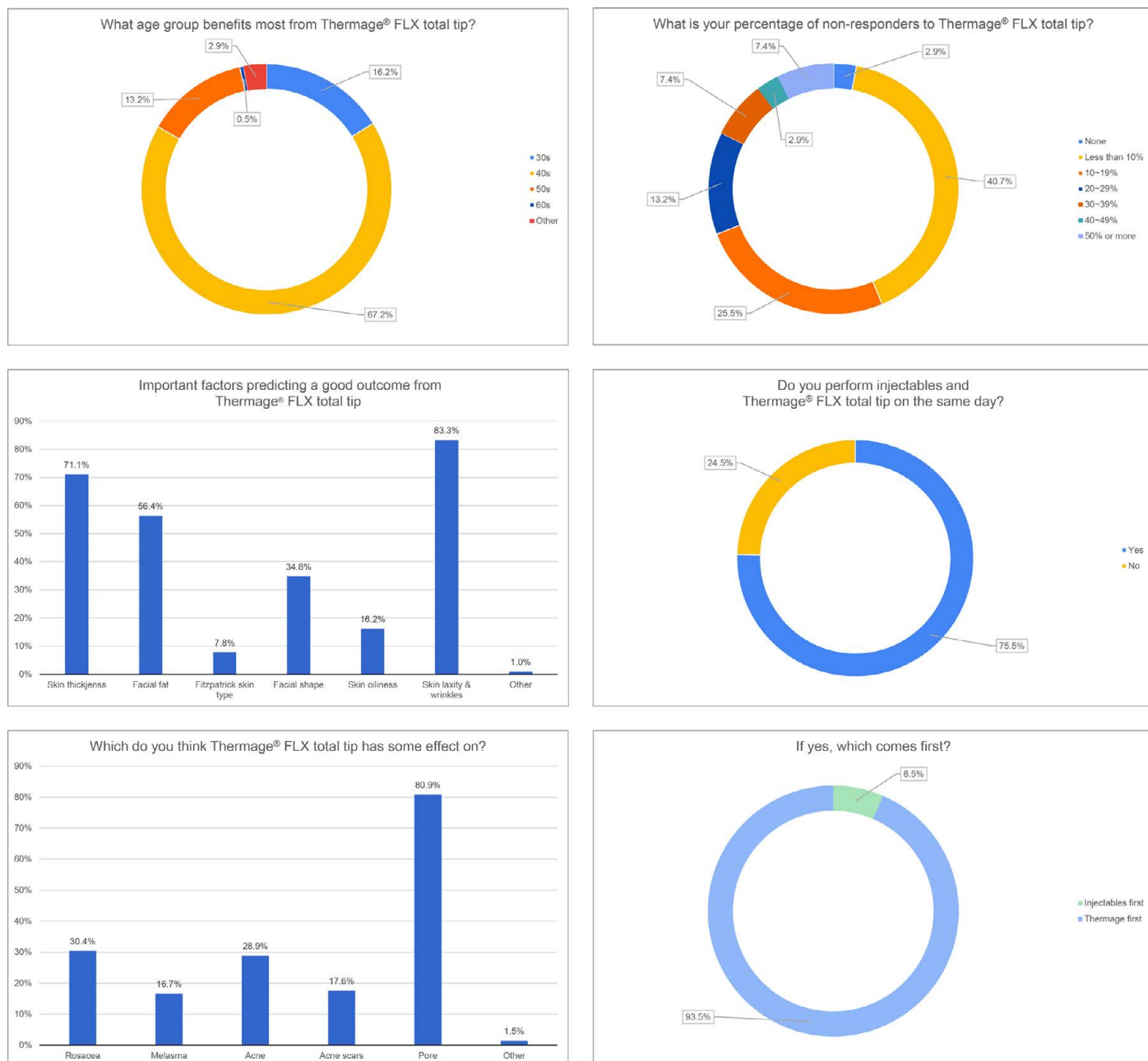


FIGURE 2B. Perceived effectiveness of Eye Thermage.

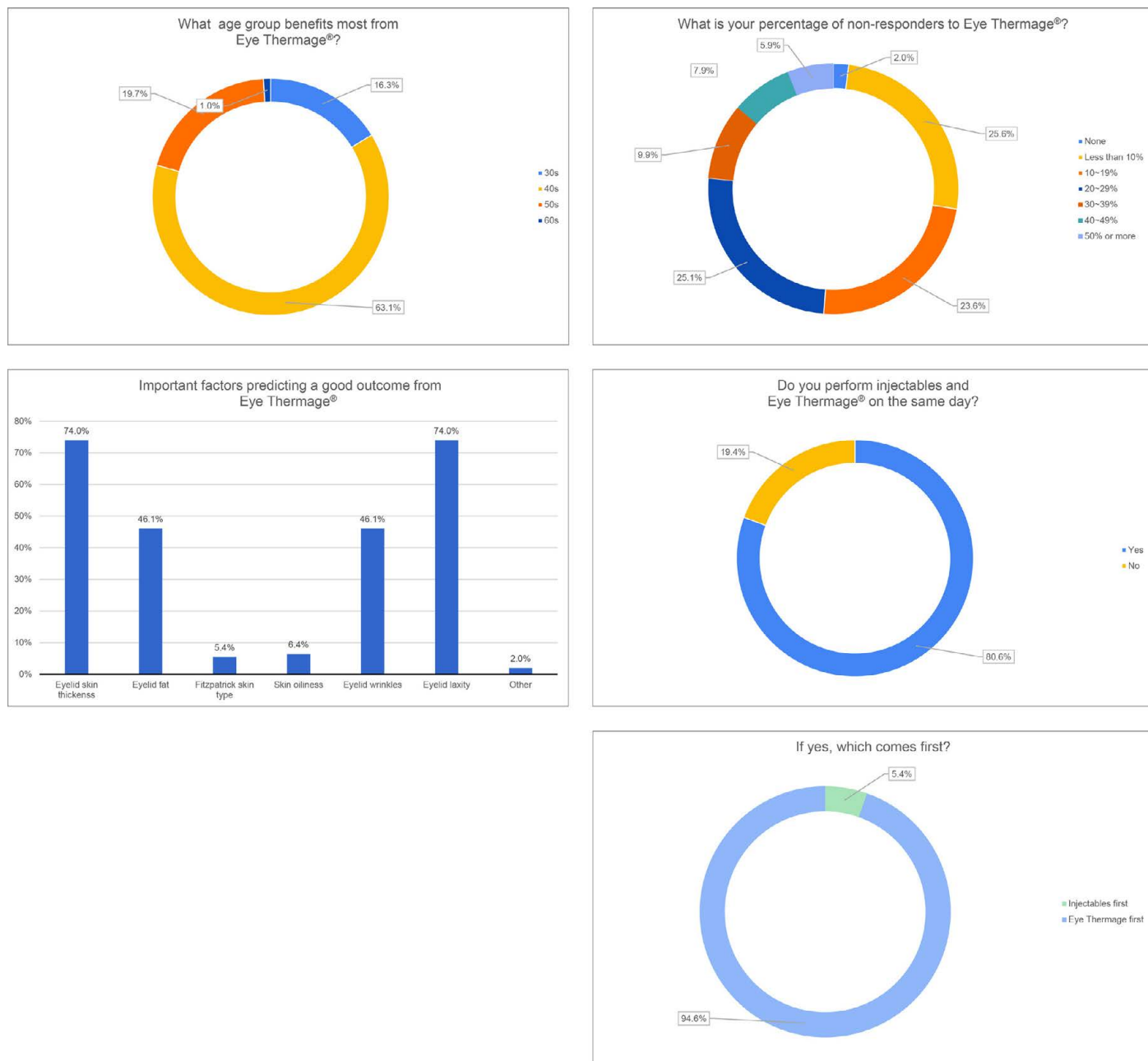


FIGURE 3A. Practice patterns of the Thermage FLX total tip.

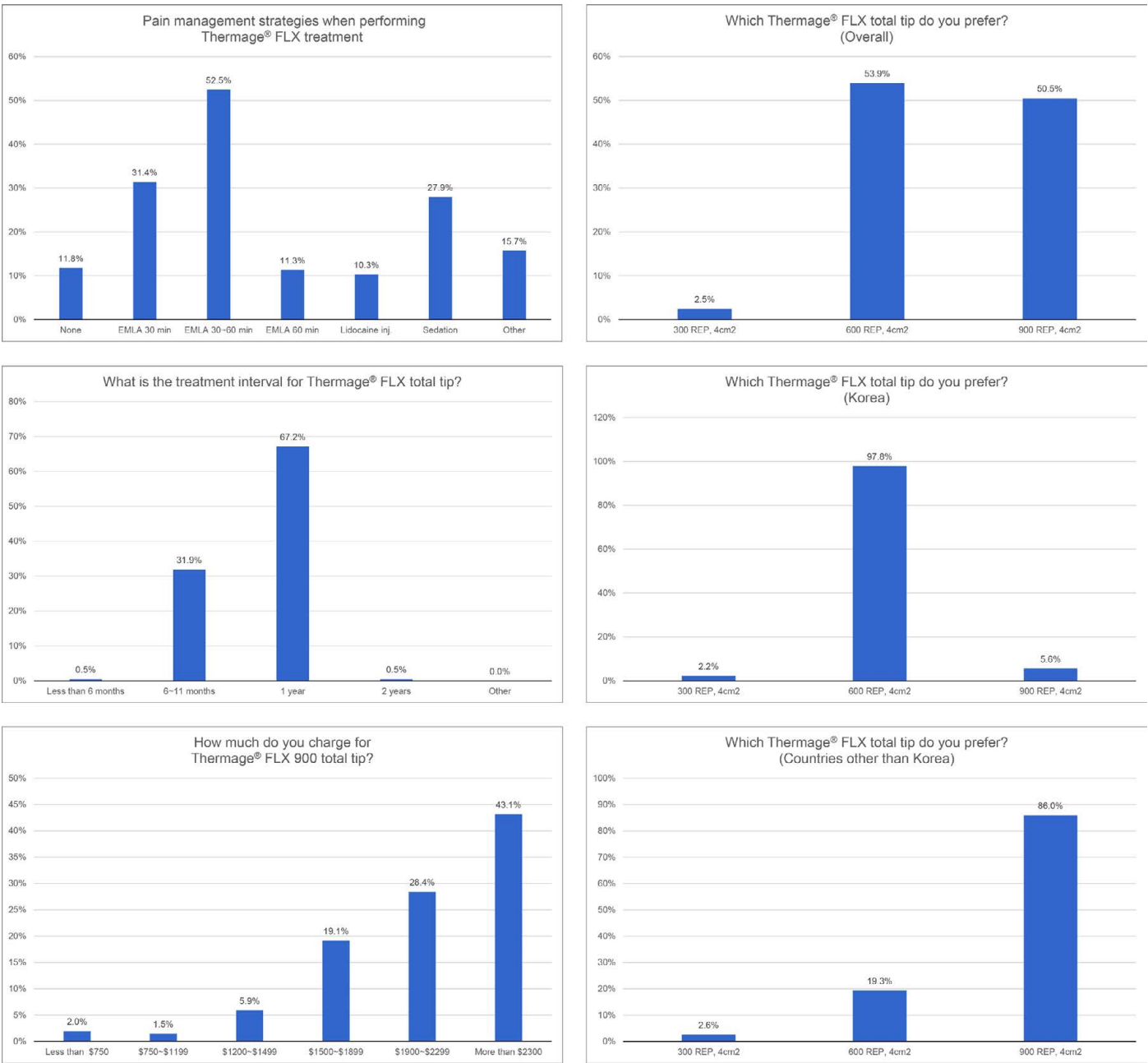


FIGURE 3B. Practice patterns of Eye Thermage.

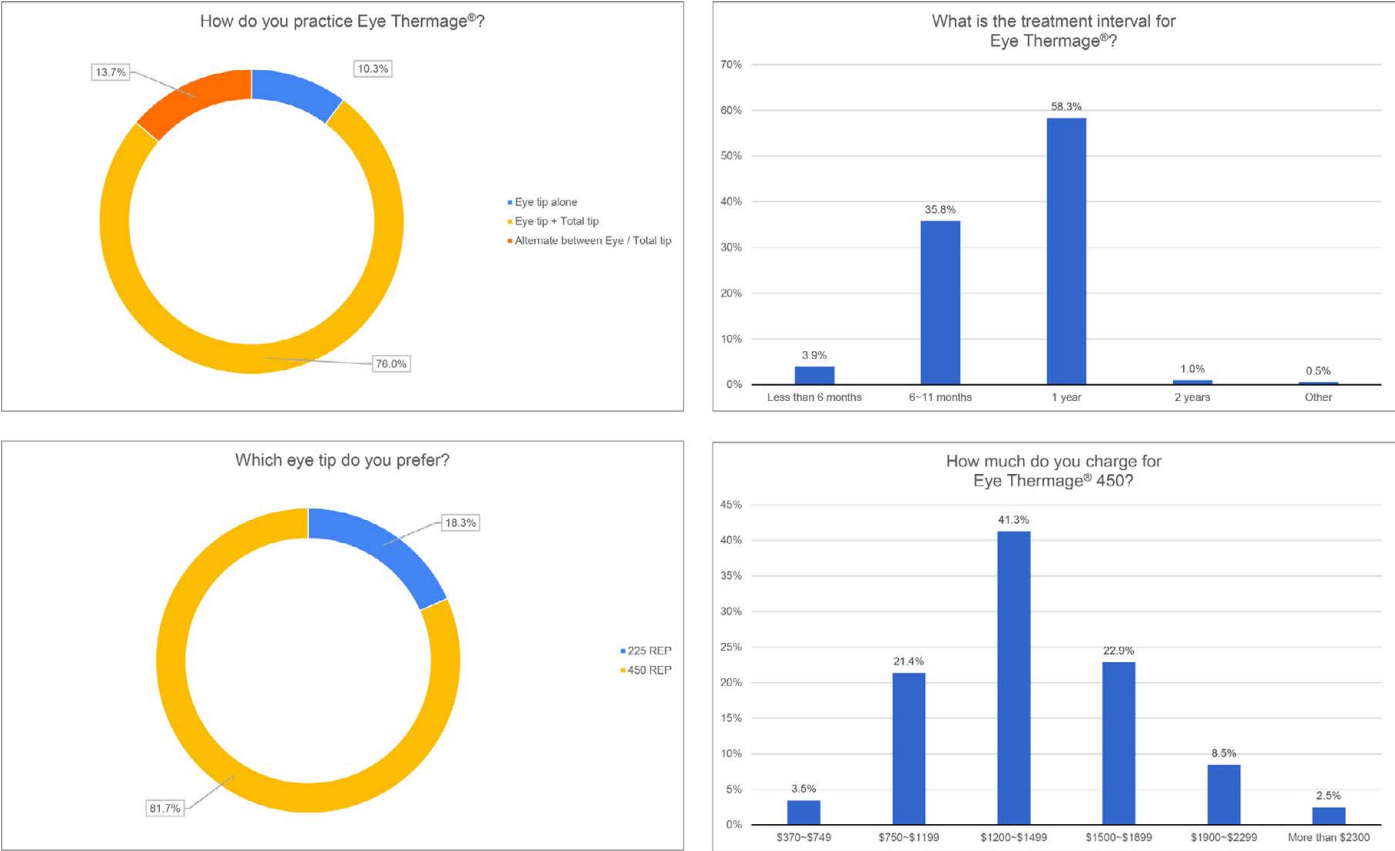


FIGURE 3C. Treatment levels used in Thermage FLX.

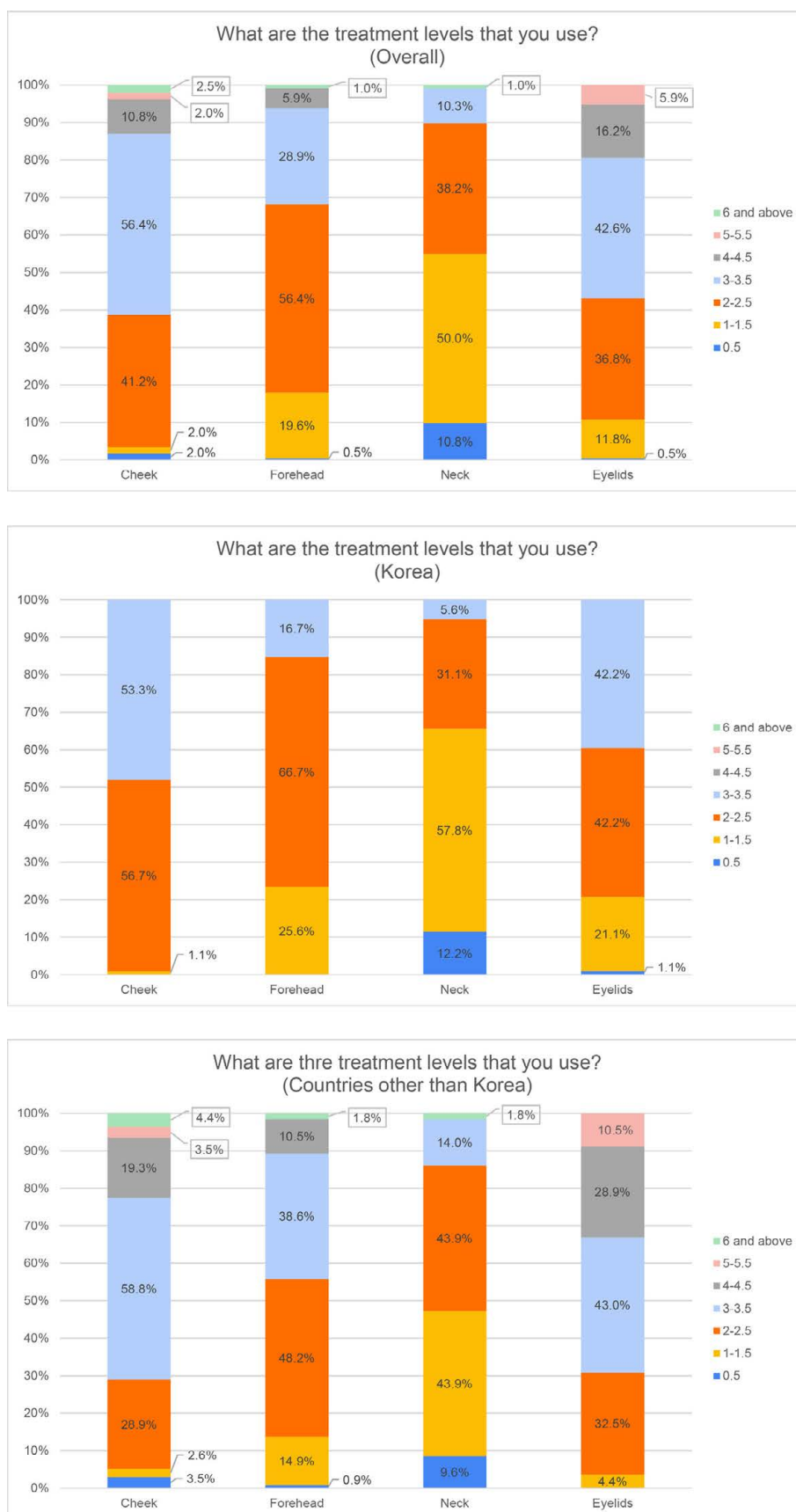


FIGURE 4. Complications experienced with Thermage FLX.

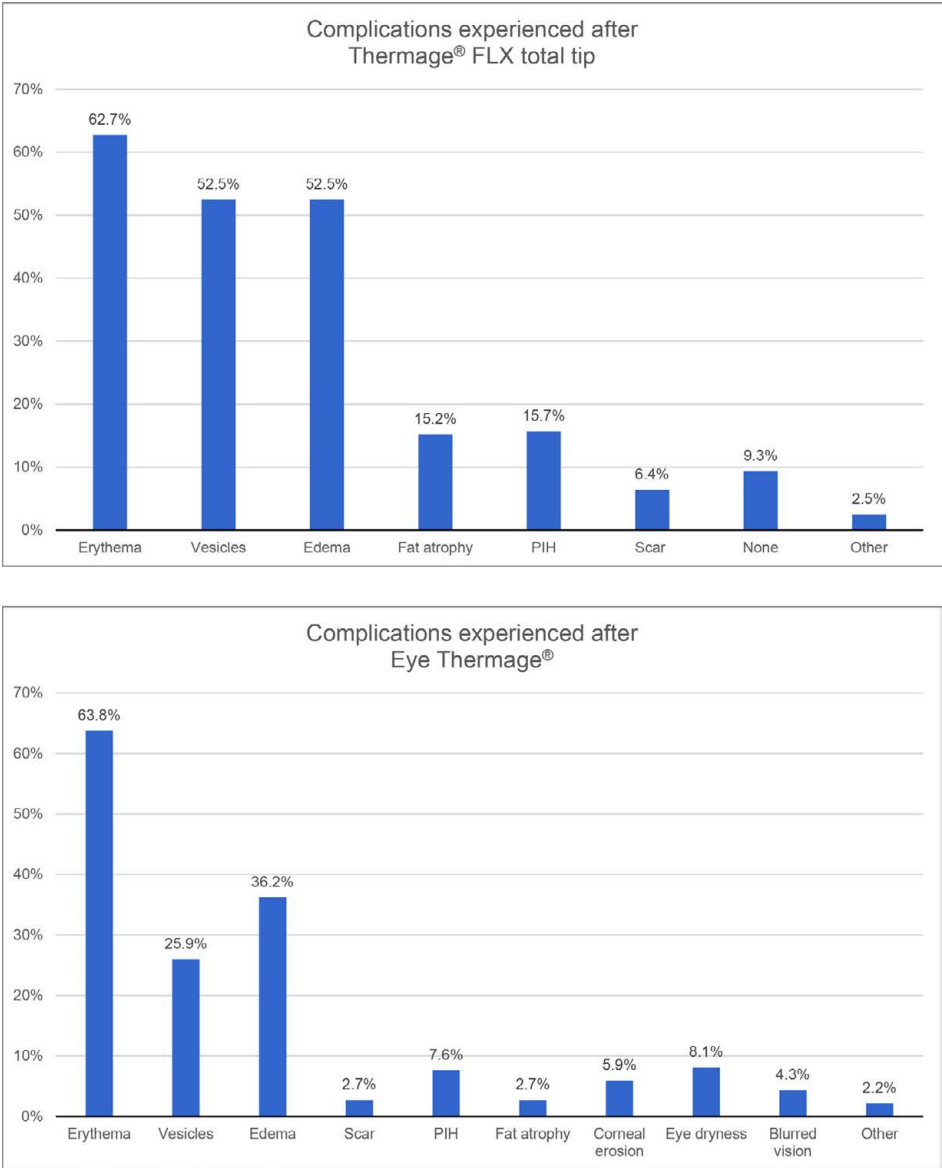




FIGURE 5B. Data regarding physicians' self-experience with Eye Thermage.



CONCLUSION

Thermage FLX represents a significant advancement in non-invasive skin rejuvenation and is widely endorsed by Asia-Pacific physicians, with high rates of satisfaction and self-experience. While results are gradual and often require annual sessions, the device is considered ideal for patients in their 40s with mild to moderate skin laxity. Combination protocols involving the total (600 REP 4 cm² tip or 900 REP 4 cm² tip) and eye (450 REP 0.25 cm² tip)—often with injectables—are common, with monopolar RF typically administered first. Serious complications are rare, and patient comfort can be effectively managed with EMLA cream. Conservative energy settings, particularly for delicate areas like the neck, are advised to reduce risks. We hope the insights from this 2024 survey support clinicians in optimizing their Thermage FLX practice.

DISCLOSURES

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Social Media Analysis of #LipFiller: Content and Quality

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INTRODUCTION

The popularity of fillers for lip enhancement—commonly referred to as “lip fillers”—has grown substantially in recent years.^{1,2} A 2024 survey reported a 3.4% global increase in aesthetic procedures.¹ As lip fillers become more widely offered in medical offices and medspas, there has been a corresponding rise in social media content related to these treatments.^{2,3} Visual social media platforms, such as Instagram, use the hashtag #lipfiller as digital repositories of user-generated content, provider marketing, patient testimonials, and educational materials, subsequently shaping public perception and influencing consumer behavior.³ As the range of providers who perform lip filler procedures has expanded from MD/DOs to mid-level providers and aestheticians, there remains the question of discrepancies in information quality among posts between providers.^{2,4} However, there are no studies to date evaluating the educational content and quality of the top social media posts containing content about lip fillers.

This study aims to evaluate Instagram posts tagged with #lipfiller across two domains: information content and quality. We hypothesize that posts from MDs/DOs will feature higher-quality educational material compared to those from non-physician providers. We aim to better understand how lip filler procedures are portrayed online and to identify gaps, biases, or misrepresentations that may shape patient expectations and clinical practice.

MATERIALS AND METHODS

A cross-sectional study was conducted on April 10, 2025, in order to evaluate the content and quality of the top 50 #lipfiller Instagram posts. Three independent reviewers analyzed each post and extracted data, including content category, comment number, number of followers, QQS scores, and mDISCERN scores. Posts were analyzed by the type of provider posting content, which included dermatologists, plastic surgeons, dentists, other physicians (MD, DO), nurse practitioners, registered nurses, physician assistants, aestheticians, and brand representatives. Modified DISCERN (mDISCERN) and Global Quality Scale (QQS) were used to assess the reliability and quality of top #lipfiller Instagram posts, respectively. Higher mDISCERN and QQS scores indicate higher degrees of reliability

and quality. For statistical analysis, one-way analysis of variance (ANOVA) with Tukey's multiple comparison test was used to compare mean mDISCERN and QQS scores among different post types. Statistical significance was defined as $P < 0.05$. Data were analyzed using GraphPad Prism (GraphPad Software, San Diego, CA).

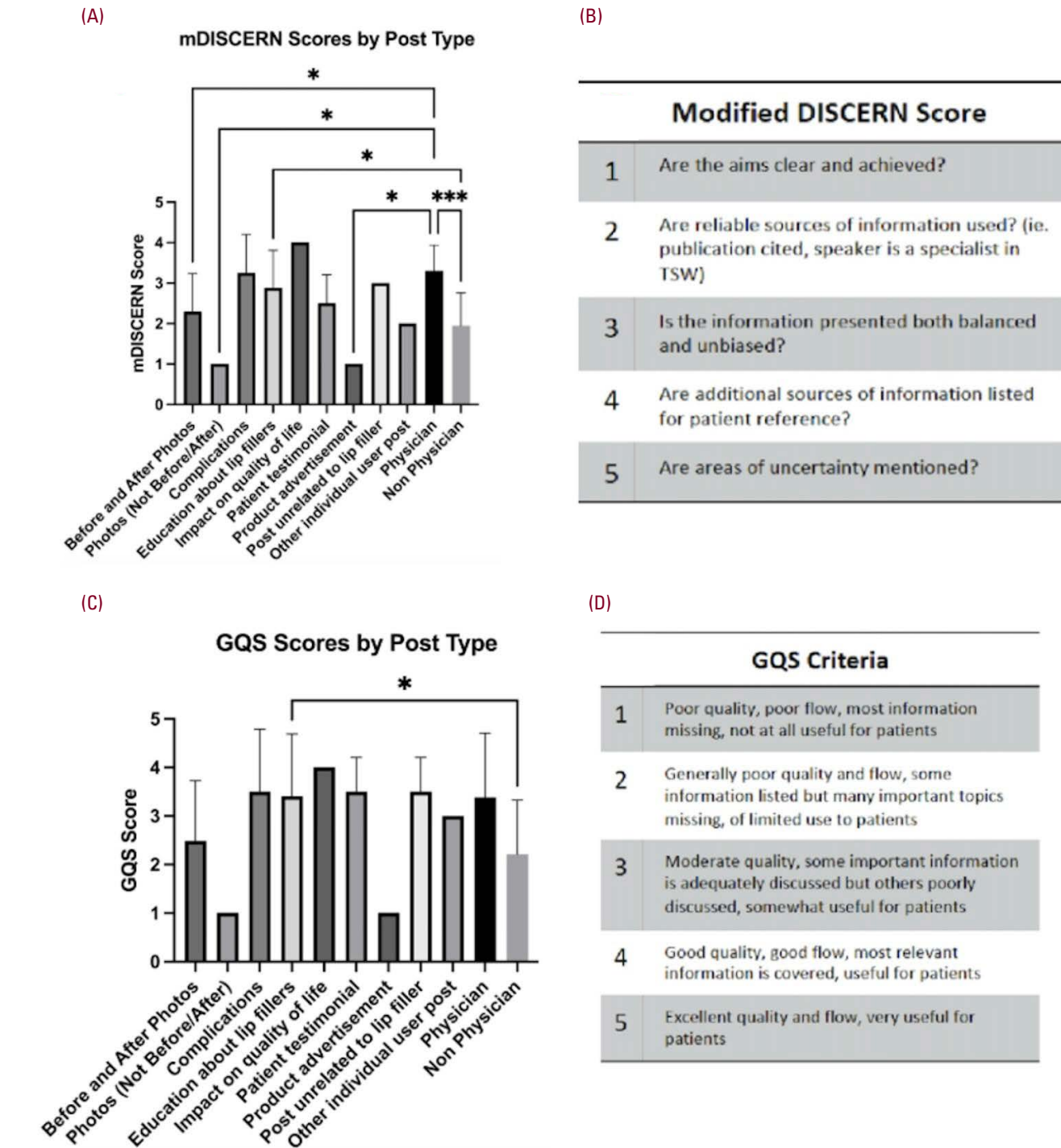
RESULTS

Only 26% of the top 50 #lipfiller Instagram posts were made by physicians. The average mDISCERN scores of physicians were 3.31 (SD=0.65), while the mDISCERN score for non-physicians was 1.95 (SD=0.81). Among all posts, aestheticians accounted for 34%, nurse practitioners for 16%, brand/product representatives for 12%, physician assistants for 8%, registered nurses for 6%, dentists for 4%, plastic surgeons for 4%, and individual users for 2%. Interestingly, only 1/50 posts were made by a dermatologist. The average QQS scores for physicians and non-physicians were 3.38 (SD =1.3) and 2.21 (SD =1.1), respectively. The mDISCERN scores for posts made by physicians were significantly higher than posts made by non-physicians ($P=0.0001$). The most popular posts contained before and after photos, education about lip filler, patient cases that were not before and after, and complications of lip filler use.

DISCUSSION

Social media functions as a powerful tool to disseminate information about dermatological procedures. However, the educational quality of popular Instagram posts is poor across all creators. Posts created by physicians had significantly higher scientific reliability than posts made by non-physicians. The most common content contained in these posts was before and after photos with limited educational content. Given the widespread popularity of social media posts containing content related to lip filler, it is crucial that dermatologists implement evidence-based, scientifically accurate information in posts containing #lipfiller. While patient testimonials and before-and-after photos offer meaningful insight into personal patient experiences, it is important for healthcare providers to disseminate reliable information about lip filler injections to prevent the dissemination of inaccurate and possibly harmful misinformation about cosmetic injectables.

FIGURE 1. mDISCERN and GQS scores based on content and creator type. Three independent reviewers calculated mDISCERN and GQS for each post. To calculate mDISCERN scores, one point was given for an answer of “yes” and zero points were given for a score of “no”, with scores ranging from 0 to 5 (B). GQS calculations were made by assigning a score ranging from 1-5 based on the listed criteria (D). ANOVA one-way with multiple comparisons was used to compare mDISCERN (A) and GQS (C) scores by post type.



*represents significance $P<0.05$; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$.

CONCLUSION

The overall educational content and quality of the most popular lip filler posts on Instagram are poor. Dermatologists should prioritize distributing content with high educational quality when creating and disseminating lip filler content on Instagram.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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Unveiling Artificial Intelligence's Diagnostic Power and Challenges in Dermatology for Skin of Color: A Review

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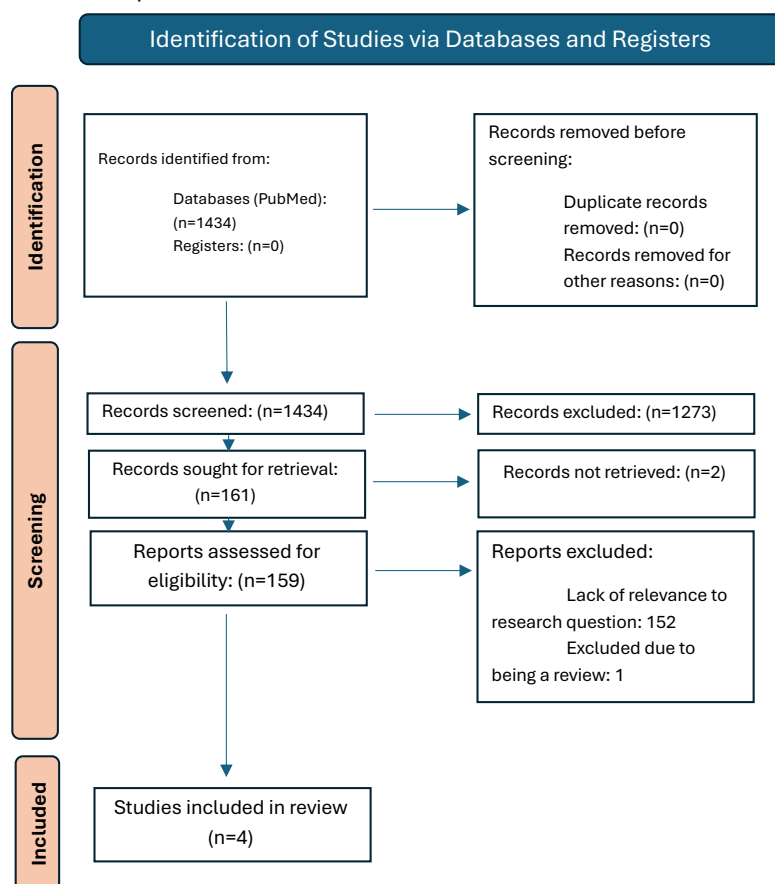
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INTRODUCTION

Artificial intelligence (AI) has the ability to revolutionize the diagnostic outcomes and accessibility of dermatology.¹ This study scrutinizes the application of AI in dermatology, specifically assessing its effectiveness in diagnosing skin conditions in skin of color (SOC), while synthesizing the emerging trends of dermatologic AI and SOC,

thus serving as a resource to address the bias toward lighter skin tones—a fundamental shortcoming of AI— which is vastly understudied.² The goal is to help guide researchers and developers on ways to create more inclusive tools for equitable diagnostic use, highlighting limitations and providing insight into ways to mitigate bias and make change toward equitable and reliable AI dermatologic outcomes.

FIGURE 1. This figure shows how the authors picked the studies used in this review.



Four authors jointly analyzed posts via PubMed from December 10th, 2023 to May 21st, 2024. The keyword searches included: (Artificial Intelligence dermatology). 1434 articles were identified, and ultimately 4 were included in the review.

An analysis of the sources in this review found significant disparities in the ability of AI models to diagnose skin disease in individuals of darker skin tones (Fitzpatrick skin types 5 and 6) when compared to individuals with lighter skin tones. An inherent bias is revealed in two studies as evidenced by AI originally trained with lighter skin toned images having lower metric performance in the areas of sensitivity, specificity, positive predictive value, negative predictive value, F1 score, and area under the receiver operating characteristic curve when diagnosing basal cell carcinoma and melanoma in images of darker skin tones as compared to lighter skin tones.

Recognizing this disparity, researchers have found that the use of unsupervised image-to-image translation in medical AI image recognition models by synthetically darkening light skin images while retaining lesion-specific features has the potential to improve accuracy across diverse skin tones. Early findings show that these modified images can improve model adaptability for darker skin tones and pave an innovative path for enhancing AI diagnostic equity.

A major limitation remains the limited availability of skin lesions from individuals with darker skin types. Large, diverse datasets are crucial for closing the performance gap. One study aimed to address this gap by introducing a resource called the Diverse Dermatology Data Set Images, finding that AI models trained with this data set performed better on darker skin types.

AI shows great promise for the future of dermatology; however, a key challenge identified is the performance disparity of AI algorithms on darker skin tones, likely due to biased training datasets and a lack of clinical images depicting darker skin tones. This affects diagnostic reliability and raises ethical concerns about healthcare equity, as AI tools may perpetuate disparities in racially diverse populations if not properly addressed.

Future research is needed and should focus on expanding datasets to better represent diverse skin tones and exploring techniques such as unsupervised image-to-image translation to improve AI performance in racially diverse contexts. The emerging evidence in the field of AI and SOC addressed in this review underscores data-driven avenues for creating regulatory standards and reducing diagnostic inequity in dermatology.

DISCLOSURES

The authors have no conflict of interest to declare.

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Prevalence of Pruritus in Type 2 Diabetic Patients on GLP-1 Agonist Therapy

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INTRODUCTION

Chronic pruritus is a commonly underestimated comorbidity in type 2 diabetes mellitus (T2DM) patients, affecting between 18.4% to 27.5% of diabetics.¹ Glucagon-like peptide-1 (GLP-1) agonists have reportedly decreased itch in diabetics with concurrent psoriasis²; however, their role in targeting itch specifically remains unknown. To investigate the association of GLP-1 agonists and pruritus prevalence in T2DM, we conducted a retrospective cohort study utilizing the TriNetX database.

Four cohorts were defined as T2DM patients prescribed semaglutide, dulaglutide, liraglutide, or tirzepatide. The control cohort included T2DM patients without any GLP-1s. GLP-1 therapy was also compared with T2DM patients prescribed metformin. Additionally, the effects of GLP-1 therapy were analyzed between diabetics without neuropathy versus those with neuropathy. Sources of infectious itch and injection site pruritus were excluded from all groups. Cohorts were propensity matched for demographics, comorbidities, and comedications. Pruritus prevalence was evaluated at 14 days, 3 months, 6 months, and 12 months post-GLP-1 therapy (Table 1).

Compared to controls, all GLP-1 medications were associated with significantly decreased pruritus after two weeks. Following one year, semaglutide, dulaglutide, and tirzepatide further decreased itch prevalence versus 14 days. Relative to metformin, liraglutide did not significantly decrease pruritus at any point. Conversely, after two weeks, semaglutide, dulaglutide, and tirzepatide all lowered itch rates. After one year, semaglutide and tirzepatide were again associated with significantly decreased itch compared to two weeks. Additionally, semaglutide, dulaglutide, and liraglutide significantly improved pruritus in diabetics without neuropathy compared to those with neuropathy. Tirzepatide was associated with similar itch improvement in both groups.

Compared to controls, GLP-1 agonists were effective in decreasing pruritus prevalence. Semaglutide, dulaglutide, and tirzepatide also demonstrated superior itch relief relative to metformin. This suggests that these GLP-1 agonists' benefits on pruritus extend beyond glucose or hemoglobin A1c improvement. Additionally, approximately 50% of diabetics experience pruritus in the context of diabetic neuropathy.¹ However, diabetics without neuropathy were associated with greater or similar itch improvement after

TABLE 1.

Pruritus Prevalence at Various Time Points After GLP-1 Treatment				
Cohorts	GLP-1 agonist	14 days	6 months	1 year
GLP-1 vs Control	Semaglutide	0.32 (0.33-0.36)	0.29 (0.28-0.31)	0.23 (0.22-0.25)
	Liraglutide	0.58 (0.54-0.63)	0.56 (0.51-0.60)	0.51 (0.47-0.56)
	Dulaglutide	0.46 (0.44-0.49)	0.43 (0.41-0.46)	0.39 (0.36-0.41)
	Tirzepatide	0.23 (0.21-0.25)	0.15 (0.13-0.17)	0.09 (0.08-0.11)
GLP-1 vs Metformin	Semaglutide	0.50 (0.46-0.54)	0.42 (0.39-0.47)	0.34 (0.30-0.38)
	Liraglutide	0.95 (0.81-1.12)	0.88 (0.74-1.05)	0.94 (0.77-1.14)
	Dulaglutide	0.79 (0.70-0.88)	0.72 (0.64-0.82)	0.66 (0.57-0.76)
	Tirzepatide	0.29 (0.25-0.35)	0.11 (0.08-0.15)	0.11 (0.08-0.14)
GLP-1: No Diabetic Neuropathy vs. Diabetic Neuropathy	Semaglutide	0.67 (0.60-0.75)	0.65 (0.56-0.75)	0.64 (0.53-0.76)
	Liraglutide	0.69 (0.57-0.82)	0.73 (0.59-0.91)	0.61 (0.48-0.78)
	Dulaglutide	0.63 (0.56-0.70)	0.59 (0.51-0.67)	0.64 (0.55-0.74)
	Tirzepatide	0.79 (0.55-1.13)	1.38 (0.87-2.17)	1.41 (0.76-2.63)

GLP-1 therapy compared to diabetics with neuropathy. As such, it is unlikely that GLP-1s decrease itch through neuropathy relief. Instead, although the exact mechanism is currently unclear, it is possible that GLP-1 agonists' anti-inflammatory effects dampen itch. These medications downregulate inflammatory markers, such as interleukin (IL)-6 and IL-17, which play a role in pruritus pathogenesis.^{3,4} GLP-1 therapy decreases expression of IL-23, IL-22, and tumor necrosis factor- α , key pro-inflammatory cytokines linked to inflammatory skin diseases associated with both diabetes and itch.⁵

Limitations include unaddressed confounding variables, patient medication adherence, dosage details, ICD code misclassification bias, and lack of causal conclusions. However, our findings strongly suggest an association between semaglutide, tirzepatide, and dulaglutide therapy with decreased pruritus prevalence. Semaglutide and tirzepatide also appear to have a stronger effect on itch over time.

DISCLOSURES

There are no potential conflicts or conflicts of interest.

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NEWS, VIEWS, AND REVIEWS

From Misdiagnosis to Resistance: The Need for Antifungal Stewardship in Dermatology

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INTRODUCTION

Dermatophytoses, fungal infections of the skin, hair, and nails, affect approximately 25% of the global population, and reports of antifungal therapy-resistant infections have risen over the past decade.¹ A major contributor to this trend is the widespread practice of empirically treating suspected fungal infections without diagnostic confirmation.¹

Misdiagnosis is common, as dermatophytoses exhibit considerable clinical variability and mimic numerous inflammatory dermatoses, including secondary syphilis, annular psoriasis, and pityriasis rosea.² Reflecting these challenges, the American Academy of Dermatology's Choosing Wisely campaign recommends avoiding empiric oral antifungal therapy without confirmatory testing for suspected onychomycosis.³ Nevertheless, dermatologists frequently prescribe antifungals without confirmatory testing.⁴ This review examines the diagnostic gaps that contribute to inappropriate antifungal prescribing, the role these practices play in antifungal resistance (AFR), and stewardship strategies to improve accuracy and treatment outcomes.

Diagnostic Gaps in Dermatophytoses

The diagnostic evaluation of dermatophytoses includes potassium hydroxide (KOH) microscopy, fungal culture, polymerase chain reaction (PCR) testing, and histopathology.¹ KOH preparations provide inexpensive, rapid diagnosis, yet they are frequently underutilized in the clinical setting^{1,4} (Figure 1). In a survey of 308 dermatologists, 20.9% "rarely" or "never" performed fungal examinations prior to prescribing antifungals, and 19.9% reported "sometimes" doing so.⁴

Figure 1. Example of a clinical presentation of tinea incognito (left) and corresponding KOH microscopy (right).



The belief that clinical examination alone is sufficient remains a major barrier, despite evidence demonstrating the high rate of visual misclassification caused by the varied presentations of dermatophytoses.⁴ For example, Yadgar et al conducted an image-based survey, in which dermatologists were asked to categorize 13 clinical images as either fungal or non-fungal infections; only 8 out of 13 cases were correctly categorized more than half of the time, with only one case achieving >90% diagnostic accuracy.²

Diagnostic confirmation is even less common in onychomycosis, as a recent study by Gupta et al demonstrated that among 120,000 patients with suspected onychomycosis, only around 10% of patients who received oral antifungals and 16% who received topical antifungals underwent confirmatory testing.⁵ This gap may be attributed to the higher costs of KOH preparation and periodic acid-Schiff (PAS) evaluation compared to empiric terbinafine treatment.⁶ However, recent studies report that confirmatory testing may ultimately be less expensive than the downstream costs associated with misdiagnosis and treatment failure.^{5,6}

Consequences of Empiric Antifungal Treatment

Empiric antifungal treatment for non-fungal conditions delays accurate diagnosis and care while contributing to selective pressure that fosters resistance.^{2,7} AFR has become increasingly recognized globally, with terbinafine-resistant *Trichophyton rubrum* and *T. indotineae* most prominently implicated.¹ The first US case of *T. indotineae* resistant to oral terbinafine was reported in 2023, confirming AFR as a worldwide issue.¹ Resistance has since been documented across both fungicidal (eg, terbinafine) and fungistatic (eg, azoles) drug classes, reinforcing the need for stewardship.¹

In addition to empiric use, prescribing antifungals for non-fungal conditions, such as seborrheic dermatitis (SD), adds to unnecessary exposure and may promote AFR. SD is a chronic skin disorder affecting areas of the body rich in sebaceous glands.⁸ Though *Malassezia* yeast overgrowth is one of multiple driving factors of SD, in addition to epidermal skin barrier disruption and a dysregulated inflammatory response, it is not considered a true fungal infection; yet topical ketoconazole (1% over the counter (OTC); 2% prescription) shampoo remains first-line therapy for SD of the scalp.⁸ Studies have reported elevated minimum inhibitory concentrations (MICs) in *Malassezia* isolates for azoles and terbinafine in SD patients,

suggesting that chronic antifungal use may drive resistance.⁹ Although prospective resistance studies in SD are limited, the broad OTC availability of antifungal shampoos highlights the need to better understand the effects of their repeated use over time. SD treatment also includes anti-inflammatory agents such as once-daily roflumilast 0.3% foam, which has been proven effective in recent clinical trials and may decrease the potential risk of breeding AFR compared to antifungal shampoos.¹⁰

Antifungal Stewardship

The lack of diagnostic testing for suspected fungal infections, along with the rise in AFR calls for antifungal stewardship (AFS) programs. AFS aims to optimize the diagnosis, treatment, and prevention of fungal infections while minimizing the emergence of antifungal resistance.⁷ Although antimicrobial stewardship programs are widely established, most are centered on antibiotic stewardship, and few formally integrate AFS, despite increasing reports of treatment failures and resistant dermatophyte strains.⁷ The World Health Organization has identified antifungal resistance as a major public health concern, underscoring the need for coordinated efforts across clinical and public health systems.⁷

A core principle of AFS is ensuring diagnostic confirmation prior to treatment and discouraging empiric antifungal therapy.^{1,7} At a minimum, KOH with microscopy, fungal culture, or PCR should be performed before prescribing antifungals, particularly for recurrent infections or atypical presentations.⁷ Molecular-based diagnostic tools, including PCR and genomic sequencing of the internal transcribed spacer (ITS) region, should be considered when resistant dermatophytoses are suspected.⁷

Expert recommendations emphasize the importance of collaboration among dermatologists, academic centers, public health agencies, and professional societies to monitor resistant strains and coordinate effective response strategies.¹ Clinicians should report unusual or recalcitrant cases to state health departments or the Centers for Disease Control and Prevention (CDC) and avoid unnecessary antifungal exposure, including topical steroid–antifungal combination products, to minimize selection pressure.

An important yet understudied area is practitioner training. Limited research exists on dermatology residents’ training in KOH preparation, their comfort with the procedure, and their willingness to perform it. This gap highlights a need for further investigation, as it may help inform strategies for addressing AFS.

CONCLUSION

The rising prevalence of antifungal resistance underscores the urgent need to strengthen diagnostic accuracy and reduce unnecessary antifungal exposure. Misdiagnosis of dermatophytoses remains common, and the reliance on empiric therapy contributes to treatment failures, delayed care, and selective pressures that promote resistance.^{4,7} Antifungal stewardship programs provide a

framework for addressing these gaps by emphasizing diagnostic confirmation before therapy, the adoption of molecular diagnostic tools, and improved coordination among clinicians, laboratories, and public health agencies.⁷ Future studies assessing dermatology residency training on dermatophyte diagnostics may further strengthen stewardship strategies.

DISCLOSURE

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Field (Cancerization) Tested: Patient and Provider Perspectives on Klisyri

In **Field (Cancerization) Tested: Patient and Provider Perspectives on Klisyri**, guest host **Dr. Vishal A. Patel**, Associate Professor of Dermatology and Medicine/Oncology at the George Washington University School of Medicine and Health Sciences and Director of Cutaneous Oncology at the GW Cancer Center, speaks with **Amanda Caldwell, DNP, FNP-C**, dermatology nurse practitioner at U.S. Dermatology Partners and President of the Society of Dermatology Nurse Practitioners (SDNP). Drawing on her experience as both a clinician and a patient treated with Klisyri (tirbanibulin 1%) as well as other field therapies, Ms. Caldwell shares how her personal journey has deepened her advocacy for early detection, field therapy awareness, and patient-centered care. Together, they discuss evolving strategies for managing actinic keratosis and field cancerization, comparing experiences with various field treatments and highlighting the unique profile of Klisyri. The conversation offers practical, evidence-based pearls for dermatology professionals and advanced practice providers — as well as valuable firsthand insights for patients navigating their own treatment decisions for actinic keratosis.



HOST
Dr. Vishal A. Patel



GUEST
Amanda Caldwell,
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‡An 11-week clinical study on n=50 women with Fitzpatrick skin phototypes III-VI (2023, India). Mela B3 Serum was used twice daily for 8 weeks in conjunction with a sunscreen (AM) and lightweight moisturizer (PM). Sunscreen and moisturizer were continued for the remaining 3 weeks.

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