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JOURNAL OF DRUGS IN DERMATOLOGY

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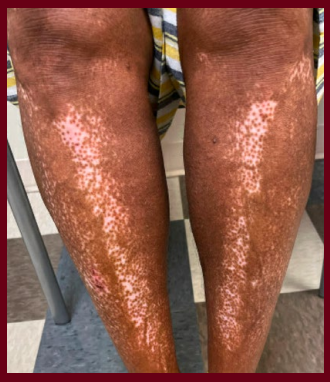

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Sebaceous Hyperplasia: Perceptions, Utilization, Cost

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Cysteamine Isobionic-Amide Complex Versus Kligman's Formula for the Treatment of Melasma: Equal Efficacy and Rapid Onset of Action

Mukta Sachdev MD,[a] Pearl E. Grimes MD,[b] Valerie Callender MD,[c] Corey L. Hartman MD,[d] Susan C. Taylor MD,[e] Nada Elbuluk MD MSc,[f] Ashraf Badawi MD,[g] Yoko Funasaka MD PhD,[h] Joyce Lim MD,[i] Chau Yee Ngee MD,[j] Seemal R. Desai MD[k]

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ABSTRACT

Background: Modified Kligman's formula (mKF) is the gold standard treatment for melasma; however, its prolonged use is not recommended due to side effects. Cysteamine is a potent, safe, and effective depigmenting agent. Here, we conducted a double-blind, randomized, and placebo-controlled clinical trial to assess the efficacy of cysteamine isobionic-amide — a complex with enhanced depigmenting efficacy — and compared it to mKF for the treatment of melasma.

Methods: This study involved a total of 80 patients divided into 3 groups: cysteamine-isobionic amide, placebo, or mKF. The modified Melasma Area Severity Index (mMASI) score and spectrophotometric evaluation were conducted at baseline, week 4, week 8, and week 16. Dermatological assessment, patients' feedback, and satisfaction including quality-of-life scores were also collected.

Results: At week 4, cysteamine isobionic-amide and mKF groups showed an equivalent onset of action in terms of mMASI and skin pigmentation contrast reduction. The 2 groups significantly reduced melasma severity and improved the overall skin condition with a comparable efficacy at week 16. Quality of life of melasma patients was significantly improved in the cysteamine isobionic-amide group at week 8 and further at week 16 ($P<0.001$) compared to the mKF group. Patients' feedback and satisfaction were higher with the cysteamine isobionic-amide product compared to mKF.

Conclusion: Cysteamine isobionic-amide provided a rapid onset of action and was as effective as the mKF for the treatment of melasma. The data suggest that cysteamine isobionic-amide could potentially be an acceptable alternative to mKF for the long-term treatment of melasma.

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INTRODUCTION

Melasma is an acquired, pigmentary disorder characterized by the appearance of light brown to dark macules on sun-exposed areas of the body, most commonly occurring on the face. It can affect all racial and ethnic groups but is more common in women and individuals of color.[1] Melasma is known to significantly impact the psychological health and therefore the quality of life of the people affected.[2,3]

Over the years, a wide range of depigmenting compounds have been introduced for the treatment of melasma.[4–7] Hydroquinone (HQ) is an effective depigmenting agent used for the treatment of epidermal melasma. Several mechanisms of action have been proposed for HQ over the years, such as tyrosinase inhibition, modification of melanosome formation, or reduction of DNA and RNA synthesis with concomitant melanosome degradation and melanocyte destruction.[8–12]

In 1975, Kligman and Willis investigated ways to enhance the depigmenting effect of hydroquinone.[13] At that time 2 observations were made. First, the skin of patients with acne who were treated for several months with topical retinoic acid occasionally showed a light hypopigmentation. Second, a loss of pigment was observed after intradermal injection of corticosteroids into darker skin types. Thus, these researchers had the idea to combine HQ with retinoic acid and corticosteroids.[13] Surprisingly, rather than an additive effect, this combination showed a synergistic depigmenting action, which was not explainable at that time. To date, we know that retinoic acid not only acts as a depigmenting agent via increasing keratinocytes shedding off from the epidermis (increasing melanin loss) but is also an inhibitor of glutathione S-transferase, the latter protecting melanocytes against the melanocytotoxic activity of HQ.[14] Retinoic acid thus increases the susceptibility of melanocytes to the cytotoxic action of HQ.[14]

Numerous clinical studies have, since that time, confirmed the high efficacy of modified Kligman's formulas (mKF) for the treatment of many disorders of hyperpigmentation and a gold standard treatment for melasma. Over the years, the mKF has been modified regarding the type of corticosteroids and the vehicles used. Due to the significantly high efficacy as well as the rapid onset of action, mKF have become the most widely used HQ-based products for treatment of melasma.[15,16]

Cysteamine is the simplest aminothiol present in nature. It is an endogenous molecule produced in mammalian cells during the Coenzyme A metabolic pathway.[17] Endogenous cysteamine has been shown to play several roles in human biology. Among others, it acts as an intracellular antioxidant.[18,19] Oral cysteamine has also been used for the treatment of different pathologies, such as cystinosis, and neurodegenerative disorders.[19,20]

In 1966, Chavin and Schlesinger injected cysteamine hydrochloride into the skin of a black gold fish model and surprisingly discovered that cysteamine acts as a potent skin depigmenting agent.[21] Two years later, independent studies by Frenk et al and Bleehen et al showed higher depigmenting efficacy of topical cysteamine compared to HQ in the black Guinea pig model.[22,23] Despite these results, cysteamine was never developed into a topical formula due to its very unstable nature, its offensive odor produced upon oxidation, and its high irritant potential.[24,25]

In 2012, a technology was developed by Dr. B. Kasraee to stabilize cysteamine and significantly reduce its odor. For the first time, stabilized cysteamine 5% cream became available (Cyspera® Scientis SA, Switzerland). Several vehicle-controlled, double-blind clinical studies evaluated the efficacy and tolerability of stabilized cysteamine for the treatment of hyperpigmentation disorders.[26,27] These studies confirmed the potential efficacy of stabilized cysteamine as a depigmenting agent. In recent years, different formulations have been developed to enhance the depigmenting efficacy of topical cysteamine. Some of such formulations were successfully compared to known depigmenting agents, such as HQ and tranexamic acid, in clinical studies.[26–29] The most recent of these formulations combines cysteamine with isobionic- amide from the pyridine family of molecules (pyridine-4-carboxamide) and claims a high skin depigmenting efficacy.[30]

Some literature also points to the possibility of these cysteamine formulations being as effective or more effective than mKF.[31,32] The present study is a double-blind, randomized, and placebo-controlled clinical trial comparing the efficacy of cysteamine isobionic-amide combination with that of mKF for the treatment of melasma.

MATERIALS AND METHODS

A single center randomized, and double-blind clinical trial was conducted at MS Clinical Research Pvt. Ltd, India. The study protocol was conducted in compliance with the World Health Organization, International Conference on Harmonization's (ICH) Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, and Declaration of Helsinki. The study was approved by an Independent Ethics Committee.

Study Participants

Written informed consent was obtained from all patients prior to enrollment. Female patients (N=80) between ages 25-50 years with facial melasma, but otherwise healthy, were recruited. The treatment period was 16 weeks. The inclusion criteria were: (1) female patients between 25-50 years of age; (2) Fitzpatrick skin types III, IV, and V; (3) having moderate-to-severe mMASI scoring; (4) having epidermal or mixed melasma. The diagnosis of epidermal or mixed melasma was confirmed by Wood's lamp examination. Exclusion criteria were: (1) Patients with only dermal melasma; (2) history of allergenic reaction to any components of the products; (3) oral contraceptives or planning pregnancy 4 months after the end of the study period; (5) menopausal symptoms; (6) skin lightening skin procedure in the past 8 weeks; (7) topical treatment with hydroquinone in the past 8 weeks; (8) other skin diseases.

Screening Phase

Patients were asked to wash their faces with a standard facewash (Cetaphil® Gentle Cleanser, CGC) and acclimatize for 10 minutes at a temperature of 22°C ± 5°C and relative humidity of 50% ±10%. The dermatologist assessed the melasma severity on the mMASI scale and collected the medical and gynecological history. Patients meeting the inclusion and exclusion criteria were qualified to participate in the study. The washout phase lasted 14 days. The patients were allowed to continue their usual skincare routine (recorded in the log) but discontinue any

topical or oral depigmenting treatments and medications. The baseline visit was scheduled after 2 weeks.

Study Design

At each visit to the institute (week 4, week 8, and week 16), patients were instructed to wash their faces using a provided standard facewash (CGC), then let the skin acclimatize for 10 minutes at a temperature of 22°C ± 5°C and relative humidity of 50% ± 10%. Digital high-resolution images were acquired using VISIA-CR (Canfield Scientific Inc.). On these, dermatological examinations for modified mMASI scoring and identification of lesional and non-lesional sites were performed. Visual assessment of skin attributes was carried out and skin color was evaluated using a CM-2600d spectrophotometer (Konica Minolta Inc.). Patients were asked to fill in both self-assessment and quality-of-life (QoL) questionnaires.

Topical Application

Patients were randomized into one of the treatment groups based on the randomization plan. The patients were allocated to 3 different groups each receiving 3 test products coded as follows:

1. Group A (N=30, cysteamine isobionic-amide): daily short-contact active (A1, Cyspera® Intensive), rinsed with rinse-off active (A2, Cyspera® Neutralize), followed by leave on active (A3, Cyspera® Boost).
2. Group B (N=20, Placebo): daily short-contact placebo (CMC, Cetaphil® Moisturizing Cream), rinsed with rinse-off placebo (CGC, Cetaphil® Gentle Cleanser), followed by leave-on placebo (CML, Cetaphil® Moisturizing Lotion).
3. Group C (N=30, mKF): daily short-contact placebo (CMC), rinsed with rinse-off placebo (CGC) followed by leave on comparator active (mKF, Tri-Luma®).

The Cyspera® Intensive system provides a 3-step application involving 3 different products that are meant to be used sequentially. Therefore, to guarantee the blinding of the clinical trial, all the other groups also included 3 products: one short contact, a rinse-off, and a leave-on product (Figure 1).

Patients were instructed to apply on the entire face a thin layer of short-contact product on unwashed skin once per day in the evening. After 15 minutes of exposure, patients applied a cleansing product that was rinsed off and then followed by an application of a thin layer of a leave-on formulation. All patients were instructed to apply a broad-spectrum sunscreen twice daily, in the morning and at mid-day.

Cyspera® Intensive, Neutralize, and Boost were provided by Scientis SA. The comparator product includes the mKF, which is available upon prescription as Tri-Luma®. The placebo includes Cetaphil® Moisturizing Cream (CMC), Cetaphil® Gentle Cleanser (CGC), and Cetaphil® Moisturizing Lotion (CML).

Clinical Assessment

Spectrophotometry

Spectrophotometric analysis of skin color was performed using a portable spectrophotometer (CM-2600d, Konica Minolta). At baseline, 3 lesional and adjacent non-lesional skin sites were identified and marked on high-resolution images acquired by VISIA CR. Spectrophotometric measurements were performed on such marked skin sites at baseline, week 4, week 8, and week 16. Lesional skin sites are defined as areas in which melasma is uniform and discrete, whereas non-lesional sites are areas adjacent to lesional skin in which there are no signs of hyperpigmentation.

mMASI score

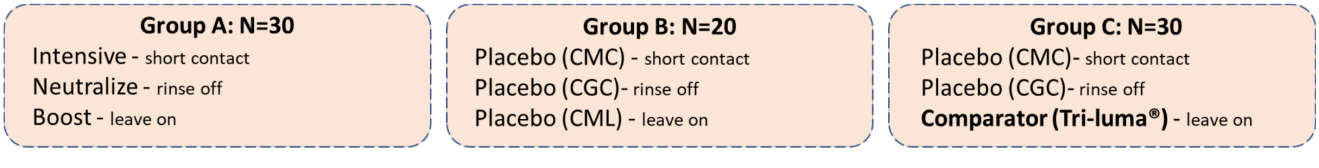
Clinical evaluations were performed by the same investigators during visits at baseline, at 8 weeks, and the end of the study (16 weeks) for all patients. A numerical score was assigned to each facial area (forehead, right malar, left malar, and nose) by adding the corresponding value from each of the categories listed below. The mMASI score was calculated as follows:

Scoring of Pigmentation (D)	Scoring for Area of Involvement (A)	mMASI Score
(0) normal skin color without evidence of hyperpigmentation (1) barely visib hyperpigmentation (2) mil yperpigmentation (3) moderat yperpigmentation (4) sever yperpigmentation	(0) 0% involvement (1) < 10% involvement (2) 10 – 29% involvement (3) 30 – 49% involvement (4) 50 – 69% involvement (5) 70 – 89% involvement (6) 90 – 100% involvement	Forehead 0.3 (D) A + right malar 0.3 (D) A + left malar 0.3 (D) A + Nose 0.1 (D) A

*mMASI, Melasma Area Severity Index.

The mean mMASI was calculated and compared across the study groups. The change in mMASI as well as spectrophotometry at 4 months were the primary endpoints for the study.

FIGURE 1. Overview of treatment groups and products.



Dermatological Assessment

Adverse events including erythema, dryness, itching, burning sensation, and irritation as well as severe adverse reactions were monitored and recorded during the study. The skin of the patients was visually inspected by the dermatologist and skin attributes, such as skin hydration, skin texture, skin clarity, overall skin tone, hyperpigmentation, and roughness/smoothness were assessed and graded using a 1–5-point scale.

Patients' Assessment

Patients' viewpoints on treatment efficacy were determined by asking patients to fill in a self-evaluation questionnaire. To collect feedback on the impact of melasma on quality of life, the patients were asked to fill in the Melasma Quality of Life Scale by using a 1 (not bothered at all) to 5 (bothered all the time) scale.

Statistical Analysis

Shapiro-Wilk test was performed on baseline values using R software (R- ver.3.1.2) for each parameter. When the *P*-value was less than 0.05, the data were considered as non-normally distributed and a non-parametric test (ie, the Wilcoxon signed-rank test) was performed to compare each visit with baseline. When the *P*-value was more than 0.05, the data was considered as normally distributed and a parametric test (ie, paired t-test paired) was performed to compare each visit with baseline.

RESULTS

The age of the patients ranged from 25 to 45 years. The average age for the 3 groups was: 42.57 ± 5.46 for Group A, 42 ± 5.58 for Group B and 40.5 ± 5.79 for Group C. Overall, 14 patients (18%) had Fitzpatrick skin type III, 57 patients (71%) had Fitzpatrick skin type IV and 9 patients (11%) had Fitzpatrick skin type V. Sixty-nine patients completed the study.

The Effect of Cysteamine Isobionic-Amide Compared to mKF on Skin Pigmentation Contrast

Statistically highly significant increase in L* value could be observed for all groups at week 4, week 8, and week 16 in comparison to baseline in both lesional and non-lesional skin sites. However, when considering the difference in L* (ie, pigmentation contrast) between lesional and nonlesional skin sites, only Group A and Group C showed significant changes. These effects were observed at week 4 ($P<0.05$) and particularly at week 8 ($P<0.001$) and week 16 ($P<0.001$; Figure 2). Group A showed a higher reduction of the delta L* between lesional and non-lesional sites between week 8 and week 16 compared to Group B (placebo), and Group C (mKF) (Figure 3).

The Effect of Cysteamine Isobionic-Amide Compared to mKF on mMASI

Statistically highly significant reduction of mMASI scores were observed in Group A (cysteamine isobionic-amide complex, N=26) and Group C (mKF, N=27). The 3 study groups had comparable mean mMASI scores at baseline: 10.48 for Group A, 10.67 for Group B, and 10.51 for Group C. No significant mMASI score reduction compared to baseline was observed for Group B (placebo, N=16), except at week 16 ($P=0.03$). The mean reduction of mMASI score at week 4 for Group A was 2.33 (-22% from baseline) and 2.54 (-24% from baseline) for Group C, with no significant difference between the two groups ($P=0.5$). Whereas, at week 16, the mMASI score reductions were 4.26

FIGURE 2. Difference in L* between lesional and non-lesional skin sites for the 3 groups after 4, 8, and 16 weeks of treatment. Group A (cysteamine isobionic-amide, blue), Group B (placebo, gray), and Group C (mKF, orange). Statistical significance vs baseline is reported as follows: ***, $P<0.001$.

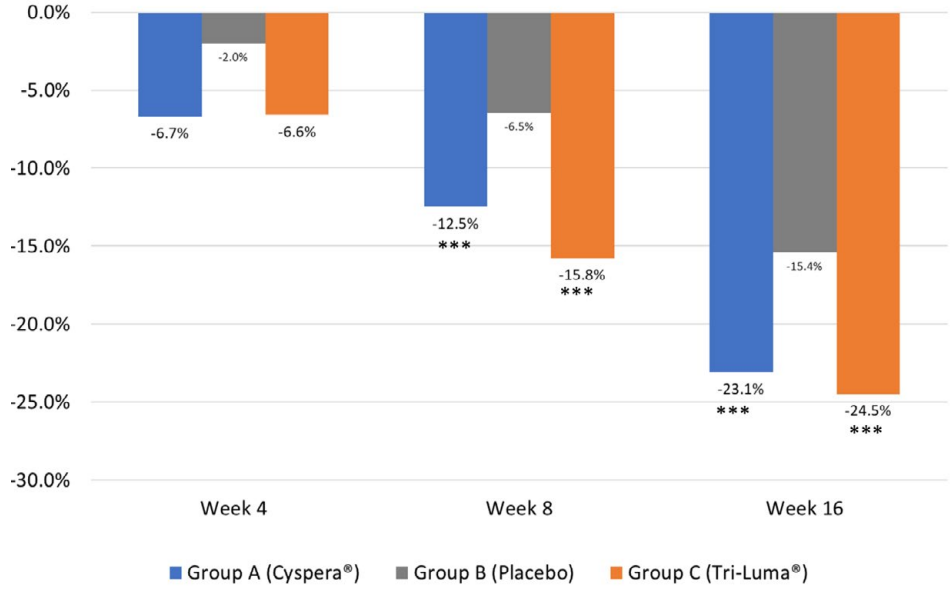
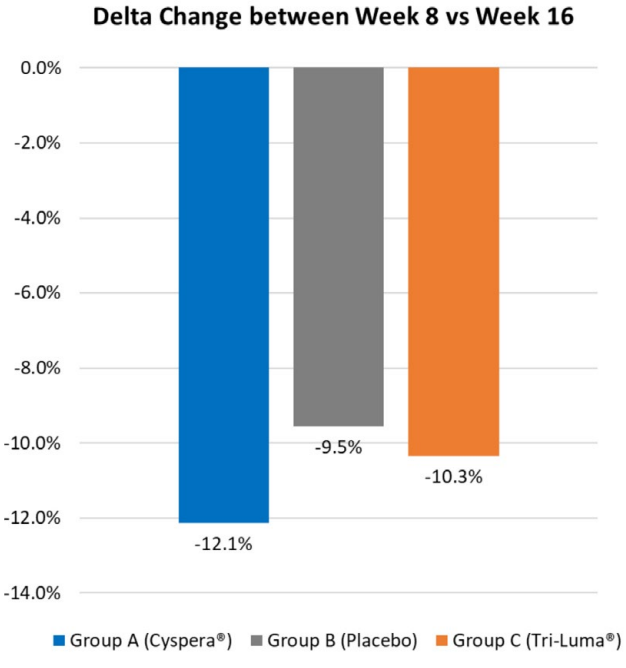


FIGURE 3. Skin pigmentation contrast reduction between lesional and non-lesional skin sites. A lower value indicates a more even skin tone across lesional and non-lesional areas of the skin.



(Group A, -41% from baseline, *P*<0.001) and 4.50 (Group C, -43% from baseline, *P*<0.001). No statistically significant difference between the 2 active groups was found (*P*=0.7) (Figure 4).

The difference in mMASI reduction between week 8 and week 16 was 1.33 (18% reduction) for Group A and 1.10 (15% reduction) for Group C (Figure 5). A highly significant reduction in mMASI score between week 8 and week 16 could be observed in Group A (cysteamine isobionic-amide regimen) compared to Group B (placebo, *P*=0.0006), whereas no significant reduction was observed when Group C (mKF) was compared to Group B (placebo, *P*=0.077).

The Effect of Cysteamine Isobionic-Amide Compared to mKF on Quality of Life

Data resulting from the Melasma Quality of Life Scale showed that the quality of life of the patients significantly improved in all groups compared to baseline. Group B (placebo) saw an improvement after 4 weeks; however, the quality-of-life scores did not further improve and reached a plateau during the following weeks. Patients in Group A (Cyspera®) saw a significant improvement in the quality of life (*P*<0.0001) at week 8 and week 16 compared to both patients of Group B (placebo) and Group C (mKF) (Figure 6).

FIGURE 4. Difference in L* between lesional and non-lesional skin sites for the 3 groups after 4, 8, and 16 weeks of treatment. Group A (cysteamine isobionic-amide, blue), Group B (placebo, gray), and Group C (mKF, orange). Statistical significance vs baseline is reported as follows: ***, *P*<0.001.

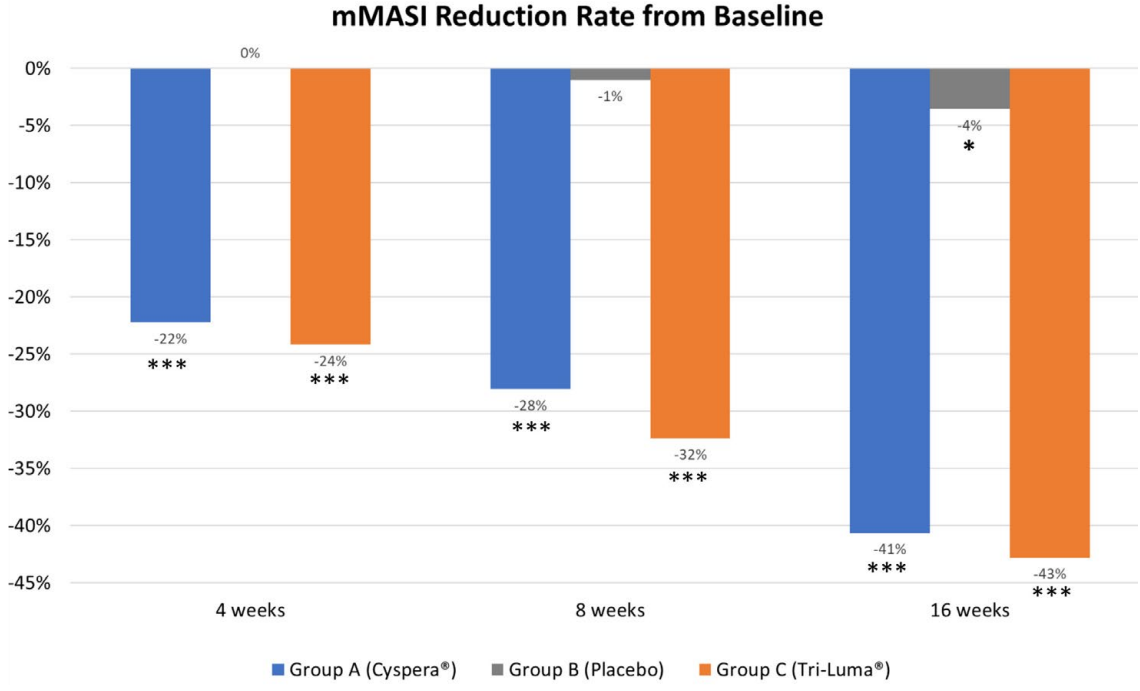
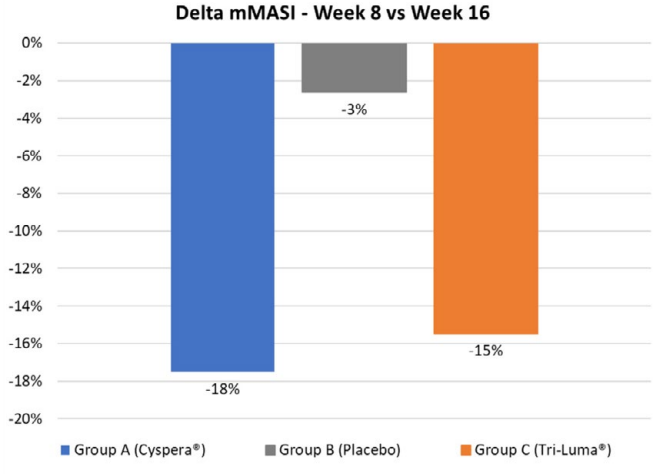


FIGURE 5. Reduction (%) of mMASI score between week 8 and week 16 for the treatment groups receiving cysteamine isobionic-amide (Group A, blue line), placebo (Group B, gray line), or mKF (Group C, orange line). ns, not significant; ***, *P*<0.001.



Furthermore, it was found that there was an overall significant positive relationship between the severity of melasma (mMASI) and the quality-of-life scores (r = 0.82, *P* = 0.001). When performing a group analysis, Group A (r = 0.93) and Group C (r = 0.97) resulted in higher correlation coefficients than Group B (r = 0.5).

Patient's Self-Assessment

During the initial 2 weeks of the treatment, 9 subjects belonging to Group A reported mild transient stinging and 1 patient reported mild itching. The sensation was recorded as a transient effect upon short contact product application. By week 4, the subjects reported tolerance and the test product was reported to be compatible with skin in regular use. At the end of the 16 weeks, the patients reported a higher degree of satisfaction (score 4.69/5.00) with the cysteamine isobionic-amide treatment. A higher overall skin improvement (score 4.85/5.00) was also reported by the patients applying cysteamine isobionic-amide.

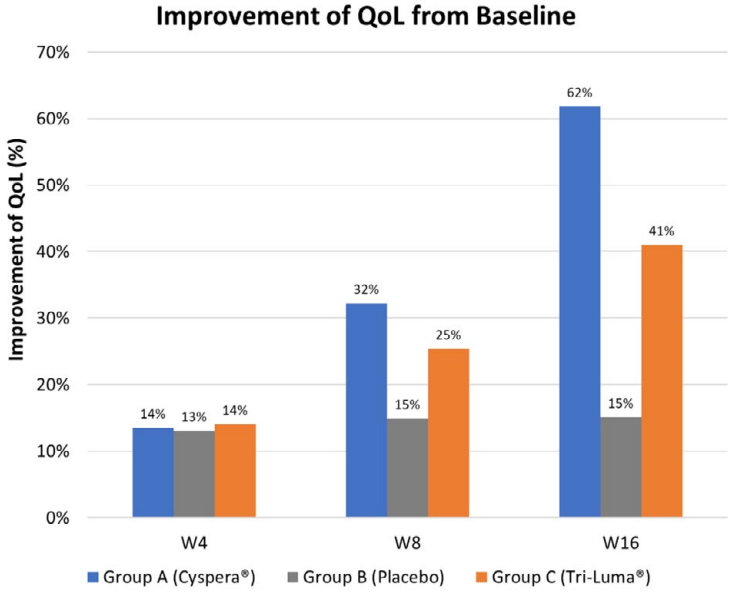
Dermatological Assessments

Cysteamine isobionic-amide was noted to produce mild erythema in 3 patients at week 4 and moderate erythema in 1 patient at week 16. However, the latter did not report any discomfort in the self-assessment or subject diary. None of the reported incidences required any intervention or rescue therapy. The test regimen under controlled application was overall tolerable with no clinically significant occurrence and/or severity of adverse effects or skin intolerances. Significant improvements in skin hydration, skin texture, skin clarity, skin tone, hyperpigmentation, and skin smoothness were observed already at week 4 in Group A (cysteamine isobionic-amide) and Group C (mKF). Group B (placebo) showed a significant improvement only after week 8.

DISCUSSION

This study was aimed at investigating the efficacy and tolerability of cysteamine isobionic-amide complex in comparison to those of mKF for the treatment of melasma. The mKF has been regarded as the gold standard treatment for melasma over the last 4 decades. However, long-term use is limited due to the risk of adverse effects from long-term use of HQ. Furthermore, a

FIGURE 6. Improvement of quality of life over 16 weeks of treatment is shown as a percentage improvement from baseline. Group A (cysteamine isobionic-amide, blue line); Group B (placebo, gray line); Group C (mKF, orange line). ***, *P*<0.001.



maintenance therapy consisting of twice-weekly application of mKF may still result in relapse, as suggested by some authors, especially if patients suffer from severe melasma.[33] Additionally, long-term use is not recommended due to various side effects, such as exogenous ochronosis, skin atrophy, and skin irritation/photosensitivity, caused, respectively, by HQ, corticosteroids, and retinoic acid.[32,34] Therefore, the challenge consists in identifying a safe and efficient treatment that allows patients not only to be treated with but also to be able to maintain the results with long-term usage.

Cysteamine, an endogenous molecule, is the product of natural degradation of L-cysteine biosynthesized during the co-enzyme A metabolism and has intrinsic antioxidant and depigmenting properties. It has been used for decades in medicine for the treatment of cystinosis as well as other medical conditions and has a long history of safety for human use.[35,36] Cysteamine is an inhibitor of the melanogenic enzymes tyrosinase and peroxidase; thus having depigmenting effects.[31] Its efficacy as topical therapy for the treatment of melasma has already been revealed and confirmed in several well-controlled clinical trials, some comparing its efficacy to that of other depigmenting agents, such as HQ and tranexamic acid.[26–29,31] The combination of cysteamine with isobionic-amide evaluated in this study is effective in inhibiting the epidermal pigmentation pathway at 2 different levels: cysteamine inhibits melanogenesis whereas isobionic-amide, belonging to the B3 group of vitamins, inhibits melanosomal transfer from melanocytes to keratinocytes (unpublished internal data, Scientis SA). Given cysteamine's safety history and proven efficacy, cysteamine-based topical formulations could represent potential candidates as safer alternatives to current therapies for melasma.

The results of this study showed that the cysteamine isobionic-amide complex is as effective as the mKF for the treatment of melasma with a comparable onset of action. The spectrophotometric data revealed that the pigmentation contrast between lesional (melasma-affected) and non-lesional skin sites could be significantly reduced as early as 4 weeks after the beginning of the treatment with cysteamine isobionic-amide complex as well as with the mKF. A further improvement with a statistically significant reduction of pigmentation contrast was observed with both the cysteamine isobionic-amide complex and mKF after 8 and 16 weeks of treatment. However, when focusing on the last 8 weeks of treatment, the cysteamine isobionic-amide complex group showed a greater reduction in skin pigmentation contrast. The mMASI value reductions were in excellent accordance with the above changes. Taken together, the spectrophotometric, as well as mMASI evaluation data, unequivocally confirmed that, unlike mKF, the cysteamine isobionic-amide complex continues to reduce melasma lesions throughout the last 8 weeks of application, suggesting that a continuation of the treatment could potentially provide additional improvements.

The improvement in the quality of life reported by the patients also showed a statistically significant difference between the 2 groups. A significant increase in quality of life was reported by the patients in the cysteamine isobionic-amide group compared to those in the mKF group. This finding alongside the significantly higher patient treatment satisfaction suggests that the improvement in the overall skin appearance might contribute to this higher quality of life improvement in the cysteamine group compared to the mKF group.

The Unmet Need for Long-Term Maintenance Treatments

Despite the availability of a number of effective treatments for melasma, such as mKF, oral tranexamic acid, etc., and the acceptable remission for melasma during the acute treatment phase, the recurrence of melasma occurs very frequently upon the cessation of the treatment. Thus, the need for a safe and effective treatment that permits the long-term maintenance therapy of melasma remains necessary. Currently, available treatments do not permit such a long-term therapy due to side effects associated with their long-term use. Cysteamine has been used during the last 10 years for the treatment of melasma. Most melasma patients treated with cysteamine were recommended not to discontinue the application of the product according to its instructions for use. To date, other than a few cases of skin irritation, cysteamine treatment has not been associated with any

TABLE 1.

Comparison Between Cysteamine Isobionic-Amide Complex and Modified Kligman's Formula		
	Cysteamine	Modified Kligman Formula
Onset Of Action	Improvements within 4 weeks	Improvements within 4 weeks
Long Term Use	Suitable	Unsuitable*
Side Effects	Not reported	Reported
Skin Atrophy	No evidence	Evidenced (corticosteroids)[13,31]
Ochronosis	No evidence	Evidenced (HQ)[34,39]
Mutagenicity	Anti-mutagenic[37]	Evidenced in vitro (HQ)[40]
Carcinogenicity	Anti-carcinogenic[37,38,41]	Evidenced in animal models, but not in humans (HQ)[40,42]
Photosensitivity	Not	Yes

*Treatment with mKF is generally discontinued after 8 to 12 weeks.

reported cases of ochronosis, skin atrophy, photo sensitization, or other side effects. Cysteamine seems to reverse some side effects of prolonged use of topical corticosteroids such as skin hypopigmentation and telangiectasia.[31] The available medical literature indicates that cysteamine exerts antimutagenic, anticarcinogenic, and antimelanoma effects in vivo.[37,38] Table 1 summarizes some comparison points between cysteamine and mKF.

CONCLUSION

This study shows that the cysteamine isobionic-amide complex has equivalent efficacy and onset of action to that of mKF. Additionally, quality of life and patient satisfaction with the cysteamine isobionic-amide treatment were significantly higher compared to mKF. Taken together the results of this study suggest that cysteamine isobionic-amide could potentially be an acceptable alternative to mKF for the long-term treatment of melasma. However, longer-term, larger studies are needed to further assess the long-term effects of the current formulation.

DISCLOSURES

Drs Sachdev, Hartman, Grimes, Callender, Taylor, Elbuluk, Badawi, Funasaka, Lim, Ngee, and Desai have served as consultants and/or investigators for Scientis Pharma in the past.

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ORIGINAL ARTICLE

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Outcomes for Psoriasis by Self-Identified Racial Groups in Ixekizumab Clinical Trials: A Pooled Analysis

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ABSTRACT

Background: Biologics have shown promising outcomes in psoriasis clinical trials. However, there is a paucity of data exploring the potential differences in outcomes between self-identified racial groups.

Objective: To evaluate treatment response to ixekizumab in patients with psoriasis across different self-identified racial subgroups.

Methods: This study analyzed pooled data from 5 clinical studies (UNCOVER-1, UNCOVER-2, UNCOVER-3, IXORA-R, and IXORA-S) with patients of different self-identified racial subgroups, who were treated with an on-label dose of ixekizumab for psoriasis through 12 weeks. Treatment response to ixekizumab was assessed using the Psoriasis Area and Severity Index (PASI) and static Physician's Global Assessment response rates. Patient Global Assessment of Disease Severity, Itch Numeric Rating Scale, Skin Pain Visual Analog Scale, and Dermatology Life Quality Index were used to evaluate the patient-reported outcomes (PROs) and impact on quality of life (QoL).

Results: A total of 1825 ixekizumab-treated patients from 5 pooled studies were included. Consistent with the clinical outcomes from the overall population, all self-identified racial groups showed rapid improvement in PASI through week 12, although the response was somewhat slower in American Indian/Alaska Native patients. Differences in PROs and QoL assessments were observed among racial groups, especially in patients who identified as Black/African American and American Indian/Alaska Native.

Conclusion: Ixekizumab is effective through 12 weeks of treatment for psoriasis across different self-identified racial groups. Sample sizes for some racial groups were small (N≤12), therefore, further research is required to understand potential differences in psoriasis treatment with ixekizumab between various racial groups.

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INTRODUCTION

Psoriasis is a chronic, immune-mediated skin disease affecting approximately 125 million people worldwide, with a higher reported prevalence in the White population (3.6%) than in people with skin of color (African American: 1.9%; Hispanic: 1.6%; and other race groups: 1.4%).[1,2] Recent studies, however, indicate an underestimation of prevalence in non-White patients.[3] This may be attributed to healthcare and economic gaps, misdiagnosis, or underrepresentation of psoriasis in patients with skin of color due to different clinical presentations.[3-5]

Despite similarities in psoriasis across different racial groups, differences have been noted in terms of prevalence, clinical presentation, genetics, disease severity, diagnosis, and treatment response.[3,6] Current treatment strategies, including biologics, have demonstrated safety and efficacy across diverse racial groups, although these therapies have been tested in clinical trials conducted primarily on White patients.[7,8] There are only a limited number of studies that investigate racial differences in treatment response to different therapies.[6] Therefore, there is a need to consider data from diverse phenotypes when deciding a treatment strategy in patients with psoriasis.

The objective of this analysis was to determine the efficacy of ixekizumab, an interleukin (IL)-17A antagonist, across different racial subgroups through 12 weeks of treatment for psoriasis. This is a pooled analysis of 5 pivotal clinical studies in patients with psoriasis (UNCOVER-1, UNCOVER-2, UNCOVER-3, IXORA-R, and IXORA-S),[9-11] which assesses skin clearance, patient-reported outcomes (PROs), and quality of life (QoL) for ixekizumab treatment response based on racial subgroups.

MATERIALS AND METHODS

Study Design and Participants

This is a pooled analysis with data from 5 pivotal studies that evaluated the efficacy of ixekizumab in psoriasis (UNCOVER-1 [NCT01474512], UNCOVER-2 [NCT01597245], UNCOVER-3 [NCT01646177], IXORA-R [NCT03573323], and IXORA-S [NCT02561806]).[9-11] Patients from different racial subgroups (based on their self-identified race) were included in the analyses, and all patients received on-label dosing of ixekizumab (starting dose of 160 mg, followed by 80 mg every two weeks) through 12 weeks of treatment.

Detailed study designs and patient eligibility criteria have been previously reported.[9-11] Briefly, these studies included adult patients (≥18 years old) with chronic plaque psoriasis diagnosed at least 6 months before baseline. Other key eligibility criteria included body surface area (BSA) involvement ≥10% at both screening and baseline, static Physician Global Assessment (sPGA) score of 3 or more, and Psoriasis Area and Severity Index (PASI) score of 12 or more at both screening and baseline.

All studies were done in accordance with the ethical principles of the Declaration of Helsinki and were approved by the local ethics review boards. All patients were required to give written informed consent for participation in the clinical studies.

Assessments

The efficacy of ixekizumab with respect to racial subgroups was assessed using PASI and sPGA. PASI score evaluates the extent of body area involvement in four anatomical regions (head and neck, trunk, arms, and legs) in terms of severity of scaling, redness, and plaque induration.[12] Percent improvement from baseline in PASI, PASI 90 (at least 90% improvement in PASI score from baseline), and PASI 100 (a 100% improvement in PASI score from baseline, ie, complete resolution of plaque psoriasis) response rates were assessed in different subgroups. sPGA, a physician-reported global assessment of psoriasis lesions in terms of induration, erythema, and scaling at a given time point,[13] was used to calculate sPGA (0,1) and sPGA (0) response rates.

Improvements in health outcomes and QoL in different racial subgroups were evaluated using PROs including Patient Global Assessment (PatGA) of Disease Severity (0), Itch Numeric Rating Scale (NRS) (0), Skin Pain Visual Analog Scale (VAS) (0), and Dermatology Life Quality Index (DLQI) (0,1) response rates.

Statistical Analyses

This integrated analysis of data from 5 studies included intent-to-treat patients who were eligible per the protocol of each trial and were treated with on-label dosing of ixekizumab through 12 weeks. Data were summarized by self-identified racial subgroups. Results for categorical data, including response rates to various assessments, are presented as observed rates with 95% confidence intervals (CIs). Continuous data, such as percent improvement from baseline in PASI, are presented as mean ± standard errors (SE) for each racial subgroup.

RESULTS

Demographic and baseline disease characteristics for patients treated with ixekizumab for psoriasis, categorized by self-reported racial groups from 5 pooled studies, are presented in Table 1. The integrated dataset was composed of 1825 patients across 6 different racial groups: 1656 (90.7%) White; 77 (4.2%) Asian; 59 (3.2%) Black/African American; 12 (0.7%) American Indian/Alaska Native; 6 (0.3%) Native Hawaiian/Other Pacific Islander; 11 (0.6%) multiple, and 4 patients with non-reported race. The baseline characteristics were mainly consistent between the racial groups; however, slightly higher mean skin pain was noted among Black/African American, American Indian/Alaska Native, and Native Hawaiian/Other Pacific Islander. In addition, a higher mean DLQI total score was reported among Black/African American and Native Hawaiian/Other Pacific Islander.

TABLE 1.

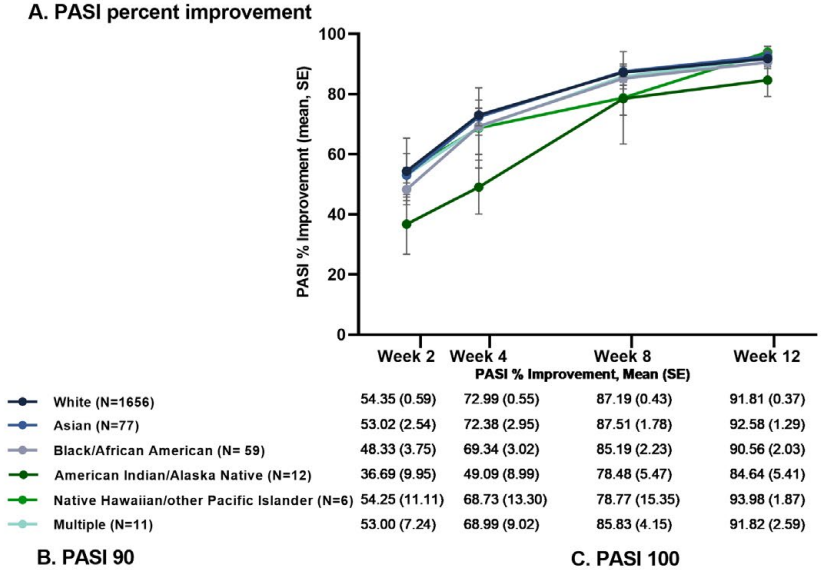
Demographics and Baseline Disease Characteristics for Ixekizumab-treated Patients Across Different Racial Groups from 5 Pooled Studies

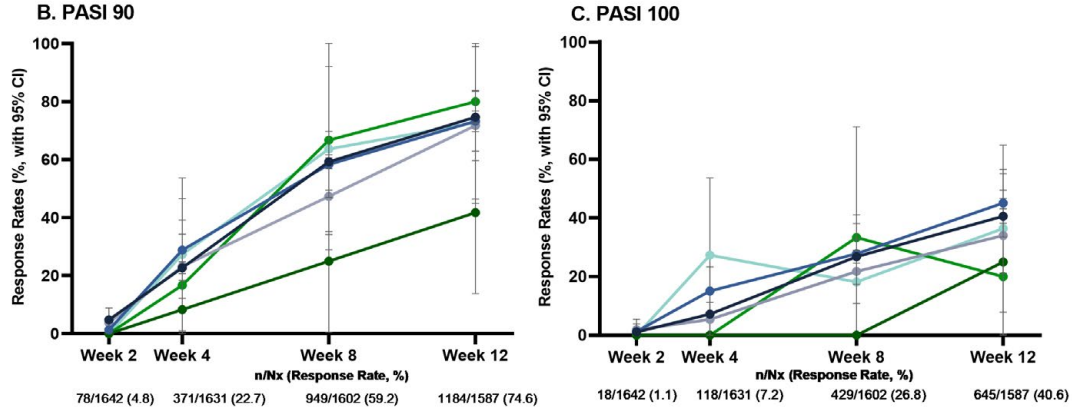
	White[a] (N=1656)	Asian (N=77)	Black/ African American[b] (N=59)	American Indian/ Alaska Native (N=12)	Native Hawaiian/ Other Pacific Islander (N=6)	Multiple[c] (N=11)
Age (years), mean (SD)	46.2 (13.3)	44.1 (13.9)	46.0 (13.9)	40.2 (9.1)	45.7 (10.7)	44.4 (12.4)
Female, n (%)	1082 (65.3)	58 (75.3)	30 (50.8)	10 (83.3)	4 (66.7)	9 (81.8)
sPGA, mean (SD)	3.5 (0.6)	3.7 (0.7)	3.6 (0.6)	3.8 (0.6)	3.8 (0.8)	3.5 (0.5)
PatGA, mean (SD)	4.1 (1.0)	4.3 (0.9)	4.4 (0.9)	4.4 (0.7)	3.7 (1.6)	3.9 (0.9)
Skin pain, mean (SD)	45.1 (30.7)	44.6 (34.1)	56.6 (29.1)	69.3 (20.5)	63.3 (31.7)	44.8 (34.1)
Itch, mean (SD)	6.7 (2.5)	7.2 (2.4)	7.9 (2.0)	8.1 (1.4)	7.0 (3.2)	6.3 (2.1)
DLQI, mean (SD)	12.5 (6.9)	13.9 (6.8)	16.1 (6.7)	13.8 (6.3)	17.3 (6.5)	11.5 (8.4)

Data for every outcome are not available for each patient. [a]The baseline response rate for sPGA, PatGA, skin pain, itch, and DLQI in the White racial subgroup was calculated with data from 1655, 1644, 1637, 1655, and 1650 patients, respectively. [b]The baseline response rate for sPGA, PatGA, itch, and DLQI in the Black/African American racial subgroup was calculated with data from 59 patients, while data from 58 patients were used for skin pain. [c]The baseline response rate for sPGA, PatGA, itch, and DLQI in the Multiple racial subgroup was calculated with data from 11 patients, while data from 10 patients were used for skin pain.
DLQI=Dermatology Life Quality Index; IXE=ixekizumab; N=total number of patients; n=number of patients; PatGA=Patient Global Assessment; SD=standard deviation; sPGA=static Physician's Global Assessment of Disease.

The pooled analysis demonstrated that ixekizumab was effective through 12 weeks for different racial groups. All 6 racial groups showed rapid mean PASI percentage improvement from baseline, which continued through 12 weeks (mean percentage change [SE] from baseline: 84.6% [5.41], 92.6% [1.29], 90.6% [2.03], 94.0% [1.87], 91.8% [0.37], and 91.8% [2.59] in American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and multiple racial groups, respectively), though the progress was slower in American Indian/Alaska Native patients (Figure 1A). Moreover, at week 12, patients of all racial subgroups demonstrated similar PASI 90 response rates with clear or almost clear skin (Black/African American [71.7%], Asian [73.2%], White [74.6%], multiple [72.7%], and Native Hawaiian/Other Pacific Islander [80.0%]), except American Indian/Alaska Native patients who had lower PASI 90 response rates (41.7%) (Figure 1B). No consistent trend was observed in PASI 100 response rates, though the response was lower for American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander (Figure 1C). The sPGA response rates were consistent for White, Asian, Black/African American, and multiple racial groups. American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander demonstrated slightly lower sPGA (0) and sPGA (0,1) response rates, although the 95% CIs overlapped between different subgroups (Figure 2).

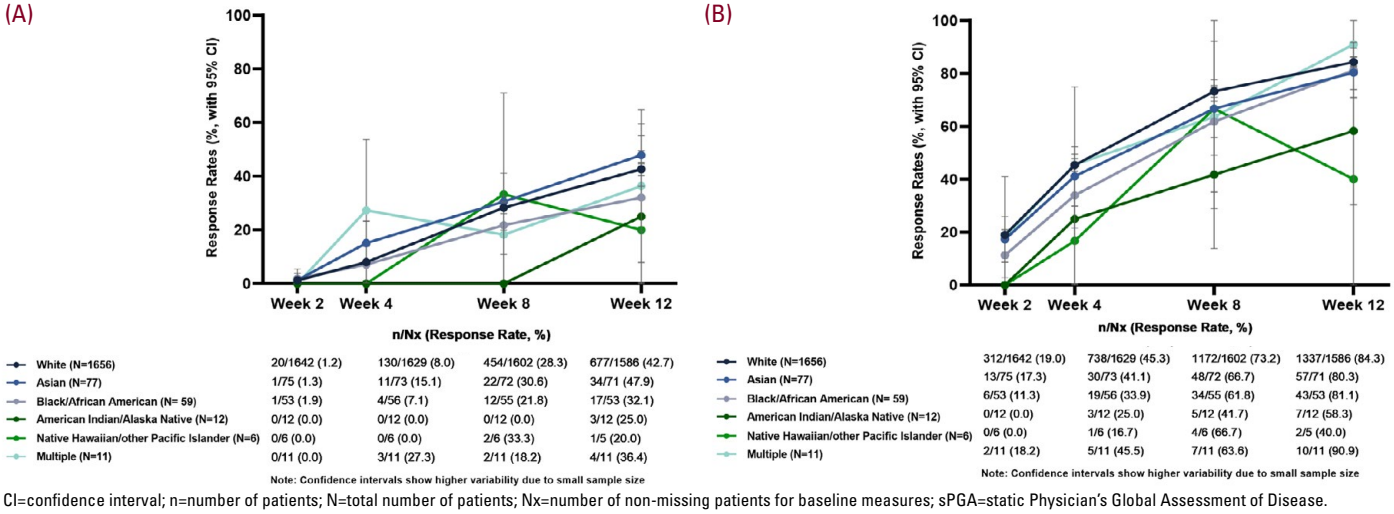
FIGURE 1. Pooled analysis for PASI response rates through week 12 by racial subgroups in patients treated with ixekizumab from 5 clinical trials. (A) PASI percent improvement (mean ± SE) from baseline through week 12, (B) Percentage of patients in each racial subgroup with 90% or greater reduction from baseline in PASI through week 12 (PASI 90), and (C) Percentage of patients in each racial subgroup with 100% reduction from baseline in PASI through week 12 (PASI 100). The 95% CIs (represented by error bars) show higher variability due to a small sample size.





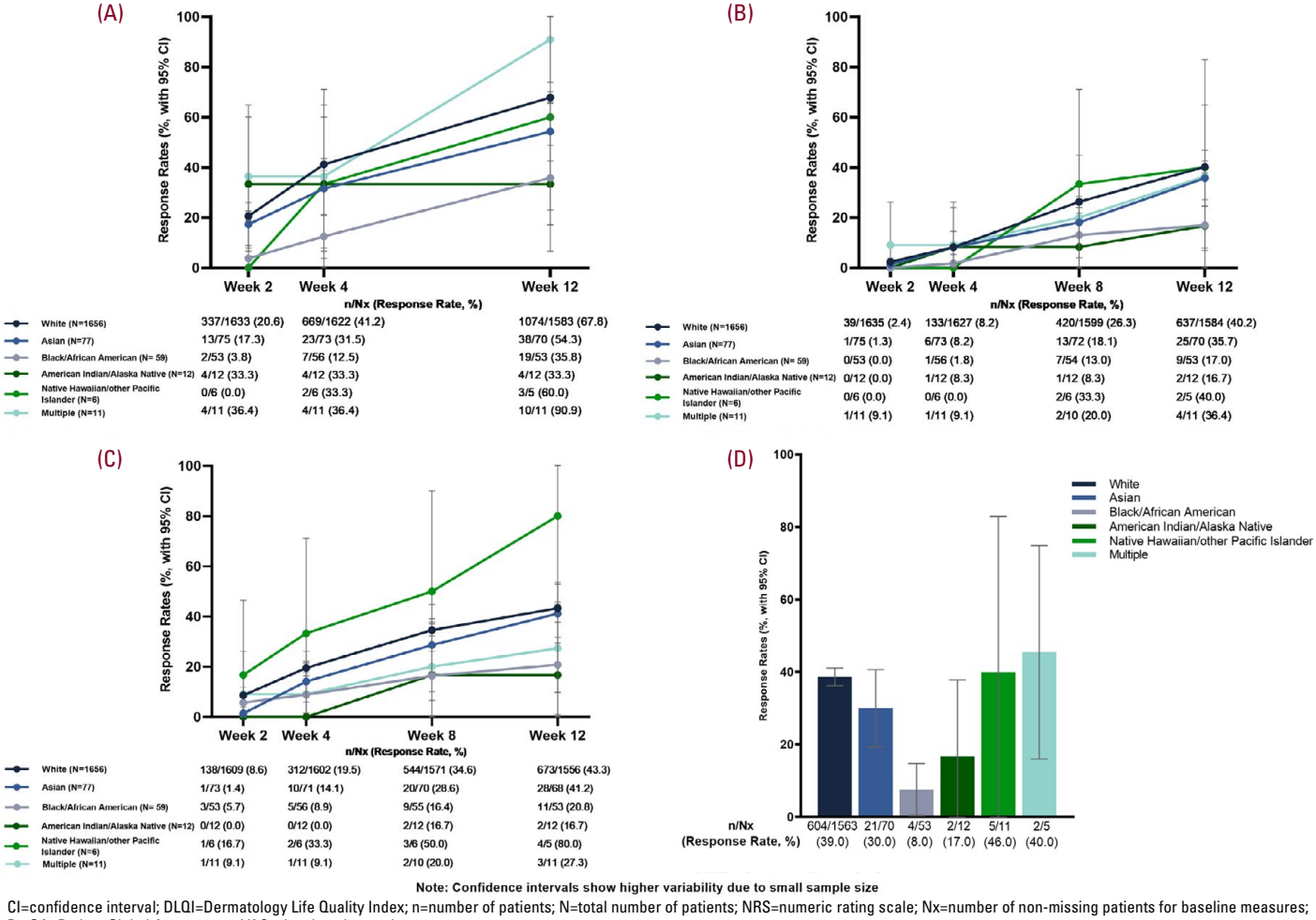
CI=confidence interval; n=number of patients; N=total number of patients; Nx=number of non-missing patients for baseline measures; PASI=Psoriasis Area and Severity Index; PASI 90=at least 90% improvement in PASI score from baseline; PASI 100=100% improvement in PASI score from baseline; SE=standard error.

FIGURE 2. Response rates to sPGA through Week 12 by racial subgroups in patients treated with ixekizumab from 5 clinical trials. (A) Percentage of patients in each racial subgroup with sPGA score of 0 through Week 12, and (B) Percentage of patients in each racial subgroup with sPGA score of 0 or 1 through Week 12. The 95% CIs (represented by error bars) show higher variability due to a small sample size.



CI=confidence interval; n=number of patients; N=total number of patients; Nx=number of non-missing patients for baseline measures; sPGA=static Physician's Global Assessment of Disease.

FIGURE 3. Patient-reported outcomes and quality of life through week 12 by racial subgroups in patients treated with ixekizumab from 5 pooled studies. (A) DLQI (0,1), (B) PatGA (0), and (C) Itch NRS (0) are presented through week 12, while (D) Skin Pain VAS (0) was evaluated at a single time-point of week 12. The 95% CIs (represented by error bars) show higher variability due to a small sample size.



CI=confidence interval; DLQI=Dermatology Life Quality Index; n=number of patients; N=total number of patients; NRS=numeric rating scale; Nx=number of non-missing patients for baseline measures; PatGA=Patient Global Assessment; VAS=visual analog scale.

In terms of health outcomes and QoL, differences in response were noted among racial groups for certain PROs (Figure 3). DLQI (0,1) response rates were similar for the White (67.8% [65.5, 70.1]), Native Hawaiian/Other Pacific Islander (60.0% [17.1, 100.0]), and multiple (90.9% [73.9, 100.0]) racial categories, while Black/African American (35.8% [22.9, 48.8]) and American Indian/Alaska Native (33.3% [6.7, 60.0]) showed lower response rates with no overlap in 95% CIs with White racial category (Figure 3A). PatGA (0) response rates indicating patient's assessment of disease severity were consistent between different racial categories, however, lower response rates were observed for Black/African American and American Indian/Alaska Native groups (Figure 3B). No consistency was noted in the Itch NRS (0) response rates among different racial categories, although Black/African American and American Indian/Alaska Native groups showed comparatively lower response rates (Figure 3C). A similar trend was noted for Skin Pain VAS (0), with a consistent response rate across the racial categories except for lower response rates in Black/African American and American Indian/Alaska Native (Figure 3D).

DISCUSSION

Ixekizumab was efficacious in patients with psoriasis from different racial groups in this integrated analysis from 5 pivotal clinical trials (UNCOVER-1, UNCOVER-2, UNCOVER-3, IXORA-R, and IXORA-S). In line with the overall clinical data from ixekizumab studies, all racial groups showed rapid PASI improvement from baseline through 12 weeks.[9-11,14] Although American Indian/Alaska Native patients had a somewhat slower response, there were no significant differences in PASI improvement or PASI 90 response rates at week 12 across different racial groups. Likewise, sPGA response rates were consistent across the racial groups, except for American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander who showed numerically lower response rates. A difference was also observed for PROs and QoL across racial groups. The American Indian/Alaska Native group consistently showed lower response rates for skin clearance, PROs, and QoL. The Black/African American group had consistent skin clearance in terms of PASI and sPGA response rates, but lower response rates were noted for PROs and QoL assessments.

Several studies have examined responses to treatment strategies, including biologics, across diverse racial and ethnic groups. In a recent systematic review, patients from different racial and ethnic groups showed varied responses to biologic treatments; ixekizumab provided the highest PASI 90 response rate for Asian and Latino patients compared to White patients, while brodalumab and ustekinumab showed the highest PASI 90 scores for Asian patients followed by White, Latino, and Black patients.[6] Assessments of PROs and QoL are consistent with another report that indicates the effect of psoriasis on QoL varies with race, with a greater psychosocial impact reported in non-White patient populations. A cross-sectional analysis of data from more than 10,000 patients with psoriasis reported a significant difference in mean DLQI scores across racial groups, and a greater impact on QoL in Black, Asian, and Hispanic patients than White patients.[15] This may be attributed to various factors including disease severity, dyspigmentation, and cultural differences.[16,17]

These results should be considered with caution, however, as studies on treatment strategies for patients with skin of color are lacking, possibly due to the disproportionate representation of certain racial groups in the clinical trials and to a limited number of studies reporting outcomes based on race and/or ethnicity. Another systematic review assessing the diversity of dermatology clinical trials found that, across 58 studies conducted entirely in the United States that reported race, 74.4% of participants were White. Moreover, disease type was noted to be associated with the degree of racial diversity in a study with the lowest number of non-White participants in the psoriasis studies and 84.3% of total participants being White.[7] A study evaluating the representation of race and ethnicity in 75 pivotal clinical trials in dermatology reported that White patients were over-represented (80.4%), while other races (Black: 9.8% and Asian: 5.5%) were under-represented.[8]

Apart from skin clearance efficacy, differences in response rates could also be based on diagnosis, access to healthcare, and knowledge gaps in diverse racial groups. For instance, a prominent clinical presentation of psoriasis observed in patients with skin of color is post-inflammatory pigmentation, which can occur while the psoriatic lesion is healing and may persist even after the resolution of lesions.[18] This may take longer to resolve and pose a greater negative impact on QoL for patients with skin of color. Moreover, differences have been reported in the presentation of psoriasis in patients with darker skin. Erythema may appear violaceous or red-brown and could be mistaken for post-inflammatory hyperpigmentation. There may be hypo- or hyperpigmented patches characteristic of post-inflammatory pigment alteration, which may further impact the diagnosis and treatment regimen.[16,18] In terms of healthcare, the odds of receiving biologics as treatment was found to be 69% lower among Black patients compared to White patients,[19] thus highlighting the inequitable access to care in non-White patients, which may be due to the high cost of care, lack of awareness, or perception of available therapies.[4,20] The high cost of care as a barrier to medical treatment could be attributed to the difference in total income that exists between White and non-White populations.[4] Patients who go undiagnosed are more likely to be non-White or have lower household income compared to patients who received a diagnosis for psoriasis.[5] Health care is still limited in many countries and therefore, patients from low- and middle-income countries often face barriers in diagnosis and treatment of psoriasis due to a lack of

sufficient health professionals, absence of dermatologists, and insufficient public funding for healthcare.[21]

This analysis has a limitation in that sample sizes for some of the racial groups were small (N≤12) and results should be interpreted within this context; however, these analyses may still reflect differences in treatment response among patients from different racial groups.

In conclusion, although only a limited number of studies evaluate treatment response based on race, treatment strategies should consider the effect of race and ethnicity in patients with psoriasis, for informed clinical decision-making and setting treatment expectations. Further analyses with greater sample sizes are needed to understand psoriasis and outcomes in patients treated with ixekizumab and other treatments for psoriasis across different racial groups.

DISCLOSURES

AM is a consultant at Eli Lilly and Company, UCB Pharma, Pfizer, AbbVie, Sanofi, Bristol Meyers Squibb, Janssen, and Johnson and Johnson; Grant/investigator: Galderma and Incyte. VC is a consultant at Acne Store, Aerolase, AbbVie, AVAVA, AVITA Medical, Beiersdorf, Cutera, Dermavant, Eli Lilly and Company, EPI Health, Juenes Aesthetics, L'Oréal, OrthoDerm, Scientis, Sente, SkinCeuticals, and UCB; Investigator: Almirall, AbbVie, Eli Lilly and Company, Galderma, L'Oréal, Pfizer, Prollenium, SkinBetter Science, Symatese, and Teoxane. HW-L is a consultant at Johnson and Johnson, Bausch and Lomb, DermTech, Incyte, L'Oréal, and LiVDerm; Speaker: Eli Lilly and Company, Incyte, Ortho Dermatologics, and L'Oréal; Investigator: Vyne Therapeutics, Eirion Therapeutics, AbbVie, Arcutis, and Pfizer. KH is a former employee and stockholder at Eli Lilly and Company. KS and AG are current employees and stockholders of Eli Lilly and Company. AA is a consultant/advisory board member at LEO, Galderma, Pfizer, Sanofi-Regeneron, Dermavant, Beiersdorf, Ortho, L'Oréal, Bristol-Meyers-Squibb, Bausch Health, UCB, Vyne Therapeutics, Arcutis, Janssen, Allergan, Almirall, AbbVie, Sol-Gel, Amgen, VisualDx, Eli Lilly and Company, Swiss American, Cutera, Cara, EPI Health, and Incyte; Grants (funds to institution): LEO, Novartis, Almirall, Bristol-Myers-Squibb, Amgen, Vyne Therapeutics, Galderma, Valeant (Bausch Health), Cara, Arcutis, Dermavant, AbbVie, and Castle; Speaker: Regeneron, Sanofi-Genzyme, Pfizer, and Bristol-Meyers-Squibb; Royalties: Springer, Wiley-Blackwell, Wolters Kluwer Health.

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ORIGINAL ARTICLE

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Targeting the Aryl Hydrocarbon Receptor to Address the Challenges of Atopic Dermatitis

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic relapsing–remitting disease with a multifactorial etiology involving epidermal barrier and immunologic dysfunction. Topical therapies form the mainstay of AD treatment, but options are limited by adverse effects and restrictions on application site, duration, and extent of use. Tapinarof (VTAMA®; Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved for the treatment of plaque psoriasis. AhR is a ligand-dependent transcription factor with wide-ranging roles, including regulation of homeostasis and immune response in skin cells. AhR expression and signaling are altered in many inflammatory skin diseases, and clinical trials with tapinarof have validated AhR as a therapeutic target capable of delivering significant efficacy. Tapinarof cream 1% once daily demonstrated efficacy versus vehicle in adults and adolescents with AD and is being investigated in the ADORING trials for the treatment of AD in adults and children down to 2 years of age.

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INTRODUCTION

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor regulating gene expression in various cells, including immune and epithelial cells.[1] AhR is expressed ubiquitously throughout the body, has roles in many physiologic processes, and is activated by a wide range of ligands.[2-5] AhR also affects signaling through interaction with other proteins, such as the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2).[1]

Atopic dermatitis (AD) is an inflammatory skin disease associated with changes in AhR signaling, reduced Nrf2 activity, abnormal immune responses, impaired skin barrier function, and oxidative stress.[1,6-8] Increased T helper (Th)2 cell cytokine expression, particularly interleukin (IL)-4, IL-5, IL-13, and IL-31, has been implicated in AD pathogenesis.[9-11] Management of AD includes reducing symptoms and improving the quality of life for patients and caregivers.[12]

There is a need for efficacious and well-tolerated therapies that can be used by children and adults, without restrictions on the duration or extent of use, or sites of application.[13] Clinical trials with tapinarof (VTAMA®; Dermavant Sciences, Inc.) validate AhR as a therapeutic target in inflammatory skin diseases. Tapinarof is an AhR agonist that downregulates cytokines, promotes skin-barrier normalization, and reduces oxidative stress.[1,14,15] Tapinarof cream 1% once daily (QD) is approved for the treatment of adults with plaque psoriasis,[16] and is under investigation for the treatment of psoriasis in children down to 2 years of age and for the treatment of AD in adults and children down to 2 years of age, having demonstrated efficacy in adults and adolescents with moderate to severe AD in previous trials.[17,18]

This review discusses the rationale for targeting AhR in the treatment of AD based on the current understanding of the role of tapinarof in the treatment of inflammatory skin disease.

Rationale for Targeting AhR

Overview of AhR

AhR is a ligand-dependent transcription factor expressed in most cell types, including skin, immune, and epithelial cells,[3] and acts as a master regulator of homeostasis in healthy cells, mediating responses to low-molecular-weight ligands from endogenous,

dietary, xenobiotic, and environmental sources.[1,19-21] Depending on the ligand and cellular context, AhR signaling results in the induction or repression of different genes with diverse responses in a wide range of tissues.[1]

Ligand-dependent AhR activation induces cytoprotective responses in the skin by upregulating antioxidant pathways and skin-barrier protein and ceramide lipid production.[1,14,22] After AhR binds to a ligand in the cytoplasm, conformational changes result in nuclear translocation,[23,24] where the AhR–ligand complex heterodimerizes with AhR nuclear translocator (ARNT) and binds to specific DNA recognition sites to control transcription of AhR-responsive genes.[23,24]

Classical AhR signaling pathways were initially elucidated in determining the toxicologic effects of polycyclic aromatic hydrocarbons, which may explain the association between atmospheric pollution and AD and asthma.[25-28] In addition to regulating gene expression as a nuclear receptor, AhR interacts with other genes and proteins to modulate genomic and cytosolic pathways.[29]

The AhR is a Master Regulator of Epithelial Homeostasis

In vitro, ex vivo, and in vivo models point to a key role for AhR as a regulator of homeostasis in immune and epithelial cells, via multiple pathways, including alteration of the transcriptional program of regulatory T (T_{reg}) cells and epithelial cells.[30] AhR also signals through Nrf2 to induce cytoprotective antioxidant responses, and mediates antioxidative and cytoprotective signaling when activated by flavonoids and azoles.[1,31-33] Additionally, AhR regulates epithelial homeostasis, via immune-mediated skin responses and skin barrier effects.[1,34-36] AhR is widely expressed in skin cells, including keratinocytes, macrophages, dendritic cells, T-cell subtypes, T_{reg} cells, mast cells, neutrophils, and resident memory T cells (T_{RM}).[37,38] In immune cells, AhR signaling reduces the Th2 differentiation and cytokine expression implicated in AD, including IL-4, IL-5, and IL-13.[9,37,39] Furthermore, AhR signaling regulates the differentiation of $CD4^+$ Th cells that produce inflammatory cytokines[1,37] and decreases major histocompatibility complex class II expression and the production of Th2- (IL-4, IL-5, and IL-13), Th1 and Th17- cytokines (IL-21 and IL-22).[40,41]

AhR signaling also regulates keratinocyte differentiation, promotes skin-barrier integrity, and prevents transdermal water loss.[35,42] To normalize skin-barrier integrity, AhR signaling upregulates barrier components including proteins such as filaggrin, loricrin, hornerin, and involucrin, as well as ceramide lipids.[22,24] AhR-mediated activation of the Nrf2 transcription factor induces cytoprotective antioxidant responses that suppress oxidative stress, which further promotes skin homeostasis.[24,43]

AhR in Dermatologic Inflammatory Diseases

Alterations in AhR expression are known to occur in inflammatory skin diseases, including psoriasis and AD.[6,14] Targeting AhR in inflammatory skin diseases may therefore provide an innovative approach to alter multiple disease mechanisms via a single receptor, in contrast to therapeutic agents that inhibit specific cytokines or enzymes.[42,44,45] AD is multifactorial and heterogenous, thus modulation of multiple upstream mechanisms via AhR could be advantageous in restoring homeostasis to address underlying pathophysiologic processes (disease modification) in addition to improving symptoms.

Burden of AD and Limitations of Current Therapies

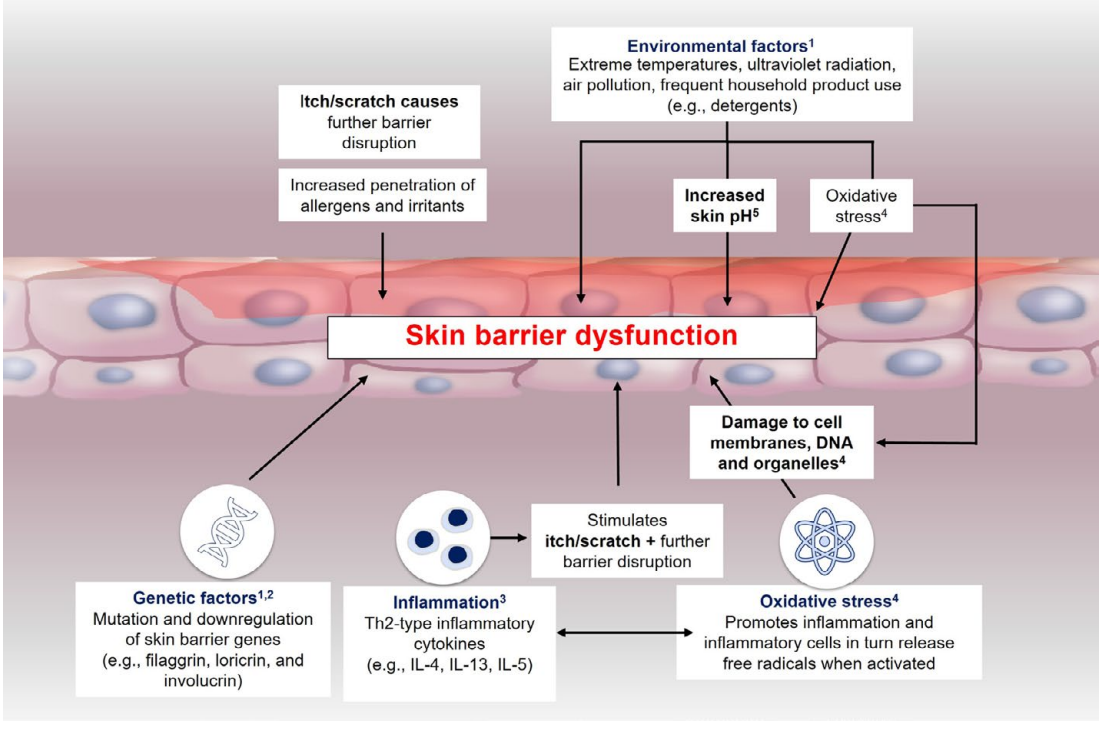
AD is a chronic relapsing-remitting disease affecting approximately 25% of children and 7–10% of adults worldwide. About 40% of adults and 33% of children with AD have moderate to severe disease.[46,47] Patients with AD are at high risk of developing other type 2 inflammatory diseases, food allergies, allergic rhinitis, and asthma. AD has an impact on sleep, and psychosocial functioning due to persistent pruritus and stigma associated with visibly affected skin.[12,18]

There is no curative therapy for AD and treatment aims to reduce inflammation, relieve core symptoms such as pruritus, and reduce the frequency and severity of flares to improve quality of life.[18] Topical agents form the mainstay of treatment in patients with mild to moderate AD, with initial options including topical corticosteroids (TCSs) or topical phosphodiesterase-4 inhibitors; and topical calcineurin inhibitors or Janus kinase (JAK) inhibitors as second-line options.[48] With increasing severity, more potent TCSs may be used, however, concerns exist regarding application location, extent of body surface area treated, and long-term use, especially for mid- and high-potency TCSs.[49,50] Adverse events with TCSs, some of which are irreversible, include acne, rosacea, perioral dermatitis, facial erythema, hirsutism, skin thinning and atrophy, striae, telangiectasia, ecchymosis, dyschromia, and withdrawal phenomena.[49] Consequently, the use of TCSs is often limited or restricted, especially in sensitive skin regions (eg, face and skin flexures/intertriginous areas) and in infants and younger children who are at increased risk of systemic absorption and potential adverse events. Therefore, a need remains for efficacious non-steroidal topical therapies that can be used without these restrictions in patients down to 2 years of age.

Etiology of AD

The etiology of AD is multifactorial, involving epidermal barrier and immunologic dysfunction, genetics, and environmental factors (Figure 1).[51] A healthy epidermal barrier protects against water loss, pathogens, and inflammatory stimuli. In AD, changes

FIGURE 1. The pathogenesis of atopic dermatitis.



IL, interleukin; Th, T helper.
1. Ständer S. *N Engl J Med.* 2021;384:1136–43; 2. Furue M. *Int J Mol Sci.* 2020;21:5382; 3. Nakajima S, et al. *Cytokine.* 2021;148:155664; 4. Ji H, Li XK. *Oxid Med Cell Longev.* 2016;2016:2721469; 5. Hendricks AJ, et al. *Br J Dermatol.* 2020;183:16–23.

in skin-barrier integrity are associated with inflammation and immune-cell infiltration, alongside alterations in the expression of epithelial barrier proteins, such as filaggrin.

More than 30 risk loci for AD have been identified, including genes involved in epidermal differentiation, innate immunity, and T-cell function.[39,52] The strongest genetic risk for AD involves the filaggrin gene,[53,54] which plays a role in skin-barrier integrity.[52] Th2 cytokine genes, such as those encoding IL-4 and IL-13, are also associated with AD.[52]

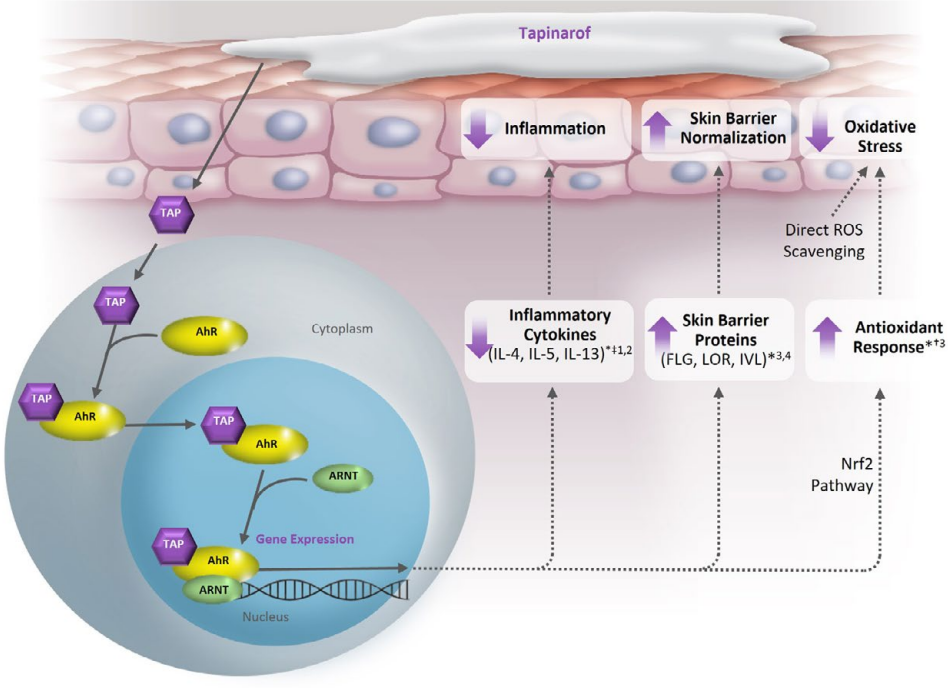
Oxidative stress is also implicated in AD, resulting in increased dermal inflammation and skin-barrier dysfunction.[55] Environmental factors implicated in the etiology of AD include pollutants, irritants, and microbial dysbiosis.[56] Pollutants, including polyaromatic hydrocarbons, induce oxidative stress, skin-barrier dysfunction, and immune dysregulation, and are linked to the development and exacerbation of AD and asthma.[22-25,57,58]

Th2 cytokines, such as IL-4, IL-5, and IL-13, are associated with AD pathogenesis.[59] Increased expression of IL-4 induces immunoglobulin E production, inflammation, and pruritus in vivo[59,60] and suppresses expression of the terminal keratinocyte differentiation proteins, filaggrin, loricrin, and involucrin.[60] IL-5 contributes to eosinophilia, which is characteristic of lesions in AD.[59,61] IL-13 is an inflammatory mediator of pruritus, skin-barrier dysfunction, and inflammation in AD.[62]

Tapinarof in the Treatment of Psoriasis and AD

Tapinarof is a first-in-class, non-steroidal, topical AhR agonist approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults,[16] and under investigation for the treatment of psoriasis in children down to 2 years of age, and for AD in adults and children down to 2 years of age. Tapinarof cream 1% QD demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two identical, 12-week, pivotal phase 3 trials.[63] Efficacy improved beyond 12-weeks in the long-term extension trial, with a high rate of complete disease clearance (Physician Global Assessment [PGA]=0; 40.9% [n=312]), an approximately 4-month remittive effect defined as off-treatment maintenance of a PGA score of 0 (clear) or 1 (almost clear), and durability of response when on therapy for up to 52 weeks.[64] The efficacy of tapinarof is attributed to its specific binding and activation of AhR, resulting in downregulation of pro-inflammatory cytokines, normalization of skin-barrier function, and antioxidant effects.[14] The remittive effect off therapy in psoriasis may be attributed in part to an observed reduction in the activity and persistence of pathogenic resident memory T cells (T_{RM}).[65,66]

FIGURE 2. Proposed mechanism of action of tapinarof in atopic dermatitis.



*Demonstrated in vitro. †Demonstrated ex vivo. ‡Demonstrated in mouse models.
AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; IL, interleukin; IVL, involucrin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

Adapted from Bissonnette R, et al. *J Am Acad Dermatol.* 2021;84(4):1059-67.
1. Dermavant Data on File [DMVT-505 Th2 Polarization; Apr 2015]; 2. Dermavant Data on File [DMVT-505 AD Mouse Model; Oct 2016]; 3. Smith SH, et al. *J Inv Dermatol.* 2017;137:2110–2119; 4. Kim BE, et al. *Allergy Asthma Immunol Res.* 2018;10:207–215.

Tapinarof cream 1% QD resulted in minimal-to-no systemic exposure in the phase 3 plaque psoriasis pivotal trials[67] and in patients with plaque psoriasis covering up to 46% of their body surface area (BSA).[68] This pharmacokinetic profile underlies the low potential for systemic adverse effects and drug interactions with topical tapinarof, no QT interval effects, and no requirement for dose modifications based on renal/hepatic dysfunction.[16]

Tapinarof activates AhR, resulting in downregulation of Th2 cytokines implicated in the pathogenesis of AD (Figure 2).[14,15] AhR activation by tapinarof restores the epidermal barrier by increasing the expression of the skin-barrier proteins filaggrin, loricrin, hornerin, and involucrin, as well as ceramide lipid components.[14,15,42] Tapinarof increases antioxidant responses through the Nrf2 pathway and by direct oxygen scavenging.[14] In addition to activation of Nrf2 through AhR, tapinarof directly binds to and activates Nrf2.[14]

Tapinarof cream 1% QD demonstrated significant efficacy and tolerability in adults and adolescents with AD in early clinical trials.[17,18] In a phase 2 clinical trial evaluating tapinarof cream 1% QD in adults and adolescents with moderate to severe AD, efficacy was maintained 4 weeks after completing the 12-week treatment period.[18] This remittive effect off therapy is in alignment with findings in adult patients with plaque psoriasis treated with tapinarof[64] and is being further investigated in the ADORING phase 3 trial program. Moreover, consistent with the pharmacokinetic profile in psoriasis, tapinarof cream 1% QD demonstrated minimal-to-no systemic exposure in adolescents and children down to 2 years of age with extensive AD, with up to 90% BSA affected.[69]

The ADORING phase 3 program is a year-long evaluation of the efficacy and safety of tapinarof cream 1% QD for the treatment of AD in adults and children down to 2 years of age. The program comprises two 8-week, vehicle-controlled pivotal trials (ADORING 1 [NCT05014568] and 2 [NCT05032859]) and a 48-week open-label long-term extension trial (ADORING 3 [NCT05142774]). In the pivotal trials, patients with AD received tapinarof or vehicle QD. The primary endpoint of a Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline at week 8, was highly statistically significant in the tapinarof cream 1% QD group versus vehicle at Week 8 in both ADORING 1 and 2: 45.4% vs 13.9% and 46.4% vs 18.0% (both $P<0.0001$), respectively.[70]

Eligible patients were permitted to enroll in ADORING 3 for a further 48 weeks of treatment based on their vIGA-AD™ score, whereby patients with a vIGA-AD™ score of 0 (clear) discontinue treatment and are monitored for remittive effect (maintaining a vIGA-AD™ score of 0 or 1 when off treatment).

CONCLUSION

AhR signaling has an important role in the regulation of skin health. Clinical trials with tapinarof, an AhR agonist, validate AhR as a therapeutic target for the treatment of inflammatory skin diseases. The targeting of transcription factors such as AhR represents a novel approach to AD therapy, distinct from treatments that target specific cytokines and enzymes.

Tapinarof cream acts locally at sites of application, with minimal-to-no systemic exposure. Tapinarof demonstrated efficacy and favorable tolerability in adults and adolescents with AD and is being evaluated in the ADORING trials in adults and children down to 2 years of age.

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L.F.E. has served as a consultant, advisor, or investigator for AbbVie, Almirall, Amgen, Arcutis, Arena, Aslan, Dermavant Sciences, Inc., Eli Lilly, Forté, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, and UCB Pharma. J.I.S. has received honoraria or grants, and/or has served as a consultant, advisory board member, or speaker for Afyx, Aobiome, Arena, Asana, BioMX, Bluefin Biomedicine, Bodewell, Boehringer Ingelheim, Celgene, Dermavant Sciences Inc., Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, LEO Pharma, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, and Sanofi Genzyme. A.A.H. has received research support paid to the medical school from AbbVie, Arcutis, Dermavant Sciences Inc., and Pfizer; honoraria received from GSK, Sanofi Regeneron, and Ortho Dermatologics (as part of a Data Safety Monitoring Board); honoraria received from Dermavant Sciences, Inc., Incyte, LEO Pharma, Pfizer, Arcutis, Sun Pharma, Galderma, Novan, and Verrica. R.C. has served as an advisor, consultant, speaker, and/or investigator for AbbVie, Apogee, Arcutis, Argenx, ASLAN, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant Sciences, Inc., Eli Lilly and Company, Galderma, Genentech, Incyte, LEO Pharma, L'Oréal, Novan Inc., Pfizer Inc., Regeneron, Sanofi, and UCB Pharma. P.M.B., K.A.M., D.S.R., and A.M.T. are employees of Dermavant Sciences, Inc., with stock options.

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ORIGINAL ARTICLE

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Perceptions, Utilization, and Cost Assessment of Sebaceous Hyperplasia Treatment Modalities: A Pilot Survey

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ABSTRACT

Background: Sebaceous hyperplasia (SH) is a common, benign but cosmetically bothersome skin condition preferentially affecting older adults. Despite multiple treatment options, there is no universally accepted first-line treatment for SH nor standard pricing for said approaches.

Methods: A survey aimed at evaluating treatment approaches and their respective costs was disseminated on the Orlando Dermatology Aesthetic and Clinical Conference email listserv.

Results: Out of 224 dermatologists who participated in the survey (response rate 9.2%), most treated patients with SH (95.98%). In-office procedures were used more than pharmacologic treatments (P=<0.05). Treatments most used by respondents included electrodesiccation (ED; 83.9%), cryosurgery (35.3%), oral isotretinoin (32.6%), and carbon dioxide (CO2) laser (19.2%). Cryosurgery and ED priced between <$200 to $400. Most reported 1 to 2 sessions to achieve lesion clearance for ED, CO2 laser, and cryosurgery. Twenty-one percent reported 3-4 sessions with cryosurgery. Chemical peels, diode lasers, and photodynamic therapy required between 2-4 sessions. Respondents indicated lesions were most unlikely to recur with ED and CO2 laser. Most dermatologists (86.39%) agreed or strongly agreed that they were exposed to new treatments methods for SH through this survey and 86.49% of dermatologists were interested in learning about treatments employed by others.

Conclusion: SH is a common issue that presents in the dermatologist's office. These data highlight the perception that ED is the most common approach employed, associated with lower costs, and requiring fewer sessions to achieve resolution. More data is needed and wanted to better determine best practices for the management of SH.

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INTRODUCTION

A recent literature review suggested that the effectiveness of sebaceous hyperplasia (SH) treatment was attributed to lesion severity, patient-specific qualities, and cost, rather than a specific treatment modality.[1] Ambiguity surrounding the effectiveness of SH treatments stems from the limited comparative potential of studies in the current literature due to varying primary outcomes, study designs, parameters for determining lesion improvement, and literature reviews focusing on a sole treatment method.[1] This study investigates the variability of SH treatment approaches among dermatologists and aims to identify the most cost-effective, first-line treatment option.

MATERIALS AND METHODS

An IRB-approved (protocol NCR213612) 19-question survey was designed using the online platform, SurveyMonkey, and sent via a single email to dermatologists on the Orlando Dermatology Aesthetic and Clinical Conference listserv in August 2021. The email included a brief description of the study's objectives, the voluntary nature of the survey, and a direct link to the questionnaire.

The mean total cost of procedural-based treatments for SH was estimated using survey responses, which included procedure-specific cost per session and the average number of sessions to achieve lesion clearance. Weighted averages were used to compare values. Number of sessions rather than the duration of treatment was investigated given that there is greater interval variability between treatment sessions.

The mean total cost of pharmacologic-based therapy for SH took into account medication dosage, administration frequency, and treatment duration provided by participating dermatologists in combination with the average daily medication price. The cost of each specific pharmacologic agent was obtained from Medi-Span Price Rx using UpToDate. All costs are presented in United States dollars.

RESULTS

The demographics and clinical practice descriptions of respondents are detailed in Table 1. The majority of respondents were female (59.4%) and worked in a private practice (69.6%), with 24% of participants practicing outside of the United States.

TABLE 1.

Demographics of the Dermatologists Who Participated in the Study	
Demographics, Values Reported as n (%)	
Gender (n=224)	
Male	88 (39.29)
Female	133 (59.38)
Non-binary	1 (0.45)
Prefer not to answer, or "other"	2 (0.89)
Age (n=224)	
25-34	38 (16.96)
35-44	65 (29.02)
45-54	44 (19.64)
55-64	45 (20.09)
65+	31 (13.84)
Prefer not to answer, or "other"	1 (0.45)
Years in Practice (n=224)	
Less than 10 years	94 (41.96)
11 to 20 years	49 (22.88)
21 to 30 years	39 (17.41)
31 years or more	42 (18.75)
Practice Type (n=224)	
Private Practice	156 (69.64)
Academic Institution/VA	37 (16.52)
Community Hospital/Multispecialty Clinic	17 (7.59)
HMO	1 (0.45)
Combination	11 (4.91)
Other	2 (0.89)
Clinical Focus (n=224)	
Medical dermatology	173 (77.23)
Cosmetic dermatology	76 (33.93)
Dermatologic surgery	48 (21.43)
Dermatopathology	6 (2.68)
Other	5 (2.23)
Practice Setting (n=224)	
Large metropolitan area	110 (49.11)
Small metropolitan area	56 (25.00)
Suburban	50 (22.32)
Rural	8 (3.57)
Region of Practice (n=224)	
South (ie, DE, DC, FL, GA, MD, NC, SC, VA, WV, KY, MS, TN)	60 (26.79)
West (ie, AZ, CO, ID, NM, MT, UT, NV, WY, AK, CA, HI, OR, WA)	44 (19.64)
Northeast (ie, CT, ME, MA, NH, RI, VT, NJ, NY, PA)	40 (17.86)
Midwest (ie, IN, IL, MI, OH, WI, IO, KS, MN, MO, NE, ND, SD)	26 (11.61)
US Territory	2 (0.89)
Other, below: Europe Non-USA, Unspecified South America Southeast Asia South Asia Africa Middle East Canada Central America	53 (22.66) 13 (5.80) 10 (4.46) 9 (4.02) 6 (2.68) 3 (1.34) 3 (1.34) 3 (1.34) 3 (1.34) 2 (0.89)
Treats Sebaceous Hyperplasia in Practice (n=224)	
Yes	215 (95.98)
No	9 (4.02)

TABLE 2.

Dermatologist Awareness and Use of Available Sebaceous Hyperplasia Treatment Modalities, N (%)				
Treatment Modality	**Utilize**	**Aware But Does Not Utilize**	**Unaware**	**No Response**
Electrodessication	188 (83.9%)	32 (14.3%)	3 (1.3%)	1 (0.5%)
Cryosurgery	79 (35.3%)	115 (51.3%)	28 (12.5%)	2 (0.9%)
Oral Isotretinoin	73 (32.6%)	119 (53.1%)	30 (13.4%)	2 (0.9%)
Salicylic Acid Superficial Peels	49 (21.9%)	120 (53.6%)	52 (23.2%)	3 (1.3%)
Carbon Dioxide Laser	43 (19.2%)	164 (73.2%)	16 (7.1%)	1 (0.5%)
Trichloroacetic Acid Peels	42 (18.8%)	134 (59.8%)	43 (19.2%)	5 (2.2%)
Photodynamic Therapy	22 (9.8%)	96 (42.9%)	104 (46.4%)	2 (0.9%)
Minocycline	21 (9.4%)	52 (23.3%)	149 (66.5%)	2 (0.9%)
Diode Laser	29 (12.9%)	123 (54.9%)	68 (30.40%)	4 (1.9%)
Bichloracetic Acid Peels	19 (8.5%)	84 (37.5%)	117 (52.2%)	4 (1.9%)
Tetracycline	20 (8.9%)	25 (11.2%)	168 (75.0%)	6 (2.7%)
Vitality Institute Peels	7 (3.1%)	84 (37.5%)	126 (56.3%)	7 (3.1%)
Zileuton	1 (0.5%)	24 (10.7%)	192 (85.7%)	7 (3.1%)

Ninety-six percent of respondents treated SH in their practice. Of the dermatologists included in this study, the majority (77.2%) reported medical dermatology as their clinical focus. With the survey option to select more than one clinical focus, some providers reported the focus of their practice crossed multiple specialties, including: cosmetic dermatology (33.9%), dermatologic surgery (21.4%), dermatopathology (2.7%) and other (2.2%). Forty-two percent of practitioners surveyed have been in practice for less than 10 years, with 19% in practice for 31 years or more, and the largest group of participants fell between the ages of 35 to 44 years.

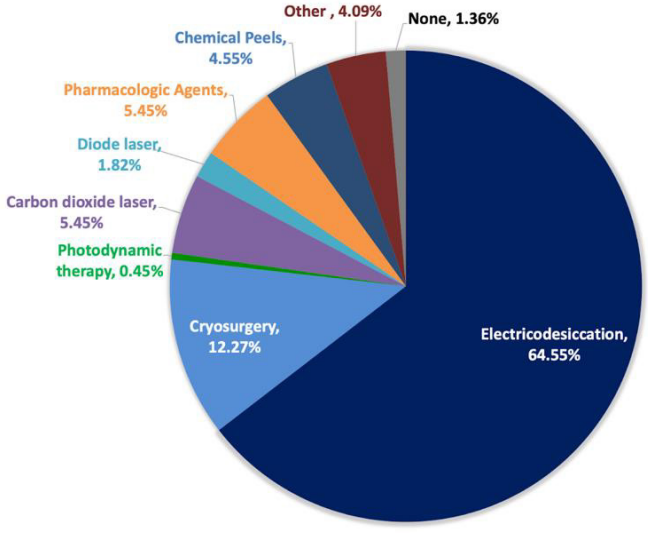
Sebaceous Hyperplasia Treatment

Seventy-seven percent of the providers either agreed or strongly agreed that they felt comfortable treating SH, with 70.3% feeling knowledgeable about the available treatment options. Eighty-two percent of providers were more likely to treat SH with in-office non-pharmacological therapy compared with 11% of providers who reported being more likely to treat SH with pharmacological treatment.

There are a variety of treatment methods available for SH. Table 2 provides an extensive list of available SH treatments stratified by participating providers' degree of awareness or utilization. Electrodessication (ED) was the treatment method most used by dermatologists (83.9%) followed by cryosurgery (35.3%) and oral isotretinoin (32.6%). While carbon dioxide (CO2) lasers were only used by 19.2% of dermatologists, 73.2% of providers were aware of its utility in SH. Zileuton was the most under-recognized treatment (85.7% unaware), used by only one practitioner.

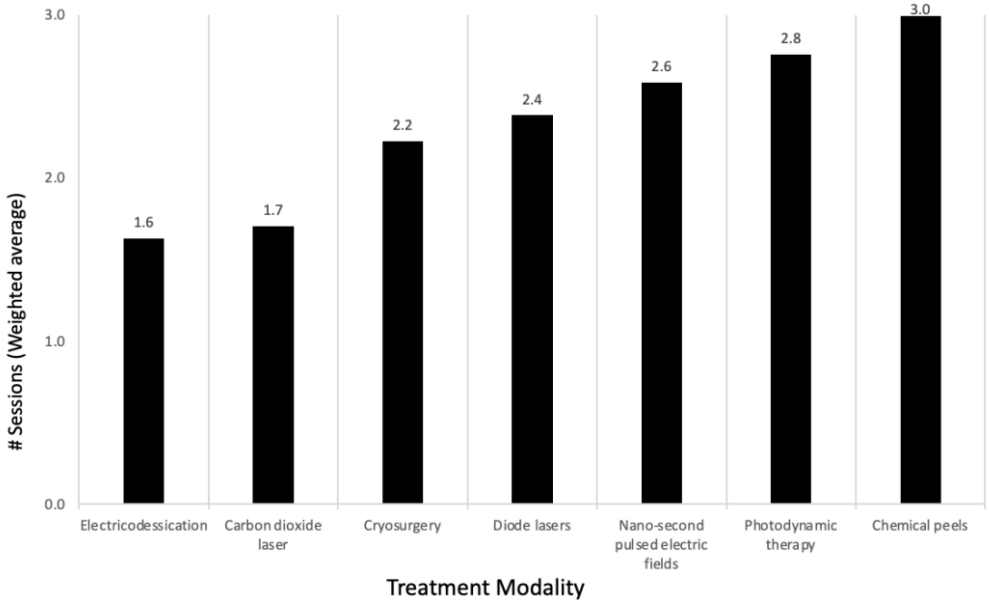
Separately, dermatologists provided their single most preferred first-line approach to treat SH (Figure 1). The leading first-line approaches were ED (65%), cryosurgery (12.3%), CO2 laser (5.5%), pharmacologic agents (5.5%), and chemical peels (4.6%). The pharmacologic agents selected as first-line were isotretinoin (n=8), topical retinoid (n=3), and minocycline (n=1). Out of the chemical peels, salicylic acid (n=4) and trichloroacetic acid (TCA) (n=4) peels were most popular, followed by bichloracetic acid peels (n=2).

FIGURE 1. First-line treatments used by participants for sebaceous hyperplasia.



SH often requires multiple sessions of non-pharmacological treatment for lesion clearance. For ED, 46% of providers estimated patients need only one session and 40% estimated 2 sessions. For cryosurgery, 31% of providers estimated a

FIGURE 2. Number of treatments expected for each modality.



2-session requirement, and 21% estimated needing either 3 to 4 sessions or only one session. Chemical peels required the most sessions, with up to 5+ sessions being recommended by 7.5% of providers. Figure 2 highlights the expected number of sessions according to treatment.

With regards to pharmacologic therapy, 36% of providers anticipated a treatment duration of 2 to 4 months when using minocycline or tetracycline for SH. Oral isotretinoin was anticipated to require a longer duration of use, with 35% of dermatologists recommending 5 to 7 months of use. Only 25 dermatologists provided estimations on the duration of Zileuton treatment: less than 2 months (36%), 2 to 4 months (32%), 5 to 7 months (16%), >12 months (12%), and 8 to 12 months (4%).

The strength and frequency of the pharmacologic regimens varied among providers. Minocycline 50 mg and 100 mg were more commonly prescribed than 75 mg. Once-daily dosing of minocycline 100 mg was the most popular (71.4%). Tetracycline 250 mg and 500 mg were prescribed similarly with every other day, once daily, and twice-daily dosing. Only tetracycline 250 mg was prescribed to patients at a frequency of four times daily. The providers that treated with isotretinoin tended to prescribe weight-based dosages of 0.25 mg/kg/day (39%, n=37) to 0.5 mg/kg/day (33%, n=32). Less popular isotretinoin regimens included 1 mg/kg/day (16%, 1=15) and less than 0.25 mg/kg/day (13%, n=12). Zileuton 600 mg was prescribed once daily, every other day, and twice daily. Zileuton 1,200 mg was only prescribed every other day or once daily.

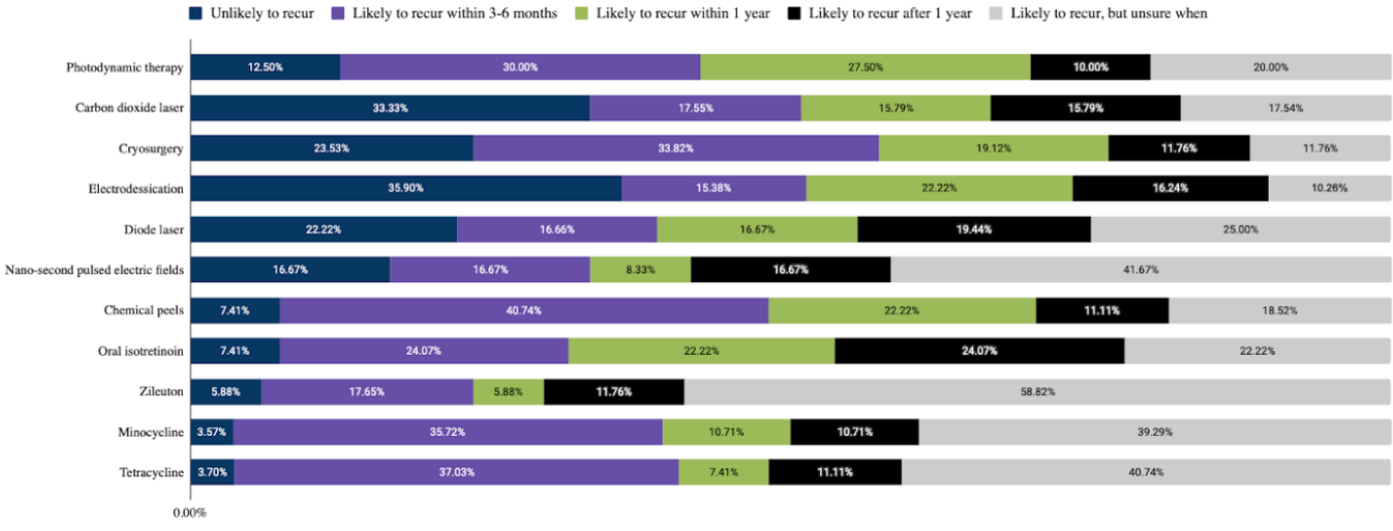
Lesion Clearance and Recurrence

The majority of providers reported first noticing clearance of SH lesions within one month of treatment for most of the procedural therapies discussed: ED (88.6%), CO2 (83%), diode laser (75.8%), cryosurgery (74.2%), nano-second pulsed electric fields (66.7%), and PDT (58.1%). Chemical peels were more likely to achieve lesion clearance within 2 to 3 months (47%) than within one month (36.7%). Around 16% of respondents anticipated clearance for both chemical peels and nano-second pulse stimulation to take greater than 4 months.

Pharmacological therapies including oral isotretinoin, zileuton, minocycline, and tetracycline had a lower expectation for early lesion clearance when compared with the procedural interventions. The majority of respondents expected lesion clearance to occur within 2 to 3 months: isotretinoin (68%), minocycline (65.4%), tetracycline (63.7%), and Zileuton (54.5%). An average of 24% of participants expected more than 4 months to achieve lesion clearance for all pharmacological treatments.

When asked about the likelihood of SH lesion recurrence following cessation of pharmacological intervention, most providers felt lesions were likely to recur but were unsure of timing (Figure 3). Provider responses were more definitive regarding the recurrence of SH lesions after stopping non-pharmacological therapies. Thirty-six percent and 24% of providers indicated that lesions were unlikely to recur after ED and CO2 laser treatment, respectively. Most providers expected recurrence of lesions within 3 to 6 months after chemical peels

FIGURE 3. Likelihood of lesion recurrence after treatment cessation.



and cryosurgery (40.7% and 33.8%, respectively). In addition, after treatment with nano-second pulsed electric fields and diode lasers, the majority of providers expected recurrence but were unsure of the timeframe for when SH lesions would recur.

Cost Analysis

ED and cryosurgery were the most cost-conscious treatment modalities, reported to cost less than $200 per single session of full-face treatment (15+ lesions). Most dermatologists expected TCA peels and bichloracetic acid peels to cost <$200 as well. A greater proportion of providers anticipated the price of a diode laser session to cost between $200 and $400, and CO2 laser therapy was expected to be the most expensive therapy, with cost estimations falling between $1000 to $3000. PDT and vitality institute (VI) peels were most quoted to cost $400 to $600. The majority of responses (75%) regarding the price of nano-second pulsed electric fields were "I don't know". Taking into account the average number of sessions required to treat a full face, the total cost of procedural treatment of SH lesions was calculated and shown in Figure 4.

FIGURE 4. Total expected cost per treatment modality, taking into account weighted average cost per session and number of sessions to achieve clearance.

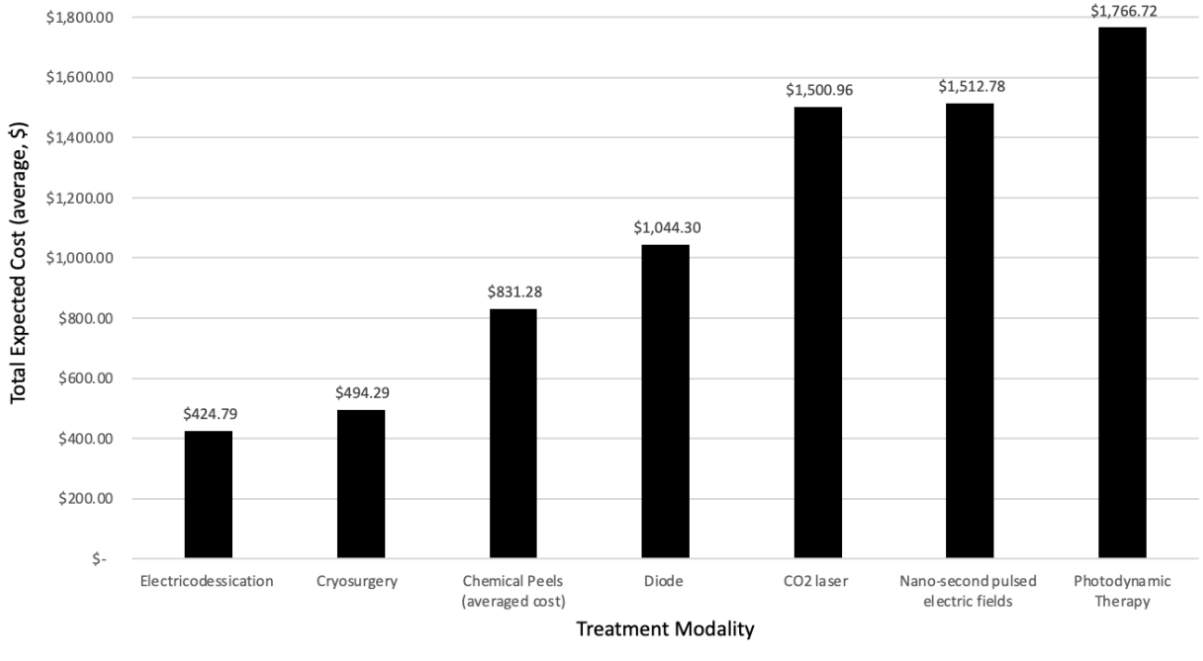


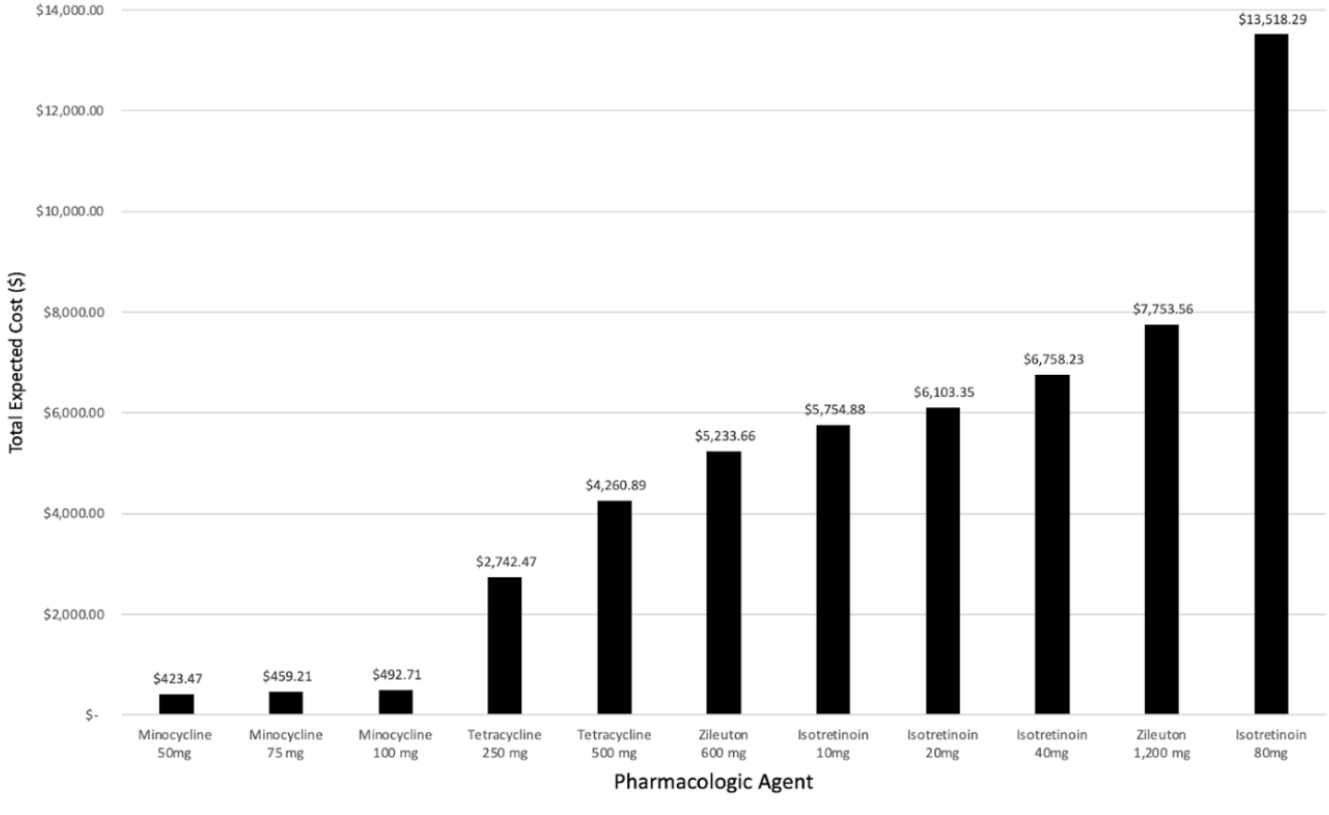
TABLE 3.

Average Total Expected Cost of Treating Sebaceous Hyperplasia With Pharmacologic Modalities. (Values represent weighted averages).

Pharmacologic Modality	# Pills/Day (Weighted Average)	Price Per Pill	Treatment Duration In Months	Treatment Duration In Days	Total Estimated Cost
Minocycline 50 mg (capsule)	1.38	$1.70	6.012820513	180.3836154	$423.47
Minocycline 75 mg	1.29	$1.98	6.012820513	180.3836154	$459.21
Minocycline 100 mg	1.14	$2.39	6.012820513	180.3836154	$492.71
Tetracycline 250 mg	1.78	$7.88	6.512820513	195.3846154	$2,742.47
Tetracycline 500 mg	1.38	$15.75	6.512820513	195.3846154	$4,260.89
Zileuton 600 mg	1.05	$37.59	4.42	132.6	$5,233.66
Zileuton 1,200 mg	0.78	$75.18	4.42	132.6	$7,753.56
Isotretinoin 10 mg	1	$31.46	6.097560976	182.9268293	$5,754.88
Isotretinoin 20 mg	1	$33.37	6.097560976	182.9268293	$6,103.35
Isotretinoin 40 mg	1	$36.95	6.097560976	182.9268293	$6,758.23
Isotretinoin 80 mg	1	$73.90	6.097560976	182.9268293	$13,518.29

The prices associated with various pharmacologic treatment modalities are shown in Figure 5. The price per individual pill, average number of pills per day, and treatment duration were taken into account to estimate the total cost of treatment (Table 3). Of note, the reported cost for minocycline relates to capsule formulations; however, tablets were found to be more expensive. For the weight-based dosing of isotretinoin, the average weight of an adult human in the United States was used to estimate the isotretinoin pill dosage that would be used. The most popular dosage of isotretinoin selected was 0.25 mg/kg/day (30.6%, n=26) and 0.5 mg/kg/day (34.1%, n=29). For an average human of 80 kg, this would be equivalent to 20 mg and 40 mg of isotretinoin, respectively.

FIGURE 5. Total expected cost of treating sebaceous hyperplasia with pharmacologic modalities.



Overall, the most cost-conscious pharmacologic agent was minocycline capsules; however, the effectiveness is questionable due to the high likelihood of recurrence. Minocycline tablets were more expensive than the capsules; the total expected cost for minocycline tablets, in increasing order of dosage, is $969.00, $1,332.12, and $1,241.05.

Provider Perspective of Survey

Eighty-six percent of providers felt this survey exposed them to alternative SH treatments they were previously unaware of. In addition, 86% of providers were interested in understanding how other dermatologists treat SH. Only 48% of providers predicted that most dermatologists have the same first-line treatment for SH, and 59% agreed that they have a first-line treatment for SH that they use in practice. However, this demonstrates that 41% of dermatologists did not have a first-line treatment.

DISCUSSION

Sebaceous hyperplasia is a common dermatologic condition that, while benign, can cause patients cosmetic distress and frustration.[2] Many available treatment options vary in effectiveness and cost; however, without a consensus on the most effective and cost-effective method, practice guidelines are not feasible. The treatment options for SH fall into pharmacological or non-pharmacological categories. Our study supports the findings of a recent review of the literature that non-pharmacological therapies are more commonly employed.[1]

Within the non-pharmacological therapies, ED was the most utilized procedure and represented the first-line approach for most providers. It was also perceived to be the least expensive option requiring only one session – occasionally two – to achieve lesion clearance. It was expected to have the lowest likelihood of recurrence after treatment cessation, which are findings similar to those reported in other studies.[3,4] Taking all this into consideration, we conclude that ED is the most cost-effective treatment option for SH.

Similarly priced to ED, cryosurgery is another less expensive option for treating SH. Although it is less likely to be considered a first-line approach, cryosurgery was the second most utilized treatment in our study and required only 2 sessions for successful lesion clearance. Other advantages include short preparation time and no need for injectable anesthesia.[5] Unfortunately, lesions were expected to recur within 6 months to 1 year. Other studies investigating cryosurgery for SH did not follow patients beyond 4 months, so long-term recurrence rates remain unknown.[5] One study found that cryotherapy was less efficacious and associated with inferior cosmesis compared with ED.[1]

While CO2 lasers are effective in treating SH, they are expected to be the costliest treatment modality. In our study, CO2 lasers were considered to have the second lowest likelihood of recurrence. However, Noh et al reports a recurrence of lesions within 6 months after completing 2 sessions with a CO2 laser. In their study, maintenance of lesion clearance was later achieved with a third session followed by 2 years of isotretinoin therapy.[6] Other studies that investigate the use of CO2 lasers in SH reported improvement in lesion appearance, but the lack of adequate follow-up, the absence of clearly defined parameters to measure the degree of improvement, and the use of combination treatments make it difficult to assess response.[7,8,9] Since many patients with SH may have received treatment with isotretinoin at any time point throughout their therapy, it is important to note that isotretinoin is absolutely contraindicated within the 6 months preceding CO2 laser therapy.[10]

The total cost of chemical peels was influenced by a higher session requirement. In our study, chemical peels required at least 3 sessions for SH clearance and were more likely than other modalities to require 5+ sessions. With high rates of expected recurrence within 6 months, this therapy is also not considered to be as effective as other available options. Out of the chemical peels, salicylic acid peels were slightly less expensive and used more often than bichloracetic acid and TCA peels. VI peels were the most expensive and used the least often.

Diode lasers lead to successful lesion clearance, with most dermatologists expecting 2 to 4 sessions to achieve clearance. These findings are in line with other studies that required 2 to 5 sessions for clearance of SH lesions.[11,12] A disadvantage is that lesion recurrence is anticipated to occur around one year after treatment, and there are no studies that report long-term recurrence rates for comparison. This therapy option is of moderate cost, with treatment falling between $300 and $500 per session.

Of note, when asked about utilized treatment options, 3 participants selected "other", and reported the use of mechanical resurfacing procedures such as excision, curettage, and radiofrequency. Four dermatologists also mentioned the use of an Erbium laser as a modality to treat SH. One study reported significant cosmetic outcomes with a low recurrence rate of SH lesions with Erbium laser therapy.[13] Regarding pharmacological treatment options, a few dermatologists reported using spironolactone (n=1) for 5 to 7 months or topical retinoids (n=3) for a range of 2 to 7 months in the "other" category. These options were not offered as an option in the distributed survey due to limited literature supporting their use for the treatment of SH.

Pharmacological therapies were expected to require long treatment durations, with tetracycline and minocycline expected to be used for 5 to 8 months. The most prescribed dosages for tetracycline were 250 mg twice daily, and 50 mg

once or twice daily for minocycline. Oral isotretinoin was also anticipated to require a long duration of use (5-7 months), with a recommended prescription of 0.25 or 0.5 mg/kg/day. This is similar to the duration reported in other studies in which lesion recurrence was expected after discontinuing therapy.[3] Since Zileuton is an unfamiliar medication for this indication to most of the responding dermatologists, the response rate regarding this medication was low. Of those who responded, the recommendation for zileuton is 600 mg twice daily for approximately 4 to 6 months. While the recurrence rate of lesions after these pharmacological therapies is expected to be high, the timeline of lesion return was unclear. Though the cost of minocycline is the lowest of the pharmacologic agents, followed by tetracycline, due to the high likelihood of recurrence, pharmacologic therapies are not as practical in treating SH based on these data.

Dermatologists tended to gravitate towards procedural SH treatments over pharmacologic options, and the results from this study show that the common procedural modalities are more cost-effective. A newer treatment option for SH is the Pulse Bioscience' Cell FX System Nano-Pulse Stimulation (NPS). Munavalli et al investigated outcomes in SH with NPS technology and showed 99% lesion clearance, with only a small percentage requiring a second session.[14] However, dermal volume loss, manifested as cutaneous depressions, was an unwanted side effect that may be minimized with lower NPS energy.[15]

LIMITATIONS

This study used a voluntary survey for data collection, and thus is limited by response rate and bias from provider-specific experience with prior treatment and training. In addition, we had variable response rates for rarer treatment options, such as Zileuton. For our cost-analysis of therapies, we did not take into account insurance coverage; but due to the likely cosmetic nature of treatment indication, insurance coverage may be limited. In addition, when calculating the mean total cost of treatments, rate of lesion recurrence was not accounted for; thus, the total cost may be higher if re-treatment is expected. Nevertheless, ED has the least reported risk of recurrence, and therefore, remains the preferred choice.

The total duration of procedural treatments may vary depending on session interval times; therefore, the number of sessions rather than duration of treatments was investigated. This study did not define what was meant by lesion clearance and, upon review of literature, there is variability in the definition of lesion clearance, with some studies setting criteria and other studies describing the changes in size and appearance of individual SH lesions.

In addition, this study does not consider out-of-pocket expenses such as travel costs and production losses at work, which includes work time lost due to clinic visits for initial consultation and subsequent treatments. Furthermore, procedural treatments may leave skin with temporary signs of redness or trauma, such that a patient may opt to take time off from work after therapy. In contrast, pharmacologic options may not require as much time off, although medications such as isotretinoin often require laboratory monitoring and side effects from medications are not to be overlooked.

The procedural interventions that were investigated may not apply to all skin types and may be associated with side effect profiles or post-operative recoveries that influence a patient's decision. Those with darker skin tones should avoid traditional resurfacing lasers as well as the new Cell FX System, as these modalities are only approved for lighter skin types and may lead to permanent skin pigmentation changes in darker skin types.[16,17] Most cases of SH reported in the literature are in patients with lighter skin tones. However, combination treatment of lasers and PDT showed promising results in patients with darker skin tones.

CONCLUSION

SH is a common issue that presents to the dermatologist's office. Our data highlight the cost-effective nature of electrodessication, as it is one of the cheaper treatment options and requires few sessions to achieve successful outcomes based on practitioner feedback. More data are needed to better determine best practices for the management of SH; however, our study provides the first cost-effective analysis of the various modalities used to treat SH.

DISCLOSURES

None of the authors has any conflicts of interest to disclose.

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A 2023 Arcutis survey of 93 adults diagnosed with seborrheic dermatitis found that an average of 15 products (including over-the-counter, alternative, and prescription treatments) were reportedly used on a yearly basis.[2]

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

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

The most common adverse reactions (≥1%) include nasopharyngitis (1.5%), nausea (1.3%), and headache (1.1%).

Please see brief summary of full Prescribing Information for ZORYVE foam on the following page.

See the results at zoryvehcp.com/foam

References: 1. ZORYVE® foam. Prescribing information. Arcutis Biotherapeutics, Inc; 2023.
2. Data on File. Arcutis Biotherapeutics, Inc.

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

Wash hands after application.

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

ZORYVE foam, 0.3%, is for topical use only and not for ophthalmic, oral, or intravaginal use.

CONTRAINDICATIONS

ZORYVE foam, 0.3%, is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

WARNINGS AND PRECAUTIONS

Flammability

The propellants in ZORYVE foam, 0.3%, are flammable. Avoid fire, flame, and smoking during and immediately following application.

ADVERSE REACTIONS

Clinical Trials Experience

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

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 203 and STRATUM), 683 adult and pediatric subjects 9 years of age or older with seborrheic dermatitis were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks. The combined trial population was 79% White, 11% Black, and 5% Asian; for ethnicity, 79% identified as non-Hispanic/Latino and 21% identified as Hispanic/Latino. Fifty percent (50%) were male and 50% were female. The median age was 41 years (range 9 to 87 years). The median body surface area (BSA) affected was 2.5%.

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are insufficient data available on the use of ZORYVE foam, 0.3%, in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 30 and 26 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 10 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 16 and 49 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 49 times the MRHD during pregnancy and lactation periods in mice.

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

Clinical Considerations

Labor and delivery

Avoid using ZORYVE foam, 0.3%, during labor and delivery. There are no human studies that have investigated effects of ZORYVE foam, 0.3%, on preterm labor or labor at term; however, animal studies showed that oral roflumilast disrupted the labor and delivery process in mice.

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (30 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (3 times the MRHD on a mg/m^2 basis).

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

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (26 times the MRHD on a mg/m^2 basis).

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

Lactation

Risk Summary

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

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZORYVE foam, 0.3%, and any potential adverse effects on the breastfed infant from ZORYVE foam, 0.3%, or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use ZORYVE foam, 0.3%, on the smallest area of skin and for the shortest duration possible while breastfeeding. To avoid direct infant exposure, advise breastfeeding women not to apply ZORYVE foam, 0.3%, directly to the nipple or areola. If applied to the patient's chest, avoid exposure via direct contact with the infant's skin.

Data

Animal data

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

Pediatric Use

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

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

Geriatric Use

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

Hepatic Impairment

Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The systemic exposure of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE foam, 0.3%, is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C). No dosage adjustment is needed in patients with mild (Child-Pugh A) hepatic impairment.

PATIENT COUNSELING INFORMATION

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

Flammability

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

Lactation

Advise patients to use ZORYVE foam, 0.3%, on the smallest area of skin and for the shortest duration possible while breastfeeding. Instruct patients who are breastfeeding not to apply ZORYVE foam, 0.3%, directly to the nipple or areola to avoid direct infant exposure. Instruct patients to avoid inadvertent contact of treated areas with infant skin.

In DERMIS-1 and DERMIS-2, ~40% of patients achieved IGA Success and ~70% of patients achieved I-IGA Success at Week 8.[1]

DERMIS-1 and DERMIS-2 were identical Phase 3 randomized, parallel, double-blind, vehicle-controlled, multicenter studies that evaluated ZORYVE over 8 weeks as a once-daily, topical treatment for plaque psoriasis. Subjects (N=881) were randomized 2:1 to receive ZORYVE cream 0.3% (n=576) or vehicle (n=305) applied once daily for 8 weeks. Eligibility criteria included a diagnosis of mild, moderate, or severe plaque psoriasis and an affected BSA of 2% to 20%. The primary endpoint was IGA Success at Week 8 and a key secondary endpoint was I-IGA Success at Week 8.[1]

IGA Success and I-IGA Success were defined as a score of *Clear* (0) or *Almost Clear* (1) and a ≥2-grade improvement from baseline.[1,2]

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use.[1]

BSA = Body Surface Area, IGA = Investigator Global Assessment, I-IGA = Intertriginous-IGA

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

The most common adverse reactions (≥1%) include diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain (1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%).

Please see brief summary of full Prescribing Information for ZORYVE cream on the following page.

See the results at zoryvehcp.com/cream

References: 1. ZORVYE® cream. Prescribing information. Arcutis Biotherapeutics, Inc; 2023.
2. Data on File. Arcutis Biotherapeutics, Inc.

ARCUTIS BIOTHERAPEUTICS

US-COM-151-00311 01/24

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are insufficient data available on the use of ZORYVE cream in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 9 and 8 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 3 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 5 and 15 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 15 times the MRHD during pregnancy and lactation periods in mice.

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

Clinical Considerations

Labor and delivery

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

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (9 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (3 times the MRHD on a mg/m^2 basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (9 times the MRHD on a mg/m^2 basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (8 times the MRHD on a mg/m^2 basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (5 and 15 times the MRHD on a mg/m^2 basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (5 times the MRHD on a mg/m^2 basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (15 times the MRHD on a mg/m^2 basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (29 times the MRHD on a mg/m^2 basis).

Lactation

Risk Summary

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

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

Clinical Considerations

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

Data

Animal data

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

Pediatric Use

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

The safety and effectiveness of ZORYVE cream in pediatric patients below the age of 6 years have not been established.

Geriatric Use

Of the 881 subjects with psoriasis exposed to ZORYVE cream or vehicle for up to 8 weeks in 2 controlled clinical trials, 106 were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted.

Hepatic Impairment

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

PATIENT COUNSELING INFORMATION

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

Lactation

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

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ORIGINAL ARTICLE

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Benefit of Topical Combination Therapy for Acne: Analyzing Effect Size Using Number Needed to Treat

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ABSTRACT

Background: Topical acne trials often are confounded by high vehicle response rates and differing outcome measures, making it difficult to compare treatments. Number needed to treat (NNT) can be a simple, clinically meaningful way to indirectly compare treatment options without head-to-head data. NNT is the number of patients who need to be treated with an intervention to observe one additional patient successfully achieving a desired outcome versus vehicle/placebo. While treatment attributes such as adverse events may not be captured, lower NNT is a good indicator of a more effective treatment.

Methods: Following a search of combination topical treatments for acne vulgaris, all treatments that reported pivotal trial efficacy data consistent with the 2018 FDA definition of success were included in NNT analyses.

Results: Of 13 treatments, 7 reported 12-week treatment success rates in 11 phase 3 trials, with similar baseline demographics/disease severity. Treatment success ranged from 26.8% with tretinoin 0.1%/benzoyl peroxide (BPO) 3% cream to 50% with triple-combination clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel. NNTs for the triple-combination gel were 4 and 5 (from 2 pivotal trials). Adapalene 0.3%/BPO 2.5% gel had an NNT of 5. Tretinoin/BPO had the largest range between trials, with NNTs of 4 and 9. The other 4 treatments had NNTs ranging from 6 to 8.

Conclusion: A comparison of combination topical acne treatment trial data, using the same treatment outcome and similar patient populations, resulted in triple-combination clindamycin phosphate/adapalene/BPO gel and adapalene/BPO gel having the most favorable NNTs.

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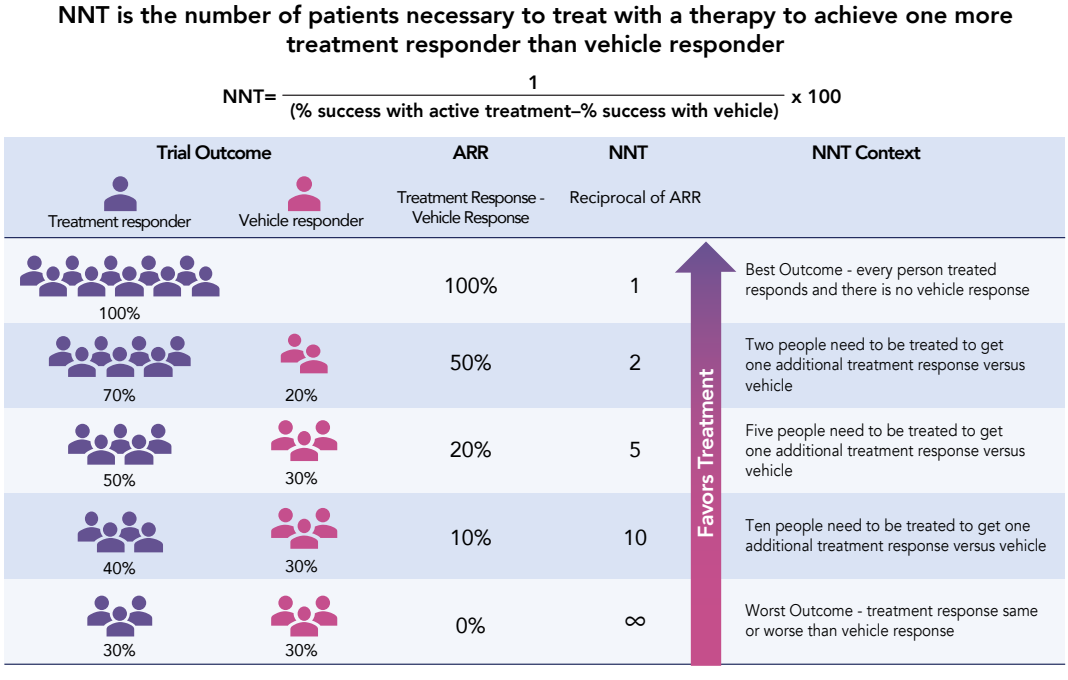
INTRODUCTION

Assuming comparable safety and tolerability, patients and healthcare providers strive to choose the most effective treatment for any given condition. For conditions with multiple treatment options, this requires evaluating the relative effectiveness of each. In the absence of head-to-head trials, a common measure of comparative clinical effectiveness is the number needed to treat (NNT).[1-3] NNT is a way to provide a clinically useful measure of treatment effect and indirectly compare data across randomized double-blind controlled trials.[2,4] Assuming other treatment-related considerations are equal (eg, side effect profile, cost, access), choosing a treatment with the lowest NNT would be a reasonable approach, as this may denote the highest efficacy in attaining a treatment outcome.

The NNT is the reciprocal value of the absolute risk reduction (ARR; Figure 1). More than *P* values and responder rates, NNT is a clinically intuitive way to determine if one treatment is better than another in a way that is likely to be noticed in routine clinical practice.[2] However, the clinical relevance of an NNT is not just based on the number. Acceptable NNTs vary widely by disease and are dictated by many factors, such as severity, epidemiology, and treatability.[3]

In the acne vulgaris literature, NNTs are rarely reported; while there is an example of NNT used as an outcome measure of treatment efficacy,[5] NNTs are more frequently calculated in secondary sources such as review articles.[6-9] In these publications, NNTs for acne treatments were less than 10 but

FIGURE 1. Description of number needed to treat (NNT).



Hypothetical trial outcomes shown here illustrate how NNT values are calculated. Lower NNT values favor active treatment over vehicle.
ARR, absolute risk reduction; NNT, number needed to treat.

were calculated using different definitions of treatment success and with different study conditions, preventing meaningful comparisons between studies.

The complex and multifactorial pathogenesis of acne has resulted in combination treatments simultaneously targeting different factors being the recommended treatment strategy for most patients.[10] Fixed-dose combination products can also simplify treatment regimens and may enhance patient adherence.[10-12] However, in the absence of head-to-head studies of acne treatments, there are no direct assessments of the comparative efficacy of fixed-dose combination topical treatments. The objective of this analysis was to calculate the NNT values of these products for the treatment of acne using treatment success, as defined by the Food and Drug Administration (FDA),[13] as the comparison metric.

MATERIALS AND METHODS

Data Collection

A literature and treatment search[14,15] were conducted to identify combination topical acne treatments. Once identified, data sources obtained for currently available treatments included Prescribing Information, Medical Review, and/or Multi-Discipline Review documents for drug approval in the United States. Medical Review and Multi-Discipline Review documents were obtained from the FDA approved drug database; prescribing information documents were obtained either from branded drug websites or Drugs@FDA.[13]

Data from the available pivotal phase 3 studies included in this analysis were inclusion and exclusion criteria (ie, participant age, acne severity), baseline disease severity and demographics, population size for active treatment and vehicle groups, and treatment success rates for active treatment and vehicle groups. NNTs were calculated from each study using treatment success as the comparator metric.

NNT Calculation Using Treatment Success (Per FDA Definition)

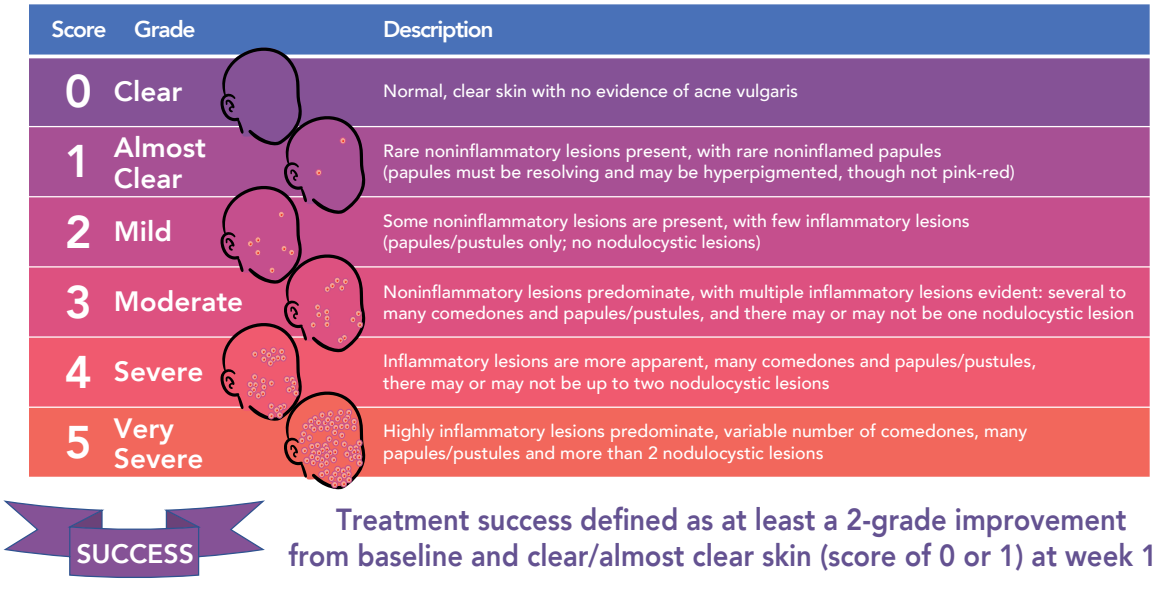
NNT calculations require the use of a binary outcome at a specific point in time.[2] The Evaluator's Global Severity Score/Investigator's Global Assessment (EGSS/IGA) is a scale used to determine acne severity, with higher scores indicating more severe acne (Figure 2).[16,17] EGSS, IGA, and Investigator's Static Global Assessment (ISGA) are considered variations of the same scale referred to by different names.[16,17] The EGSS/IGA scale can be dichotomized to success or failure, with the 2018 FDA guidelines for treating acne defining a clinically meaningful outcome for success as a ≥2-grade improvement from baseline and clear/almost clear skin (score of 0 or 1).[13] This FDA definition of treatment success was used to calculate NNT values in this analysis. Any combination topical acne treatment studies that reported other definitions of success (eg, global improvement) were not included. The same outcome measure and time point must be used to minimize non-efficacy influences when comparing the efficacy of treatments via NNTs.[18] In this analysis, the common endpoint of treatment success at 12 weeks was used to reduce this variability.

NNT is the reciprocal of ARR, which is the difference in probability of an event between active treatment and vehicle (Figure 1).[8,19] NNT for treatment success was calculated with the equation below and confirmed via an online NNT calculator (https://clincalc.com/Stats/NNT.aspx).

$$\text{NNT} = \frac{1}{(\%\ \text{success with active treatment} - \%\ \text{success with vehicle})} \times 100$$

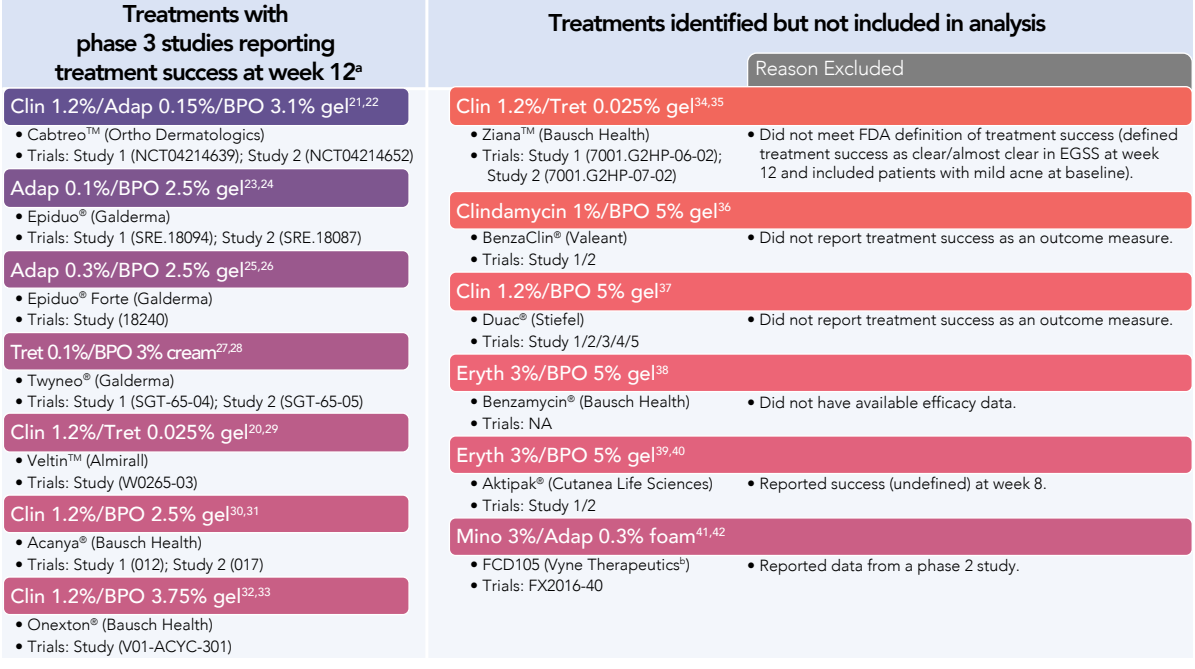
Calculated NNT values are rounded up to the nearest whole number (as a fraction of a person in the real world is not possible).[2,3,8] Calculated NNT values were summarized descriptively, with no statistical analyses performed.

FIGURE 2. EGSS/IGA scale and treatment success definition used.[17,20]



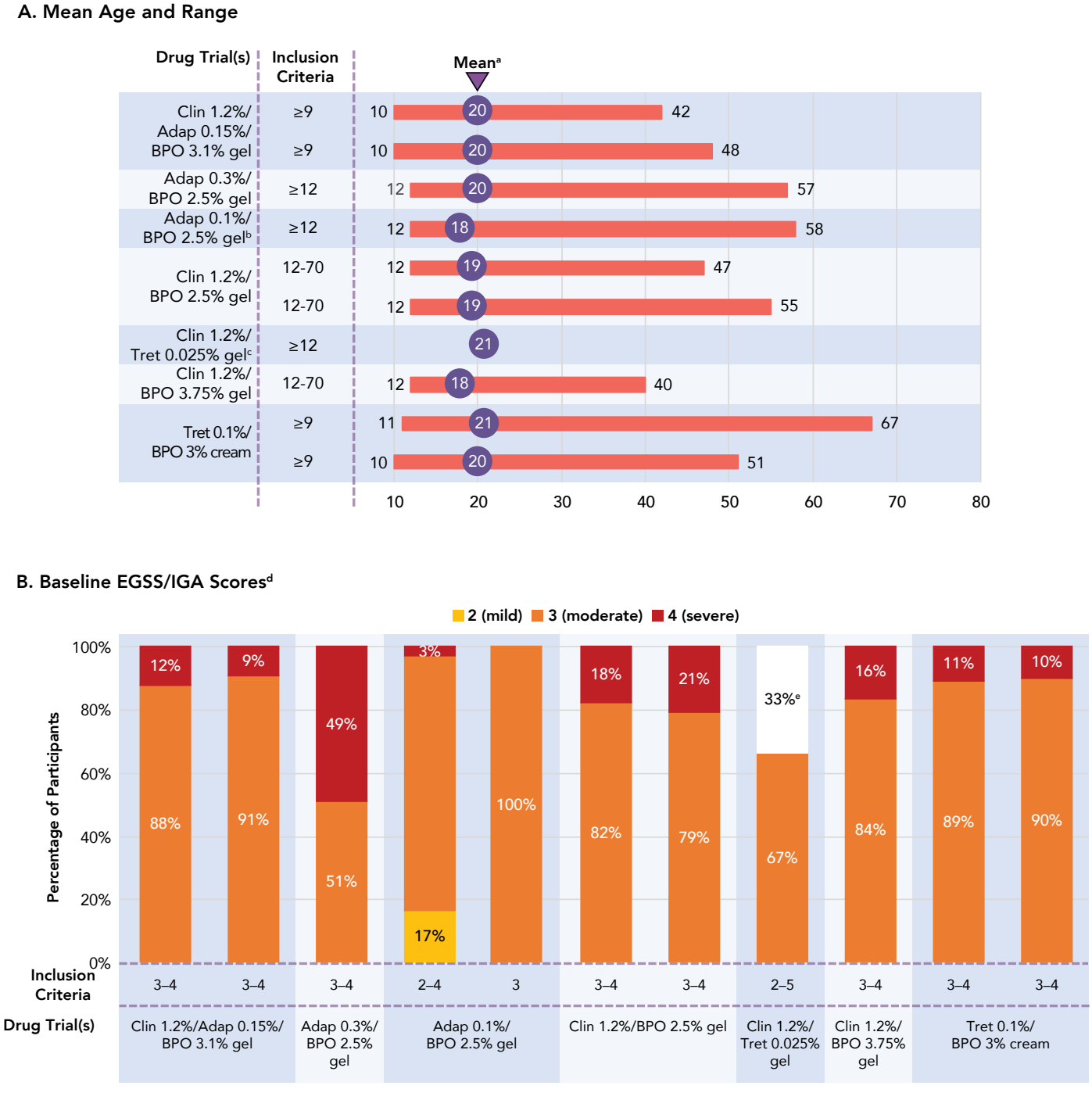
[a]Per 2018 FDA guidelines for treating acne.[13] EGSS, Evaluator's Global Severity Score; IGA, Investigator's Global Assessment.

FIGURE 3. Combination topical acne treatments evaluated.



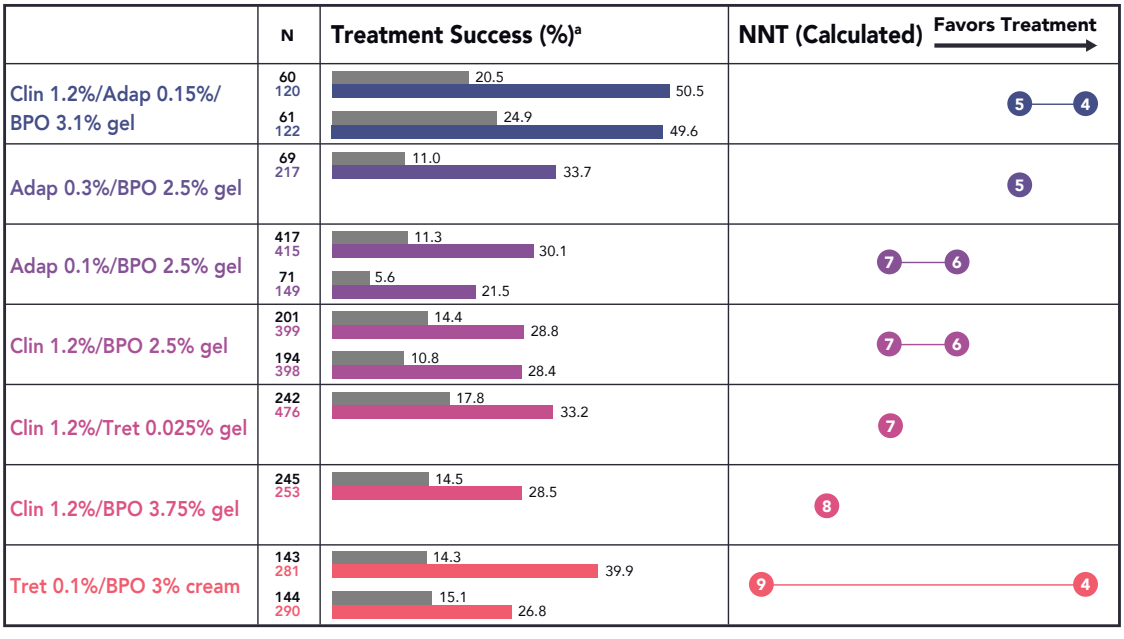
[a]Defined as percentage of participants achieving ≥2-grade reduction from baseline in EGSS/IGA and clear/almost clear skin at week 12. [b]Currently owned by Journey Medical,[43] development status unknown. Adap, adapalene; BPO, benzoyl peroxide; Clin, clindamycin phosphate; EGSS, Evaluator's Global Severity Score; Eryth; erythromycin; IGA, Investigator's Global Assessment; Mino, minocycline; NA, not available; Tret, tretinoin.

FIGURE 4. Trial Inclusion criteria and patient baseline data.



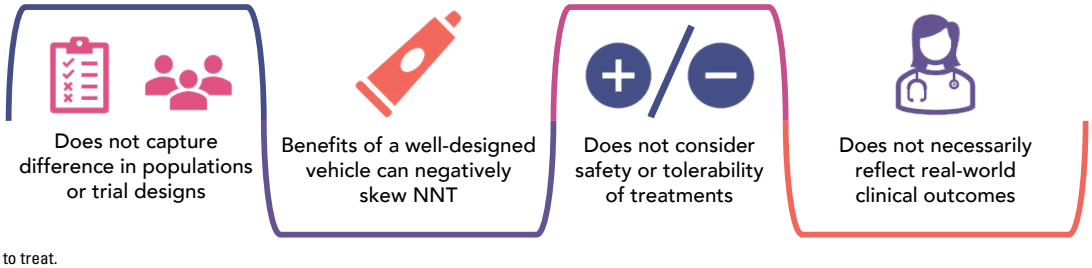
[a]Mean age and age ranges for active treatment groups.
[b]Adapalene 0.1%/BPO 2.5% gel reported combined baseline age data from two trials.
[c]Clindamycin phosphate 1.2%/tretinoin 0.025% gel source disclosed only mean age.
[d]Percentage of participants with each baseline EGSS/IGA score (2 [mild], 3 [moderate], or 4 [severe]); data for active treatment group unless otherwise noted.
[e]Clindamycin phosphate 1.2%/tretinoin 0.025% gel trial disclosed limited baseline severity data with 33% of patient baseline EGSS/IGA unknown, as indicated by the open bar; treatment and vehicle group data were combined in the source information.
Adap, adapalene; BPO, benzoyl peroxide; Clin, clindamycin phosphate; EGSS, Evaluator's Global Severity Score; IGA, Investigator's Global Assessment; Tret, tretinoin.

FIGURE 5. Treatment success and NNT for combination topical acne treatments.



Grey bars indicate vehicle and colored bars active treatment data.
[a]Defined as (or met criteria for) the percentage of patients achieving ≥2-grade reduction from baseline in EGSS/IGA and clear/almost clear skin at week 12.
Adap, adapalene; BPO, benzoyl peroxide; Clin, clindamycin phosphate; EGSS, Evaluator's Global Severity Score; IGA, Investigator's Global Assessment; NNT, number needed to treat; Tret, tretinoin.

FIGURE 6. Limitations of NNT in this analysis.



NNT, number needed to treat.

RESULTS

A total of 11 FDA-approved dual fixed-combination drugs, one FDA-approved triple-combination drug, and one dual-combination drug without phase 3 data were found (Figure 3). Of these, 7 reported treatment success rates at week 12 and were included in the analysis (Figure 3).[20-33] Most trials defined treatment success at week 12 as at least a 2-grade improvement from baseline and clear/almost clear skin, which is consistent with the 2018 FDA guidance on defining treatment success in acne trials.[13] Adapalene 0.1%/benzoyl peroxide (BPO) 2.5% gel Study 1 reported this as an intersecting definition of treatment success. Two drugs (clindamycin phosphate 1.2%/BPO 2.5% gel and clindamycin phosphate 1.2%/BPO 3.75% gel) defined success as clear/almost clear skin (score of 0 or 1); however, as they enrolled patients with moderate or severe grades (score of 3 or 4), patients had to have at least a 2-grade improvement to meet that criterion. Six combination treatments were not included in this NNT analysis for not reporting treatment success data as defined above or for not having phase 3 data (Figure 3).[32,34-42]

The 7 treatments included in the analysis had 11 total phase 3 pivotal studies (Figure 3). Patient populations were similar across the 11 studies, though there were differences in inclusion/exclusion criteria and subsequent differences in enrolled baseline demographics and disease severity (Figure 4). The inclusion criteria minimum age was either 9 or 12 years across all trials (Figure 4A). The mean age of enrolled patients in the treatment group was similar across trials, between 18 and 21 years. Though not shown, the mean ages of the vehicle groups did not vary from treatment groups. Most participants across the studies had moderate-to-severe acne at baseline (Figure 4B). Only one treatment enrolled patients with mild acne (adapalene 0.1%/BPO 2.5% gel), and most enrolled a majority of patients with moderate acne; the one exception is adapalene 0.3%/BPO 2.5% gel, which enrolled an equal percentage of patients with moderate and severe acne.

The NNTs calculated from the treatment success results for these 11 studies were all less than 10 (Figure 5). The lowest NNT values of 4 and 5 (most favorable) were found with fixed-dose, triple-combination clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel. Treatment success rates with this triple-combination gel were ~50% at week 12, the largest values seen for any treatment. Adapalene 0.3%/BPO 2.5% gel also had a trial with an NNT of 5 and a treatment success rate of 33.7%. The largest NNT range between trials was seen with tretinoin 0.1%/BPO 3% cream, for which NNT values were 4 and 9.

DISCUSSION

NNT is a descriptor of treatment efficacy, representing the number of patients needed to be administered a treatment to achieve one additional successful outcome versus placebo or vehicle. It may be used as a simple way to indirectly compare drug effects across clinical trials when head-to-head study data are not available. In this analysis, NNTs were calculated and compared for 7 fixed-combination topical acne treatments. Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel and adapalene 0.3%/BPO 2.5% gel were determined to have the most favorable (lowest) NNT values of 4-5 and 5, respectively. One study of tretinoin 0.1%/BPO 3% cream had an NNT value of 4, though the second study had an NNT of 9. NNT values for the remaining dual-combination drugs ranged from 6 to 8.

The most-recently approved topical product for acne, clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel is the only triple, rather than dual, combination product included in this analysis. It is possible that due to the multifactorial pathogenesis of acne, a triple-combination topical treatment may result in clinical success more often than seen with 2-ingredient combination products. This is supported by published phase 2 study results, in which this fixed-dose triple combination led to greater treatment success rates at week 12 (52.5%) compared with its dual-component combination dyads in the same gel vehicle (27.8-30.3%; $P \leq 0.001$ all).[44] The benefits of clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel are also supported by a recently published meta-analysis, in which triple therapies containing an antibiotic, retinoid, and BPO were among the top 2 most efficacious of all products assessed for both treatment success and total lesion count reductions.[45]

The straightforwardness of the NNT statistic offers an intuitive and easy-to-comprehend summary for both clinicians and the lay public.[3] However, limitations directly related to its simplicity have been widely discussed in many therapeutic areas.[1,18,46] Some limitations, such as outcome measure variability, can be relatively easily addressed. While the selection of treatment success at 12 weeks as the comparator outcome in this analysis did preclude the inclusion of combination topical acne drugs that did not report this outcome, it was used by many available treatments and reduced a major source of potential variability in the NNT calculation. The FDA's adoption of a standard definition of treatment success for acne vulgaris in 2018 should bolster NNT comparisons for future treatments.[13]

Other NNT limitations are persistent and particularly problematic in trial comparisons (Figure 6). Differences in baseline population and trial design are always a confounding factor in NNT comparisons.[47] There was some variability in the inclusion criteria for each trial included in this analysis, which is reflected in some differences in the baseline demographics and disease severity. However, no obvious trends were detected when comparing variations in baseline information and NNT values.

Of particular impact with implementing NNT in topical acne treatments, and all topical treatments in general, is that controls in these trials are almost always drug-free vehicles. The NNT calculation was designed with placebo controls in mind,[3] not vehicle controls. Some pharmaceutical manufacturers expend considerable effort on optimizing aspects of topical vehicles, such as effective drug delivery to the skin and hydration/moisturization.[14] Moisturization can mitigate irritation caused by active ingredients, and may indirectly enhance treatment efficacy by improving patient compliance.[48,49] Certain moisturizer ingredients, like ceramides, may have direct therapeutic effects on the skin.[50] Many acne treatment vehicles contain similar moisturizing ingredients and antimicrobial preservatives with potential direct and indirect therapeutic benefits.[49] Because the NNT calculation subtracts potential positive vehicle effects, a well-designed vehicle can lead to a higher (less favorable) NNT even though more patients overall may respond to the formulation.

This leads to another important limitation of NNT, which is it does not capture treatment emergent adverse events (TEAEs). The number needed to harm (NNH) is the calculation used to understand the number of patients treated to have one more TEAE with treatment than placebo.[2] Determining the NNH of a treatment requires the same type of data to be reported for each trial in order to make accurate comparisons. Like vehicle formulations, safety and tolerability data reporting in acne studies has evolved over the years. The highly variable standards, including terms used for TEAEs, preclude directly comparing NNH in this therapeutic area at this time. NNHs would ideally enable direct comparisons of TEAEs such as discomfort and irritation. While TEAEs, as well as tolerability, undoubtedly inform a physician's decisions to employ a particular treatment, they can also negatively influence a key issue in practical acne management: patient compliance.

Like other approaches to reporting efficacy, NNT is ultimately a single value that fails to capture many aspects of real-world treatment. In a controlled clinical trial environment—in which patient adherence may be higher than real-world use—a product

with a favorable NNT value and low irritation profile may have other unquantified effects that can affect real-world usage.[51] For example, patient compliance may be negatively influenced by a topical acne treatment that feels uncomfortable on the skin,[52] has any unpleasant odors,[53] or may bleach clothing.[54] Alternatively, a thoughtfully constructed vehicle may mitigate many of these negative traits that have become commonplace in the acne armamentarium. While not captured by NNT, these details can have a profound influence on whether a patient continues to use a product, and no product can be effective if it is not used. Product design that emphasizes both patient experience and treatment efficacy would therefore lead to a drug being preferred by patients and physicians alike. Further, the FDA's definition of treatment success utilized in clinical trials may not be fully representative of real-life acne improvements. Patients treated with topical acne medications may have clinically meaningful acne reductions without achieving clear or almost clear skin with a two-point improvement in disease severity. If the standard outcome is overly stringent, the resulting NNT may overestimate the number of patients required to see one additional success. However, the resulting bias may be less likely to affect the relative comparison across different drugs.

CONCLUSION

To better inform clinical practice, clinical trial results should be reported clearly and emphasize relevance to patient care. With treatment success rates of ~50% and 33.7%, clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% gel and adapalene 0.3%/BPO 2.5% gel, respectively, resulted in the lowest (most favorable) NNTs of the combination topical acne treatments examined in this analysis. NNT is a simple but useful method of reporting treatment efficacy.

DISCLOSURES

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ORIGINAL ARTICLE

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Halobetasol Propionate 0.01% and Tazarotene 0.045% Lotion With a Ceramide-Containing Moisturizer in Adults With Psoriasis

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ABSTRACT

Introduction: Moisturizers are often used as adjuvant therapy for psoriasis to assist with rehydration and skin barrier restoration. Fixed-combination halobetasol propionate 0.01% and tazarotene 0.045% lotion (HP/TAZ) is indicated for the topical treatment of plaque psoriasis in adults, with a demonstrated clinical profile in two phase 3 trials. However, the effect of application order with HP/TAZ has yet to be explored. This study evaluated the clinical profile of HP/TAZ applied before versus after a ceramide-containing moisturizer in adults with mild-to-moderate plaque psoriasis.

Methods: Sixteen participants were randomized to apply HP/TAZ followed by moisturizer on one side and moisturizer followed by HP/TAZ on the other side once daily for 12 weeks. Tolerability, safety, efficacy, and quality of life endpoints were assessed.

Results: Significant Investigator's Global Assessment improvement was observed across all time points ($P \leq 0.003$) regardless of application order. Total Dermatology Life Quality Index scores significantly improved at all time points ($P \leq 0.003$), and visual analog scale for itch significantly improved at weeks 4, 8, and 12 ($P < 0.008$). Four moderate adverse events were experienced by 3 participants. Two participants reported itching/irritation, which was worse when HP/TAZ was applied first.

Conclusions: The application order of moisturizer did not decrease therapeutic efficacy of HP/TAZ. Moisturizer application before HP/TAZ may reduce incidence of application site adverse events, ultimately increasing tolerability and supporting the real-world recommendation that applying a ceramide-containing moisturizer before HP/TAZ, versus after, results in a safe and effective therapeutic option for plaque psoriasis.

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INTRODUCTION

Psoriasis, a chronic inflammatory disease characterized by erythematous and scaly skin, is caused by hyperproliferation and differentiation of keratinocytes, which results in dysregulation of the skin barrier.[1,2] Typically, a healthy stratum corneum consists of corneocytes and a lipid-rich extracellular matrix organized in a brick-and-mortar arrangement.[3] Ceramides, cholesterol, and free fatty acids predominantly populate the extracellular matrix and contribute to maintenance of barrier homeostasis and hydration.[4,5] However, in patients with psoriasis, the stratum corneum becomes depleted of lipids, including ceramides, resulting in disrupted skin barrier function, elevated levels of transepidermal water loss (TEWL), and reduced stratum corneum hydration.[2,5,6] Notably, depletion of stratum corneum lipids in psoriasis is thought to be limited to lesional epidermis and may potentiate inflammation associated with psoriasis.[5,7]

As such, direct restoration of the skin barrier is crucial for patients with psoriasis and may be facilitated by using moisturizers. Some moisturizers (eg, emollients) promote retention of hydration in the stratum corneum, reduce TEWL, and normalize hyperproliferation and differentiation of keratinocytes, thereby supporting skin barrier function in patients with psoriasis.[8] Furthermore, moisturizers that contain lipids such as ceramides may further assist in skin barrier repair by supplementing the aforementioned "mortar" of the stratum corneum and increasing total skin ceramide content.[5,9] Indeed, the American Academy of Dermatology and National Psoriasis Foundation joint guidelines recommend the use of moisturizers (ie, creams, ointments, lotions, and gels) as adjuvant therapy for topical corticosteroids to help reduce itch and desquamation.[8] Despite the widespread use of moisturizers in psoriasis regimens, there is still a need to evaluate the order of application with moisturizers and prescription therapies regardless of the therapeutic agent selected.[10-13]

Fixed-combination halobetasol propionate 0.01% and tazarotene 0.045% lotion (HP/TAZ) is indicated for the topical treatment of plaque psoriasis in adults.[14] The efficacy and safety of HP/TAZ has been demonstrated in two phase 3 clinical trials in which participants were not instructed to moisturize.[15] Thus, the optimal order in which to apply moisturizer and HP/TAZ has not been explored. This study assessed the tolerability, safety, and efficacy of the application of a ceramide-containing moisturizer (CeraVe®, L'Oreal Group) before versus after application of HP/TAZ in a split-body fashion in adults with mild-to-moderate plaque psoriasis.

MATERIALS AND METHODS

Study Design

Participants with mild-to-moderate psoriasis on both sides of the body were randomized (1:1) to receive (1) HP/TAZ followed by moisturizer on the right side of their body and moisturizer followed by HP/TAZ on the left side or (2) HP/TAZ followed by moisturizer on the left side of their body and moisturizer followed by HP/TAZ on the right side. Participants applied this regimen once daily for 12 weeks. To mimic real-world application, participants were not instructed to wait for any duration between the application of each agent, allowing a once-daily treatment regimen of immediate and consecutive application of moisturizer and HP/TAZ.

Participants were screened at baseline and assessed at weeks 2, 4, 8, and 12 for the following endpoints: Investigator's Global Assessment (IGA) score, Dermatology Life Quality Index (DLQI), visual analog scale (VAS) for itch, and tolerability (itching, dryness, and burning/stinging). Adverse events (AEs) were monitored throughout the study.

Statistical Analysis

A Wilcoxon signed rank test was used to compare endpoints with baseline. One participant was lost to follow-up before the week 12 visit; values were imputed for this visit by last observation carried forward.

RESULTS

Baseline Characteristics

Sixteen participants with mild-to-moderate psoriasis and a mean age of 50 years (range, 33 to 73 years) were enrolled; 7 participants were female and 9 were male. Two self-identified as Black and 14 as White; no participants reported Hispanic or Latino ethnicity. At baseline, the sides of the body that received HP/TAZ first had IGA scores identical to the sides that received moisturizer first (mild [2], n=5; moderate [3], n=11).

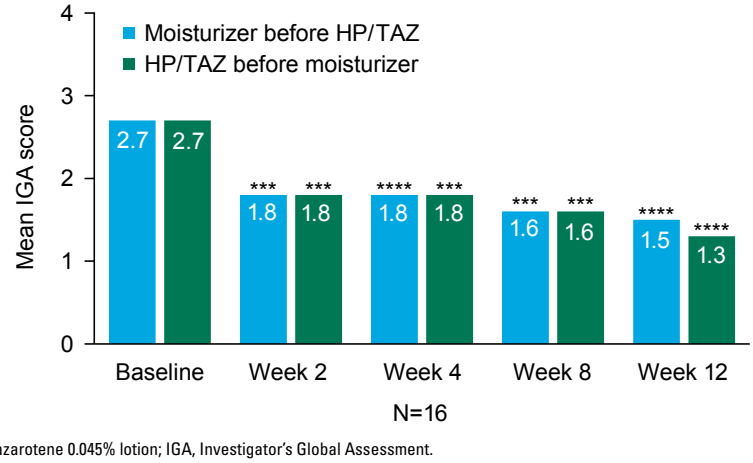
Efficacy

Statistically significant improvements in IGA from baseline were observed as early as week 2 and continued through week 12 (P<0.003 for all); results did not differ with order of application (P>0.14 for all; Figure 1). As early as week 2, both treatment regimens resulted in an IGA of 1 (almost clear) in 44% of participants. By week 12, 56% of the HP/TAZ–first regimen and 44% of the moisturizer-first regimen achieved an IGA of 0 or 1 (clear or almost clear). Because IGA improvement was similar regardless of moisturizer and HP/TAZ application order, participant data were pooled for subsequent endpoint analyses.

Quality of Life and Itch

Statistically significant improvements from baseline in total DLQI score were observed across all time points (P≤0.003 for all; Figure 2). Three individual DLQI items showed statistically

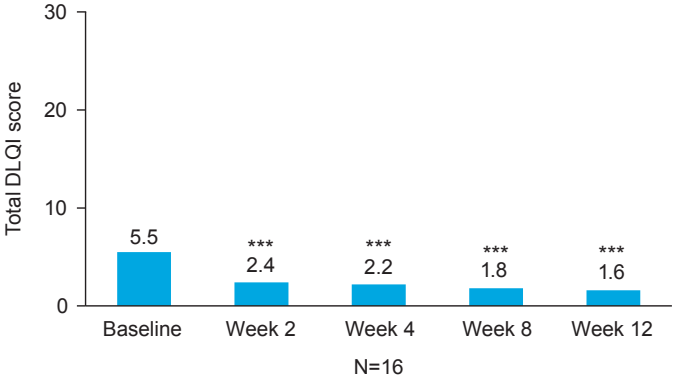
FIGURE 1. HP/TAZ treatment results in statistically significant reductions in IGA score regardless of application order. Mean IGA scores of participants who applied moisturizer before HP/TAZ or applied HP/TAZ before moisturizer were considerably decreased over time. One participant was lost to follow-up before the week 12 visit, and values were imputed for this participant by last observation carried forward.



HP/TAZ, halobetasol propionate 0.01% and tazarotene 0.045% lotion; IGA, Investigator's Global Assessment.

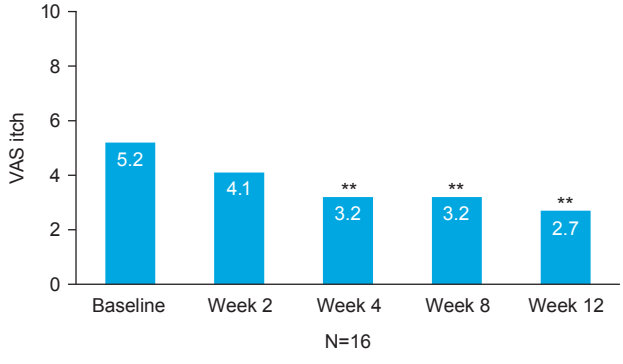
***P<0.005, ****P<0.001 compared with baseline, Wilcoxon signed rank test.

FIGURE 2. HP/TAZ treatment results in statistically significant improvements in DLQI score. Total DLQI score pooled from both treatment regimens (HP/TAZ and moisturizer in either order). One participant was lost to follow-up before the week 12 visit, and values were imputed for this participant by last observation carried forward.



DLQI, Dermatology Life Quality Index.
***P<0.005 compared with baseline, Wilcoxon signed rank test.

FIGURE 3. HP/TAZ treatment results in statistically significant improvements in VAS itch score. VAS itch scores pooled from both treatment regimens (HP/TAZ and moisturizer in either order). One participant was lost to follow-up before the week 12 visit, and values were imputed for this participant by last observation carried forward.



VAS, visual analog scale.
***P<0.01 compared with baseline, Wilcoxon signed rank test.

significant improvements from baseline: item 1 (itchy, sore, painful skin) improved at weeks 4, 8, and 12 (P<0.02 for all), and item 2 (embarrassed, self-conscious) and item 4 (influenced clothing) improved at all time points (P<0.02 and P<0.03 for all, respectively). HP/TAZ with moisturizer was also associated with a numerical improvement in VAS itch at week 2 and statistically significant improvements at weeks 4, 8, and 12 (P<0.008; Figure 3).

Safety and Tolerability

Clinically relevant improvements from baseline were observed at week 12 for itching (P=0.04), at week 12 for dryness (P=0.02), and at week 8 for burning/stinging (P=0.03). A total of 4 AEs were experienced by 3 participants. No serious AEs were reported, and no participant withdrew from the study. One participant reported moderate itch/irritation related to treatment at the application site; however, no follow-up was necessary. A second participant had a moderate case of COVID-19 (unrelated) and moderate itch/irritation possibly related to treatment; both resolved with no further complication. A third participant experienced an unrelated case of moderate COVID-19, which was resolved. Both participants reporting itch/irritation experienced a stronger sensation on the side with HP/TAZ application first. Skin atrophy, striae, telangiectasis, and folliculitis were not reported at any point during the study.

DISCUSSION

The results of this study demonstrate the tolerability and efficacy of HP/TAZ applied before and after a ceramide-containing moisturizer in adults with mild-to-moderate plaque psoriasis. Regardless of application order, HP/TAZ and moisturizer resulted in statistically significant decreases in IGA score, as well as improvements in total DLQI scores and VAS itch, indicating that moisturizer adjuvant therapy does not decrease the therapeutic efficacy of HP/TAZ. Few AEs and no serious AEs were reported (4 moderate AEs in 3 patients). However, 2 cases of itch/irritation were less severe when moisturizer was applied first, suggesting that application of moisturizer before HP/TAZ may improve the tolerability of HP/TAZ.

In addition to efficacy, treatment adherence is another goalpost for topical regimens. However, adherence to psoriasis topicals is challenged by AEs, poor quality of life, and dissatisfaction with vehicle.[16,17] Because this study suggests that application of a moisturizer adjuvant before HP/TAZ may reduce itch and irritation at the application site, moisturizer use before HP/TAZ may encourage adherence by reducing the incidence of AEs. Additionally, the improvements seen here in quality of life and itch, as well as low rates of AEs, may result in positive patient perception of an HP/TAZ moisturizer regimen and thus increase treatment adherence. In a prior study, the lotion formulation of HP/TAZ was rated by ≥93% of healthy volunteers as more hydrating, lightweight, and moisturizing than the lotion they currently use in a patient perception evaluation.[18] Additionally, HP/TAZ significantly improved patient-reported skin dryness, itching, and burning/stinging compared to vehicle in a pooled analysis of two phase 3 studies in patients with moderate-to-severe plaque psoriasis.[19,20] Altogether, increased tolerability, improved quality of life, and patient preference for the HP/TAZ vehicle may result in sufficient patient adherence when a moisturizer is applied before HP/TAZ.

Further supporting the likelihood that HP/TAZ with a moisturizer adjuvant promotes treatment adherence,[15,18] HP/TAZ is applied once daily, in contrast to twice-daily treatment regimens,

which are associated with decreased adherence.[17,21] Therefore, this study was designed to evaluate consecutive, immediate application of both topicals in differing application orders, with no lag time, representing real-world application of a once-daily treatment regimen. Observed improvements in IGA, DLQI, and VAS itch scores suggest that moisturizer application immediately before versus after HP/TAZ does not diminish its efficacy and most likely does not impede penetration. Additionally, moisturizer application order was not associated with serious AEs, and no safety concerns were raised. Because 2 participants experienced more application site itch and irritation on the side treated with HP/TAZ first, application of moisturizer first may have a positive effect on tolerability. These observations suggest that patients can apply moisturizer first and HP/TAZ second without allotting additional time to achieve an effective and tolerable outcome.

Limitations of this study are its small sample size, lack of a control group, and absence of efficacy evaluation after treatment cessation as assessed in the phase 3 trials.[15] Inclusion of a treatment cessation follow-up period would provide valuable insight regarding the probable prolonged efficacy after HP/TAZ and moisturizer application, as was demonstrated in previous trials of corticosteroid and moisturizer regimens.[10,12]

In conclusion, ceramide-containing moisturizers are valuable additions to the psoriasis treatment armamentarium and may assist in repairing the skin barrier, improving symptoms of psoriasis, and increasing patient satisfaction. Although moisturizer adjuvants are recommended in current guidelines, this study presents real-world recommendations for the use of ceramide-containing moisturizers before HP/TAZ for optimal patient outcomes.

DISCLOSURES

LK has served as a consultant, speaker, investigator, or advisory board member for Abbott Laboratories, AbbVie Inc, Allergan Inc, Almirall SA, Amgen Inc, Arcutis Biotherapeutics, Biogen Inc, Boehringer Ingelheim, Breckenridge Pharmaceutical, Bristol Myers Squibb, Celgene, Centocor Inc, Cipher Pharmaceuticals, Connetics Corporation, Coria Laboratories, Dermavant Sciences Inc, Dow Pharmaceutical Sciences Inc, Dr. Reddy's Laboratories, Eli Lilly Inc, Galderma, Genentech Inc, GlaxoSmithKline PLC, Idera Pharmaceuticals, Innovation Pharmaceuticals, Janssen Pharmaceuticals, LEO Pharma A/S, Maruho Medical, Medicis Pharmaceutical Corp, Merck Serono International SA, Merck & Co, Nimbus Therapeutics, Novartis AG, Ortho Dermatologics, Pfizer Inc, PharmaDerm Laboratories, Stiefel Laboratories Inc, Sun Pharmaceutical Industries, Taro Pharmaceutical Industries Ltd, UCB, Valeant Pharmaceuticals, Ventyx Biosciences, and XenoPort Inc. AJ is an employee of Ortho Dermatologics (a division of Bausch Health US, LLC).

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ORIGINAL ARTICLE

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Incorporating a Prognostic Gene Expression Profile Test Into the Management of Cutaneous Squamous Cell Carcinoma: An Expert Consensus Panel Report

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ABSTRACT

Background: Cutaneous squamous cell carcinoma (cSCC) is a growing health concern with a rapidly increasing incidence. Disease-specific mortality is typically preceded by a metastasis, but current staging systems have significant limitations in predicting this event. The 40-gene expression profile (40-GEP) test is a validated method of further stratifying patients based on the risk of regional or distant metastasis, but limited guidelines exist for incorporating this test into clinical practice.

Objective: To review the available literature on the use of gene expression profile (GEP) testing to assess prognosis in cSCC and create consensus statements to guide dermatology clinicians on its use.

Methods: A comprehensive literature search of PubMed, EMBASE, and Scopus was completed for English-language original research articles on the use of GEP testing to assess cSCC prognosis. A panel of 8 dermatologists with significant expertise in diagnosing and managing cSCC gathered to review the articles and create consensus statements. A modified Delphi process was used to approve each statement and a strength of recommendation was assigned using the Strength of Recommendation Taxonomy (SORT) criteria.

Results: The literature search produced 157 articles that met the search criteria. A thorough screening of the studies for relevance to the research question resulted in 21 articles that were distributed to the panelists for review prior to the roundtable discussion. The panel unanimously voted to adopt 7 consensus statements and recommendations, 6 of which were given a strength of "A" and 1 of which was given a strength of "C".

Conclusion: The 40-GEP test provides accurate and independent prognostic information beyond standard staging systems that only incorporate pathologic data. Incorporation of GEP testing into national guidelines can help further stratify patients based on risk of metastasis, and thus may improve morbidity and mortality.

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INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, occurring in 1.8 million people in the United States (US) annually.[1-4] Its incidence is on the rise, likely due to an aging population and possibly an increased emphasis on skin cancer screening.[1-5] Although typically found at a 1:4 ratio to basal cell carcinoma (BCC), the most common skin cancer in the general US population, one study identified a 1:1 ratio between cSCC and BCC in a Medicare fee-for-service population in 2012.[5] While cSCC typically carries an excellent prognosis, with 5-year cure rates greater than 90%, a subset of these tumors exhibit aggressive behavior such as local recurrence and metastasis.[6-9] The frequency of regional and distant metastasis may be underreported due to a lack of nonmelanoma skin cancer (NMSC) registries.[1,8] As a result, these numbers are primarily

estimated by retrospective cohort studies, which cite a rate between 2% to 6%.[7-10] Furthermore, disease-specific mortality is typically estimated to be 1.5% to 3%.[4,9,11,12] Despite this relatively low mortality rate, the absolute number of deaths attributable to cSCC in the US was estimated to be between 3932 and 8971 in 2012 and may already exceed deaths from cutaneous melanoma.[3,12-14] The vast majority of these deaths arise in patients with metastasis, at which point the 5-year survival rate can drop to 50% to 83% for regional metastasis and even below 40% for distant metastasis.[8,9,11]

There are several staging systems for cSCC designed to stratify patients based on the risk of recurrence and metastasis. The most commonly used systems include the individual risk factor-based National Comprehensive Cancer Network (NCCN) system, American Joint Committee on Cancer Eighth Addition (AJCC8) staging system, and the Brigham and Women's Hospital (BWH) classification.[15-17] These systems are based on clinical and/or pathological features, such as tumor size and thickness, perineural invasion, cell differentiation, and tumor location. However, these factors may be limited in their utility, as biopsy specimens are often transected, precluding accurate measurement of tumor depth.[9,12] Additionally, interobserver variability in dermatopathology has been reported throughout the literature,[18-20] with one study identifying discrepancies in 22% of the 405 cases reviewed, 40% of which related to nonmelanocytic neoplasms.[18] The combination of these limitations have resulted in a low sensitivity (23-46%) and positive predictive value (PPV) (12-13%) for these staging systems.[16,17,21,22]

Given these relatively low sensitivity and PPV values, more precise methods of predicting the risk of recurrence, metastasis, and mortality are needed for skin cancer. Precision medicine has already become commonplace throughout many specialties, including dermatology. Genomic testing with the use of gene expression profile (GEP) assays is a validated and commonly used tool to aid in diagnosis and prognostic assessment for cutaneous malignancies.[23-27] For cSCC, there is one commercially available GEP test, the 40-gene expression profile test (40-GEP), that uses formalin-fixed paraffin-embedded (FFPE), primary cSCC tissue to stratify tumors into low (Class 1), high (Class 2A), and highest (Class 2B) risk for regional or distant metastasis at 3 years after diagnosis.[14] The test was initially validated by Wysong et al in 2020,[28] but several other studies since then have demonstrated the test's analytical validity, clinical validity, accuracy, and clinical utility.[11,14,28-36] Despite the abundant data, limited guidelines exist on how to incorporate this test into clinical practice. The purpose of this study was for a panel of experts in cSCC diagnosis and management to review the available literature and produce appropriate use recommendations for dermatology practitioners for GEP testing for this cancer.

MATERIALS AND METHODS

Literature Search and Study Selection

A comprehensive literature search of PubMed, EMBASE, and Scopus was completed on December 2, 2022, using the keywords cutaneous squamous cell carcinoma, prognosis, and gene expression along with the Boolean term AND for English-language original research articles, systematic reviews, and meta-analyses without date restrictions. Articles were screened for relevance to the topic of measuring gene expression to assess prognosis in cSCC. The studies that met the inclusion criteria were then distributed to the panelists. Each member of the panel reviewed the selected articles and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[37] These levels include level 1 (good-quality patient-oriented evidence, such as systematic reviews or meta-analyses of good-quality cohort studies or a prospective cohort study with good follow-up), level 2 (limited-quality patient-oriented evidence, such as retrospective cohort studies or prospective cohort studies with poor follow-up), or level 3 (other evidence, such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[37] Of note, a level 2 or 3 designation does not necessarily indicate a deficient study, but is requisite for retrospective studies or basic science articles that focus on disease states, respectively.

Development of Consensus Statements

The panel consisted of 8 dermatologists with expertise in diagnosing and managing cSCC. They convened on January 13, 2023, to review and discuss the studies and create consensus statements to guide clinicians on the use of GEP testing to assess prognosis for cSCC. A modified Delphi process was used to reach a consensus for each statement.[38] This process requires supermajority approval to adopt a recommendation through multiple rounds of real-time voting and has been utilized frequently to create expert recommendations in dermatology.[39-42]

RESULTS

Literature Search and Study Selection

The initial literature search produced 157 articles that met the search criteria. A thorough screening of the studies for relevance to the research question resulted in 21 articles that were distributed to the panelists for review prior to the roundtable discussion.

Levels of Evidence Designation

Of the 21 articles that were reviewed, the panel assigned level 1 evidence to 2 articles,[28,35] level 2 evidence to 8 articles,[11,14,29,43-47] and level 3 evidence to 11 articles[30-34,36,48-52] (Table 1 and 2).

Consensus Statements

The panel created seven consensus statements related to cSCC and the use of GEP testing to assess prognosis. All 7 statements received a unanimous (8/8) vote for adoption. Each of the

TABLE 1.

SORT Criteria Level Of Evidence for Articles Pertaining to the 40-GEP Test	
Article	**Level of Evidence**
Wysong A, Newman JG, Covington KR, et al. Validation of a 40-gene expression profile test to predict metastatic risk in localized high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2021;84(2):361-369.	1
Saleeby E, Bielinski K, Fitzgerald A, et al. A Prospective, Multi-Center Clinical Utility Study Demonstrates That the 40-Gene Expression Profile (40-GEP) Test Impacts Clinical Management for Medicare-Eligible Patients with High-Risk Cutaneous Squamous Cell Carcinoma (cSCC). *SKIN The Journal of Cutaneous Medicine.* 2020;6(6):482–496.	1
Arron ST, Wysong A, Hall MA, et al. Gene expression profiling for metastatic risk in head and neck cutaneous squamous cell carcinoma. *Laryngoscope Investig Otolaryngol.* 2022;7(1):135-144.	2
Farberg AS, Hall MA, Douglas L, et al. Integrating gene expression profiling into NCCN high-risk cutaneous squamous cell carcinoma management recommendations: impact on patient management. *Curr Med Res Opin.* 2020;36(8):1301-1307.	2
Ibrahim SF, Kasprzak JM, Hall MA, et al. Enhanced metastatic risk assessment in cutaneous squamous cell carcinoma with the 40-gene expression profile test. *Future Oncol.* 2022;18(7):833-847.	2
Arron ST, Blalock TW, Guenther JM, et al. Clinical Considerations for Integrating Gene Expression Profiling into Cutaneous Squamous Cell Carcinoma Management. *J Drugs Dermatol.* 2021;20(6):5s-s11.	3
Au JH, Hooper PB, Fitzgerald AL, Somani AK. Clinical utility of the 40-gene expression profile (40-gep) test for improved patient management decisions and disease-related outcomes when combined with current clinicopathological risk factors for cutaneous squamous cell carcinoma (cscc): case series. *Dermatol Ther (Heidelb).* 2022;12(2):591-597.	3
Borman S, Wilkinson J, Meldi-Sholl L, et al. Analytical validity of DecisionDx-SCC, a gene expression profile test to identify risk of metastasis in cutaneous squamous cell carcinoma (SCC) patients. *Diagn Pathol.* 2022;17(1):32.	3
Hooper PB, Farberg AS, Fitzgerald AL, et al. Real-world evidence shows clinicians appropriately use the prognostic 40-gene expression profile (40-gep) test for high-risk cutaneous squamous cell carcinoma (cscc) patients. *Cancer Invest.* 2022;40(10):911-922.	3
Litchman GH, Fitzgerald AL, Kurley SJ, et al. Impact of a prognostic 40-gene expression profiling test on clinical management decisions for high-risk cutaneous squamous cell carcinoma. *Curr Med Res Opin.* 2020;36(8):1295-1300.	3
Rebeca T, Giselle P, Litchman GH, et al. Impact of gene expression profile testing on the management of squamous cell carcinoma by dermatologists. *J Drugs Dermatol.* 2019;18(10):980-984.	3

TABLE 2.

SORT Criteria Level of Evidence for Articles Related to the Measurement of Gene Expression to Assess Prognosis in cSCC but Not Pertaining to the 40-GEP Test	
Article	**Level of Evidence**
Cañueto J, Cardeñoso-Álvarez E, Cosano-Quero A, et al. The expression of podoplanin is associated with poor outcome in cutaneous squamous cell carcinoma. *J Cutan Pathol.* 2017;44(2):144-151.	2
Chen MK, Cai MY, Luo RZ, et al. Overexpression of p300 correlates with poor prognosis in patients with cutaneous squamous cell carcinoma. *Br J Dermatol.* 2015;172(1):111-119.	2
Li YY, Hanna GJ, Laga AC, et al. Genomic analysis of metastatic cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2015;21(6):1447-1456.	2
Vinicius de LV, Scapulatempo C, Perpetuo NM, et al. Prognostic and risk factors in patients with locally advanced cutaneous squamous cell carcinoma of the trunk and extremities. *J Skin Cancer.* 2011;2011:420796.	2
Xu R, Cai MY, Luo RZ, et al. The expression status and prognostic value of cancer stem cell biomarker cd133 in cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2016;152(3):305-311.	2
Al-Rohil RN, Tarasen AJ, Carlson JA, et al. Evaluation of 122 advanced-stage cutaneous squamous cell carcinomas by comprehensive genomic profiling opens the door for new routes to targeted therapies. *Cancer.* 2016;122(2):249-257.	3
Campos MA, Macedo S, Fernandes MS, et al. Prognostic significance of RAS mutations and P53 expression in cutaneous squamous cell carcinomas. *Genes (Basel).* 2020;11(7):751. Published 2020 Jul 6.	3
Kitrell BM, Blue ED, Siller A Jr, et al. Gene expression profiles in cutaneous oncology. Dermatol Clin. 2023;41(1):89-99.	3
Newman JG, Hall MA, Kurley SJ, et al. Adjuvant therapy for high-risk cutaneous squamous cell carcinoma: 10-year review. *Head Neck.* 2021;43(9):2822-2843.	3
Zilberg C, Lee MW, Yu B, et al. Analysis of clinically relevant somatic mutations in high-risk head and neck cutaneous squamous cell carcinoma. *Mod Pathol.* 2018;31(2):275-287.	3

TABLE 3.

Consensus Statements and Recommendations for Incorporating the 40-GEP Test into Clinical Practice and Their Corresponding Strengths Using SORT Criteria

Consensus Statement/Recommendation	Strength of Recommendation	Consensus Vote
There is data to support that specific genes influence cSCC clinical behavior.	A	8/8
The data supports the 40-GEP test's ability to identify a subset of cSCCs that are at a high risk for metastasis.	A	8/8
The 40-GEP test provides clinically useful data for cSCC prognosis independent of the AJCC8 and BWH staging systems.	A	8/8
Adding 40-GEP data to the AJCC8 and BWH staging systems enhances the prognostic assessment of cSCC.	A	8/8
The 40-GEP test results can increase the precision and confidence in cSCC management decisions.	A	8/8
The 40-GEP test should be considered for use on cSCC tumors with at least 1 high-risk feature per AJCC8 and/or BWH and/or NCCN guidelines.	A	8/8
The 40-GEP test should not be used on cSCC in situ or invasive cSCC without high-risk features, or for patients that are not candidates for additional procedures or therapies.	C	8/8

statements and recommendations were given a strength of recommendation according to SORT criteria (Table 3).

Statement 1: *There are data to support that specific genes influence cSCC clinical behavior. (SORT Level A)*

Several studies have demonstrated a correlation between the upregulation or downregulation of certain genes and aggressive clinicopathologic features, poor outcomes, or both.[43-52] Campos et al retrospectively evaluated 162 cases of cSCC and found that RAS mutations were more frequently associated with an infiltrative than expansive pattern of invasion and were also associated with features of local aggressiveness.[49] Additionally, p53 overexpression was shown to be a predictor of recurrence in the univariate analysis, although not in the multivariate analysis.[49] Cañueto et al analyzed podoplanin expression in a series of 94 cSCCs and found that moderate-to-intense expression was associated with the presence of desmoplasia, an infiltrative growth pattern, the presence of lymphovascular invasion, and the presence of ulceration.[43] These higher levels of expression were also associated with a higher risk of nodal metastasis during follow-up and shorter periods of disease-free relapse.[43] Additional studies have shown that overexpression of p300 correlates with decreased recurrence-free survival (RFS) and overall survival (OS),[44] and that high CD133 expression is greater in patients with advanced tumor stage and it also correlated with decreased RFS and OS.[47]

Statement 2: *The data support the 40-GEP test's ability to identify a subset of cSCCs that are at high risk for metastasis. (SORT Level A)*

The original validation study for the 40-GEP test consisted of a prospective cohort of 321 primary cSCC cases, all of which had 1 or more clinicopathologic risk factors, of which 52 had documented regional or distant metastasis vs 269 that did not. Regarding metastatic risk, the test designated 203 cases as Class 1 (low risk), 93 as Class 2A (high risk), and 25 as Class 2B (highest risk). Kaplan-Meier survival analysis then demonstrated that the 3-year metastasis-free survival (MFS) rates were 91.6% for Class 1, 80.6% for Class 2A, and 44.0% for Class 2B.[28] Furthermore, the hazard ratios for metastasis for the Class 2A and 2B cases were 2.44 and 10.15, respectively.[28]

Since that original study, several others have demonstrated that the 40-GEP test can accurately identify a subset of cSCCs at high risk for metastasis. Arron et al used the test to assess 278 cases of cSCC of the head and neck and found that 3-year MFS rates were 92.1% for Class 1, 76.1% for Class 2A, and 44.4% for Class 2B.[29] Ibrahim et al used the 40-GEP test to analyze a retrospective cohort of 420 cases of cSCC without at least 1 high-risk feature as defined by NCCN guidelines or AJCC or BWH staging systems.[11] In this study, 3-year MFS rates for Class 1, Class 2A, and Class 2B were 93.9%, 80.5%, and 47.8%, respectively.[11] All 3 studies demonstrated concordant 3-year MFS rates for each 40-GEP class and verified the ability of the test to predict the risk of metastasis.

Statement 3: *The 40-GEP test provides clinically useful data for cSCC prognosis independent of the AJCC8 and BWH staging systems. (SORT Level A)*

The utility of the 40-GEP test depends on its ability to accurately assess cSCC prognosis independent of established staging systems such as AJCC8 and BWH. Several studies compared the 40-GEP test to these staging systems and found that the test is an independent predictor of risk. In the original validation study, a 40-GEP Class 2B result had a PPV of 60% compared to 32.8%, 35.1%, and 16.7% for the AJCC, BWH, and NCCN high-risk groups, respectively.[28] Furthermore, a Class 1 result

had a negative predictive value of 91.1% compared to 87.7%, 86.3%, and 90.5% for the AJCC, BWH, and NCCN low-risk groups, respectively. Similarly, Ibrahim et al found that the PPV for a Class 2B result in their cohort was 52.2% compared with 30.0% and 33.9% for high-stage AJCC8 and BWH tumors, respectively.[11] Likewise, in a cohort of cSCCs on the head and neck, Arron et al found that the sensitivity of a Class 2 result for metastasis was significantly greater than high-stage AJCC8 T3/T4 and BHW T2b/T3 results and the specificity of a Class 2B result was significantly greater than the high-stage AJCC8 and BWH results.[29]

Statement 4: *Adding 40-GEP data to the AJCC8 and BWH staging systems enhances the prognostic assessment of cSCC. (SORT Level A)*

Not only does the literature support the independent prognostic value of the 40-GEP test, but it also establishes that incorporating these results into current staging systems and guidelines further improves prognostic assessment. Patients classified as NCCN high risk and very high risk that also received a 40-GEP result of Class 2B had a metastasis occurrence rate of 37.5% and 60.0% respectively, compared to a rate of 9.8% for NCCN high risk and a rate of 23% for NCCN very high risk alone.[11]

Statement 5: *The 40-GEP test results can increase the precision and confidence in cSCC management decisions. (SORT Level A)*

As previously noted, applying 40-GEP test results has the potential to re-categorize NCCN-defined high-risk cSCC patients into lower intensity management groups.[11,28] This can have a large impact on management decisions, such as frequency of follow-up, method of nodal assessment (ie, palpation vs biopsy), use of advanced imaging, and use of adjuvant therapy. The NCCN guidelines for high-risk cSCC are broad and have the potential to lead to overtreatment, as 63.0% of the high-risk NCCN cases in the original 40-GEP validation cohort were identified as low-risk Class 1.[28] By incorporating additional data from 40-GEP testing into management decisions, clinicians can better adjust their management intensity based on risk. In a survey of 162 dermatologists, Litchman et al showed that a 40-GEP Class 1 result caused clinicians to substantially increase their avoidance of additional interventions while a Class 2B result led clinicians to choose a higher intensity management plan with increases in recommendations for sentinel lymph node biopsy, adjuvant radiation, adjuvant chemotherapy, and shorter follow-up intervals.*34* Hooper et al also conducted a clinical utility study by surveying 34 clinicians who ordered 10 or more 40-GEP tests in its first year of availability. Using 6 real-world cases spanning the spectrum of risk levels, they found that clinicians were overall well-aligned regarding the baseline risk levels and subsequent management changes based on 40-GEP results.[33] Farberg et al analyzed a cohort of 300 NCCN-defined high-risk cSCC patients and found that 40-GEP test results, after adjusting for AJCC8 or BWH tumor stage, were able to recommend low management intensity for 53.0% or 57.7% of patients, respectively.[14]

Statement 6: *The 40-GEP test should be considered for use on cSCC tumors with at least 1 high-risk feature per AJCC8 and/or BWH and/or NCCN guidelines. (SORT Level A)*

The validation study for the 40-GEP test consisted of a cohort of patients with at least 1 high-risk feature as defined by these staging systems and NCCN guidelines.[28] Additional studies demonstrating the test's accuracy and clinical validity also utilized similar inclusion criteria.[11,14] Therefore, the panel recommends considering the test for cSCC cases with at least 1 high-risk feature in order to maximize prognostic accuracy and utility.

Statement 7: *The 40-GEP test is not recommended to be used on cSCC in situ or invasive cSCC without high-risk features, or for patients that are not candidates for additional procedures or therapies. (SORT Level C)*

Similarly, the available literature does not support the use of the test for in situ cSCC or cSCC without high-risk features. Until further studies are completed on these tumors, the use of the test would result in unnecessary healthcare costs that outweigh the benefits of the results. Additionally, if a patient is not a candidate for additional procedures or therapies, the panel believes that there is limited value in the test's results, as it will not lead to an alteration in management.

CONCLUSION

cSCC is a growing health concern with a rapidly rising incidence and poor survivability in cases of metastatic disease.[1-5,8,9,11] Existing clinicopathologic staging systems have significant limitations in their ability to predict which patients will experience a metastasis, as only 14% to 17% of patients with AJCC8 T3/T4 tumors and 24% to 38% of patients with BWH T2b/T3 tumors develop one.[16,21,22] A more accurate method of assessing this risk is critical to reduce the morbidity and mortality associated with both cSCC and unnecessary interventions. This comprehensive review demonstrated that the 40-GEP test has been validated as an independent predictor of cSCC risk of metastasis beyond AJCC8 and BWH staging systems. Furthermore, when 40-GEP testing is used in conjunction with these systems, multiple studies have shown that more accurate prognostic assessment is possible.[11,14,28]These consensus recommendations put forth by the panel can help guide dermatology clinicians on appropriate test usage to make better risk-aligned management decisions, thereby ultimately improving patient outcomes.

DISCLOSURES

DZ and NB have participated in a research fellowship partially funded by Castle Biosciences. BB has served as a consultant for Castle Biosciences. RC, TAC, JQDR, LKF, and GG have no conflicts of interest. DS has served as a consultant to DermTech.

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ORIGINAL ARTICLE

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Improvement of Chronic Venous Insufficiency Related Leg Xerosis and Dermatitis With Ceramide-Containing Cleansers and Moisturizers: An Expert-Based Consensus

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ABSTRACT

Introduction: Chronic venous insufficiency (CVI) may lead to sustained elevated pressure (aka venous hypertension) in the dermal venous microcirculation. Risk factors include advanced age, obesity, female gender, pregnancy, and prolonged standing. CVI in the lower extremities may lead to cutaneous changes such as xerosis and venous leg dermatitis (VLD). This review explores skin barrier restoration using skincare for xerosis and VLD.

Methods: Prior to the meeting, a structured literature search yielded information on fourteen draft statements. During the meeting, a multi-disciplinary group of experts adopted five statements on xerosis and VLD supported by the literature and the authors' clinical expertise.

Results: VLD and associated xerosis is a common condition requiring more attention from healthcare providers. Compression therapy is the standard CVI and should be combined with good-quality skincare to enhance adherence to treatment. Maintaining an intact skin barrier by preventing and treating xerosis using gentle cleansers and ceramide-containing moisturizers may improve the skin sequelae of CVI. Skincare is frequently lacking or overlooked as part of the treatment of patients with CVI and VLD. This skin treatment is an unmet need that can be addressed with ceramides-containing pH balanced cleansers and moisturizers.

Conclusion: Compression therapy is the mainstay of treatment for CVI and VLD. Quality skincare can improve treatment adherence and the efficacy of compression therapy. Using a skincare agent may reduce friction and help patients avoid skin trauma while putting on compression garments. A ceramide-containing moisturizer sustained significant improvements in skin moisturization for 24 hours and may offer synergistic benefits together with compression treatment.

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INTRODUCTION

Chronic venous insufficiency (CVI) comprises structural and functional pathology of the venous system. CVIs'pathophysiology most commonly results from lower extremity valvular reflux and/ or venous obstruction, which induces sustained elevated pressure (aka venous hypertension) in the dermal venous microcirculation in the dermal microcirculation.[1-4] The prevalence of CVI increases with age and is typically more predominant in women, smokers, obese or pregnant patients, as well as those with hereditary risk factors present.[1] Other risk factors include diabetes mellitus, prolonged sitting or standing, deep vein thrombosis (DVT), heart failure, and chronic lower extremity edema.[5,6] The abnormal venous flow of the lower extremities is observed in ~50% of individuals in the general population, although the estimated prevalence of CVI varies across the population studies reported.[1] A population study by Prochaska and colleagues was performed on 12,423 participants (age range: 40 to 80 years) who were part of the Gutenberg Health Study from April 2012 to April 2017. Using systematic phenotyping of CVI according to established CEAP (Clinical-Etiologic-Anatomic-Pathophysiologic) classification, they found a prevalence of CVI of 40.8% (Table 1).[1] Upwards of 6 million people in the US have advanced forms of CVI, such as leg edema and skin changes, and 2.2 million (PMID: 24625244) have venous leg ulcers.[5] The Edinburgh Vein Study found that the age-adjusted prevalence of CVI was 9% in men and 7% in women.[4] The prevalence of CVI in Asian populations has been reported to be lower than in non-Hispanic white populations. However, the prevalence in South Korea is rising due to the underdiagnosis of CVI, increased obesity, and an aging population.[4]

TABLE 1.

Clinical Staging as Part of the CEAP Classification	
Stage	**Description**
C0	No visible signs of venous disease
C1	Spider veins and reticular varicose veins
C2	Varicose veins with no signs of chronic venous hypertension
C3	Edema
C4	Skin changes
C4a	Pigmentation, dermatitis
C4b	Lipodermatosclerosis, Atrophie blanche
C5	Healed venous leg ulcer
C6	Venous leg ulcer

CEAP (Clinical-Etiologic-Anatomic-Pathophysiologic) classification

FIGURE 1. Venous edema.

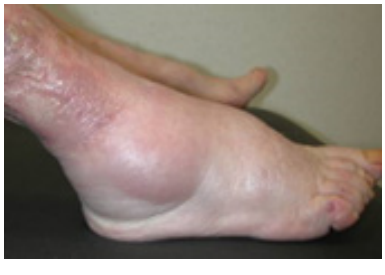
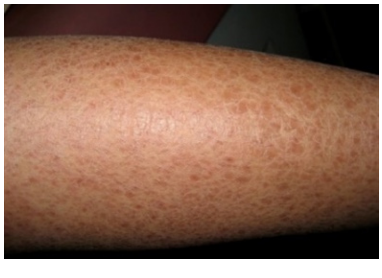


FIGURE 2. Lower leg xerosis.



CVI may lead to spider veins, reticular varicose veins, and edema (Figure 1). CVI induces inflammation and skin changes such as xerosis (Figure 2), pigmentation (Figure 3), dermatitis (Figure 4), lipodermatosclerosis, atrophie blanche, and eventually, venous ulceration (Table 2).[5,6,10,11] Venous ulcers can vary in size, can be difficult to manage and diminish quality of life, particularly if they are painful, complicated with dermatitis and xerosis, or drain profusely.[5,6,10-17] The management of leg ulcers is outside the scope of this review.

FIGURE 3. Pigmentation.

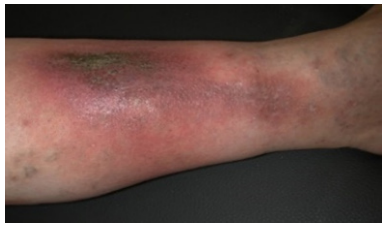
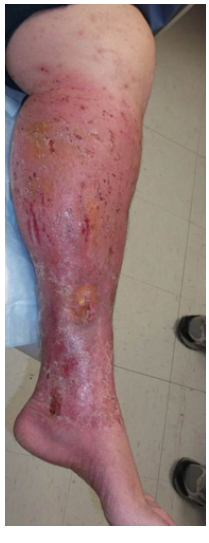


FIGURE 4. Venous dermatitis.



The prevalence of venous leg dermatitis (VLD) in patients >50 years in the US is estimated to be 6-7% (~15-20 million individuals), making this twice as prevalent as psoriasis.[18,19] VLD presents initially as poorly demarcated erythematous plaques of the lower legs bilaterally, classically involving the medial malleolus.[5-9] Duplex ultrasound is useful in demonstrating venous reflux to confirm the clinical diagnosis or when the clinical diagnosis of VLD is inadequate.[5,7]

TABLE 2.

Venous Leg Dermatitis	
Dermatologic presentation	Poorly demarcated erythematous rash, plaques, pitting edema
Associations	Advanced age, obesity, female gender, pregnancy, prolonged standing
Etiology	Venous insufficiency leading to edema and inflammation
Characteristics and location	Gravity-dependent regions such as the lower extremities
Histology	Dermal fibrosis, perivascular lymphocytic infiltrates, extravasated erythrocytes, small blood vessel proliferation
Diagnosis	Clinically, can be confirmed by venous duplex ultrasound
Treatment	Treatment of underlying venous insufficiency, compression stockings, emollients, anti-inflammatory agents

This review explores skin barrier restoration using skincare with gentle cleansers and moisturizers for CVI-related xerosis and VLD.

MATERIALS AND METHODS

The project used a modified Delphi process comprising structured literature searches and face-to-face discussions followed up online.[20,21]

Literature Review

The structured literature searches (01-November 2022) on PubMed and Google Scholar, as a secondary source, of the English-language literature (2010 – October 30, 2022) were performed by a dermatologist and a physician/scientist. They manually reviewed the selected literature for additional resources and prioritized studies on CVI, VLD and xerosis, SC barrier function, and skincare benefits using cleansers and moisturizers. The searches for CVI* VLD** and xerosis*** explored current clinical guidelines, treatment options, and therapeutic approaches using the following terms:

Group 1: *CVI*, VLD**, xerosis*** AND pathophysiology OR inflammation OR cutaneous changes OR clinical signs OR clinical symptoms OR pruritus OR skin barrier physiology OR function OR dysfunction OR depletion of stratum corneum lipids*

Group 2: *CVI*, VLD**, xerosis*** AND compression therapy OR skincare OR cleansers OR moisturizers OR emollients OR ceramides OR ce¬ramide-containing skincare OR efficacy OR safety OR tolerability*

The searches yielded 46 papers deemed clinically relevant to CVI, VLD, xerosis, and skin care to promote a healthy skin barrier and potential mitigation of xerosis and VLD using over-the-counter skincare and CER-containing cleansers and moisturizers.

Role of the Panel

The panel of six physicians (advisors) of various specialties (dermatology, vascular surgery, podiatry, and family medicine) involved in treating patients with CVI and resulting skin changes convened for a meeting. Prior to the meeting, a structured literature search yielded information on fourteen draft statements. During the meeting, the authors adopted five statements supported by the literature and the authors' clinical expertise.

RESULTS

Statement 1: *Venous dermatitis is a common inflammatory dermatosis of the lower extremities occurring in patients with chronic venous insufficiency. Risk factors include age, deep vein thrombosis, heart failure, obesity, diabetes, and prolonged sitting/standing.*

CVI leads to sustained venous hypertension (VH) upon ambulation, which causes skin changes and inflammation.[5,7-10] Dilated capillaries may trigger hemosiderin deposition in the dermis, producing hyperpigmentation (both hemosiderin and melanin), predominantly in the gaiter area.[5,7-10] Chronic VH induces thinning of the epidermis, erythema, xerosis, and VLD.[3-9] Patients with CVH frequently have pruritus, leading to scratching, skin markings, lichenification, and excoriations.[5,7-10] Further changes occur through the proliferation of small vessels, edema, spongiosis, mixed inflammatory cell infiltrates, and structural alterations in the papillary dermis.[5,7-10] Studies have shown that expression of matrix metalloproteinases (MMPs) 1, 2, and 13 is altered in the lesional skin of VLD in comparison with healthy skin, which could explain the spongiosis and structural abnormalities observed in the histology of VLD.[24]

Risk factors for developing VLD include advanced age, obesity, female gender, pregnancy, and prolonged standing.[5] Further risk factors associated with VLD include inherited disorders (such as thrombophilia) and prolonged bed rest.[1,5,6]

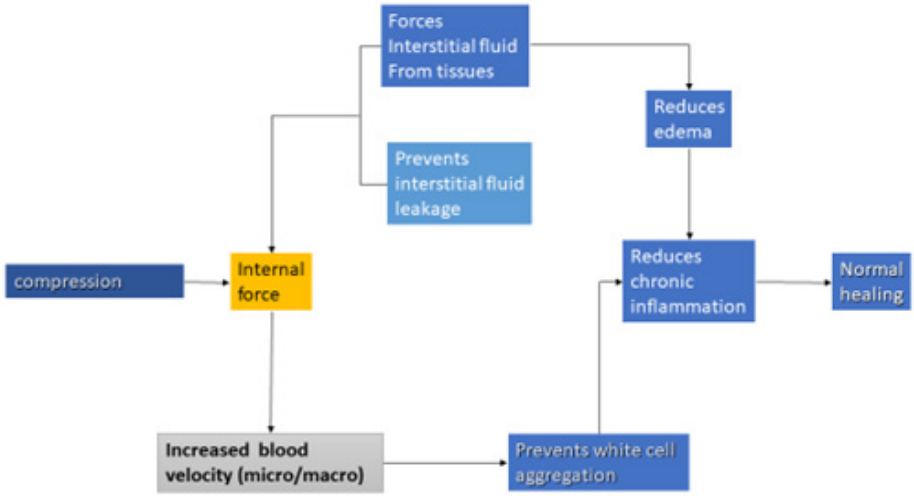
Studies have supported that the pathophysiology of venous and arterial vascular disease are commonalities; however, population-based studies confirming the clinical implications are lacking.[1,22,23] As many patients with leg ulcers never have venous studies, the advisors agreed that the term "venous leg ulcers" may not be appropriate, as the link to the venous system remains unproven in about 40% of leg ulcers.[2,3,5,22,23] Publications and algorithms should distinguish between VLD and swelling leg dermatitis (SLD) as the approach to treatment may differ.[7]

Statement 2: *Compression is the standard therapy for CVI; it has been shown to reduce edema and improve superficial skin lymphatic and venous function and transport.*

Treatment of VLD consists of addressing the VH, usually with compression therapy.[5,6-19]

Clinical guidelines and pathways for patients with CVI-related VLD should include accurate diagnosis and the use of appropriate diagnostic tools.[6] It is important to understand the individual patients' issues to achieve an optimal treatment outcome using a holistic approach.[6,18] Compression is the standard treatment for lowering VH, decreasing edema and inflammation, and enhancing tissue vascularization.[6,10-17] The underlying CVI should be treated with adequate compression that is appropriate and sustainable for the patient.[25] Before applying compression, the ankle-brachial pressure index (ABPI) is to be measured to provide information if sufficient arterial circulation is present for leaving compression safely in place day and night.[6,10-17,26] Lower extremity Doppler examination is recommended as the standard for patients with suspected peripheral arterial disease.[11,26]

FIGURE 5. Mode of action of compression.



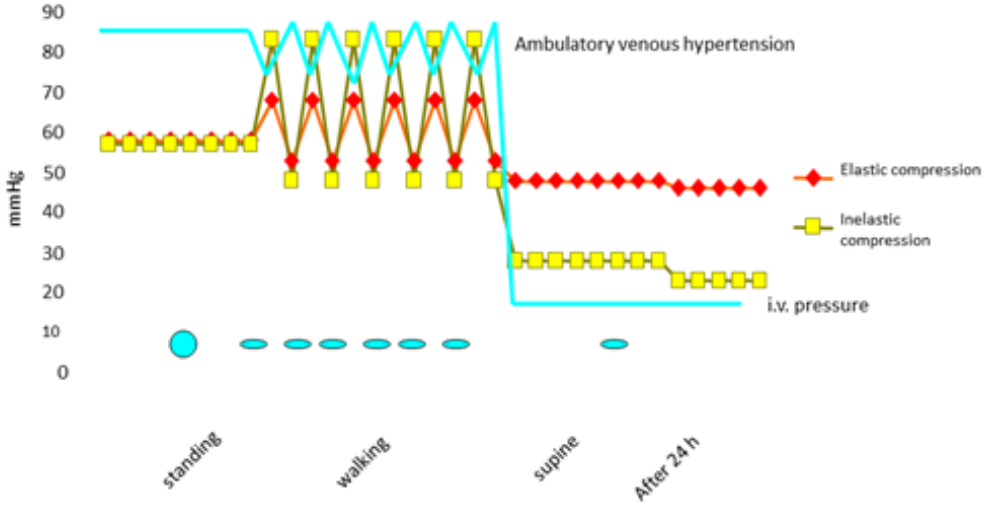
Many guidelines are available on CVI and leg ulcer management using compression.[6,11-17,19] Compression can be delivered using bandages, devices, or stockings and has been shown to reduce edema and inflammation and improve superficial skin lymphatic function and transport within the subfascial system (Figure 5).[6,10-17,25,27] Inelastic short-stretch bandages exert a massage effect during walking, reducing edema and increasing blood flow but inelastic compressions do not compress the legs when patients are at rest.[25,30] Intermittent pneumatic pressure devices have similar effects and may be tolerated in patients with concomitant arterial occlusive disease.[27,28] Elastic compression maintains a constantly high resting pressure independent of body position and has the lowest margin of safety because pressure remains high even when the patient is lying down (Figure 6).[6,30]

Skin damage has been reported even with light thromboprophylaxis stockings. Incorrect application of the bandages or fitting of the compression devices or stockings and lack of daily surveillance are important flaws in patient care, leading to adverse events.[6,29]

Statement 3: *Compression therapy should be combined with good-quality skincare to enhance adherence to and impact of treatment.*

The skin plays a vital role in assisting lymph flow and venous return and acts as a collateral route for lymph drainage.[32] In patients with VH, hyperkeratosis may occur, resulting from the over-proliferation of keratin or reduced desquamation.[34-37] Infrequent skin cleansing and poor skincare may exacerbate

FIGURE 6. Intravenous pressure measured in standing, walking, supine, and after 24 hours when using elastic and inelastic compression.



hyperkeratosis leading to colonization or infection.[34] If left untreated, lesions occur, and there is a risk for invasive infections such as cellulitis.[34-37]

Gentle skin cleansing, exfoliation, and moisturizers as adjuncts to compression or medical treatment should be part of the prevention, treatment, and maintenance of VLD. Hyperkeratosis and papillomatosis should be removed to maintain or restore skin barrier function.[8,9,34] Compression therapy, the standard treatment for patients with VLD, is less effective when hyperkeratosis is left untreated.[34,35] Exfoliation may reduce hyperkeratosis, scabs, and scales in patients with VH and associated VLD.[6-9] Removal of nonvital tissue is an accepted method to decrease biofilms and stimulate healing.[34-37]

There are various methods available for skin cleansing, including mild cleansers with a physiological pH (4-7), scrubbing, or skin massage using monofilament fiber debridement pads.[34-37] In choosing the right cleanser and cleansing device, it is important to consider aspects such as pathophysiology, skin condition, cleansing efficacy, patient tolerance, and interaction between skin condition, skin type, and the cleanser.[34] Further factors to consider are adherence to the treatment, the optimal time and method of cleansing and moisturizing, and the patient's cosmetic perception.[34]

Statement 4: *Maintaining an intact skin barrier by preventing and treating xerosis using gentle cleansers and ceramide-containing moisturizers may improve the skin sequelae of CVI.*

Ceramides, cholesterol, and free fatty acids are essential constituents of the SC.[33,40] They form highly ordered lipid lamellae and fill the space between the corneocytes.[33,40] The composition and structure of the lipid lamellae are critically important to the permeability barrier function of the skin and form an effective waterproof barrier.[33,40] Reductions in SC lipid content may be due to chronic inflammation leading to VLD.[7,8,9,33,40] A healthy skin with good elasticity facilitates an improved surface for compression and exercise in patients with CVI.[34-37] Skin care is important to address the issues associated with inflammation, xerosis, pruritus, and VLD.[8,9,12,31-37] Xerosis and VLD are often associated with pruritus, mainly involving the lower extremities.[18,19,23,31] Pruritus significantly impacts the quality of life and is reported by patients to be equally bothering as skin pain or even worse.[39] Skin changes triggered by CVI make the leg more susceptible to the entry of irritants and allergens through the skin, leading to inflammation and pruritus.[31,40] Scratching can lead to secondary infections, ulcerations, and chronic wounds.[31]

Skincare using cleansers and moisturizers and exfoliation of dry and scaly skin in atopic dermatitis has been reported in an algorithm as a standard measure for AD and may be applicable for VLD.[38] Topically applied steroids combined with moisturizers may be of benefit in acute VLD disease, as is the use of topical nonsteroidal medications such as tacrolimus.[8,9,31] Skin lipids containing moisturizers such as ceramides combat xerosis, restoring skin barrier function and may reduce pruritus.[31,40-45]

Statement 5: *Skincare is frequently lacking or overlooked as part of the treatment of patients with CVI and venous dermatitis. This skin treatment is an unmet need that can be addressed with ceramides-containing pH balanced cleansers and moisturizers.*

Ceramides are essential to the epidermal barrier and help maintain the skin's barrier function.[40] A disturbed composition of ceramides in the epidermis of patients with inflammatory disorders such as AD affects epidermal water loss and reduced water holding capacity.[40,45] It is evident from studies that the qualitative and quantitative difference in ceramide metabolism precipitates cutaneous inflammatory conditions such as dermatitis.[40,45]

Ceramide-containing moisturizers can decrease AD flares, via activation of peroxisome proliferator-activated receptor α, downregulation of inflammatory cytokines, and elevated antimicrobial peptides expression.[46] Ceramides delivered through a multi-vesicular topical product have shown clinically significant results for the management of xerosis.[41-44] Studies demonstrated that ceramide-containing skincare restored skin barrier function, reducing irritation, and was an effective and safe choice for those with xerosis or AD.[41-45]

Currently, skincare for VLD is underused.[5,31] Educating healthcare providers on the pathophysiology of CVI and related VLD is important to promote effective therapy with compression and skin care, improving patient outcomes.[5,18] Training medical assistants and nurses to assess patients for CVI on initial office visit intake may support early intervention.[18] During patient visits, handouts should be given, confirming the information on CVI and the risk of developing it due to comorbid conditions.[18]

LIMITATIONS

Although many studies have looked at atopic dermatitis and the benefits of skincare using gentle cleansers and moisturizers, robust studies on combining compression treatment with skincare for CVI, VLD, and related xerosis are lacking. Moreover, skin treatment is an unmet need for CVI, VLD, and related xerosis that can be addressed with ceramides-containing pH balanced cleansers and moisturizers and should be part of guideless and addressed in education for clinicians and patients as a standard measure.

CONCLUSION

Compression therapy is the standard CVI and VLD and should be combined with good-quality skincare to enhance adherence to

treatment. Maintaining an intact skin barrier by preventing and treating xerosis using gentle cleansers and ceramide-containing moisturizers may reduce friction and help avoid skin trauma while putting on compression garments. A ceramide-containing moisturizer sustained significant improvements in skin moisturization for 24 hours and may offer synergistic benefits together with compression treatment improving adherence to treatment and patient outcomes.

DISCLOSURES

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ORIGINAL ARTICLE

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Deucravacitinib for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

There is contrasting evidence regarding the efficacy and safety of JAK (Janus kinase) inhibitors in the treatment of psoriasis. This systematic review and meta-analysis assessed deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, as the therapy of choice for moderate-to-severe psoriasis. PubMed, Embase, and Cochrane databases were searched for randomized controlled trials, including patients with moderate-to-severe psoriasis. Outcomes of interest were serious adverse events (SAEs), the severity of illness, as measured by the validated questionnaires: Psoriasis Area and Severity Index (PASI) and scalp-specific Physician's Global Assessment (ss-PGA); and quality of life, measured by the Dermatology Life Quality Index (DLQI). Four studies with 1663 patients were included in the meta-analysis, of whom 1123 (67.5%) were treated with deucravacitinib during a 12-to-16-week follow-up. The mean age was 45.4 ± 13.3 years, and 70.2% were male. Two-thirds had a history of scalp psoriasis. Achievement of PASI 75 was significantly higher in the deucravacitinib group, as compared with placebo (RR 5.7; 95% CI 4.32-7.53; $P<0.001$). Similarly, ss-PGA 0/1 (RR 3.86; 95%CI 3.02-4.94; $P<0.001$) and DLQI 0/1 (RR 3.89; 2.89-5.22; $P<0.001$) were also significantly more frequent in the deucravacitinib group. The incidence of SAEs was similar between groups. These findings suggest that patients with moderate-to-severe psoriasis treated with deucravacitinib for 12 to 16 weeks had significantly decreased severity of illness and improved quality of life, without a concerning increase in the incidence of SAEs.

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INTRODUCTION

Psoriasis is a common multisystem chronic inflammatory disease that affects approximately 3.2% of the population. The most prominent manifestation of psoriasis is skin involvement with erythematous plaques, but often systemic inflammation also occurs, and treatment optimization with systemic non-biologic therapies has been proposed to reduce disease severity.[1,2] Several studies have recently evaluated the efficacy and safety of Janus kinase (JAK) inhibitors, and, more recently, selective tyrosine kinase 2 (TYK2) inhibitors. Deucravacitinib is an oral, selective, allosteric TYK2 inhibitor that blocks signal transduction of interleukin (IL) 23, IL-12, and type I interferons. It has been approved for psoriasis and is a promising treatment for moderate-to-severe disease.[3,4]

The recently published POETYK-PSO1 and POETYK-PSO2 trials investigated deucravacitinib treatment in adults with moderate-to-severe psoriasis, and have increased the weight of evidence in this area.[5,6] The drug demonstrated superiority versus placebo and apremilast, was well tolerated, and achieved higher rates of improvement in disease severity and quality-of-life outcomes.[5,6] Furthermore, deucravacitinib was also investigated for the treatment of psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE) in 2 recent phase 2 trials, which have shown promising results.[7,8] To this date, there is no study assessing deucravacitinib treatment efficacy and safety in psoriasis across all available data by meta-analysis. Hence, we performed a systematic review and meta-analysis of randomized clinical trials to evaluate the disease severity reduction, quality of life improvement, and adverse event profile of deucravacitinib compared with placebo, in patients with moderate-to-severe psoriasis

MATERIALS AND METHODS

Eligibility Criteria

Only studies that matched all the following eligibility criteria were included in this meta-analysis: (1) randomized controlled trials (RCTs); (2) deucravacitinib at dosages of 6 mg/day or higher compared to placebo; and (3) enrolling patients with moderate-to-severe psoriasis. We excluded studies that (1) did not have a control group; (2) enrolled patients without psoriasis; or (3) had overlapping patient populations.

Additionally, eligible studies were included only if they reported any of the 3 clinical outcomes of interest, which are: (1) validated disease severity questionnaires, such as the Psoriasis Area and Severity Index (PASI); (2) quality of life, measured by the Dermatology Life Quality Index (DLQI); and (3) adverse events. Other validated disease severity questionnaires included Psoriasis Symptoms and Signs Diary (PSSD), which evaluates changes from baseline; PSSD symptom score of 0; static Physician's Global Assessment of 0 or 1 (sPGA 0/1); scalp-specific Physician's Global Assessment of 0 or 1 (ss-PGA 0/1); and Physician's Global Assessment of Fingernail (PGA-F) of 0 or 1 (PGA-F 0/1).

Endpoints and Subgroup Analysis

The primary outcome of interest was a ≥75% reduction in the PASI score (PASI 75), which is a validated tool used to measure disease severity and extent of psoriasis, based on a thorough physician examination.[9] The sPGA is another disease severity outcome that scores erythema, induration, and scaling on all psoriatic lesions, resulting in a score ranging from 0 (clear) to 4 (severe).[9] Likewise, ss-PGA is the scalp-specific assessment of the sPGA score, and PGA-F is the corresponding score for nail disease. The PSSD is a daily patient-reported outcome where patients assign a severity score of 0 to 10 across 11 items that represent disease severity.[10] Regarding the quality of life, the DLQI is a 10-question questionnaire in which patients report the severity of symptoms and their impact on daily life, resulting in a composite score of 0 to 30.[11]

Subgroups of interest included patients affected by scalp psoriasis, who were analyzed by the reported ss-PGA scores, and patients with nail disease, assessed by the PGA-F score.

Search Strategy

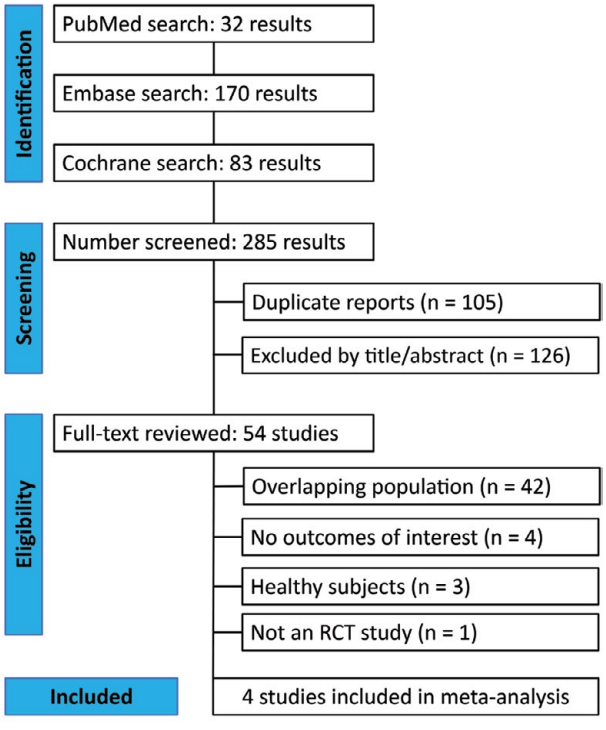
We systematically searched Cochrane Central Register of Controlled Trials, PubMed, and Embase databases for RCTs investigating deucravacitinib, meeting the eligibility criteria, and published from inception to January 2023. We used deucravacitinib, BMS-986165, and psoriasis as the search terms. Additionally, we manually searched the references of relevant reviews, meta-analyses, and unpublished clinical trials for any additional studies. Our search had no language restriction.

Three authors (PGM, CC, and PFM) independently extracted the data following predefined search criteria and quality evaluation. Disagreements on data extraction were resolved by consensus among the authors. The prospective meta-analysis protocol was registered on PROSPERO on January 23, 2023, under the protocol ID CRD42023391823.

Quality Assessment

To evaluate the risk of bias, we used version 2 of the Cochrane Risk of Bias assessment tool for RCTs (RoB 2).[12]Two independent authors (PGM and PFM) completed the risk of bias assessment. In case of divergences, a third author (OT) reviewed the studies to understand the point of conflict and resolve the disagreements. *Robvis* was used to create the RoB-2 assessment Figure.[13] Publication bias was assessed with visual funnel-plot analysis for the main outcome PASI 75 and adverse events.

FIGURE 1. PRISMA flow diagram of study screening and selection.



Statistical Analysis

This systematic review and meta-analysis were conducted and reported in accordance with the Cochrane Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[14,15]

Risk ratios (RR) with 95% confidence intervals (CI) were used to compare treatment effects of categorical outcomes. The DerSimonian and Laird random-effects model was applied for the analysis of all outcomes. Heterogeneity was evaluated using I^2 statistics and Cochran's Q test; values of $P < 0.10$ and $I^2 > 25\%$ were considered significant for heterogeneity. Pooled studies underwent sensitivity analysis through the systematic removal of each RCT and recalculating the difference between groups. Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration) was used for statistical analysis.

RESULTS

An extensive literature search yielded 285 results. After removing duplicated and unrelated studies, 54 were selected

TABLE 1.

Baseline Characteristics of Included Studies				
Study	**Armstrong 2022[5]**	**NCT04167462[17]**	**Papp 2018[16]**	**Strober 2022[6]**
Number of patients	498	220	179	766
Deucravacitinib group, n (%)	332 (66.7%)	146 (66.3%)	134 (74.8%)	511 (66.7%)
Deucravacitinib dosage	6 mg QD	6 mg QD	3 mg BID; 6 mg BID; 12 mg QD	6 mg QD
Follow up until outcome measure, weeks	16	16	12	16
Age, years (mean±SD)	46.5±13.8	40.6±12.22	45.0±13.4	47.0±13.5
BMI, kg/m² ±SD	29.9±7.1	NA	28.3±5.5	30.8±6.6
Male, n (%)	343 (68.9)	180 (81.8)	128 (71.5)	517 (67.5)
White	395 (79.3)	0 (0)	151 (84.4)	706 (92.2)
Asian	93 (18.7)	220 (100)	25 (14.0)	32 (4.2)
Duration of disease, years (median ±SD)	17.2±12.5	NA	18.3±13.7	19.7±12.9
Scalp psoriasis history, n (%)	453 (91.0)	NA	NA	672 (87.7)
sPGA score 3, n (%)	385 (77.3)	NA	NA	625 (81.6)
sPGA score 4, n (%)	112 (22.4)	NA	NA	141 (18.4)
PASI score (0-72), mean (SD)	21.4±8.6	NA	18.7±6.7	20.8±8.0
DLQI score (0-30), mean (SD)	11.8±6.7	NA	12.3±6.0	12.3±6.6
ss-PGA score ≥ 3, n (%)	330 (66.3)	NA	NA	478 (62.4)

SD: standard deviation; kg: kilogram; m²: meter squared; QD: once a day; BID: twice a day; NA: not available.

for full review. Following prespecified inclusion and exclusion criteria, a total of 4 studies with 1663 patients were included in this systematic review and meta-analysis, of whom 1123 (67.5%) were treated with deucravacitinib.[5,6,16,17]

Study populations were homogeneous in most aspects, apart from ethnicity and deucravacitinib dosage administrated to patients. One trial was fully composed of Asian patients, while the others had predominantly White patients. One study administered deucravacitinib in multiple doses with 5 treatment arms ranging from 3 mg every other day to 12 mg QD,[16] whereas 3 trials used the standard dosage of 6 mg QD.[5,6,17] Our analysis only included data on patients treated with 6 mg QD or higher. Mean patient age ranged from 40.6 to 47 years old, and most of them were male (n=1168, 70%), ranging from 67.5% to 81.8%. The characteristics of the study population are presented in Table 1.

In pooled analysis, a significantly higher number of patients treated with deucravacitinib (658/1121; 58.7%) achieved a ≥75% reduction in the PASI score compared with placebo (54/540; 10.0%) (RR 5.7; 95% CI 4.32-7.53; *P*<0.001; Figure 2).

Similarly, sPGA scores of 0 or 1 were also significantly more frequent in patients randomized to deucravacitinib (607/1121; 54.1%) than to placebo (42/540; 7.8%) (RR 6.74; 95% CI 5.02-9.07; *P*<0.001; Figure 3). Likewise, the proportion of patients with ss-PGA scores of 0 or 1 was greater in the deucravacitinib group (395/619; 63.8%), as compared with placebo (56/345; 16.2%) (RR 3.86; 95% CI 3.02-4.94; *P*<0.001; Figure 4). Moreover, among patients with nail involvement, PGA-F scores of 0 or 1 were significantly more frequent in the deucravacitinib-treated group (RR 2.73; 95% CI 1.25-5.97; *P*=0.01; Figure 5).

FIGURE 2. PASI 75 score was significantly more frequent in the deucravacitinib group, compared with placebo (*P*<0.001).

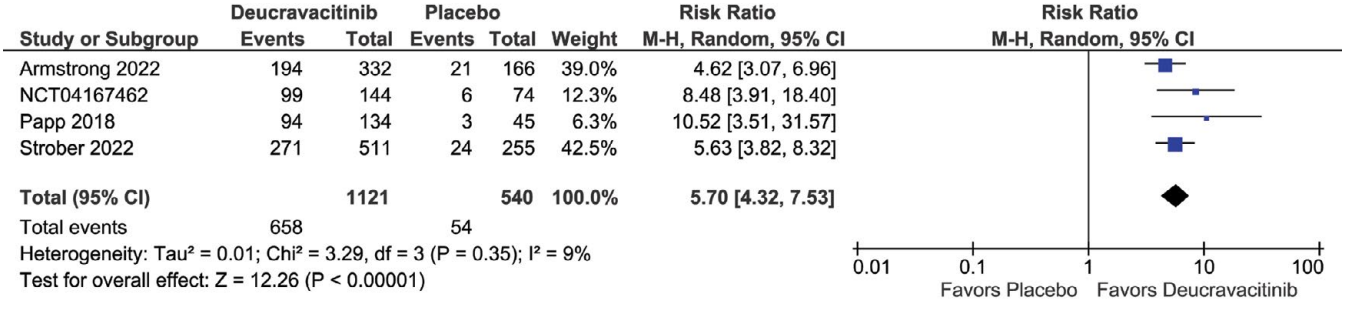


FIGURE 3. sPGA 0/1 was significantly more common in deucravacitinib-treated patients, as compared with placebo (*P*<0.001).

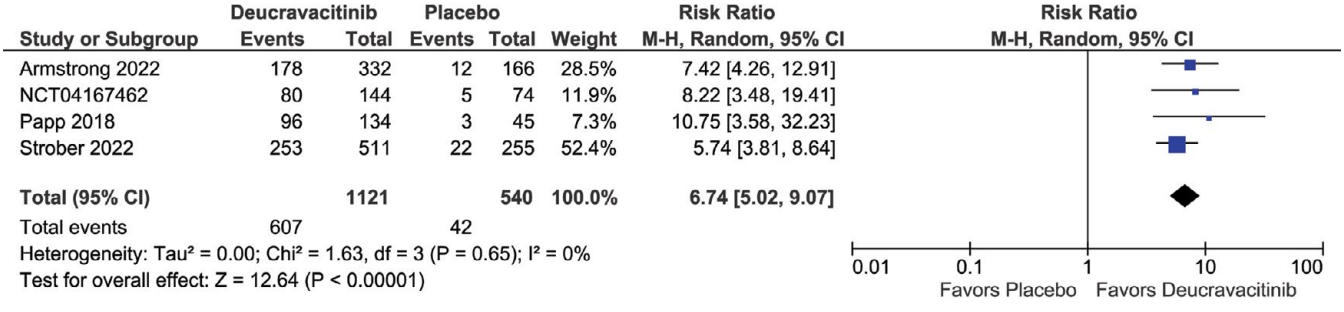


FIGURE 4. ss-PGA 0/1 was significantly more prevalent with deucravacitinib compared with placebo (*P*<0.001).

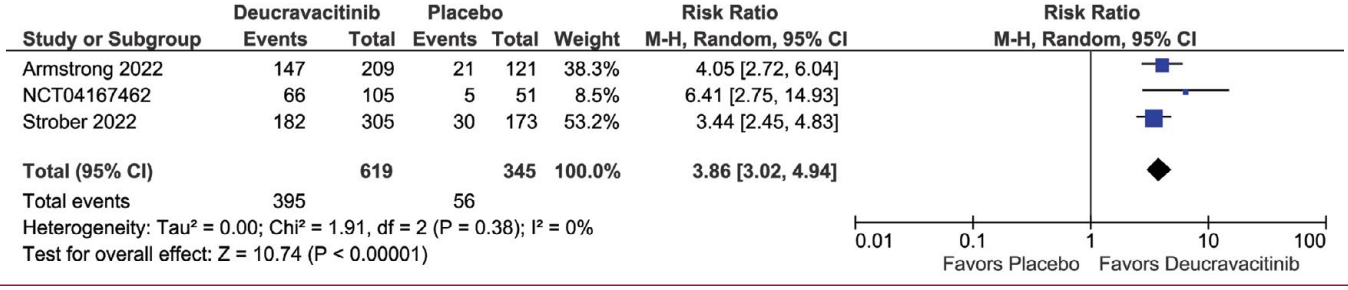


FIGURE 5. PGA-F 0/1 was significantly more frequent in the deucravacitinib group, as compared with placebo (*P*<0.001).

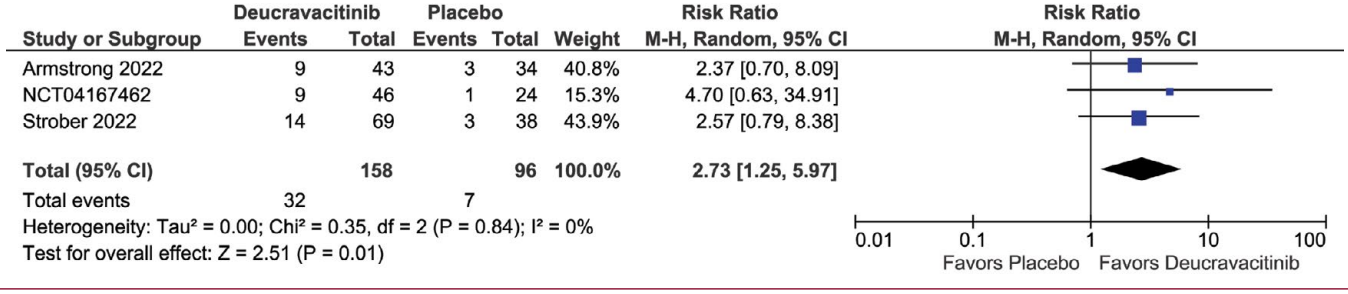


FIGURE 6. DLQI 0/1 was significantly more frequent in the deucravacitinib group, as compared with placebo (*P*<0.001).

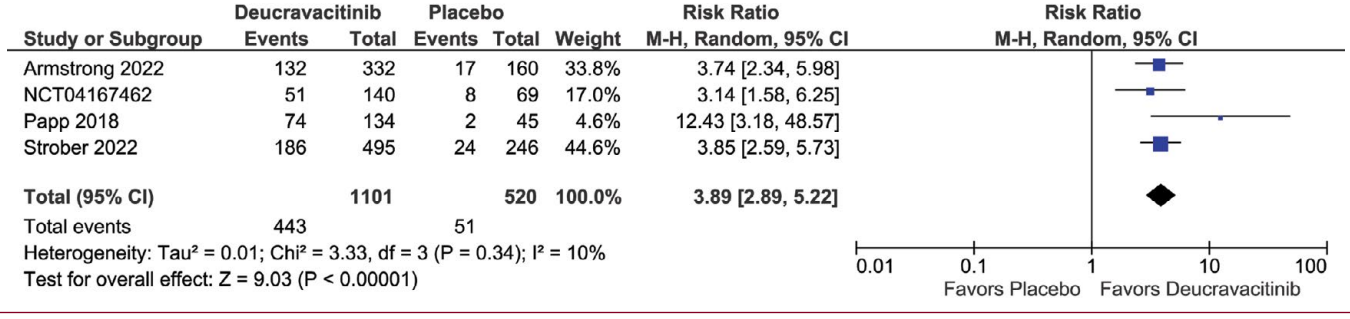


FIGURE 7. The incidence of SAEs was similar in both groups (*P*=0.37).

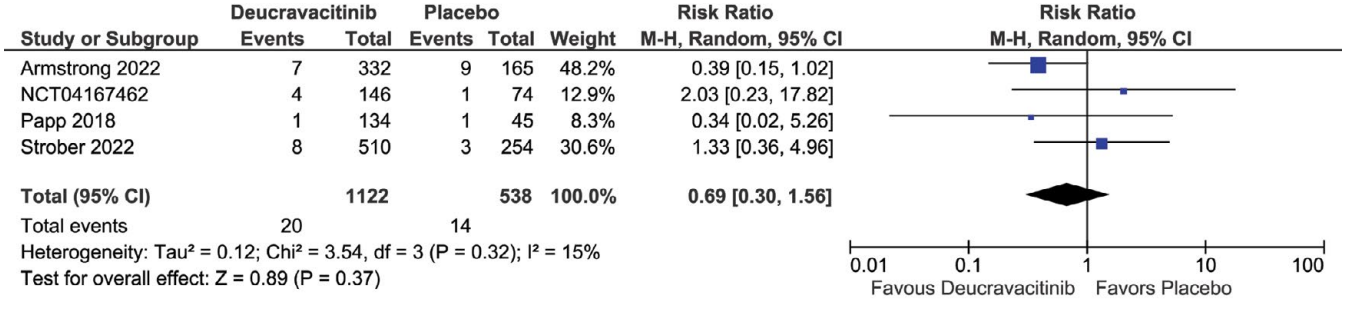
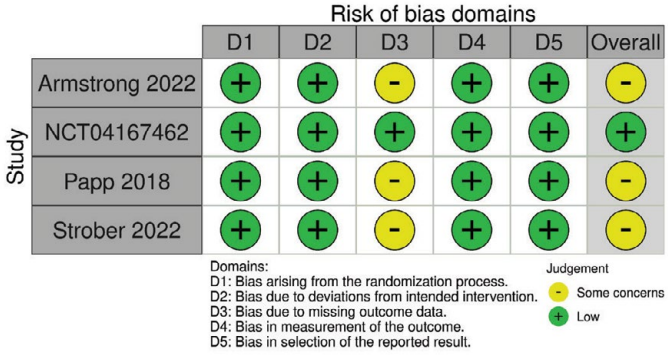


FIGURE 8. Risk of bias assessment according to RoB-2 tool.



Additionally, scores of 0 or 1 in DLQI tests were more prevalent in the deucravacitinib group (443/1101; 40.2%) versus placebo (51/520; 9.80%) (RR 3.89; 95% CI 2.89-5.22; *P*<0.001; Figure 6).

Regarding safety endpoints, the most frequent serious adverse events (SAEs) were either cardiovascular or infectious, with a total of 10 and 8 occurrences, respectively, across all patients. However, there was no significant difference between patients treated with deucravacitinib (20/1122; 1.8%) and placebo (14/538; 2.6%) when accounting for all the SAEs combined (RR 0.69; 95% CI 0.30-1.56; *P*=0.37; Figure 7). The individual incidence of different categories of SAEs are shown in Table 2.

Figure 8 outlines the quality appraisal of each individual RCT included in the meta-analysis. Most studies were considered at risk for missing outcome data bias due to a significant number of patients who left the trials, resulting in a patient discontinuation rate of 5%, 9%, 12.5%, and 14%, for NCT04167462, Armstrong 2022, Strober 2022, and Papp 2018, respectively.[5,6,16,17] Moreover, there was no mention of statistical analysis capable of avoiding bias in the premature discontinuation of patients. Otherwise, studies were considered at low risk of biases. The analysis of funnel plots did not suggest publication bias, as the studies are symmetrically distributed around the meta-analysis estimate (Figure 9A and B).

Sensitivity analyses were performed through the systematic removal of each RCT from the pooled estimates. No changes in the results for PASI 75, sPGA 0/1, ss-PGA 0/1, DLQI 0/1, PGA-F 0/1, and safety endpoints were observed after removing each study.

DISCUSSION

In this systematic review and meta-analysis of 4 studies and 1663 patients, we compared deucravacitinib with placebo as a potential treatment for moderate-to-severe psoriasis. The main findings were as follows: (1) patients treated with deucravacitinib achieved PASI 75 almost 6 times more frequently than patients on placebo over 12 to 16 weeks of follow-up (58.7% vs. 10%, respectively; *P*< 0.001); (2) sPGA

FIGURE 9. Funnel plots for PASI 75 (A) and serious adverse events (B). The symmetrical distribution of the included studies suggests no evidence of publication bias.

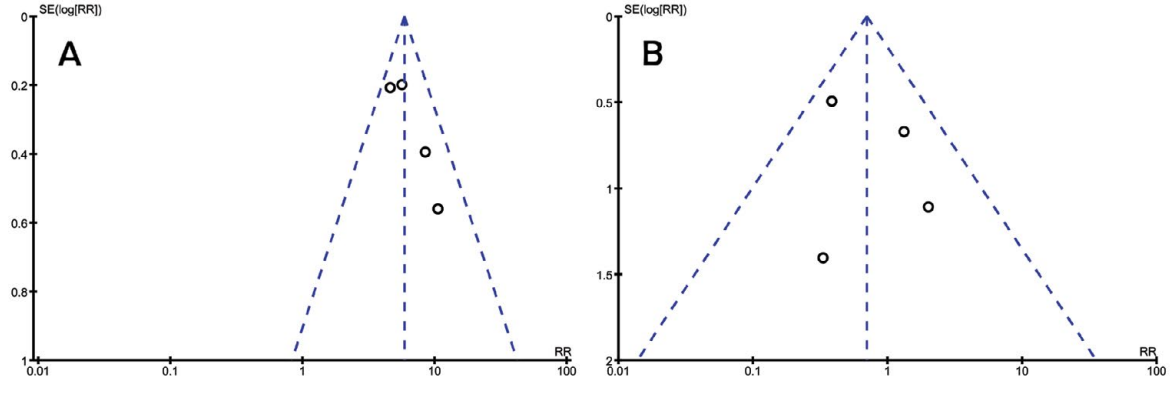


TABLE 2.

Individual Incidence of Serious Adverse Events								
Study	Armstrong 2022[5]		NCT04167462[17]		Papp 2018[16]		Strober 2022[6]	
Intervention	DEUC	Placebo	DEUC	Placebo	DEUC	Placebo	DEUC	Placebo
Infection, n	2	1	2	0	0	0	4	1
Cardiovascular, n	2	3	0	0	0	0	3	0
Others, n	3	9	3	1	1	2	3	3
Total, n	7	13	5	1	1	2	10	4

DEUC: deucravacitinib group

scores of 0 or 1 were approximately 7 times more frequent in patients randomized to deucravacitinib, compared with placebo (54.1% vs 7.8%, respectively; *P*<0.001); (3) scores of 0 or 1 in the DLQI questionnaire were almost 4 times more prevalent in the deucravacitinib group compared with placebo (40.2% vs 9.80%, respectively; *P*<0.001); and (4) there was no significant difference in the incidence of SAEs between groups (*P*=0.37).

The 2020 issue of the Joint American Academy of Dermatology-National Psoriasis Foundation guidelines on systemic non-biologic treatments for psoriasis did not mention the use of selective TYK2 inhibition as a treatment alternative, and the only JAK inhibitor present in the guideline was tofacitinib.[18] The results of our meta-analysis indicate that deucravacitinib may be considered in the therapeutic armamentarium of systemic non-biological agents for patients with psoriasis.

A unique property of deucravacitinib is its highly selective TYK2 inhibition, which happens via the drug binding to the JH2 domain of TYK2, resulting in a much lower degree of interaction with JAK1, JAK2, and JAK3 receptors, as compared with other JAK inhibitors.[19] This novel, more selective mechanism may explain the milder adverse event profile of deucravacitinib seen across RCTs. In a network meta-analysis, Zhang et al. compared the efficacy and safety of different JAK inhibitors in the treatment of plaque psoriasis.[20] Among all JAK inhibitors, patients on tofacitinib 15 mg BID were more likely to reach PASI 75 at 8 and 12 weeks, followed by tofacitinib 10 mg BID, and deucravacitinib 12 mg QD. However, these doses of tofacitinib were associated with a higher rate of opportunistic infections as compared with other JAK inhibitors. Moreover, the prior meta-analysis included only 1 study with deucravacitinib, thus limiting the power for the indirect comparisons to deucravacitinib in the network meta-analysis.

Deucravacitinib blocks signal transduction of IL-23, a cytokine linked to inflammatory pathogenesis in PsA,[21,22] as well as IL-12 and type 1 interferons, which have also been shown to participate in SLE pathogenesis.[23–25] In a phase 2 RCT, Morand et al assessed the efficacy and safety of deucravacitinib in patients with active SLE after a 32-week treatment course.[8] A significantly higher percentage of patients randomized to deucravacitinib achieved the composite disease severity outcome SLE Responder Index 4 (SRI-4), as compared with placebo. The incidence of SAEs was not significantly different between deucravacitinib and placebo groups.[8]

Recent studies have also shown deucravacitinib to be a potential candidate for the treatment of psoriatic arthritis (PsA),[7] a complication that occurs in up to 30% of patients with psoriasis.[21] In a phase 2 trial including 203 patients, there was greater improvement in the American College of Rheumatology-20 (ACR-20) response, a multidimensional outcome that measures disease activity, in patients receiving deucravacitinib, as compared with placebo.[7] No SAEs were reported in deucravacitinib-treated patients during 16 weeks of treatment.[7]

A dedicated analysis of patients with nail involvement found improved outcomes with deucravacitinib as compared with placebo in this subgroup. PGA-F scores of 0 or 1 were significantly more common in deucravacitinib-treated patients, compared with placebo (*P*=0.01). Similarly, a significantly higher number of patients with scalp psoriasis achieved ss-PGA scores of 0 or 1, as compared with placebo. A phase 3 double-blind RCT comparing the efficacy and safety of deucravacitinib versus placebo in patients with moderate-to-severe scalp psoriasis is currently ongoing. The estimated enrollment is 150 individuals, and it may further confirm the positive ss-PGA findings in this meta-analysis.[26]

The safety of systemic non-biological agents is an important issue in the treatment of patients with psoriasis.[27] In the CHAMPION trial, methotrexate achieved PASI 75 in 35.5% of patients after a 16-week treatment. However, it was associated with important hepatotoxicity.[28] Similarly, nephrotoxicity is a well-known side effect of long-term cyclosporin therapy.[29] Acitretin, another agent routinely used for psoriasis, is teratogenic, which limits its use in childbearing-age women.[27] Apremilast is inferior in efficacy, compared with deucravacitinib, although the incidence of SAEs was similar.[5,6] JAK inhibitors have been associated with neutropenia, elevated liver enzymes and creatinine levels, and dyslipidemia.[30] However, Armstrong et al and Strober et al reported no meaningful changes in these laboratory parameters with deucravacitinib, as compared with placebo,[5,6] unlike other JAK inhibitors.[30] The safety of deucravacitinib is further confirmed by our meta-analysis, which showed no difference in the incidence of SAEs.

This meta-analysis has limitations. First, follow-up was limited to 16 weeks due to the crossover design of the trials after this period. Nevertheless, two studies have shown sustained efficacy and safety of deucravacitinib in longer-term follow-up of up to 52 weeks.[5,6] The results of the ongoing POETYK-PSO-LTE randomized open-label trial are expected to provide more information into the longer-term efficacy and safety of deucravacitinib.[31] Second, there was limited representation of other ethnicities beyond White and Asian populations. Third, as shown in the risk-of-bias assessment, there was some concern of bias in missing outcome domain. However, the absence of heterogeneity indicates the consistency of findings among individual studies, and this is unlikely to have played a significant effect on the results. Finally, all studies were industry-funded, with the same sponsor. If and how this could have influenced study results in any way is unclear.

CONCLUSION

In this meta-analysis of RCTs, patients with moderate-to-severe psoriasis treated with deucravacitinib had a significant reduction in disease severity and improvement in quality of life, with no difference in the incidence of serious adverse events, as compared with placebo. These findings suggest that deucravacitinib is an effective treatment option for moderate-to-severe psoriasis, with a favorable safety profile up to 16 weeks of treatment.

DISCLOSURES

Philip J. Mease has received research grants, consultation fees, and/or speaker honoraria from Abbvie, Acelyrin, Aclaris, Amgen, Bristol Myers, Boehringer-Ingelheim, Galapagos, Gilead, GlaxoSmithKline, Inmagene, Janssen, Lilly, Moonlake, Novartis, Pfizer, SUN Pharma and UCB. Otavio A. S. Toth, Patrick F. Meldola, Pablo G. Machado, Gabriel F. C. Chiarelli, Erick Schnorrenberger, Jose L. S. Kracik, Caio C. de Carvalho, and Joao V. L. Guzatti have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Blood Monocyte Count Can Predict Early Response to Secukinumab Therapy in Patients With Psoriasis

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ABSTRACT

Early response to treatment with biologics, defined as Psoriasis Area and Severity Index (PASI) ≤ 2 six months after initiation of therapy, seems to be associated with more stable psoriasis and a lower risk of flares and treatment discontinuation. This study aimed to identify markers that can predict early response to treatment with secukinumab in patients with plaque psoriasis. Treatment with secukinumab was initiated in 29 biologic-naive patients with plaque psoriasis (75.9% males). After six months, the patients were stratified as (1) PASI ≤ 2 responders or (2) PASI > 2 responders. Patients who achieved PASI ≤ 2 six months after initiation of secukinumab therapy already had significantly greater PASI reductions after the first month of therapy compared to those with PASI > 2 six months after treatment. Baseline blood monocyte counts significantly correlated with PASI, both before and six months after initiating secukinumab therapy. A lower monocyte count with a cutoff value set at less than 0.69 × 10^3/uL (based on ROC curve analysis) was found in multivariate analysis to be an independent factor for achieving PASI ≤ 2 six months after initiation of therapy with secukinumab (R^2 = 0.7; β = -0.67; *P* = 0.03). We showed that baseline monocyte count may be useful for predicting early response to secukinumab therapy in plaque psoriasis patients. Identifying such a marker may help clinicians choose the most appropriate biologics for patients with plaque psoriasis and help avoid the expense of switching from one biologic to another.

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by the proliferation and abnormal differentiation of keratinocytes and massive infiltration of inflammatory immune cells. Discovery of the pathogenic role of cytokines such as interleukin (IL)-17 and IL-23 in psoriasis led to a shift in treatment strategies for this disease.[1] Therapeutic agents targeting these cytokines (biologics) are effective. The evaluation of psoriasis treatment is often based on severity measured with the Psoriasis Area and Severity Index (PASI).[2] However, data from clinical trials have shown that clinically similar patients with psoriasis may respond differently to biologics. Some patients achieve clear or almost clear skin (ie, PASI 90–PASI 100) within the first 4–8 weeks of therapy.[3,4] However, some patients are classified as late responders or never full responders. The clinical significance of early response to biologics is not fully understood. It has recently been stated that patients with PASI ≤ 2 six months after initiation therapy with biologics show markedly more stable psoriasis with lower risk of flares and treatment discontinuation compared to those with PASI > 2 within five years of follow-up.[5] Thus, it has been suggested that the best response to biologics should be regarded not only as a significant reduction in PASI but clear or almost clear skin (ie, PASI ≤ 2) within the first several weeks of therapy (ie, early response).

Some recent studies have shown that higher body weight and smoking may be associated with a lower probability of treatment response, as well as early response, to different biologics (ie, adalimumab, ustekinumab, secukinumab).[4,6] Identifying the factors that affect early response to biologics (ie, PASI ≤ 2 six months after initiation of therapy) could be helpful in selecting the most effective medication for patients with psoriasis and may avoid expensive switching between biologics. Thus, the main aim of this study was to identify clinical and laboratory markers of achieving PASI ≤ 2 in the first six months of treatment with secukinumab (anti-IL-17A) among patients with plaque psoriasis.

MATERIALS AND METHODS

Patients

The study included 29 patients with active plaque psoriasis (PASI ≥ 18), all aged 18 years or older. All participants had no history of systemic treatment or phototherapy for at least three months prior to entering the study. Patients with autoimmune disorders, such as thyroiditis and psoriatic arthritis, were excluded. The following patient characteristics were collected: sex, age, body weight, smoking, hypertension, hyperlipidemia, PASI and BSA, and basic blood test results such as CBC, liver, and kidney function test.

Medications for hypertension and hyperlipidemia were reported in 79% and 66% of the study participants, respectively. A total of 66% of patients had a body mass index (BMI) of 30 or higher (considered obesity). All patients received secukinumab (Cosentyx, Novartis, Basel, Switzerland) 300 mg subcutaneously once a week for five weeks and once monthly thereafter. The patients were followed for the next six months.

The study has been approved by the Bioethical Committee of the Medical University of Silesia, Katowice, Poland.

Statistical Analysis

Statistical analysis was carried out using Statistica 7.1 PL software (TIBCO Software Inc., Palo Alto, CA, USA). If not stated otherwise, data were expressed as median and minimum–maximum values. Continuous variables were compared using the Mann–Whitney U test. The chi-squared test or Fisher's exact test was used for dichotomous variables. Multivariable logistic regression analysis was used to identify independent factors. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Twenty-nine patients (75.9% males) aged 22–66 years with psoriasis (PASI ≥ 18) were enrolled in this study. All participants had at least a one-year history of disease. None had been treated with immunosuppressive agents during the preceding three months.

Overall, treatment with secukinumab resulted in PASI < 10 in all patients six months after initiating therapy.

Based on the PASI reduction after six months of therapy with secukinumab, patients were stratified into (1) PASI ≤ 2 group (n = 15) and (2) PASI > 2 group (n = 14).

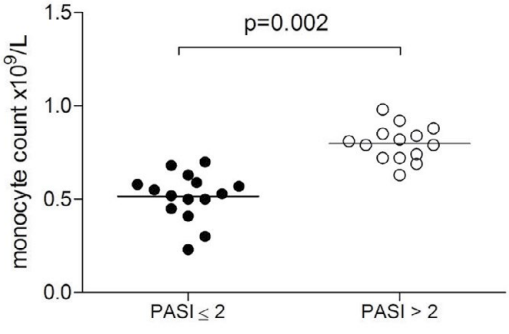
Individuals from the PASI ≤ 2 and PASI > 2 groups did not differ in basic demographic and clinical characteristics, including age, sex, and baseline psoriasis severity (Table 1). However, the PASI > 2 group had a significantly longer duration of disease (Table 1) and a higher baseline monocyte count than the PASI ≤ 2 group (Figure 1). Moreover, patients who achieved PASI

TABLE 1.

Characteristics of Patients			
	PASI ≤ 2 (n=15)	PASI > 2 (n=14)	*P*
Age	50 (21-61)	43,5 (31-66)	0.88
Males; n (%)	13 (86.7)	9 (60)	0.21
PASI at baseline	22.1 (18.2-43.3)	19.3 (18.6-29)	0.16
BSA at baseline	26 (20-76)	24 (17-47)	0.34
PASI after 1 month	6.2 (0-17.4)	11.5 (5.6-18)	0.005
% of PASI reduction after 1 month	59.8 (43.9-100)	44.8 (21.1-76.3)	0.043
BSA after 1 month	16 (0-41)	20 (8-38)	0.19
Medication for hypertension; n (%)	12 (80)	11 (78)	0.67
Medication for hyperlipidemia; n (%)	7 (47)	8 (57)	0.42
BMI ≥ 30; n (%)	9 (60)	10 (71)	0.28
Smokers; n (%)	7 (47)	5 (35.7)	0.18
Blood test results at baseline:			
Leukocytes; $x10^3$/uL	5.8 (5-8.2)	7.1 (4.7-9.9)	0.14
Lymphocytes; $x10^3$/uL	1.7 (1.4-2.3)	1.9 (0.9-3.2)	0.25
Neutrophils; $x10^3$/uL	3.4 (2.5-5.4)	4.3 (2.4-6.2)	0.18
Monocytes; $x10^3$/uL	0.5 (0.2-0.9)	0.8 (0.5-1.0)	0.002
Eosinophiles; $x10^3$/uL	0.3 (0.1-0.4)	0.2 (0.03-0.3)	0.27
Basophiles; $x10^3$/uL	0.02 (0.01-0.06)	0.03 (0-0.05)	0.67
ALT; U/L	28 (8-94)	27 (13-83)	0.81
AST; U/L	20 (9-51)	20 (14-78)	0.88
Creatinine levels; umol/L	78.1 (53.7-106)	71.4 (41.8-87.6)	0.35
CRP levels; mg/dL	2 (0.6-34)	2.7 (0.03-9.4)	0.97

Data are shown as median (min-max) or otherwise stated.
PASI: Psoriasis Area and Severity Index; BSA: Body Surface Area; BMI: Body Mass Index; ALT: alanine transaminase; AST: aspartate transaminase; CRP: C-reactive protein

FIGURE 1. Baseline monocyte count among psoriatic patients with PASI ≤ 2 and > 2 six months after therapy with secukinumab.



≤ 2 six months after therapy initiation with secukinumab had significantly greater PASI reductions after the first month of therapy compared to those with PASI > 2 six months after treatment (Table 1).

In multivariate analysis, an independent factor for achieving PASI ≤ 2 six months after initiation of therapy with secukinumab was baseline monocyte count (R^2 = 0.7; β = -0.67; P = 0.03).

The cutoff value for monocyte count at baseline for the PASI ≤ 2 group was set to be less than 0.69 × 10^3/uL based on ROC curve analysis (data not shown).

It was interesting that monocyte count after six months still significantly correlated with PASI at six months after initiation of therapy with secukinumab (r = 0.83; P < 0.0001).

DISCUSSION

T cells are the most studied immune cell population, with multiple subsets linked to the development of skin lesions in psoriasis. Meanwhile, understanding the role of innate immune cells in psoriasis pathogenesis, in particular monocytes/macrophages, is still evolving. The critical importance of the inflammatory monocyte lineage in the pathogenesis of psoriasis has recently been demonstrated. Under basal conditions, blood monocytes enter the dermis and acquire inflammatory expression. These cells differentiate into dermal macrophages. Macrophages produce IL-23 and IL-1b, subsequently promoting IL-17 production, mostly by gamma/delta T cells and Th17 cells.[7,8] It has been shown that a pharmacological reduction in monocyte migration during psoriasis significantly improves disease severity. In a mice model of psoriasis, it was recently shown that prophylactic dosing (ie, prior to an IL-23 injection model of psoriasis) of a selective CSF-1R tyrosine kinase inhibitor significantly reduced IL-17A mRNA expression in the skin.[9] Interestingly, however, after establishing inflammation, tyrosine kinase inhibitors did not affect IL-17A expression.[8] Consequently, there is presumably a need for a substantial reduction in monocyte/macrophages levels to modulate IL-17A.

Thus, treatment solely targeting IL-17A in patients with a longer duration of disease is likely not sufficient to totally and rapidly overcome the "inflammatory momentum", resulting in a partial or delayed response. The results of our study seem to support this hypothesis, since patients from the PASI > 2 group had a significantly longer duration of psoriasis. Moreover, we found that higher blood monocyte levels correlated significantly with more severe disease, longer duration of symptoms, and PASI > 2 at six months after initiation of secukinumab therapy.

In clinical trials, PASI 75 and PASI 90 are often used as efficacy responses, whereas response criteria based on absolute PASI are more suitable for real-world studies. Some recent studies have shown that a low PASI within the first six months of treatment in biologic-naive patients was associated with a more stable disease course and a lower risk of flares and treatment discontinuation.[5] It has been suggested that a treatment target of PASI = 0 or at least ≤ 2 in the first six months of treatment should be considered a desirable treatment outcome. Thus, in the current study, we decided to set the endpoint as PASI ≤ 2 at the six-month follow-up.

It seems reasonable to initiate biologic therapy for psoriasis patients with medication that can result in PASI ≤ 2 within the first several weeks of treatment. Therefore, identifying the patient characteristics associated with achieving such an early and strong treatment response to biologics in patients with psoriasis should be of special interest.

For the first time, we showed that blood monocyte levels can be a useful prognostic factor for early response to secukinumab therapy in psoriasis. Patients with higher baseline blood monocyte counts may not achieve an early response to secukinumab therapy. Monocytes/macrophages are the main source of IL-23. We can only hypothesize that patients with psoriasis with higher blood monocyte counts may benefit from initial therapy with anti-IL-23 medication. However, further studies are needed.

Recent studies have found that higher body weight and smoking reduced the odds of achieving PASI ≤ 2 after six months of treatment with adalimumab, etanercept, infliximab, secukinumab, or ustekinumab.[6,10,11,12,13] In the current study, we did not detect any differences between the analyzed groups in either body weight or smoking. In the entire group of patients, however, we found a higher percentage of individuals with BMI ≥ 30 and those who were smokers (65.5% and 41.4%, respectively).

Our study has several limitations that should be taken into consideration. First, a small number of patients were studied. However, it should be highlighted that a relatively small number of psoriatic patients require biologics. Most respond well to

topical therapy or non-biologic systemic therapy. Second, we did not assess the clinical significance of early response to treatment. We may only assume its significance based on previous studies.

In conclusion, we demonstrated that lower baseline blood monocyte counts may be associated with early response to treatment with secukinumab, defined as PASI ≤ 2, six months after initiation of therapy. Thus, blood monocyte count may serve as a prognostic factor for response to therapy with secukinumab, which may help to select patients who may benefit from such treatment and those who will not.

DISCLOSURES

All authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

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The Gastrointestinal Microbiome and Immune Checkpoint Inhibitors: A Review of Human Interventional Studies Among Melanoma Patients

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ABSTRACT

Immune checkpoint inhibitors (ICI) are widely utilized for the treatment of malignant melanoma. Interestingly, gastrointestinal microbiome composition has emerged as a predictive biomarker of immunotherapy outcomes. This review seeks to assess the effect of microbiota-modulatory interventions on the clinical and immunological response of metastatic melanoma treated with ICIs. A systematic search was performed to retrieve studies and cases involving any microbiota-modulating intervention. Three studies assessed the effect of fecal microbiota transplantation (FMT) on ICI efficacy, and one case report assessed its effect on clearance of ICI-associated colitis. Overall, 37.5% of melanoma patients who had been previously refractory to ICI immunotherapy demonstrated complete or partial response following FMT and subsequent immunotherapy. 65% of immunotherapy-naïve melanoma patients demonstrated an objective response. No severe FMT-associated adverse events were reported, and FMT depicted efficacy in the remission of ICI-associated colitis. The results suggest that FMT may be a safe and moderately effective microbiota-modulating intervention to improve the efficacy of therapy in ICI-treated melanoma patients. Large, randomized, controlled trials are needed to determine optimal FMT donors and assess other microbiota-modulating interventions, such as pre- and probiotics, in melanoma patients.

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INTRODUCTION

Melanoma and Immune Checkpoint Inhibitors

Melanoma is a malignant neoplasm of the melanin-producing cells residing in the basal layer of the epidermis.[1] Estimations depict 21.5 new cases of cutaneous melanoma diagnosed per 100,000 men and women in the United States annually.[2] While there is a 99% five-year survival rate for localized cutaneous melanoma, distant metastasis dramatically decreases survival and calls for systemic therapeutic approaches.[3]

Systemic immunotherapy, including immune checkpoint inhibitors (ICI), fosters long-term survival for some patients.[4] Immune checkpoints suppress immune cell activity due to the binding of checkpoint proteins and partner proteins. For example, upon binding to programmed death protein 1 (PD-1) on T-cells, programmed death ligand 1 (PD-L1) suppresses cytotoxic T-cell activation. Similarly, binding of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) with integral membrane protein B7 on antigen-presenting cells (APCs) downregulates T-cell activation by preventing the costimulatory interaction between B7 and CD28.[5] Malignant melanocytes can express PD-L1 and CTLA-4, suppressing and evading the immune response. ICIs are monoclonal antibodies that prevent the binding of PD-L1 and PD-1 or CTLA-4 and B7, ultimately stimulating cytotoxic T-cells and improving the endogenous immune response. However, only about 20-40% of advanced melanoma patients treated with ICIs exhibit long-term response; others demonstrate no response or develop secondary resistance.[6] Many researchers have sought to uncover potential factors mediating immunotherapy efficacy to better explain the inequitable response among patients.

The Microbiome

The microbiome refers to the collection of microorganisms sharing a common habitat. The gastrointestinal microbiome represents the largest microbiome in the body and modulates gastrointestinal, metabolic, and dermatologic diseases. In addition, its role in the pathogenesis and treatment of metastatic melanoma has become better elucidated with novel research. The gut microbiota composition has been demonstrated to change as melanoma progresses from in situ, to invasive, and ultimately metastatic disease.[7] Furthermore, microbiota composition has been shown to differ among melanoma patients and healthy counterparts.[7]

The microbiome may also modulate response to melanoma treatments and side effects. Numerous studies have assessed the impact of the gut microbiome on ICI efficacy and the occurrence of immune-related adverse events (irAEs). Microbiota-derived metabolites, such as short-chain fatty acids, elicit diverse effects on tumorigenesis and the immune system and may be implicated in immunotherapy response.[8] Microbiome composition has therefore emerged as a predictive biomarker of immunotherapy outcomes.[9]

The Microbiome and Immunotherapy

Microbiota Signatures and ICI Response in Melanoma

Studies have found differing gastrointestinal microbiota compositions among patients who respond to immunotherapy versus those who do not.[9,10] A 2022 prospective study assessed intestinal microbiota signatures and the ICI response in melanoma and denoted specific microbes associated with a positive PD-1 response and irAEs.[9] The authors performed a meta-analysis with four additional cohorts and found a significant difference between the microbiota of PD-1 responders and non-responders (P=0.002). The *Actinobacteria* phylum and *Lachnospiraceae* family were the most abundant taxa associated with responders, whereas non-responders were associated with *Bacteroides* or *Proteobacteria* taxa. Lastly, researchers found *Lachnospiraceae* or *Streptococcus spp*. to be associated with irAEs.[9] Such research provides valuable insight into the importance of gut microbiota signatures in predicting ICI treatment response and justifies the assessment of microbiota-modulatory interventions for improving ICI treatment response.

Fiber and Probiotics

Whereas oral probiotics directly alter the gastrointestinal microbiome,[12] dietary fiber, metabolized by gut microbes, indirectly alters microbiota composition and results in the production of beneficial metabolites that can influence ICI responses.[13] A 2021 observational study assessed fecal microbiota profiles, dietary habits, and probiotic use among melanoma patients.[14] Of the 128 patients receiving ICI therapy, an improved progression-free survival (PFS) was observed among those reporting sufficient dietary fiber intake compared to those with insufficient dietary fiber intake. After adjusting for clinical factors, the authors noted a 30% lower risk of progression or death for every 5g increase in intake. However, significant differences in microbial composition were not observed between those reporting sufficient vs. insufficient fiber intake. Interestingly, the greatest ICI treatment response was noted in individuals reporting sufficient dietary intake and no probiotic use.[14]

Animal Studies

Various studies have analyzed the effect of microbiome composition changes on antitumor immunity using fecal microbial transplantation (FMT) from humans to mice. A 2018 study assessed the efficacy of anti-PD-1 treatment in germ-free or antibiotic-treated mice receiving FMT from either cancer patient donors who responded to ICIs or cancer patient non-responders.[11] The authors observed improved anti-PD-1 efficacy among mice receiving FMT from ICI-responders compared to mice receiving FMT from ICI-non-responders, with efficacy assessed via tumor growth.[11] Similarly, a study utilizing melanoma patients as FMT donors found tumor size reduction in mice receiving FMT from melanoma anti-PD-1-responders compared to mice receiving FMT from melanoma anti-PD-1-non-responders.[10]

A favorable microbiota has also been shown to improve treatment with anti-CTLA-4 antibody therapy. Compared to mice with other dominating microbiota, mice who underwent FMT from melanoma donors exhibited a better response to anti-CTLA-4 antibody therapy due to colonization of B. thetaiotaomicron or B. fragilis.[15] The study highlights the role of Bacteroidales in enhancing anti-CTLA-4 treatment, specifically via interleukin 12-dependent TH1 immune responses.11 In addition to improving the anti-tumor effects of ICIs, microbiota-modulatory interventions, such as the administration of Bifidobacterium alone, may even ameliorate tumor control to the same degree as anti-PDL1 therapy.[16] These studies depict the potential utility of microbiota-modulating interventions to enhance ICI outcomes.

Human Interventional Studies

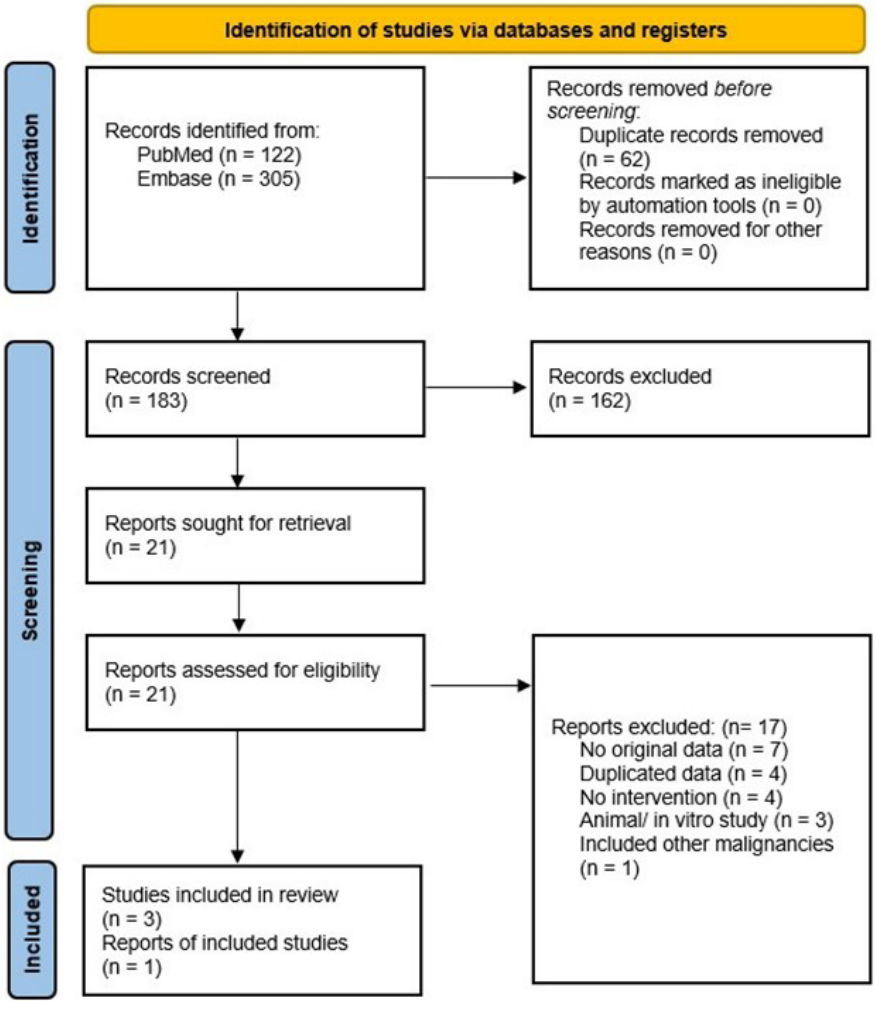
A systematic search was conducted to retrieve studies assessing the effect of microbiota-modulatory interventions on the clinical and immunological response to ICI-treatment among melanoma patients. Exclusion criteria included in vitro, animal, and non-interventional studies. 3 studies and 1 report met the inclusion criteria (Figure 1) and are listed in Table 1.

Efficacy and Adverse Events

Although any microbiota-modulatory interventions were sought for analysis, FMT comprised the intervention in all four manuscripts. In 2021, Baruch et al published an open-label Phase I clinical trial assessing ICI efficacy among metastatic melanoma patients receiving FMT from one of two donors who achieved a complete response to anti-PD-1 therapy.[17] Ten ICI-refractory patients underwent a 72-hour native microbiota depletion protocol with oral vancomycin and neomycin, followed by FMT intervention administered via colonoscopy and stool capsules. Subjects underwent standard-dosed nivolumab (anti-PD-1) infusions and maintenance FMT capsule administration every 14 days until day 90. Objective tumor regression was assessed via imaging according to iRECIST criteria.

The authors observed an objective response (OR) to treatment

FIGURE 1. PRISMA flow diagram. The literature search conducted with PubMed and Embase yielded 427 records. Following duplicate removal, 183 records underwent title and abstract screening. 21 full-text reports were sought for retrieval and assessed for eligibility, and 17 reports were excluded for various reasons. Three studies and 1 case report met the inclusion criteria.



with three participants, all of whom received FMT from Donor 1.[17] Two subjects depicted a partial response, and one subject depicted a complete response. All three responders met the six-month PFS milestone. Although seven patients failed to respond to ICI treatment despite FMT intervention, gut sample analysis of all recipients depicted an up-regulation of genes implicated in peptide presentation by APCs, and recipients from Donor 1 experienced an up-regulation of genes implicated in APC activity, innate immunity, and interleukin-12.[17] An overall pretreatment vs posttreatment comparison of lamina propria-infiltrated CD68+ cells, representing APCs, depicted a significantly increased posttreatment infiltration (353 vs 569 cells/mm^2 , P=0.05), providing insight into potential mechanisms implicated in microbiome-associated immunomodulation.

No FMT-related serious adverse events (SAEs) were observed. One subject experienced mild bloating between days 3-15. Grade 1 irAEs were observed, although no moderate to severe irAEs were observed. This is clinically significant, as half of the patients had previously experienced moderate to severe irAEs from previous ICI therapy.[17] Despite the moderate success noted by this phase I clinical trial, the small sample size hinders the generalizability of results. Furthermore, the inclusion of two separate FMT donors may have impacted efficacy results, further complicated by the fact the study design was not intended for inter-donor comparison. Lastly, the lack of a control group and prevention of observer bias reduce study quality. Still, this was the first study to assess a microbiota-modulating intervention on ICI therapy among melanoma patients and provided preliminary evidence for the potential efficacy of FMT coupled with systemic immunotherapy.

TABLE 1.

Efficacy and Safety of Microbiota-Modulating Interventions in Conjunction With ICI Therapy Among Melanoma Patients

Author (Year)	Population (n)	Intervention	Design	Outcome Measure	Efficacy	Safety
Baruch (2021)	MM patients who progressed on 1+ anti-PD-1 therapy (n=10)	Antibiotic-induced microbiota depletion + FMT with two MM donors who achieved a complete response to anti-PD-1+ nivolumab	Open-label, uncontrolled	Objective tumor regression, iRECIST criteria PET-CT imaging completed before trial and on day 65	3 recipients depicted ORs: 1 complete and 2 partial All responders crossed the six-month PFS	No severe FMT-related AEs Several grade 1 immune related AEs noted, arthralgia with the greatest incidence No moderate to severe irAEs despite 6 developing irAEs during prior anti-PD-1 therapy
Davar (2021)	MM patients refractory to anti-PD-1 therapy (n=16)	FMT derived from 7 MM patients with ORs to anti-PD-1 therapy+ pembrolizumab	Open-label, uncontrolled	Objective tumor regression, RECIST v1.1 Radiographic assessment every 12 weeks	3 recipients depicted OR to treatment 3 patients depicted durable, stable disease lasting >12 months Remaining patients progressed despite FMT Median PFS and overall survival in all patients were 3 and 7 months, respectively Among the 6 responders, medial PFS and overall survival were 14 and 14 months, respectively	All patients experienced at least 1 AE: 72.9% grade 1, 20.0% grade 2 Grade 3 AEs occurred in 3 patients: 2 cases of fatigue, and 1 peripheral motor neuropathy
Miller (2022)	Immunotherapy-naïve MM patients (n=20)	FMT+ anti-PD-1 treatment one week later	Open-label, uncontrolled	OR via RECIST 1.1	65% OR rate 3/20 complete response 75% clinical benefit rate	FMT-related AEs: grade 2 diarrhea (2/20), hypophosphatemia (1/20), GI toxicities (13/20) Grade 3 irAEs: myocarditis (1/20), nephritis (1/20), fatigue (1/20) Anti-PD-1 therapy was discontinued for toxicity in 2 patients
Chen (2022)	MM of the palate patient treated with Toripalimab who experienced treatment-associated colitis (n=1)	FMT on day 56 of colitis, following other failed colitis treatments	Case report	Colitis remission	N/A	Inflammation and erosion of colon mucosa subsided following FMT No remaining signs of inflammation Colitis returned following re-initiation of ICI, initiated 6 months following colitis remission

AE: Adverse event; irAEs: Immune related adverse events; FMT: fecal microbiota transplantation; MM: Metastatic melanoma; OR: Objective response; PFS: Progression-free survival

Davar et al (2021) designed an open-label trial to evaluate the efficacy of FMT among sixteen PD-1-refractory melanoma patients.[18] Donors included seven melanoma patients who exhibited long-term response to anti-PD-1 therapy, similar to the donors utilized by Baruch et al.[17] Four donors demonstrated a complete response and three donors had a partial response, with a median PFS of 56 months.[18] Following the initial FMT, subjects received pembrolizumab (anti-PD-1) therapy every three weeks until disease progression or signs of toxicity. Three patients demonstrated an OR, and three patients demonstrated stable disease (SD) lasting >12 months. Although the overall median PFS and overall survival were observed to be 3 and 7 months, respectively, the median PFS and survival specifically among the six responding patients was 14 and 14 months, respectively.

All patients experienced at least one AE. Of these AEs, 72.9% and 20.0% were grade 1 and 2, respectively. Hypothyroidism requiring hormone therapy was noted in 17.6% of patients. Grade 3 AEs occurred in three patients, with two cases of fatigue and one case of peripheral motor neuropathy.[18] However, whereas Baruch et al described AEs experienced by subjects during their initial failed immunotherapy,[17] allowing comparison to AE incidence throughout the study, Davar et al did not specify the incidence of AEs during initial treatment (prior to study intervention). Hence, it is difficult to determine whether FMT reduced or contributed to AEs experienced throughout the study. Overall, the authors observed SD or OR in 6 of 16 previously anti-PD-1-refractory patients following FMT. The small sample size and omitted control group suggests evidence quality is comparable to that of the Baruch et al study.[17]

Miller et al (2022) published an open-label Phase I trial to analyze the effects of FMT on safety and anti-PD-1 response in 20 patients with advanced melanoma and no prior anti-PD-1 treatment.[19] The patients were given 80-100g of healthy donor stool via oral capsules and underwent anti-PD-1 therapy one week later. Response was measured with RECIST v1.1, depicting a 65% OR rate and a 15% complete response rate. Responders demonstrated an increase in IL-17 and Th17 in peripheral blood post-FMT.[19]

FMT-related AEs included grade 2 diarrhea (n=2) hypophosphatemia (n=1), and grade 1 gastrointestinal toxicities (n=13). Grade 3 irAEs included myocarditis (n=1), nephritis (n=1), and fatigue (n=1). Two patients discontinued anti-PD-1 therapy due to toxicity. As the patients included in this study had no prior anti-PD-1 treatment, it is unclear if FMT contributed to the objective response rate (ORR) or if these observations are the direct result of immunotherapy. As an uncontrolled open-label study with 20 subjects, evidence quality is comparable to that of the prior two studies.

Lastly, Chen et al (2022) published a case report detailing the successful remission of treatment-refractory ICI-associated colitis with FMT.[20] The patient was previously treated with Toripalimab (anti-PD-1) for melanoma of the palate and subsequently developed colitis. The patient's immunotherapy was temporarily terminated, and a variety of other colitis treatments failed to result in colitis remission. After 56 days, the patient received three consecutive treatments of FMT every other day. Colonoscopy revealed subsided erosion of the colon mucosa with no remaining signs of inflammation. The patient achieved full remission of colitis following FMT intervention.[20] However, six months later, the patient began ICI treatment and experienced colitis relapse, suggesting FMT maintenance may be required to prevent ICI-associated colitis. Although this case report did not assess the impact of FMT on ICI efficacy, it depicted the potential utility of FMT in the prevention or modulation of irAEs. However, given the single efficacious case presented, this report is of the lowest evidence quality presented, and a larger, controlled trial is necessary for the generalization of results.

The studies depict the potential utility of FMT coupled with ICI among melanoma patients, including those who had progressed on at least one line of anti-PD-1 therapy and those without prior anti-PD-1 treatment. Overall, 46 patients were assessed for OR and AEs, and one additional patient was assessed for the remission of ICI-associated colitis. 47.8% depicted an objective partial or complete tumor response, and no severe FMT-associated adverse events were reported. Furthermore, Baruch et al reported less irAEs following FMT than during initial, failed anti-PD-1 therapy,[17] and Chen et al described the successful clearance of ICI-associated colitis with a single FMT.[20] These results suggest FMT is both safe and moderately efficacious in promoting OR to ICI immunotherapy. However, no controlled studies were included in the analysis, and evidence quality is further limited by small sample sizes.

DISCUSSION

Despite 47.8% of melanoma patients demonstrating OR or CR, the population of melanoma patients differed between studies. The studies conducted by Baruch et al and Davar et al included patients who were previously refractory to anti-PD-1 treatment. 6/16 patients demonstrated partial or complete responses (37.5%), and an additional three patients depicted SD lasting >12 months. Due to previous ICI failure, the efficacious results demonstrated by these studies are likely due to the FMT intervention. In contrast, Miller et al enrolled anti-PD-1 treatment-naive MM patients in their study and observed a 65% ORR.[19] As these patients had never undergone anti-PD-1 immunotherapy, it is unclear whether the greater ORR was the result of immunotherapy or due to FMT intervention prior to immunotherapy.

In addition to different melanoma populations, the studies also included different populations of FMT donors. Both Baruch et al and Davar et al utilized donors who had previously achieved a response to anti-PD-1 therapy, while Miller et al and Chen et al utilized healthy donor stool. Furthermore, Baruch et al included an initial antibiotic regimen to prime recipients for FMT.[17] Further work is required to determine the most effective FMT protocol for ICI efficacy and the reduction of irAEs.

Beyond OR, Baruch et al additionally sought to examine the pre-treatment and post-treatment microbiota composition among participants.[17] Although there were no statistically significant differences in pre-treatment composition among subjects, the group receiving FMT from Donor 1 depicted a greater post-treatment relative abundance of taxa such as *Bifidobacterium adolescentis*, and the group receiving FMT from Donor 2 had a higher relative abundance of taxa such as *Ruminococcus bromine*. Both taxa had been previously described as favorable for immunotherapy interventions.[17] A 2015 mouse-model study found *Bifidobacterium* was associated with antitumor effects, both in isolation and synergistically with PD-L1 blockade treatment.[16]The authors found enhanced CD8+T-cell priming and accumulation secondary to augmented dendritic cell function to mediate this antitumor effect. Similarly, a human study found a greater relative abundance of *Ruminococcaceae* bacteria among anti-PD-1 responders, with effects hypothesized to be mediated by increased antigen presentation and improved effector T-cell function.[10]

Furthermore, ICI responders depicted a higher relative abundance of *Enterococcaceae, Enterococcus*, and *Streptococcus australis*, and a lower relative abundance of *Veillonella atypia*.[17] Yet, the

authors note some non-responders and pre-treatment samples depicted similar patterns, hindering the ability to associate such bacterial taxa with clinical response. Ultimately, despite the treatment efficacy noted in three patients, authors were unable to determine specific response-inducing microbiota.[17]

In contrast, Davar et al were able to determine phyla associated with favorable and unfavorable responses, and they found no significant differences in gut microbiota composition in patients who received infusions from complete or partial ICI responders.[18] *Actinobacteria* (*Bifidobacteriaceae* and *Coriobacteriaceae* families) and Firmicute (*Lachnospiraceae* and *Ruminococcaceae* families) were associated with favorable responses, while members of *Bacteroidetes* and *Proteobacteria* phyla were associated with unfavorable responses. This observation aligns with the results of the systematic review assessing taxa associated with melanoma non-progression and progression.[9] The review similarly found the *Actinobacteria* phylum and *Lachnospiraceae* family to be associated with PD-1 responders, and *Bacteroidetes* and *Proteobacteria* taxa to be associated with PD-1 non-responders.[9]

Davar et al found gut microbiota composition shifted greatly towards donor microbiota uniformly in responders, but not in non-responders.[18] In addition, responders depicted higher percentages of CD56+CD8+ T-cells and increased granzyme B after treatment. They displayed decreased levels of IL-8, IL-18, MCP1, IL-12p70, and IFN-γ, which are associated with negative anti-PD-1 outcomes.[18] Lastly, FMT was found to decrease cytokine and chemokine levels, including IL-8, IL18, and MCP1, which are associated with adverse responses to anti-PD-1.

Chen et al additionally described the potential role of FMT interventions in reducing irAEs, specifically ICI-associated colitis.[20] However, as the case detailed 56 days of failed colitis treatment prior to FMT intervention, it remains unclear whether early FMT differentially impacts patient prognosis in comparison to late FMT. Future research is necessary to determine the utility of FMT for ICI-associated colitis among a greater number of patients, in addition to assessing the potential utility of FMT intervention for other irAEs.

Limitations and Future Research

The small number of eligible studies or reports and the small sample sizes of included studies reduce the robustness of our conclusions and the generalizability of results. In addition, FMT donor populations differed in the included studies, with some utilizing healthy donors and others utilizing MM patients who achieved clinical responses with ICI treatment.

Future work could strive to determine the donor source and baseline microbiota composition that predicts the greatest efficacy among melanoma recipients. It is also necessary to better understand patient or tumor factors and FMT frequency that predicts beneficial response to ICI following FMT. Lastly, future work may explore the efficacy of other microbiota-modulating interventions, such as probiotics, on ICI response.

CONCLUSION

The results of this review suggest FMT is a safe and moderately effective microbiota-modulating intervention to improve ICI efficacy in melanoma patients, among both immunotherapy-naive patients and those who have failed on at least one line of ICI therapy. 47.8% who underwent FMT and subsequent ICI therapy and were assessed for OR depicted an objective partial or complete response. No FMT-associated SAEs were reported, and FMT depicted efficacy in the clearance of ICI-associated colitis, depicting the potential utility of FMT for both ICI efficacy and the reduction of irAEs. These preliminary studies provide promising results and highlight the potential role of microbiota-modulating interventions in conjunction with ICI immunotherapy for melanoma patients.

DISCLOSURES

James Grichnik MD PhD is a consultant to Galileo Group and Canfield Scientific and serves on the Skin Advisory Board for Regeneron and Dermatology Advisory Council for Melanoma Research Foundation. Clinical trial support from Novartis, Eli Lilly, Dermira, Elorac, Boehringer, and Amgen. The remaining authors have no relationships to disclose.

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ORIGINAL ARTICLE

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Sensitive Skin: A Survey of Dermatology Resident Physicians' Perspectives and Educational Exposures

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ABSTRACT

Sensitive skin (SS) is a common patient complaint presenting to the dermatology office, but there exists a lack of consensus on defining criteria and evidence-based management approaches. Furthermore, incorporation of SS training into the dermatology residency curriculum is unknown, and therefore the authors herein sought to determine dermatology resident physicians' exposure to education about SS, perspectives on SS, and management approaches.

Ninety-nine percent of residents believe that SS should be included in some capacity in their dermatology residency training. However, less than half of responding residents received education specifically about SS during their training and less than one-fourth of residents reported feeling very knowledgeable about SS diagnosis, clinical evaluation, or management. Residents who had received specific education about SS were significantly more likely to self-describe as "very knowledgeable" about all queried topics. Residents reported challenges with all aspects of SS patient care, and cited heterogenous approaches to SS patients. These data highlight a gap in residency education, as indicated by limited consensus over diagnostic and management approaches to SS.

J Drugs Dermatol. 2024;23(2):85-89. doi:10.36849/JDD.7830

INTRODUCTION

Sensitive skin (SS) is a subjective syndrome of cutaneous hyperreactivity, characterized by symptoms of redness, itching, burning, tightness, or stinging in response to innocuous stimuli.[1,2] SS is common, with an estimated global prevalence between 40% and 70%.[3] Currently, there is an incomplete understanding of SS pathophysiology and a lack of consensus on diagnostic and management approaches. Nevertheless, dermatologists must be knowledgeable about SS; an estimated 60% to 80% of individuals with SS and without primary skin disease have seen a dermatologist in the past.[4,5] Further, given the frequency with which SS patients seek dermatologic care, diagnosis, and management of SS based on the current and available evidence on SS should be an expected competency achieved during residency training. To date, there have been no studies assessing the inclusion of SS in dermatology residency curricula. We sought to assess dermatology resident physicians' educational exposure to SS and to gauge residents' perspectives and management approaches to SS.

MATERIALS AND METHODS

A 26-question survey was developed by the authors and approved by the George Washington University Institutional Review Board (#NCR224549). Survey questions were uploaded to SurveyMonkey, a cloud-based survey tool, and the survey link was e-mailed to dermatology resident physicians registered to the Orlando Dermatology, Aesthetic, and Surgical Conference (ODAC) e-mail list. Participation in the survey was optional, and no personally identifiable information was collected. The response rate was 28%. Survey responses were compiled for analysis. Statistical testing was performed with GraphPad Prism software, using Fisher's exact tests (significance=P<0.05).

RESULTS

Demographics

There were 214 survey respondents – demographic information is included in Table 1. Residents at all levels of training were represented, and residency program locations varied among all regions of the United States.

Exposure to Sensitive Skin Education

Ninety-nine percent of dermatology residents agreed that it is very (65%) or somewhat (34%) important for SS to be included in their dermatology residency training. Additionally, 84% of residents reported having personal experience with patients presenting with a chief complaint of SS during their residency training. However, only 48% of residents reported receiving specific education about SS, with 51% having received non-specific education about SS in the context of other skin diseases and 1% received no education.

TABLE 1.

Study Respondent Self-reported Demographic Information		
		% of respondents
Gender	Female	67.1
	Male	32.9
Age	25-34	92.1
	35-44	7.48
	45-54	0.47
Current Practice Setting	Academic/University program	85.5
	Community program	14
	Military Program	0.5
Level of Training	PGY-2	26.2
	PGY-3	36.9
	PGY-4	35.5
	PGY-5	0.9
	Recent graduate	0.5
Residency Program Size	≤5 residents	7.5
	5-10 residents	33.6
	10+ residents	58.9
Program Location	Northeast US	29.9
	Southeast US	14.5
	North Central US	20.6
	South Central US	10.8
	Northwest US	2.8
	Southwest US	13.6
	Midwest US	7
	Other	0.01

Perspectives on Sensitive Skin

Residents had disparate opinions regarding whether SS should be a unique clinical diagnosis; 31% believed SS should be a unique diagnosis rather than symptom, while 22% disagreed and 46% were unsure. A majority of residents reported the primary etiology of SS to be skin barrier alteration (69%). Other selected options included external/environmental factors (11%), immune dysregulation (8%), results/symptoms of another dermatosis (8%), primary neuropathy (1%), and other non-listed factors (3%).

Self-Reported Knowledge

Dermatology residents were asked to describe their general knowledge level on SS diagnosis, clinical evaluation, and management; aggregate results can be seen in Figure 1A. For further analysis, residents were stratified into those who had received specific education about SS, and those who had received no education or non-specific education about SS in the context of other diseases (Figure 1B). Residents who received specific education about SS were significantly more likely to report being "very knowledgeable" about SS diagnosis ($P<0.0001$), clinical evaluation ($P<0.0001$), and management ($P<0.0001$) than residents who did not receive specific education about SS. Additionally, residents who did not receive specific SS education were more likely to report feeling "not at all knowledgeable" about all 3 topics ($P<0.001$).

Approaches to SS

Residents were asked to indicate their approach to diagnosis, counseling, and management of SS patients; results are in Table 2. Residents who had received specific education on SS were more likely to gather history about allergies ($P=0.0015$) and past reactivity to skin products ($P=0.003$) compared with residents who did not receive SS education. Additionally, residents who received SS education were more likely to counsel patients to avoid common environmental triggers for SS ($P=0.01$), review a

FIGURE 1. Dermatology residents' self-reported knowledge level about sensitive skin diagnosis, clinical evaluation, and management. (A) presented in aggregate; (B) stratified by whether residents received specific education on sensitive skin.

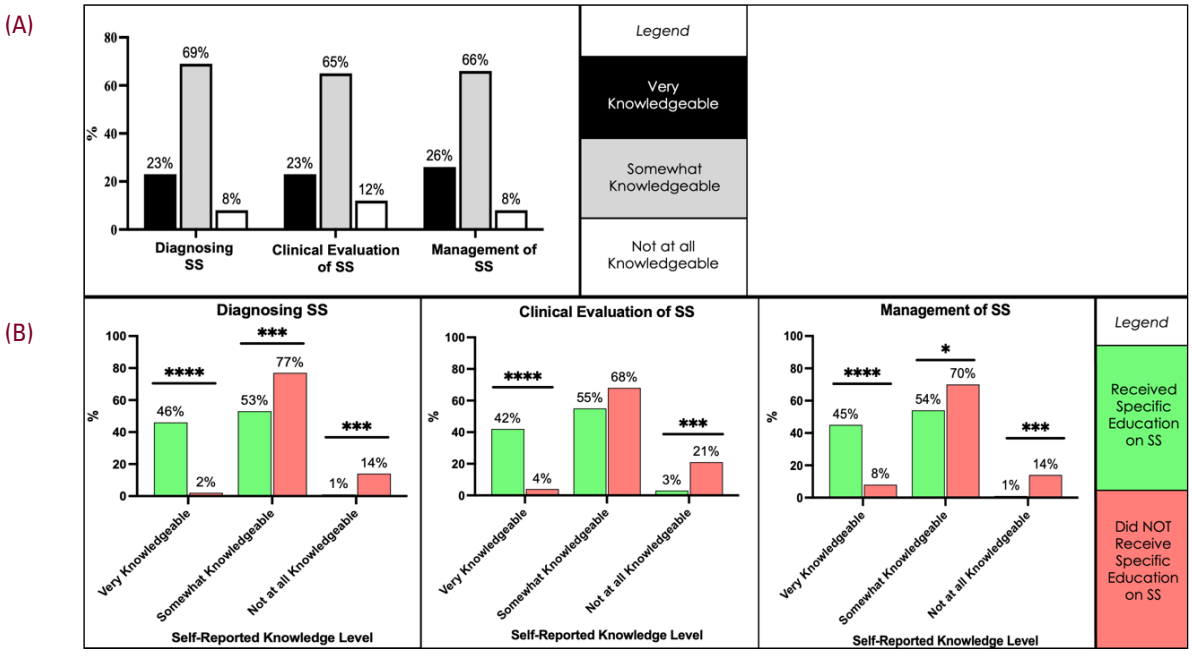
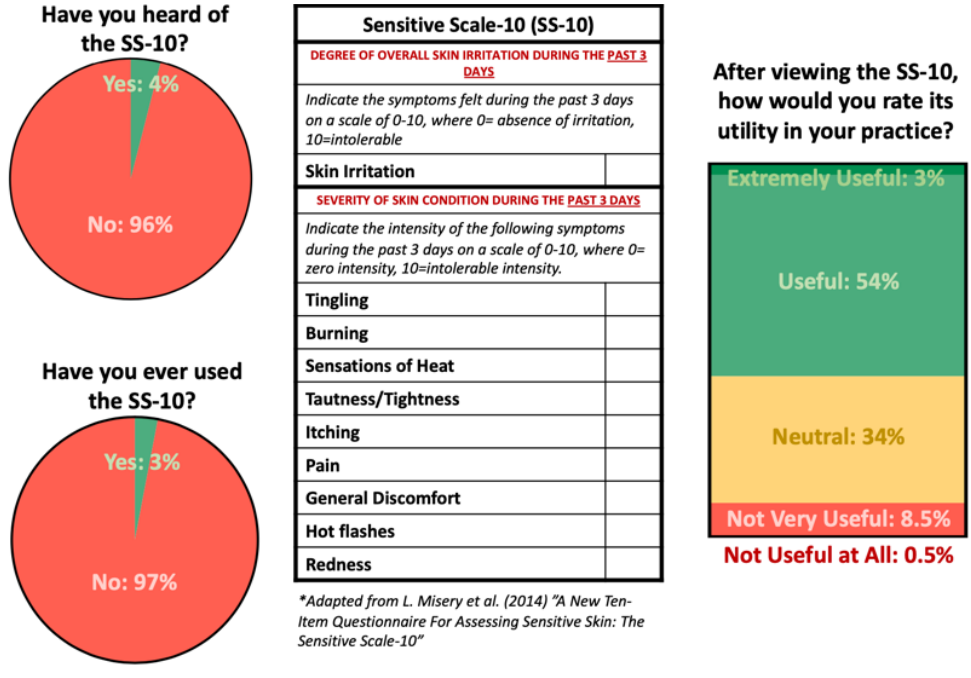


TABLE 2.

Resident Physicians' Approaches to Diagnosis, Counseling, and Management of Patients With Sensitive Skin	
Questions Asked During History-Gathering	**%**
All skin products or cosmetics a patient is currently using	87
All current and past dermatologic diseases	87
Personal history of reactivity to skin products	85
Personal history of allergy	83
All medical conditions including non-dermatologic diseases	52
Family history of sensitive skin	39
Counseling Topics	**%**
Avoidance of fragrances	93
Importance of moisturizing and maintaining skin hydration	92
Avoidance of irritating ingredients in topical formulations	91
Avoidance of common environmental triggers for sensitive skin	72
Management Strategies: Over-the-Counter (OTC) Therapies	**%**
Recommend use of OTC products formulated for sensitive skin	73
Review of all current skin products and recommending discontinuation of irritating products	71
Recommend OTC oral anti-histamines	37
Recommend use of OTC pain medications	4
Management Strategies: Prescription Therapies	**%**
Prescribe topical steroids	54
Prescribe topical immunomodulators (ex. tacrolimus, pimecrolimus)	44
Recommend patch testing	42
Recommend phototherapy or light therapy	15
Prescribe systemic immunosuppressive medications (ex. cyclosporine, mycophenolate, methotrexate)	7
Prescribe small molecule inhibitors or biologics	7

FIGURE 2. Dermatology resident physicians' experiences with and opinions on the Sensitive-Scale 10.



patient's current skin products and recommend discontinuation of irritating products (*P*=0.03), and recommend use of over-the-counter products formulated for SS (*P*=0.0007). Lastly, residents with education on SS were more likely to prescribe topical immunomodulators (*P*=0.02) and topical steroids (*P*=0.016), and to recommend phototherapy/light therapy (*P*=0.02).

Ninety-six percent of residents had not heard of the Sensitive Scale-10 (SS-10),[6] a validated scale to measure SS severity; and only 3% had used the SS-10. However, 64% of residents stated that they would use a tool or questionnaire for diagnosis or longitudinal symptom tracking of SS, and after reviewing the SS-10, 57% indicated that it would be useful in their practice (Figure 2).

Challenges

Challenges were reported with all aspects of SS patient care, including diagnosis (6%), counseling (24%), giving product recommendations (23%), prescribing/medical management (22%), and assessing improvement over time (25%). Only 29% of residents believed there was sufficient guidance for the management of SS. Of the remaining, 36% complained of a lack of guidance, and an additional 35% were unsure if guidance was sufficient. Forty percent reported that there are sufficient treatment options for patients with SS, 30% reported that there are not, and 30% were unsure.

Preferred Educational Formats and Topics

Previous SS education had occurred through formal lectures by residents (55.19%), faculty (52.83%), conference speakers (34%), or visiting speakers (26%), as well as industry presentations (41.51%). When asked about their preferred format to receive SS education, a majority of residents selected formal lectures led by faculty (80.84%). Next, residents would prefer teaching in a clinical setting (67%), visiting speakers (58%), industry presentations (39%), off-site conferences (33%), and resident-led lectures (32%). No residents indicated that they would prefer not to receive education about SS. Topics that residents were particularly interested in learning more about included product recommendations for SS (78%), counseling SS patients (77%), reviewing scientific research about SS (70%), diagnosing SS (67%), how to use the SS-10 in clinical practice (48%), and clinical research updates on SS (40%).

DISCUSSION

The survey results provide important feedback about the need for SS education during residency training; only half of dermatology residents had received specific SS education, yet nearly all agree it is an important educational topic. Currently, less than one-fourth of residents feel very knowledgeable about SS diagnosis, clinical evaluation, or management.

Residents responding to this survey described varying definitions and management strategies for SS. An expert panel designated by the International Forum for the Study of Itch defined SS to be a syndrome exclusive from other skin diseases using the Delphi consensus method: 85% of the panel agreed with this definition.[7] However in this survey less than one-third of residents reported the belief that SS was a unique condition.

Further, residents' management approaches to SS were heterogeneous. Although there is no definite consensus about SS management, a practical approach to the acute SS patient should include exclusion of primary skin diseases and discontinuation of irritating skin products.[7,8] Longitudinal SS management relies on identification/avoidance of triggers (both environmental and/or products coming into contact with skin), and daily skincare to improve skin hydration and maintain integrity of the stratum corneum.[8] In this study, residents who had received specific education on SS were significantly more likely to adhere to a majority of these recommended management steps.

Limitations of this study include response bias and our inability to verify self-reported data due to respondent anonymity. Still, these survey data support that SS should be included in residency training; residents who had received specific SS education tended to be more knowledgeable about SS and follow management approaches consistent with currently available evidence. The general lack of consensus on how best to define, diagnose, and manage SS within the field of dermatology likely contributes to the discrepancies in opinions and approaches cited in this survey of residents. A crucial intermediate step in improving SS education during dermatology residency will be to improve available evidence and bolster research on this topic.

DISCLOSURES

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ORIGINAL ARTICLE

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New Insights Into Systemic Drivers of Inflammation and Their Contributions to the Pathophysiology of Acne

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ABSTRACT

Acne Vulgaris (AV) is a prominent skin disease commonly affecting teenagers. It often persists into adulthood and is associated with adverse physical and psychosocial impacts. The pathophysiology of AV is conventionally correlated with 4 factors within and around the pilosebaceous unit: increased sebum production, follicular hyperkeratinization, *Cutibacterium acnes* proliferation, and localized immune responses. As such, conventional therapeutic approaches for AV have primarily focused on these factors. In addition to this primarily localized pathophysiology, there is a progressively emerging body of evidence indicating that underlying systemic factors contributing to a generalized immuno-inflammatory response can contribute to or exacerbate AV. In this article, we introduce and provide the supporting data, for 6 patient-centric systems that may be implicated in the development of AV: psycho-emotional stress, diet and metabolism, dysbiosis of the gut and skin microbiome, hormonal fluctuations, oxidative stress, and immune response. Identifying these pathways and their contributions in a patient-centric approach may provide expanded therapeutic opportunities for treating patients with AV.

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INTRODUCTION

Acne vulgaris (AV) is the eighth most prevalent disease globally, and a condition reported to affect at least 50 million people in the United States.[1] Because AV affects 80% of teenagers, it is generally categorized as a condition of adolescence, yet recent literature indicates that AV can affect both pre-teens and adults, with 40%-50% of women experiencing AV that occurs past the teenage years.[2-4] Physical and psychosocial sequelae associated with AV include dyschromia, scarring, poor self-image, depression, anxiety, and avoidance of social interaction.[5,6]

The pathophysiology of AV is conventionally viewed as resulting from 4 factors occurring at the pilosebaceous unit (PSU): increased sebum, follicular hyperkeratinization, proliferation of *Cutibacterium acnes*, and inflammation induced by localized immune responses.[5] Collectively, this sequence of pathophysiologic events causes marked inflammation in and around the PSU, which results in visible AV lesions and can ultimately lead to both persistent and post-inflammatory hyperpigmentation (PIH) and/or post-inflammatory erythema (PIE) and various forms of scarring.[7]

However, there is emerging evidence that many dermatologic conditions are associated with generalized underlying immune-inflammatory systemic responses. Psoriasis, once viewed and treated only as a skin disease, is now accepted as a systemic, inflammatory disease managed primarily by immunomodulatory therapies.[8] Atopic dermatitis is now approached, based on scientific evidence, as a disorder driven by a variety of pathways of inflammation, both systemic and cutaneous.[9] Hair loss and thinning, once thought of as primarily having local pathogenesis, is now accepted as a multi-factorial systemic condition with more similarities than differences across the hair loss disorder spectrum.[10]

Likewise, evidence now suggests that the localized pathophysiology of AV is not an isolated event but may be induced or exacerbated by an interconnected web of external and internal stressors propagated by various inflammatory signaling pathways.[5] Therefore, an important question to address is what systemic drivers are likely to directly contribute to the pathophysiologic development of AV occurring within and around the PSU. If we can address this question, we might then develop and provide a wider range of therapeutic options.

In this article, we use a systems-wide perspective to identify 6 relevant associations serving as contributory factors of systemic inflammation that may promote the development and/or augment the severity of AV. These include psycho-emotional stress, an unbalanced diet and metabolism, dysbiosis of the gut and skin microbiome, hormonal fluctuations, oxidative stress, and immune response. Many of these factors have long been cited as playing a role in AV through personal observation or case reports. Presently, clinical and mechanistic evidence suggests the involvement of these factors in the pathophysiology and severity of AV.[5,11] Below, we review the current literature supporting these systemic stressors and how they may drive AV lesion formation.

MATERIALS AND METHODS

Systems-Wide Pathophysiology of Acne Vulgaris

The pathophysiology of AV, whether talking about local or systemic cascades that contribute to AV lesion formation or their sequelae, begins and ends with the presence of inflammation, which is subclinical prior to the onset and after the visible resolution of active (palpable) AV lesions.[5,12] Our conventional approach to AV management, whether using topical and/or systemic medications, has been to target the 4 major pathophysiologic mechanisms that correlate with the development of AV lesions: follicular hyperkeratosis (microcomedo formation), *C. acnes* proliferation, increased sebum, and inflammation resulting from local immune responses.[12] Over time, publications on AV added to the importance of skin care and exogenous agents, and in more recent years, other considerations such as diet and the microbiome have emerged in the literature.[13-17]

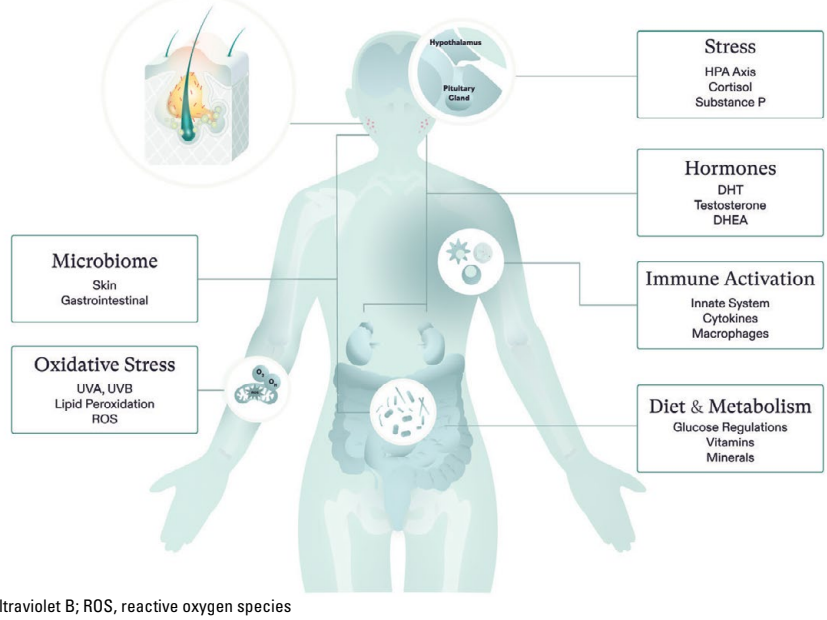
From the time benzoyl peroxide was discovered for AV in the 1960s, we had little information beyond data on how medications for AV worked until more recently.[18] In addition, more attention is being paid to development of approaches to AV management that limit or avoid antibiotic use due to the emergence of antibiotic resistance, which has widespread implications.[19,20]

In this article, the authors conceptualize beyond just the correlation of how individual medications modify pathways of AV lesion formation. Instead, a broader view of the individual affected by AV is taken, with consideration of other underlying factors that are believed to contribute to a systemic imbalance or dysregulation, all of which provide their contribution to the development of AV. Figure 1 conceptualizes 6 patient-centric factors noted to play a role in a systemic imbalance, and depicts their suggested connection to the underlying inflammation seen in AV.

The Skin Response to Psychological Stress

AV flares are often reported in association with increased stress.[21-23] Stress is a *triple-edged sword* in people with AV. It can contribute to the development of AV flares, it increases after a flare of AV, and/or "hangs overhead like a dark cloud" as many

FIGURE 1. Conceptualization of underlying patient-centric factors contributing to the development of acne vulgaris. An increase in stress severity is connected to a cutaneous inflammatory response through the release of cortisol and Substance P.[27] Hormonal fluctuations driven by androgens stimulate sebum production and pro-inflammatory cytokines.[67] Diet and metabolism of macronutrients, vitamins, and minerals affect cutaneous health.[37] Dysbiosis of the microbiome in the skin and/or gastrointestinal tract drives a systemic inflammatory response.[17] Oxidative stress from external sources (UVA, UVB) or internal sources (lipid peroxidation) leads to cellular damage from ROS.[78] Lastly, immune activation in response to these factors drives a systemic inflammatory response, leading to the development or exacerbation of acne.[60]



Abbreviations: UVA, ultraviolet A; UVB, ultraviolet B; ROS, reactive oxygen species

individuals are stressed with the anxiety of wondering when the next AV flare will occur, since most are not predictable.[22,23] A recent cross-sectional study analyzed AV severity in female medical students and found that an increase in stress severity was strongly correlated with increased AV severity.[24] In another study, job stress was associated with increased severity of AV in women.[25,26] These results truly resonate, especially as many adult women are noted to have AV that recurs or persists beyond adolescence or develop new-onset AV usually during or after their mid-twenties. Higher stress levels and having a psychologically stressful job also correlated with localized, mandibular AV in women.[25] On a physiological level, it has been reported that the skin actively responds to stress through neurotransmitters, cellular immune responses, and hormonal fluctuations.[21] The generalized stress response generated by the hypothalamic-pituitary-adrenal axis (HPA axis) releases corticotropin-releasing hormone (CRH), which is responsible for the release of androgenic and glucocorticoid hormones such as dehydroepiandrosterone sulfate (DHEA-S) and cortisol respectively, both known to play contributory roles in the development of AV lesions.[27,28] Interestingly, AV lesions from female patients were found to have significantly higher levels of CRH in the sebaceous glands compared to healthy control skin.[29]

Specifically, within the PSU, systemic stress induces a localized, cellular inflammatory response directly within the skin. Keratinocytes express receptors for pro-inflammatory neurotransmitters (ie, nerve growth factor, histamine), making them an important link for neuro-endocrine interaction at the PSU level.[30] Moreover, keratinocytes, immune cells, and mast cells are all capable of synthesizing CRH,[31] which mediates lipid synthesis within sebocytes, thus modulating the PSU lipid composition.[31] Substance P (SP), a key neuro-inflammatory mediator released during local stress and noxious stimuli, accumulates around sebaceous glands.[32] In this location, SP may induce mast cell degranulation, which can augment the perilesional inflammatory processes by increasing the expression of the pro-inflammatory mediators interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α).[32] SP has also been shown to act directly on the PSU by promoting proliferation and differentiation of the sebaceous gland and upregulating lipid synthesis by sebocytes.[32]

On a broader scale, daily stress can prolong wound healing time, believed to be an integral contributor to the resolution of AV flares, likely due to cortisol release, which can inhibit early inflammatory responses.[33] In a study of caregivers, a responsibility known to be psychologically stressful, wounds remained larger and took longer to heal compared to non-stressed controls.[34] The proinflammatory cytokine IL-1β response was impaired in the stressed caregiver group during exposure to lipopolysaccharides.[34] The involvement of IL-1β was later confirmed by studying the wound healing response in dental school students undergoing the acute stress of school exams compared to summer break.[35] IL-1β plays an important role in fibroblast chemotaxis and production of collagen, as well as immune response to foreign bodies, indicating that psycho-emotional stress can disrupt a healthy immune response, which is critical for normal wound healing.[33]

A systems-wide approach to understanding the multiple contributory factors that can drive AV development also allows us to consider the role of stress on other inflammatory cascades that impact AV. For example, chronic stress has been linked to oxidative stress in the skin, possibly through the renin-angiotensin system.[36] Angiotensin II stimulates NADPH oxidase-dependent reactive oxygen species (ROS) production in neutrophils, which also triggers the release of inflammatory mediators at the PSU, compounding the impact that stress may have in the development of AV.[36] The role of oxidative stress in the development of AV is discussed further in this review.

Diet and Metabolism

Dermatologists have long suspected a correlation between diet and AV development and/or flares, especially with excessive carbohydrate intake, high sugar-containing foods, and high dairy (milk) intake. There is now a more convincing body of evidence supporting the association between diet and AV.[15,37,38] It has been shown that a modern Western diet high in processed sugars and simple carbohydrates and low in fiber has increased the incidence of diabetes and unbalanced insulin levels, which correlates with AV severity.[38,39] A 2015 study showed that fasting insulin levels are higher in patients with severe AV than in a healthy control group.[39] Another study showed that participants who consumed a diet of low glycemic load substituted with high protein had a marked decrease in the total AV lesion counts compared to a group consuming a traditional high glycemic load diet.[38]

The modern hypothesis explaining the correlation between sugar intake and AV focuses on the glycemic load, blood glucose, insulin, and the association between insulin-like growth factors (IGFs) and cutaneous endocrine responses.[25-27] Receptors for insulin, the peptide hormone that regulates carbohydrate metabolism, and insulin-like growth factor-1 (IGF-1), an important trophic hormone that promotes bone and tissue growth, are both expressed in epidermal keratinocytes.[40] In fact, IGF-1 in patients with AV is significantly elevated compared to controls.[41] IGF-1 indirectly stimulates the nutrient sensitive kinase mammalian target of rapamycin (mTOR), which is a key regulator of cellular proliferation and lipid synthesis.[15] When activated, there is an increase in sebocyte growth and sebaceous lipogenesis, as well as increases in androgen hormone secretion.[15,42] High insulin levels also lead to altered proliferation of keratinocytes in the PSU.[15] Indirectly, low glycemic index foods also reduce free

androgens, mitigating the effects of hormonal dysregulation involvement in AV.

Besides carbohydrates and simple sugar consumption, some key vitamins and minerals may have contributory effects on the clinical manifestations and severity of AV. Zinc is a key cofactor in the regulation of protein and lipid metabolism and, specific to AV, it has been shown to be bacteriostatic against *C. acnes*, as well as reduce the pro-inflammatory cytokine TNF-α.[43] Deficiency in selenium has also been reported in AV patients.[44] Additionally, selenium supplementation has been shown to play a role in hormone regulation by decreasing the levels of the testosterone precursor dehydroepiandrosterone (DHEA) in female patients with polycystic ovary syndrome (PCOS), an endocrine disorder associated with AV as an established manifestation of androgen excess.[45] Additionally, low levels of vitamin D have been correlated with AV severity, predominantly visibly inflammatory AV lesions.[46] Supplementing with vitamin D in these patients has been noted to exhibit some improvement in the number of inflammatory AV lesions.[47] Finally, low levels of folate have been observed in AV patients.[48] Folate has many roles, but one of the most potential links to AV is its inhibitory effects on homocysteine (HCY) levels, which have been documented to be markedly elevated in patients with moderate-to-severe AV.[49] HCY degrades structural components of skin, stimulating the production and enzymatic activity of matrix metalloproteases (MMPs); some MMPs function to degrade elastin and collagen and can modulate AV lesion resolution and scarring potential.[50,51] Folate also has been hypothesized to play a role in the evolutionary adaptation to ultraviolet (UV) radiation to provide important repair mechanisms to photodamage.[52] Although the role of vitamins and minerals in AV warrants additional study, the rationale for proper supplementation based on the collective data reviewed above is well founded and can also provide other positive health benefits beyond just the skin.

The intake of essential vitamins and minerals is vital for good health, including for skin. For example, vitamin A is essential for immune activity, epithelial barrier function, and cell differentiation, but is not synthesized by the human body, so it must be consumed in amounts that are needed physiologically.[53] The correlation of oral vitamin A and its therapeutic effects for AV was first shown in a clinical study in 1942.[54] This eventually became the basis for the development of tretinoin in the 1960s and isotretinoin in the 1970s.[5,54] It has also been observed that low levels of vitamin C are associated with poor wound healing and compensatory thickening of the stratum corneum.[53] Taken together, these data suggest that appropriate levels of these and other vitamins and minerals could contribute to improving AV by supporting several of the important physiological mechanisms needed for healthy skin, with some observations more closely related to AV pathophysiology.

Skin and Gut Microbiome

Treatment of AV with systemic antibiotics has been well-established to be effective over several decades of experience and data, suggesting a bacterial component in the pathophysiology of AV.[55,56] It remains apparent that colonization with pro-inflammatory strains of *C. acnes* is a direct contributor to AV pathophysiology and reduction in these strains correlates with improvement in AV.[57] However, we recognize that *C. acnes* does not exist in a vacuum in the skin, and that there is a relationship of microorganisms within the skin microbiome, and even within the gastrointestinal (GI) tract, that can affect AV pathophysiology.[16,58] Differences in host response to strains of *C. acnes* and other microbiome changes that occur in AV may also affect AV severity.[12]

The top 4 major phyla on the skin are the same for both AV and healthy patients, with differences in diversity of some major microbes shown to correlate with individuals presenting with or without AV.[16,58,59] Moreover, the common use of topical and systemic antibiotics contributes to changes in diversity in the gut and skin microflora, allowing resistant bacterial strains to persist often over several months to years after discontinuation of antibiotic therapy.[58] The overpopulation of pro-inflammatory strains of *C. acnes* on the skin triggers several immune responses. These include stimulation of the release of inflammatory mediators (IL-17A and IFN-γ, IL-1α, IL-8, and TNF-α) through Toll-like receptors (TLR) on T lymphocytes; secretion of proteases, lipases, and hyaluronidases leading to tissue damage; accumulation of sebum due to lipogenesis by sebocytes; induction of antibacterial resistance to agents and host inflammatory cells; and contribution to AV scar formation through the release and modulation of MMPs.[12,58,60]

More recently, dysbiosis of the gut microbiome has been associated with many chronic inflammatory conditions, including AV, with 54% of AV patients reported to have marked changes showing dysbiosis in the GI tract microflora; these include a decrease in some organisms known to exhibit positive probiotic effects.[16,61,62] With >70% of the immune system reportedly found within the GI tract, the gut is an important location for many inflammatory and potentially pathophysiologic triggers.[63,64] Many factors contribute to changes in the gut microbiome, such as host physiology and genetics, antibiotic use, stress, diet, and underlying disease states.[65] Participants consuming a Western diet have been shown to often exhibit altered levels of gut microbes, highlighting the potential upstream implications of diet and metabolism on overall health, including AV development.[61,66] AV patients have been reported to have a decrease in gut microbial diversity and a loss of commensals such as *Faecalibacterium* and *Clostridiales*.[61] Dysbiosis of the gut microbiome has been linked to diminished intestinal barrier integrity (increased intestinal permeability) and increased

lipopolysaccharide endotoxins in circulation, potentially triggering a generalized inflammatory response through TLR-4 and CD14.[66] Overall, research to date supports a link between microbiome alterations, systemic inflammation, and overall health. We are in the early stages of understanding and defining details related to the microbiome, both overall and within specific body systems such as skin. Thus far, there is good evidence to show that the status of the microbiome plays an important role in maintaining overall health homeostasis and can contribute to the pathophysiology of specific disease states including AV.

Hormones

The role of the endocrine system, especially androgens, is well-established as a mandatory component in the development of AV.[67] In the 1930s, the correlation between a woman's menstrual period and AV led doctors to label AV as "chastity pustules," for which they prescribed laxatives to help rid the body of the build-up of toxins.[68] Over almost a century, our understanding of the skin and AV has come a long way, and we now know that hormones, primarily androgens, drive AV in both men and women. It is also now recognized that the skin itself is an endocrine organ, capable of synthesizing androgens, such as dihydrotestosterone, within itself.[67,69,70] A systematic review of over 1,000 studies found that testosterone and progesterone may be elevated in AV patients, but that estrogen is significantly lower in AV patients.[71] Specifically, excess circulating androgens can be associated in some patients with AV, but many exhibit normal androgen levels on blood testing, supporting the important role of local androgen production in AV-affected skin.[41,71] It has been shown that patients with AV produce higher levels of testosterone and 5α-dihydrotestosterone (DHT) in their skin than healthy individuals.[41] It is also established that the sebocytes possess all the necessary enzymes for both synthesizing androgens and for converting testosterone to DHT, making the local skin environment the primary site for androgen activity in AV in most affected patients.[71,72] DHT exerts its effects via the nuclear androgen receptor. It has been shown to directly stimulate TNF-α and IL-6, indicating a strong correlation between androgen activity in the skin and pro-inflammatory cytokine production in AV.[73,74] The hormone DHEA also regulates sebum production and has been indicated as an important target in postmenopausal women.[72] It also has been shown to be correlated with IGF-1 levels, which are higher in men and women with AV.[72] As noted above, PCOS, an endocrine disorder induced by hyperandrogenism, is characterized clinically by the presence of AV as one of the visible manifestations of androgen excess.[75]

Oxidative Stress

The skin, and particularly the face, is regularly exposed to exogenous pollutants and irritants as well as UV radiation and ozone, leading to an accumulation of reactive oxygen species (ROS).[76] These ROS, which are highly reactive and unstable chemical entities, have been shown to accelerate adverse skin changes including the appearance of aging and pigmentation, roughness, and wrinkles.[76]

Clinical evidence also indicates that oxidative stress may play a role in AV.[77] Biomarkers for lipid peroxidation, such as blood serum levels of malondialdehyde (MDA), are significantly higher in patients with AV than in their controls.[78] Enzymes with antioxidant capacity such as catalase, superoxide dismutase, and total antioxidant capacity are also significantly lower in patients with AV compared to controls, likely reflecting their consumption, at least partially, by interacting with ROS exposure with inadequate reserve.[78] Accumulation of lipid peroxide (LPO) and sebum oxidation are also higher in comedones of patients with AV than from the facial stratum corneum.[79] In addition to LPO, the inflammatory mediators IL-1α and NF-κB were also found to be higher in comedones, indicating a potential link between oxidative stress, inflammation, and AV lesion formation.[79]

On a mechanistic level, both intrinsic and extrinsic stressors can be a source of ROS generation: as a normal byproduct of mitochondrial metabolism; chronic psychological stress; environmental pro-oxidant factors including UVA, UVB, visible light, and infrared light exposure; and ozone exposure.[76,80] ROS due to these stressors include superoxide radicals, hydrogen peroxide (H2O2), hydroxyls, singlet oxygens, peroxyl radicals, and nitric oxide (reactive nitric species).[81] Our intrinsic antioxidant defense system is responsible for scavenging ROS and neutralizing them.[81,82] This system includes enzymatic antioxidants, such as superoxide dismutase and catalase; non-enzymatic antioxidants such as glutathione, and vitamins C and E; and transcriptional activation of inflammatory responses in the follicular epithelium.[80,83]

Over time, and with overwhelming exposure to ROS sources, accumulation of ROS leads to oxidative damage to cellular components such as proteins, lipids, nucleic acids, and the cell membrane.[80] Lipid peroxidation of the cell membrane, if subtoxic, may trigger repair mechanisms through antioxidant defense or signaling pathways that are adaptive.[80] Otherwise, when the oxidative stress overwhelms the capacity of the cell to repair, it will trigger cellular damage, with functional impairment and sometimes necrosis, contributing directly to skin senescence.[80] There are a few ROS-generating pathways specifically implicated in AV. Accumulation of neutrophils at the site of comedones leads to an increase in the generation of ROS.[77] *C. acnes* has also been shown to induce neutrophil secretion of ROS.[77]

Lipid peroxidation, the oxidative degradation of lipids, is an important mechanism involved in the pathophysiology and progression of AV.[80] Indeed, lipid peroxides, the chemical product, are higher in comedones of patients with AV and have been shown to affect keratinocyte proliferation and

stimulate pro-inflammatory cytokine release.[79,80] They also bind to the peroxisome proliferator activated receptor-gamma (PPAR-γ), triggering the production of lipids from sebocytes.[84] Activation of PPAR-γ has also been shown to be involved in androgen-mediated signaling and regulation of glucose and lipid metabolism, once again suggesting cross-talk between many potential pathophysiologic cascades in the development of AV.[74] Interestingly, these links on cursory review appear to be unrelated and involve distinctly different body systems and functions, however, cross-talk that can affect pathophysiology has been identified.

Immune Function

Immunologic responses, both local and systemic, have become progressively recognized as important in AV pathophysiology. Studies suggest that *C. acnes* can trigger immune responses in AV through multiple, direct pathways.[12,60] A primary immune response occurs through interaction with specific TLRs, which are innate pattern recognition receptors, expressed on numerous cell types present within the skin, such as keratinocytes, sebocytes, dendritic cells, lymphocytes, mast cells, and resident macrophages.[60] The innate immune system also responds to *C. acnes* proliferation and cellular interactions through inflammasomes — receptors that induce inflammation in response to microbes, and by stimulating antimicrobial peptide (AMP) activity, small molecules that have a wide range of inhibitor effects against bacteria, fungi, parasites, and viruses, but can respond in disease states such as AV that involve a pathogenic commensal organism.[60] Finally, *C. acnes* induces the production of MMPs, which are zinc-dependent protease enzymes that can degrade many structural components of the extracellular skin matrix, with involvement in modulation of AV-affected skin including potential scarring.[60,85]

Subclinical inflammation of the skin begins early in the development of AV.[12,74] Based on data evaluating the sequence of AV lesion formation, perilesional lymphocyte accumulation with the recruitment of inflammatory mediators is thought to precede or occur simultaneously with follicular hyperkeratinization (microcomedone formation) in the PSU. In vitro studies show that the application of pro-inflammatory cytokines such as IL-1 on PSU induces hyperkeratinization.[85] In addition, other pro-inflammatory cytokines such as TNF-α and interleukins such as IL-8 have been shown to be higher in AV lesions compared to uninvolved skin, suggesting that many cytokines and other mediators contribute collectively to the development of AV lesions.[86]

Beyond the direct involvement of the immune-inflammatory response at the PSU, other noxious stimuli indirectly trigger heightened immune responses. Oxidative stress causes direct and immunologic cellular damage.[77] Microbiome dysbiosis can activate the innate immune system to defend from proliferation of pathogenic microbial organisms.[65] High glycemic index diets and insulin fluctuations can induce a generalized inflammatory response, and stress can promote a heightened immune response on both local and systemic levels.[36,42] DHT upregulates sebaceous lipid formation and pro-inflammatory cytokine production (ie, TNF-α, IL-6) by sebocytes on the PSU, supporting a link between hormonal interactions and an immune-inflammatory response.[71] Once activated, many inflammatory mediators such as TNF-α, IL-6, SP, and TGF-β, are expressed, generating "a pro-inflammatory soup" at the PSU.[27] With this, neutrophils are recruited to the site of inflammation, further damaging the sebaceous gland and follicular epithelium.[27] This follicular wall damage causes porosity within the wall structure, resulting in leakage of follicular contents into the surrounding dermis which induces both direct and indirect inflammation, even in the absence of obvious follicular wall rupture.[12]

CONCLUSION

The underlying causes of AV have conventionally focused on the major individual pillars of pathophysiology and how individual medications can mitigate these pathways to improve AV. In this article, this prior approach is not discarded. Rather, there is a strong suggestion, with good underlying support, to integrate a more comprehensive management approach to include other underlying systemic factors, many of which are likely to relate directly to AV. In this review, we have identified the 6 major underlying patient-centric factors: psycho-emotional stress, diet and metabolism, hormonal fluctuations, microbiome dysbiosis of the skin and gut, oxidative stress, and immunologic responses. Each of these contributes to an overall generalized dysregulation that includes a variety of immunologic and inflammatory responses, with many believed to contribute to the development and/or exacerbation of AV. This broadened perspective on AV management allows for a more expanded therapeutic approach, beyond only the long-standing conventional method of matching medications with what visible AV lesions are present, coupled with good general skin care.

As a second part of this review, Burgess et al[87] will present supporting clinical evidence for various ingredients to address these 6 underlying patient-centric factors.

DISCLOSURES

Dr Del Rosso and Dr Harper are clinical investigators for Nutraceutical Wellness LLC but have not received compensation or services for any aspect of the submitted work. Dr Farris is a paid advisor for Nutrafol and Nutraceutical Wellness LLC. Dr Baldwin declares no conflict of interest. Dr Hazan and Dr Raymond are employees of Nutraceutical Wellness LLC.

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CASE REPORT

Journal of Drugs in Dermatology

Atopic Dermatitis as a Paradoxical Reaction to Secukinumab in a Patient With Plaque Psoriasis

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ABSTRACT

Paradoxical reactions to biologic agents used in the treatment of psoriasis are rare but have been reported with tumor necrosis factor (TNF) blockers and, more recently, with interleukin (IL)-17A inhibitors. Secukinumab, an IL-17A inhibitor, is an effective treatment for moderate-to-severe plaque psoriasis but has been implicated in the development or exacerbation of eczematous-like reactions in rare cases. We present a patient with a history of plaque psoriasis who developed an eczematous eruption after four months of secukinumab therapy, necessitating systemic intervention for adequate control. Five months after a loading dose of dupilumab, the patient appeared in the clinic with the return of classic, thick psoriatic plaques, affecting 15% body surface area (BSA). The patient declined further treatment and was subsequently lost to follow-up despite multiple attempts to contact her. This case adds to the limited, but growing body of knowledge on IL-17 blocker-induced eczematous reactions and underscores the need for careful monitoring and prompt recognition of this adverse event in patients receiving this class of drugs.

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INTRODUCTION

Paradoxical reactions refer to unexpected adverse events that occur during or after treatment with a medication that is contradictory to the medication's intention. In dermatology, these reactions have been observed with various systemic therapies, including biologic agents used to treat psoriasis. While tumor necrosis factor (TNF) blockers are most commonly associated with paradoxical reactions, more recent biologics, such as interleukin (IL)-17A inhibitors, have also been implicated. Although effective in treating moderate-to-severe plaque psoriasis, secukinumab, an IL-17A inhibitor, has been reported to cause the development or exacerbation of eczematous-like reactions in rare cases.[1] The appearance of these reactions is poorly understood and not well-documented in the literature. In this report, we present the case of a patient with a history of plaque psoriasis who developed an eczematous eruption after secukinumab therapy. Our case underscores the importance of recognizing paradoxical reactions and addressing the limited knowledge surrounding their mechanism and management.

CASE

A 45-year-old female with plaque psoriasis on four months of secukinumab therapy presented via teledermatology with an intensely pruritic, 10-day-long rash on the forearms, trunk, and legs. On exam, there were erythematous, crusted papules coalescing into eczematous plaques on the trunk and extremities, particularly severe on the volar surfaces. She was prescribed

FIGURE 1. Eczematous eruption with impetiginization post treatment with secukinumab on the right axilla (A), left axilla (B), left arm (C), and medial arms (D).

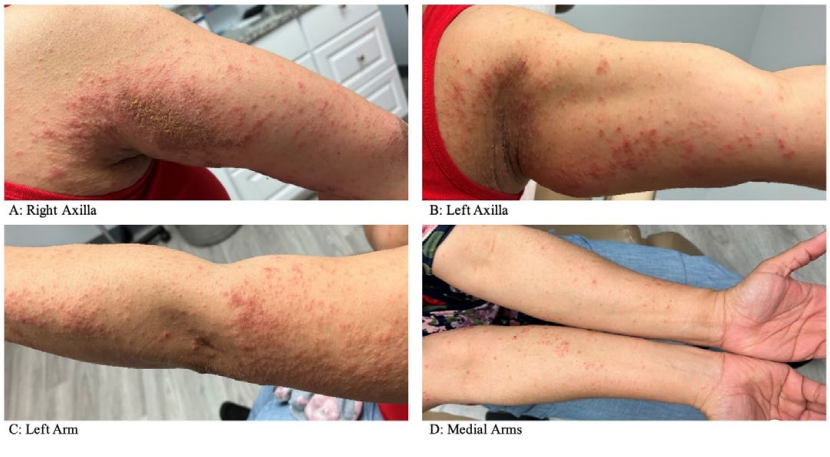
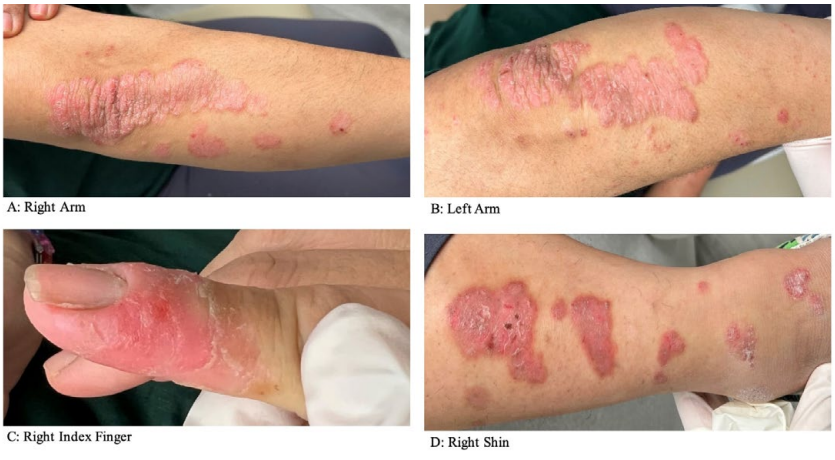


FIGURE 2. Psoriatic eruption post dupilumab on the right arm (A), left arm (B), right index finger (C), and right shin (D).



a 10-day course of prednisone along with topical clobetasol. Subsequently, she presented 4.5 weeks later with impetiginized eczematous plaques involving the skin flexures (Figure 1 A-D). The patient also had generalized erythematous papules on her abdomen and upper and lower extremities, suggestive of an autoeczematization reaction. Two punch biopsies demonstrated spongiotic dermatitis consistent with a dermal hypersensitivity to a systemically administered medication, and cultures collected were positive for MSSA. After 1.5-weeks of a 60 mg prednisone taper, oral doxycycline, topical corticosteroids, and topical mupirocin, she was significantly improved and transitioned to topical therapy. The patient subsequently experienced a severe flare of atopic dermatitis, which occurred after a COVID-19 infection and was started on dupilumab and topical ruxolitinib.

Interestingly, 5 months after the loading dose of dupilumab, the patient appeared in the clinic with classic, thick psoriatic plaques covering her trunk and extremities, affecting 15% BSA (Figure 2 A-D). She was restarted on secukinumab, as those were the only samples available in the office, but with the plan to transition to an IL-23 agent, JAK inhibitor, or methotrexate. The patient declined treatment with either methotrexate or a JAK inhibitor out of concern for their safety profiles and was subsequently lost to follow-up despite multiple attempts to contact her.

DISCUSSION

Though psoriasis and atopic dermatitis (AD) are both common inflammatory skin conditions, their immune profiles exhibit differing T-cell polarity and cytokine activation.[2] Under the current disease model, psoriasis is driven by endogenous activation of the Th17 pathway.[2] This understanding paved the way for IL-17 blockers, such as secukinumab, to emerge as effective therapeutic interventions. Conversely, atopic dermatitis is linked to Th2 activation associated with elevations in IL-4 and IL-13,[2] making IL-4 blockade a potent treatment.

Though rare, paradoxical reactions have been reported in patients taking biologics for psoriasis, especially with the TNF blockers. The most commonly reported reaction associated with IL-17 blockers is an eczematous eruption. These reactions typically occur within 4 months of initiation of the biologic,[3] as was the case with our patient. Though the mechanism for these eczematous reactions is poorly defined, disruption of the cytokine milieu is a suggested theory.[3] It proposes that inhibition of the Th17 pathways results in polarizing toward Th2 activation and invigoration.[3] Cohen et al argue that paradoxical reactions are immunologically distinct from the dermatoses they mimic. Based on mRNA in situ hybridization studies, they suggest that the underlying immunologic process persists in the background of the skewed T-cell polarization so that both immune axes may be active concurrently.[4] Furthermore, genetic polymorphisms in AD genes may explain why certain individuals are more susceptible to these biologic-induced eczematous reactions.[3]

Though previous reports have attempted to elucidate the IL-17 blocker-induced paradoxical AD reaction in psoriasis patients, there have been a relatively limited number of cases and there remains a knowledge gap. In a systematic review, Messina et al. reported that eczema and eczematous-like reactions occurred with a prevalence of 3.8% from pooled data from 23 studies on secukinumab.[5] Burlando et al reported a case of a mild paradoxical AD reaction to secukinumab. The condition was responsive to secukinumab discontinuation, but psoriasis recurred after a period of clinical remission requiring topical treatment.[6] Mendez Roncada et al reported a case of severe paradoxical AD on secukinumab, which was successfully controlled with cyclosporine.[7] However, these paradoxical AD reactions remain poorly characterized and may be underreported.

Our case study highlights a severe paradoxical reaction to secukinumab, necessitating systemic intervention for adequate control. Additionally, the patient experienced a relapse of moderate plaque psoriasis after a period of clinical remission. Our case report adds to the growing body of information on IL-17 blocker-induced eczematous paradoxical reactions. However, further studies are needed to fully characterize the disease process, and the disease prevalence, and to identify potential risk factors. As more cases of this reaction are reported and analyzed, clinicians should remain aware of this rare but potential adverse event.

One limitation of our study is that the patient received a 10-day course of oral corticosteroids before presenting with the more severe impetiginized eczematous eruption. Of note, she did not develop pustular psoriasis, which is a potentially serious complication of treating psoriasis patients with prednisone. However, oral corticosteroids are associated with provoking flares of both psoriatic disease and eczematous disease. Thus, it is unclear whether our patient would have developed a severe enough eczematous reaction to require dupilumab had she not received the oral corticosteroids.

DISCLOSURES

Melissa P. Zundell has no disclosures. Roselyn Stanger has no disclosures. Alice B. Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and Xbiotech and has received research/educational grants from AnaptypsBio, Moonlake Immunotherapeutics AG, Novartis, Bristol-Myers Squibb, and UCB Pharma, (all paid to Mount Sinai School of Medicine).

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CASE REPORT

Journal of Drugs in Dermatology

Sarecycline as a Potential Treatment for Steroid-Induced Rosacea/Perioral Dermatitis: A Case Report

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INTRODUCTION

Steroid-induced rosacea (SIR), also known as perioral dermatitis, is a withdrawal phenomenon that can occur following prolonged use of topical steroids on the face, especially with higher potency corticosteroids. This condition presents with symptoms similar to those of rosacea, which is characterized by the appearance of erythema, telangiectasia, and pustules. This is thought to be due to the steroid induced epidermal atrophy, rebound inflammation, vasodilation, and proinflammatory cytokine release, resulting in steroid rosacea. Although conventional treatments, such as topical antibiotics, second generation tetracycline antibiotics (eg, doxycycline), and antihistamines, are commonly used, SIR can still be challenging to manage.[1] Novel therapeutic approaches are needed to address this condition. We report a case of a patient with reactive steroid rosacea who experienced significant improvement with the third-generation tetracycline, sarecycline.

CASE REPORT

Our patient, a 54-year-old woman, was taking clobetasol steroids periodically for 15 years due to itchy dry patches on her scalp. On examination, the patient exhibited red papules and pimples with scales on her face that were accompanied by scaling, peeling, and a waxy texture (Figure 1). The patient was not currently on medications but had previously used tacrolimus, ketoconazole, and clobetasol. After her diagnosis of steroid rosacea, she was recommended to stop all steroids, start ruxolitinib cream twice daily, and if improvement, start laser therapy for erythema. After almost one month of no improvement, sarecycline was added to the current regimen. One month later the patient showed significant improvement with less inflammation, however, the skin was still spotty and not smooth (Figure 2). Upon continuing sarecycline for one more month the patient's face was clear of perioral dermatitis.

FIGURE 1. Right face, (a) before, (b) after.

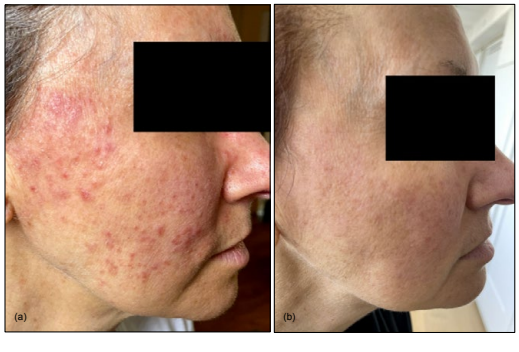
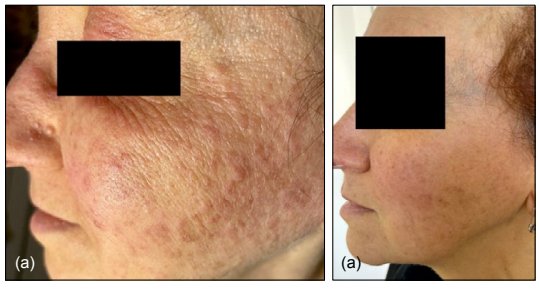


FIGURE 2. Left face, (a) before, (b) after.



DISCUSSION

Steroid-induced rosacea is a well-recognized adverse effect of long-term topical or systemic steroid use, which paradoxically induces proinflammatory gene expression, leading to rebound inflammation upon discontinuation. Furthermore, steroid rosacea has been associated with a dysregulated skin microbiome enriched with Propionibacterium acnes (*P. acnes*).[2] In the present case report, we describe a patient with treatment-refractory SIR who achieved significant improvement with sarecycline, a novel third-generation tetracycline-class antibiotic. Sarecycline's potent activity against P. acnes likely contributed to the suppression of the dysbiotic microbiome, whereas its anti-inflammatory properties may have mitigated the rebound inflammation by modulating the upregulated immune response.[3] Additionally, sarecycline's narrow spectrum of antibacterial activity yields a lower side effect profile than standard protocol broad spectrum antibiotics as it leaves most of the beneficial bacteria unaffected.[4] These findings suggest that sarecycline may represent a promising therapeutic option

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for steroid-induced rosacea. However, further studies are warranted to confirm the efficacy and safety of this antibiotic in this population.

CONCLUSION

This case report is novel in that it demonstrates effective therapy for patients with SIR by sarecycline, a third-generation tetracycline antibiotic. SIR is a refractory disease that can be hard to manage effectively. This patient had refractory SIR resistant to all standard treatment protocols and showed significant improvement with sarecycline. This third-generation tetracycline was efficacious in treating SIR with a lower side effect profile than doxycycline, the previous generation tetracycline. Further investigation of the efficacy and safety of sarecycline in the treatment of patients with SIR, particularly for those for whom the condition has been more long-standing, is warranted.

DISCLOSURES

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CASE REPORT

Journal of Drugs in Dermatology

Atypical Dyschromia in Skin of Color

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ABSTRACT

Dyschromia is a concern for many patients, especially persons of color. Postinflammatory hypopigmentation and depigmentation can affect all skin types; however, it is more apparent in those with darker skin. Some members of the dermatology community may not comprehensively understand the mechanisms of these reactions and the extent of the psychosocial effect they have on persons of color. Skin of color patients experiencing a decrease or loss of pigmentation are left with few treatment options, with no available evidence-based treatment established from a sufficient sample size. Several diseases may present with hypopigmentation and/or depigmentation despite this not being a major criterion for these conditions, including atopic dermatitis, lichen planus, discoid lupus erythematosus, polymorphous light eruption, and scleroderma. Here, we present three cases of atypical dyschromia in skin of color to highlight the underlying hypo- and depigmentation that may present with active disease and persist despite appropriate treatment.

Practice Points
1. These cases foreground the potential for a range of dermatologic conditions to result in atypical pigment changes in persons of color.
2. Postinflammatory hypopigmentation or depigmentation may persist in skin of color despite the regression of active disease.

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INTRODUCTION

Dyschromia is often the result of an external or internal insult to the skin.[1] It is a concern for many patients, especially persons of color.[2,3] In black patients, dyschromia is a common diagnosis and substantially affects their quality of life.[2-4] Current literature focuses on post-inflammatory hyperpigmentation and treatment options. However, literature on etiologies of secondary hypopigmentation and depigmentation is sparse.[1] Hypopigmentation and depigmentation can affect all skin tones; they are more apparent in darker skin.[1] Literature suggests several diseases that may present with hypopigmentation and/or depigmentation despite this not being a major criterion for these conditions.[5-11] Inflammation associated with atopic dermatitis (AD) may result in hypopigmented change and has been reported in several cases.[5-7] There have been three reports of lichen planus (LP) presenting in skin of color as hypopigmented macules.[8] Hypopigmentation is unusual for LP as it presents classically with hyperpigmentation.[8] Discoid lupus erythematosus (DLE) often presents with erythema, induration, and follicular plugging.[9] Presentation of DLE as depigmentation has been reported in seven cases and remains a rarely reported occurrence.[9-11] Similarly, scleroderma-associated depigmentation has also been reported.[12-15] Here, we present three cases of atypical dyschromia in skin of color to highlight the underlying hypo- and depigmentation that may present with active disease and persist despite appropriate treatment.

Report of a Case of Depigmentation From AD

A 66-year-old African American woman presented to our clinic for a complete body examination of AD. She reports that her AD started around age 52 at menopause, with itching on the legs. Her AD worsened in the past 2-3 years and was particularly bothersome in the summer. She had been treated previously at an outside dermatology office and had tried Dupilumab for a short time; she developed a rash and stopped this medication. She had also tried ultrapotent topical steroids, and topical calcineurin inhibitors, none of which controlled her pruritus or outbreaks.

Pertinent findings on skin exam included lichenified scaling hyperpigmented plaques on the upper arms from the upper arm to the wrists. The anterior shins showed severe lichenification and hypopigmented linear vertical plaques. Her presentation was consistent with severe atopic dermatitis. She was started on Methotrexate systemically which gave her improved control of her pruritus and atopic flares. On subsequent visits, depigmentation was persistent on her shins despite improved control of her disease (Figure 1).

FIGURE 1. Case of depigmentation from AD, in the shins of a 66-year-old African American female.

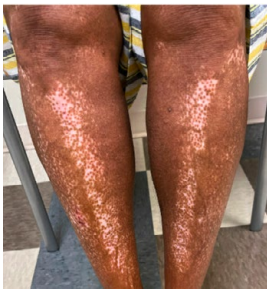


FIGURE 2. (A, B) Case of hypopigmentation from polymorphous light eruption in the arms of a 52-year-old African American female. (C) Trichoscopy showing hypopigmentary progress from polymorphous light eruption in the arms.

(A) (B) (C)

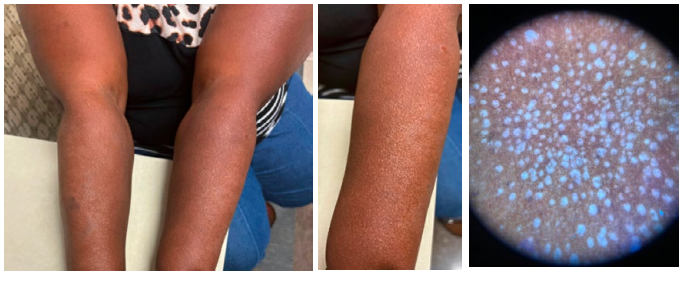
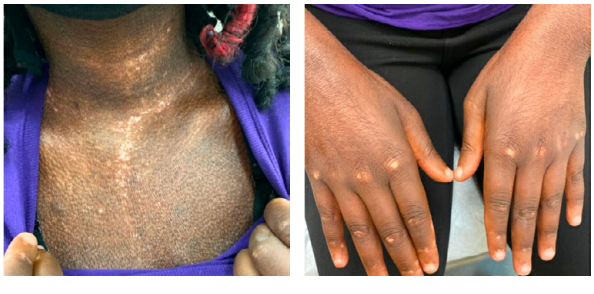


FIGURE 3. Case of depigmentation from scleroderma in the chest (A) and hands (B) of a 19-year-old African American female.

(A) (B)



Report of a Case of Hypopigmentation From Polymorphous Light Eruption (PMLE)

A 52-year-old African American woman presented to our clinic with a new pruritic rash on her forearms. The rash started three months prior to presentation. According to her report, sun exposure and high temperatures seemed to worsen the eruption. She had no relevant past medical history and an unremarkable complete review of systems. On skin examination, there were small hypopigmented 1-2 mm- shiny papules on bilateral dorsal forearms extending into dorsal hands (Figure 2). Given the history of worsening with sun exposure, a diagnosis of PMLE was made. On trichoscopy, a hypopigmentary process was observed. The patient was started on midpotency topical steroid cream for her rash in a tapering fashion. Sun protection with sun protective clothing and inorganic tinted sunscreen was recommended.

Report of a Case of Depigmentation From Scleroderma

A 19-year-old African American woman presented for evaluation and treatment of a scleroderma diagnosis made one year prior by rheumatology. She reported dry skin and tried ceramide-containing moisturizer without improvement. She stated that her chest and back were the worst areas. She had not tried prescription medication for this concern at the time of presentation. She was taking hydroxychloroquine for maintenance of her systemic symptoms. She was also treated with systemic corticosteroids and intravenous immunoglobulin for her systemic disease without improvement in her skin complaints. Her physical exam was significant for diffuse hyperpigmented ichthyotic and asteatotic plaques over the back and chest. Tightening of the skin and hypopigmentation in areas of the chest and fingers were also observed (Figure 3). Tapering of the fingertips was noted. Her condition was consistent with scleroderma. The patient was initiated on topical ammonium lactate moisturizers and topical calcineurin inhibitors for the diffuse plaques on the chest and back.

DISCUSSION

Dyschromia in skin of color is common and one of the most frequent chief complaints in dermatology for persons of color.[2,3] Possible mechanisms for secondary hypopigmentation include melanocyte loss and decreased melanin production.[1] Ruiz et al proposed a theory, 'individual chromatic tendency,' that relates post-inflammatory hypopigmentation to genetic factors, where specific individuals have "weak" melanocytes that are easily affected by inflammation.[16] The first case discussed demonstrated hypopigmentation in the setting of AD and progressed to depigmentation, an atypical form of dyschromia from AD. The persistence of the dyschromia despite improvement in activity of disease suggests that the expectation of complete repigmentation, even with appropriate treatment, may not be fulfilled. Hypopigmentation from PMLE is not well documented in the literature; the second case discussed here indicates that the inflammatory process associated with PMLE can lead to a change in pigmentation, as indicated by the physical exam and underscored elegantly by dermoscopy. This description may help to clarify the diagnosis if this pattern of hypopigmentation or depigmentation is observed. Case three discusses an unusual presentation of scleroderma with associated depigmented patches on the chest and hands. Again, recognition of this pattern of depigmentation may help to delineate the scleroderma diagnosis if other diagnoses are being considered.

Research is limited on treatment options for hypopigmentation and depigmentation in skin of color.[15] Treatment recommendations focus on the identification and treatment of the primary disease process.[15] Cosmetic topical and procedural therapies are also available.[15] Two studies reported moderate to excellent repigmentation in skin of color patients treated with topical Psoralen + ultraviolet light A.[17,18] Reszko et al reported complete repigmentation in an African American male with post-inflammatory hypopigmentation using 17 treatments of Q-switched Ruby Laser.[19] However, this has not been reported in a large number of skin of color patients and could lead to worsening of dyschromia in patients with dark skin.

Postinflammatory hypopigmentation and depigmentation remain a challenge faced by patients and providers. The impact of this process is more apparent in those with darker skin. Some members of the dermatology community may not comprehensively understand the mechanisms of these reactions and the extent of the psychosocial effect they have on persons of color. Skin of color patients experiencing a decrease or loss of pigmentation are left with few options for treating this process, with no available evidence-based treatment established from a sufficient sample size.

DISCLOSURES

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CASE REPORT

Journal of Drugs in Dermatology

Neoadjuvant PD-1 Inhibitors: A Tale of Two Cases

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ABSTRACT

Treatment responses for locally advanced cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC) are often short lived and are marred with recurrences. The introduction of adjuvant PD-1 inhibitors has demonstrated significant improvement in both, response rates, and duration of response. For patients with high-risk resectable disease, adjuvant treatments have not demonstrated an ability to reduce recurrence risk. However, there is an opportunity in the neoadjuvant setting to alter recurrence risk. Here we demonstrate two cases of neoadjuvant treatment of cSCC and MCC with impressive results.

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INTRODUCTION

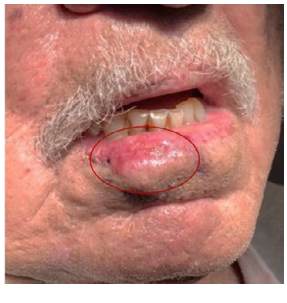
The use and implementation of PD-1 inhibitors are revolutionizing cancer treatment. This is evident in the treatment of metastatic Merkel cell carcinoma (MCC) and squamous cell carcinoma (SCC). Metastatic MCC has been amenable to chemotherapy, however, the duration of response is short, 4 to 15 months.[1] Advanced SCC that is not amenable to surgery or radiation has typically been treated with platinum-based regimens or epidermal growth factor receptor antibodies. Unfortunately, the treatment responses to these regimens are often brisk and plagued by recurrences.[2] With response rates upwards of 50% and durability of responses lasting 6 to 24 months, it is easy to see how PD-1 inhibitors have become the leading treatment for advanced SCC and MCC.[3,4]

For patients with high risk resectable MCC and SCC, there are currently no approved, effective adjuvant treatment options to reduce the risk of recurrence. Therefore, neoadjuvant treatment is the only current opportunity to alter recurrence risk. The early clinical trials are yielding impressive results which may alter our future treatment of these difficult malignancies.[5,6] Here we present a case series of neoadjuvant PD-1 inhibitors.

CASE 1

In March 2021, an 85-year-old male noticed an enlarging lesion on his right inferior lip. Subsequently, he noticed enlarging lymph nodes on the right side of his neck which prompted him to seek advice from his primary care physician. The lip lesion was biopsied and pathology was compatible with MCC. In May 2021, the patient was referred to medical oncology, where the palpable lymph node underwent fine need aspiration (FNA), and a positron emission topography/computed tomography (PET/CT) scan was performed. The FNA confirmed metastatic MCC and the PET/CT scan demonstrated uptake in the lip, right-sided cervical lymph nodes, and unknown left-sided cervical nodes. No distant foci were demonstrated. The patient was diagnosed with stage IIIB disease (Figure 1).

FIGURE 1. Merkel cell carcinoma of the right lower lip upon initial evaluation.



Treatment options were discussed and the patient was agreeable to off label neoadjuvant therapy with one cycle of nivolumab followed by Mohs micrographic surgery (MMS), lymph node dissection, and adjuvant radiation therapy.

The patient received one cycle (480 mg) of nivolumab one week after his initial visit and was scheduled for MMS 3 weeks later. A Repeat PET scan prior to surgery demonstrated a marked reduction in size and metabolic activity at all sites of disease. Clinically, the lip area appeared considerably smaller (Figure 2). Histopathologic examination of the first MMS layer showed inflammation with no residual tumor. Lymph node dissection

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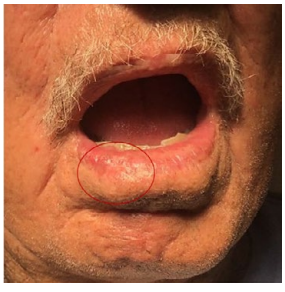
FIGURE 2. Merkel cell carcinoma of the right lower lip, 3 weeks status post nivolumab.



by the surgical oncologist also demonstrated a complete pathologic response. The patient has had no sign of recurrence at 12 months and his response is ongoing.

CASE 2

In July 2019, a 78-year-old male had MMS for a 3 cm invasive SCC on his right frontal scalp. In December 2020, the patient noted an enlarging mass in his R upper cervical neck and was promptly seen for follow up by his dermatologist. The patient was sent for an ultrasound guided FNA biopsy, which was diagnostic for metastatic SCC. A follow-up PET/CT scan demonstrated a hypermetabolic 2.8 cm lymph node posterior to the right parotid gland in the right upper cervical neck. In February 2021, the patient then underwent a modified radical neck dissection which demonstrated a 4 cm mass involving at least 3 lymph nodes that were positive for metastatic poorly differentiated SCC. The patient subsequently started adjuvant radiation but refused to complete therapy due to side effects.

The patient returned the following August with an enlarging lesion anterior to his right ear and complete right sided facial paralysis. An FNA of the parotid nodule was confirmatory for recurrent squamous cell carcinoma. Magnetic resonance imaging (MRI) demonstrated encapsulation of the right facial nerve, (Figure 3) PET/CT demonstrated no other foci. After a multidisciplinary discussion, it was decided that the patient would undergo two cycles (400 mg) of pembrolizumab, 6 weeks apart, and then undergo resection of the mass.

FIGURE 3. Magnetic resonance imaging demonstrating cSCC infiltration into the right facial nerve.

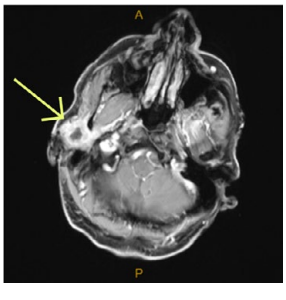
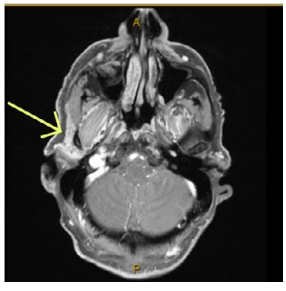


FIGURE 4. Magnetic resonance imaging 5 weeks post-pembrolizumab demonstrating resolution of cSCC infiltration.



At follow-up after the first dose of pembrolizumab, the patient reported resolution of the right-sided mass and significant improvement of his right sided facial paralysis. The patient continued treatment and received an MRI approximately 5 weeks after completing neoadjuvant therapy demonstrated complete resolution (Figure 4). At follow-up after MRI, the patient's facial paralysis had completely resolved. The patient and multidisciplinary team decided to forego surgery and continue pembrolizumab for one year. The patient has not demonstrated any sign of recurrence for 9 months.

DISCUSSION

These cases demonstrate the real-world efficacy of neoadjuvant use of PD-1 inhibitors in the setting of advanced resectable MCC and SCC. The patients in these cases showed significant responses and when defined by RECIST criteria, case 1 had complete pathologic response, and case 2 had complete radiographic response. The importance of these responses should not be understated. There are multiple studies now that demonstrate the positive correlation between the systemic response to neoadjuvant PD-1 inhibitors and favorable long-term outcomes.[7]

The response to systemic therapy should not be the only favorable outcome. Changes in treatment plans that improve the patient's quality of life must also be considered. In case 1, only one layer of MMS was taken with a straightforward repair and excellent functional and cosmetic outcomes. In case 2, the patient was spared from undergoing surgery that would have resulted in the sacrifice of his facial nerve and ipsilateral facial paralysis. Therefore, neoadjuvant can reduce surgical morbidity, while also potentially reducing the risk of recurrence.

As with all medications, there can be adverse effects, however, in these two patients, no ill effects were noted. In previous clinical trials with PD-1 inhibitors, the most common adverse reactions were lichenoid and spongiotic dermatitis, pruritus, asthenia, and fatigue.[6] More severe adverse events have a wide range from colitis to skin infections.[4,6] However, PD-1 inhibitors are generally well tolerated and were demonstrated to be in this case series.

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In conclusion, the implementation of systemic immunotherapies may have a profound effect on our treatment strategies in the future, decreasing the size of inoperable tumors eliminating some tumors outright, and giving patients lasting durable responses.

DISCLOSURES

The authors have no conflicts of interest to declare.

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CASE REPORT

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Psoriasis and Palmoplantar Pustulosis Following Pembrolizumab Therapy Successfully Treated With Topical Tapinarof Cream 1%

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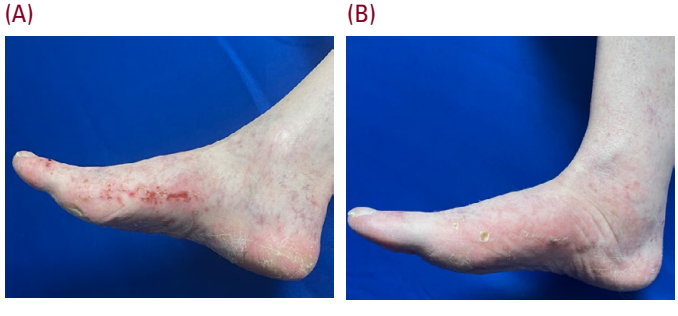
INTRODUCTION

Immune checkpoint inhibitors (ICIs) have altered the landscape for treating advanced malignant tumors. ICIs are monoclonal antibodies that target cytotoxic T lymphocyte–associate antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed death ligand 1 (PD-L1),[1] Adverse cutaneous events from ICIs are among the earliest and most common from these medications.[2] In this report, we present a case of ICI-related plaque psoriasis and palmoplantar pustulosis (PPP) following pembrolizumab therapy for recurrent cutaneous squamous cell carcinoma of the face and the use of topical tapinarof cream 1% for the treatment of both conditions.

CASE REPORT

An 83-year-old Caucasian male with a history of numerous cutaneous squamous cell carcinomas (SCC) presented with a recurrent well-differentiated cutaneous SCC of the left central malar cheek with new onset facial numbness for 3 to 4 weeks. The site was initially treated with surgery in 2014. He underwent re-excision with Mohs procedure in Sept 2021, requiring three stages. After the procedure, he exhibited paresthesia and pain at the site of surgery. He then underwent an MRI of the head and neck, which revealed perineural invasion with nerve enhancement and thickening. Subsequent positron emission tomography (PET) scan and clinical exam revealed no clinical lymph node involvement. Given perineural invasion without lymph node involvement, the tumor was staged as T3N0M0 (Stage III) according to the AJCC-8 staging system for cutaneous SCC of the head and neck.[3] He underwent complete full excision with clearance and then initiated immune checkpoint inhibitor (ICI) pembrolizumab 200 mg every 3 weeks from January 2022 to November 2022 without disease progression. The patient stopped pembrolizumab in November 2022 due to the development of a progressive rash rated as a Grade 3 ICI-related adverse event. He then presented in March 2023 with scaly nummular pink plaques involving his extremities and trunk, as well as erythematous patches, vesicles, pustules, and erosions with collarettes of scale on the palms and soles with significant pain while walking (Figure 1A). Exam findings were consistent with ICI-induced plaque psoriasis and palmoplantar pustulosis. The patient was then treated with tapinarof cream 1% daily to the affected areas for one month with significant improvement in lesion appearance and pain while walking (Figure 1B).

FIGURE 1. ICI-related plantar pustulosis of the right foot following treatment with pembrolizumab (A) pre- and (B) post-treatment with tapinarof cream 1% daily for one month.



DISCUSSION

Pembrolizumab is a monoclonal antibody that binds to the programmed cell death receptor 1 (PD-1) and prevents the inhibition of the cytotoxic T cell response allowing the immune system to eliminate tumor cells.[1] While there is an important therapeutic benefit of pembrolizumab, adverse cutaneous effects are seen in nearly 17% of patients.[2] Pembrolizumab is also less commonly known to cause or exacerbate psoriasis in patients.[2] Cases of palmoplantar pustulosis (PPP) specifically following pembrolizumab therapy are rare but have also been reported.[4] Treatment for psoriasis or PPP from pembrolizumab consists of stopping the offending drug and utilizing topical/oral corticosteroid therapy, methotrexate, and various biologics.[2]

In PPP, the primary area of inflammation is the acrosyringium indicating that eccrine sweat glands contribute to skin immunity and barrier function. Abnormalities of the gland in the palmoplantar region promote the development of vesicles and pustules filled with neutrophils or eosinophils.[5] Biopsies of these lesions show increased production of several cytokines, including interleukin-8 (IL-8), IL-1α, IL-1β, IL-17A-F, IL-22, IL-23A, and IL-23 receptor.[6] While the role of the IL-17 pathway in the pathogenesis of PPP is not fully clear, several studies have found a significant increase in the expression of IL-17A in the palms and

soles of patients with PPP.[7] The upregulation of IL-17 activates keratinocytes to produce IL-6, which mobilizes neutrophils and monocytes and triggers a chemotactic cascade attracting granulocytes to the epidermis to form the pathognomonic pustules and vesicles.[8] It is hypothesized that IL-23 also plays a role in PPP, as it is one of the many cytokines that regulates IL-17A indirectly through T cell differentiation into Th17.[7] In contrast to canonical plaque psoriasis lesions which contain extensive amounts of cytokines produced by Th17 cells (ie, IL-12, IL-17, and IL-23), in PPP lesions display a different pattern. Bissonnette et al found that in PPP there is an isolated increase in IL-17 without significant increases in IL-12 and IL-23, pointing to an underlying neutrophilic process rather than a Th17 lymphocytic response.[7]

Given the role of IL-17 in PPP, anti-IL-17 therapeutics, such as secukinumab, have successfully treated cases of pembrolizumab-induced psoriasis.[9] Our patient responded well to daily monotherapy of topical tapinarof cream 1%. Tapinarof is a novel small molecule that modulates the aryl hydrocarbon receptor (AhR), and is an approved treatment for adult plaque psoriasis.[10] Tapinarof has been shown to reduce levels of IL-17 leading to a reduction in skin inflammation and restoration of skin barrier function.[10] Our patient's condition improved significantly following tapinarof therapy with abatement of plantar pain and near complete resolution of skin lesions (Figure 1B). Therefore, tapinarof topical monotherapy may be a useful treatment for ICI-related psoriasis and PPP.

DISCLOSURES

The authors have no conflicts of interest in funding to declare.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

A New Tool to Improve Communication Between Hidradenitis Suppurativa Patients and Health Care Providers

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ABSTRACT

Background: Hidradenitis suppurativa (HS) patients tend to experience diagnosis delay, misdiagnosis, and embarrassment due to their condition. To address these issues, the International Dermatology Outcome Measure (IDEOM) HS Workgroup collaborated with patients to modify an existing Novartis questionnaire to better suit the needs of HS patients. This quality improvement project aimed to use the resulting Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire to enhance communication between HS patients and providers, improve clinical experience for HS patients, and gather relevant demographic data.

Method: Patients with HS presenting to Mount Sinai Union Square over a 9-month long period were invited to complete the Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire before seeing their providers. After the visit, patients rated their overall clinical experience and the helpfulness of the survey on a 5-point scale.

Results: The analysis cohort (n=30) consisted of a racially and ethnically diverse patient population. On a scale of 0-4, the mean helpfulness rating was 3.1 (SD=1), and the mean clinical experience rating was 3.5 (SD=0.78). There was a positive correlation between survey helpfulness and overall clinical experience and a moderately strong relationship by linear regression analysis (r=0.73, R^2=0.53). 80% reported frequent flares, 54% reported >10 years of symptoms, and the most commonly affected areas were the axillae, gluteal cleft, groin, and inguinocrural folds. The mean pain rating was 8 out of 10 (SD=2.55, Var=6.5). The majority of patients reported scars, tunnels, open wounds, ER/Urgent Care visits, inflammatory skin symptoms, and systemic symptoms. 39% had a positive HS family history. Biologics were the least common previous treatment reported (43%). Emotional burden was reported by nearly all patients, and comorbidities included depression, heart disease, arthritis, polycystic ovary syndrome (PCOS), diabetes, and irritable bowel disease (IBD).

Conclusion: The Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire was successful in improving HS patient-provider conversations, enhancing the overall clinical experience for HS patients, and collecting insightful demographic data. Healthcare providers should consider incorporating the questionnaire as part of their routine care for HS to enhance clinical discussion and improve outcomes for patients.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin condition characterized by abscesses, nodules, fistulae, draining sinus tracts, and scarring.[1] Though the pathogenesis of HS is not fully understood, the disease process centers around the pilosebaceous apocrine unit.[1] Thus, disease activity is generally high in the warm, wet areas, where these pilosebaceous-apocrine units are enriched, such as the axillae and the groin.[2] The condition can be severely disfiguring and be a source of embarrassment, pain, and diminished quality of life for patients.[1] HS is often misdiagnosed as abscesses, acne, or folliculitis.[3] On average, it may take patients 10 years and seeing more than 3 different providers before receiving their correct HS diagnosis.[3] This delay is associated with increased disease burden and quality of life impairment.[3] Due to patient embarrassment, frequent misdiagnosis, diagnosis delay, and disease severity, there exists a need to improve clinical discussion and experience for HS patients.

The International Dermatology Outcome Measure (IDEOM) is a nonprofit organization with the mission to establish patient-centered outcome measures within dermatology to improve both treatment and research efforts.[4] The Shine a Light on HS Doctor Conversation Starter is a 15-item questionnaire developed by Novartis to help patients self-diagnose their HS and talk to their dermatologists about their symptoms. The IDEOM HS Workgroup modified this questionnaire. Patients and HCPs met at the 2022 IDEOM annual meeting and then subsequently worked to improve the questionnaire using

patient input. Through a multi-round process, the questionnaire was updated to better serve the needs of HS patients with targeted prompting for information important to providers and patients. The resulting 12-item questionnaire asks patients about their HS history, experience with the condition, and concomitant symptoms and diagnoses.

We launched a 9-month long quality improvement project using the Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire. Our quality improvement project had 3 specific aims: (1) To facilitate more productive conversations between HS patients and their providers, (2) To improve the overall clinical experience of HS patients, and (3) To collect relevant demographical data characterizing the HS history of the patients presenting to a tertiary care center.

MATERIALS AND METHODS

Patients with HS presenting to the Mount Sinai Union Square tertiary care center from July 2022 to March 2023 were identified by chart review and asked to complete the 12-item Shine a Light on HS as Modified by IDEOM HS Workgroup Questionnaire at the clinic before seeing their providers. All patients with HS

FIGURE 1. The Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire.

Shine a light on HS as modified by the IDEOM HS workgroup. June 2022.

Get help navigating your skin condition by answering a few of these questions. Talking about your symptoms—and the impact they're having on your life—with a dermatologist who has experience diagnosing and treating hidradenitis suppurativa (HS) can help.

Tell your doctor (primary care, OB/GYN or dermatologist) about any bumps, boils, or abscesses (for children, include pimples and blackheads not only on the face) you've experienced over the 6 months.

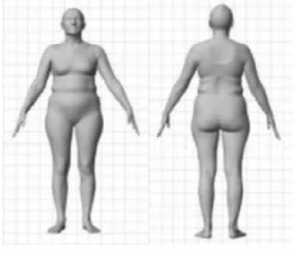
If possible, take a few photos of your skin signs with your phone and bring them with you to show your doctor.

1. How many times have these bumps, boils, or sores (abscesses) occurred over the past 6 months?

   ☐1-2 times ☐3-4 times ☐More than 5 times

2. How many years ago did you first notice symptoms?

3. Circle all the areas of your body that have been affected:



Tell your doctor how these symptoms make you feel physically.

4. Check all the symptoms that you have experienced with the bumps, boils or sores (abscesses):

   ☐Pain ☐Swelling ☐Itching
   ☐Leakage or draining pus and/or blood
   ☐Odor ☐Joint pain ☐Redness
   ☐Fatigue ☐Inflammation
   ☐Other: _____

5. If these symptoms cause pain, how bad is it? Select the number that reflects the extent of the pain. (0 – No pain; 10 – Worst pain imaginable)

   0 1 2 3 4 5
   6 7 8 9 10

6. How have these bumps, boils, or sores (abscesses) affected your skin? Check all that apply.

   ☐They have left scars
   ☐They have caused tunnels (also called sinus tracts) underneath my skin that drain when pressed
   ☐Open Wounds
   ☐Other: _____

Tell your doctor about your medical history and family history.

7. Have you had to visit the emergency room or urgent care because of your symptoms in the last year?

   ☐Yes ☐No

   If yes:
   How many times? ____

   What did they do for you there?
   _____
   _____
   _____
   _____

   Where are your medical records and are they available?
   ☐Yes ☐No
   _____
   _____
   _____

8. Has anyone else in your family had similar symptoms?

   ☐Yes ☐No

How have you managed your symptoms in the past?

9. Check any treatment that you have used or that have been prescribed to you:

   ☐Over-the-counter NSAIDs for pain relief (e.g., acetaminophen, ibuprofen)
   ☐Over-the-counter creams/ointments
   ☐Prescription corticosteroid creams/ointments
   ☐Antibiotics
   ☐Incision and drainage
   ☐Injections into lesions
   ☐Biologics
   ☐Home remedies
   ☐None of the above
   ☐Other: _____

Tell your doctor how your symptoms have impacted your life.

10. Describe how your symptoms have impacted you emotionally. Have your symptoms made you (Check all that apply):

    ☐Feel down or depressed
    ☐Feel embarrassed
    ☐Feel anxious or nervous
    ☐Lack sexual desire
    ☐Poor self image
    ☐None of the above
    ☐Other: _____

11. Describe any other ways that your life has been negatively affected by your symptoms. Check all that apply.

    ☐Sleep
    ☐Bathing
    ☐Choosing what to wear
    ☐Going to work
    ☐Ability to study or concentrate
    ☐Physical activity (or exercise)
    ☐Avoiding social events
    ☐Missing family activities
    ☐Relationships
    ☐Engaging in sexual activity
    ☐Financial
    ☐Water sports
    ☐Other: _____

12. Have you been diagnosed with any of the following medical conditions? Check all that apply.

    ☐Heart disease
    ☐Diabetes
    ☐Polycystic ovary syndrome
    ☐Inflammatory bowel disease
    ☐Arthritis
    ☐Depression
    ☐Other: _____

Additional notes to talk over with your doctor:

Please answer the following questions at the end of your visit today.

On a scale of 0 – 4, how helpful was this survey in facilitating your conversation about your HS with your doctor today? Circle the number that best describes your evaluation.

Not Helpful	Barely Helpful	Helpful	Quite Helpful	Very Helpful
0	1	2	3	4

Please rate your overall clinical experience today on a scale of 0 – 4. Circle the number that best agrees with your rating.

Poor	Fair	Good	Very Good	Excellent
0	1	2	3	4

were invited to participate with no exclusion. Repeat clinic visitors were invited to participate only once. Specifically, the questionnaire (Figure 1) asked patients about symptom incidence, condition duration, body areas affected, symptoms experienced, pain, skin impact, ER or urgent care visits, HS family history, prior treatments, emotional impact, breadth of symptom impact, and medical history.

After seeing their providers, patients were asked to complete 2 quality measure questions. They were asked to rate both the "helpfulness of the survey in facilitating their conversation about their HS with their provider" and their "overall clinical experience" on a 5-point scale from 0 to 4 (0: Not helpful/Poor, 1: Somewhat helpful/Fair, 2: Helpful/Good, 3: Quite helpful/Very good, 4: Very helpful/Excellent).

Incomplete questionnaires were included in the analysis if the 2 quality measure questions were answered. Descriptive statistics and content analysis were used to analyze quantitative and qualitative data, respectively.

RESULTS

Respondents included 30 patients for a response rate of 91%. The overwhelming majority (97%) of patients reported the survey was helpful to very helpful with a rating of 2-4. The mean rating was 3.1 with a standard deviation of 1.0. Additionally, 100% of our patients reported a clinical experience that was good to excellent with a rating of 2-4. The mean rating was 3.5 with a standard deviation of 0.78. There was a positive correlation between survey helpfulness and overall clinical experience (r=0.73). Linear regression analysis revealed a moderately strong relationship (R^2=0.53). Results from our 2 quality improvement measure questions are summarized in Table 1.

We were also able to collect important demographical information about our HS patient population and their symptom history and burden. The mean age of our patients was 37 years old with a female to male ratio of 4:1. Our patient population demonstrated both racial and ethnic diversity with patients self-identifying their race as African American (43%), White (10%), Asian (6%), and Other (40%) and their ethnicity as Hispanic (27%), Non-Hispanic (47%), and Unknown (27%). The demographic distribution of our patients is summarized in Table 2. 80% of our patients reported more than 5 instances of symptom flare over the last 6 months. At least 54% of our patients have been experiencing symptoms for 10 years or more. In order, the most commonly affected areas were the axillae (77%), the gluteal cleft (60%), the groin (53%), and the inguinocrural folds (43%). The overwhelming majority of our patients experienced inflammatory skin symptoms, such as redness, pain, leakage, swelling, inflammation, itching, and odor. A majority of our patients also experienced systemic symptoms such as fatigue (57%) and joint pain (43%). On a pain scale of 0-10, the mean pain rating was 8 (SD=2.55, Var=6.5). The overwhelming majority of our patients reported their HS caused scars, tunnels, and open wounds. 53% of our patients have had to visit the ER or Urgent Care due to their HS over the last year. 39% of our patients reported a positive HS family history. The most common previous treatments were antibiotics (83%), injections into lesions (67%), OTC NSAIDs (63%), prescription corticosteroid creams/ointments (63%), and incision and drainage (63%). Biologics were the least common previous treatment reported (43%). Nearly all patients reported significant emotional burden from their HS and are impacted across all domains of their lives. Patients reported comorbidities of depression (50%), heart disease (17%), arthritis (13%), PCOS (13%), diabetes (10%), and IBD (7%). The survey responses characterizing the HS history, burden, and symptom impact of our HS patient population are summarized in Table 3.

TABLE 1.

Response Summary for Quality Improvement Measure Questions		
	Survey Helpfulness	Overall Clinical Experience
Rating		
0	0% (n=0)	0% (n=0)
1	3% (n=1)	0% (n=0)
2	37% (n=11)	17% (n=5)
3	3% (n=1)	20% (n=6)
4	57% (n=17)	63% (n=19)
Mean	3.1	3.5
Standard Deviation	1.0	0.78
Variance	1.1	0.60
Median	4	4
Mode	4	4

TABLE 2.

Patient Demographics		
Age	Mean: 37 years	
Gender		
Female	80%	(n=24)
Male	20%	(n=6)
Race		
African American	43%	(n=13)
White	10%	(n=3)
Asian	6%	(n=2)
Other	40%	(n=12)
Ethnicity		
Hispanic	27%	(n=8)
Non-Hispanic	47%	(n=14)
Unknown	27%	(n=8)

TABLE 3.

Survey Responses Characterizing HS History Summary			
Characteristics	**n (%)**	**Characteristics**	**n (%)**
HS History		**HS History (continued)**	
Symptoms over past 6 months		HS Family History	
1-2 times	3 (10)	Yes	11 (39)
3-4 times	3 (10)	No	17 (61)
>5 times	24 (80)	Previous treatments	
Years since symptom onset		Antibiotics	25 (83)
<5 years	4 (17)	OTC NSAIDs	20 (67)
5-9 years	7 (29)	Injections	20 (67)
>10 years	13 (54)	Prescription corticosteroid creams/ointments	19 (63)
Affected body areas		Incision & drainage	19 (63)
Axillae	23 (77)	OTC creams/ointments	15 (50)
Gluteal cleft	18 (60)	Home remedies	15 (50)
Groin	16 (53)	Biologics	13 (43)
Inguinocrural folds	13 (43)	Other	3 (10)
Buttocks	11 (37)	None of the above	2 (7)
Submammary	10 (33)	Emotional impact	
Legs	7 (23)	Down/depressed	18 (60)
Back	6 (20)	Embarrassed	24 (80)
Abdomen	5 (17)	Anxious/nervous	19 (63)
Suprapubic	4 (13)	Lack of sexual desire	16 (53)
Breast	4 (13)	Poor self-image	19 (63)
Chest	3 (10)	None of the above	3 (10)
Face	3 (10)	Impact on quality of life	
Intermammary	2 (7)	Sleep	21 (70)
Feet	1 (3)	Bathing	20 (67)
Scalp	1 (3)	Choosing what to wear	26 (87)
Symptoms		Going to work	13 (43)
Pain	28 (93)	Ability to study/concentrate	17 (57)
Swelling	26 (87)	Physical activity/exercise	22 (73)
Itching	24 (80)	Avoiding social events	12 (40)
Leakage/draining	28 (93)	Missing family activities	12 (40)
Odor	24 (80)	Relationships	18 (60)
Redness	29 (97)	Engaging in sexual activity	19 (63)
Inflammation	26 (87)	Financial	15 (50)
Fatigue	17 (57)	Water sports	9 (30)
Joint pain	13 (43)	Past Medical History	
Skin impact		Heart disease	5 (17)
Scars	29 (97)	Diabetes	3 (10)
Tunnels	23 (77)	PCOS	4 (13)
Open wounds	23 (77)	IBD	2 (7)
ER/Urgent Care in last year		Arthritis	4 (13)
Yes	16 (53)	Depression	15 (50)
No	14 (47)		

DISCUSSION

We were able to characterize significant HS historical information about our diverse patient population seeking care from a renowned HS specialist at a tertiary care center. As such, many of our patients experienced significant disease burden, the severity of which frequently goes overlooked. Nearly all patients identified significant morbidity and impact across all domains of their lives. The emotional impact of HS is often under-appreciated, but more than half of our patients have been diagnosed with depression. Heart disease, arthritis, PCOS, diabetes, and IBD were other commonly reported comorbidities, suggesting that clinicians should support screening for these conditions as a part of comprehensive care. Though the overwhelming majority of our patients report having active disease with a mean pain rating of 8, less than half of them have been treated with biologic medications. The subset of patients who tried biologics were characterized by the following: 54% of those with >5 flares in 6 months, 62% of those with >10 years of symptoms, and 41% of those with a pain rating of >8. With adalimumab already FDA-approved for HS and novel biologics coming to market, these numbers expose a potential gap in care for patients who are failing their current therapies. Our survey results underscore the necessity of improving HS patient care.

The overwhelming majority of our patients found the Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire helpful to their clinic visit. This sentiment positively correlated with overall clinical experience. It is important to note that patients were visiting a tertiary care center to be seen by an HS specialist, so patient-provider conversation at baseline is likely above average when compared to non-specialist counterparts. As such, while our results are impressive, they may underestimate the value of this survey. Potential applications to maximize the utility of the Shine a Light on HS as Modified by the IDEOM HS Workgroup Questionnaire include general dermatology, private practice dermatology, family medicine clinics, OBGYN clinics, and primary care practices where providers may not be as well versed in HS. The survey can be downloaded free of charge on the IDEOM website (https://www.dermoutcomes.org/workgroups/hidradenitis-suppurativa.php).

DISCLOSURES

Melissa Peri Zundell has no conflicts to disclose. Alice B. Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and Xbiotech and has received research/educational grants from AnaptypsBio, Moonlake Immunotherapeutics AG, Novartis, Bristol-Myers Squibb, and UCB Pharma, (all paid to Mount Sinai School of Medicine).

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BRIEF COMMUNICATION

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Number of Affected Nails Is the Primary Determinant of Efinaconazole 10% Solution Usage for Onychomycosis

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ABSTRACT

Good adherence to treatment is necessary for the successful treatment of onychomycosis and requires that an appropriate amount of medication be prescribed. Most prescriptions for efinaconazole 10% solution, a topical azole antifungal, are for 4 mL per month but there are no data on patient factors or disease characteristics that impact how much medication is needed. Data from two phase 3 studies of efinaconazole 10% solution for the treatment of toenail onychomycosis were pooled and analyzed to determine monthly medication usage based on the number of affected toenails, percent involvement of the target toenail, body mass index (BMI), and sex. Participants with two or more affected nails required, on average, >4 mL of efinaconazole per month, with increasing amounts needed based on the number of nails with onychomycosis (mean: 4.39 mL for 2 nails; 6.36 mL for 6 nails). In contrast, usage was not greatly impacted by target toenail involvement, BMI, or sex. Together, these data indicate that the number of affected nails should be the major consideration when determining the monthly efinaconazole quantity to prescribe.

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INTRODUCTION

Topical onychomycosis therapies require extended treatment durations, and incomplete treatment can contribute to high relapse rates.[1] Excellent treatment adherence is vital to optimize outcomes[2] and requires that an adequate quantity of medication is prescribed. Efinaconazole 10% topical solution, an azole antifungal indicated to treat onychomycosis in patients aged 6 years and older, is available in 4 or 8 mL bottles. Perhaps because published data are lacking on factors impacting quantity of efinaconazole needed, 87% of efinaconazole prescriptions in 2022 were for one 4 mL bottle/month.[3] Using clinical data, we analyzed the quantity of efinaconazole used by baseline patient demographics and clinical characteristics to estimate drug quantity to be prescribed for a given patient.

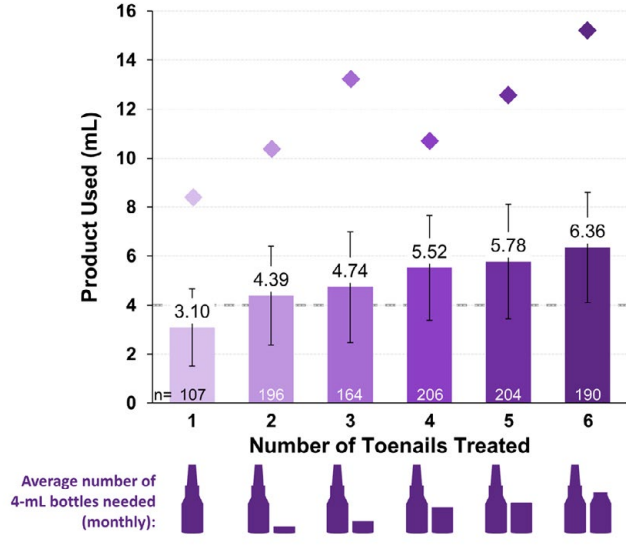
MATERIALS AND METHODS

In two identical, double-blind, phase 3 studies (NCT01008033; NCT01007708), adult participants (18 to 70 years; N=1655) with mild-to-moderate distal lateral subungual onychomycosis affecting 20% to 50% of ≥1 great (target) toenail were randomized 3:1 to treatment with efinaconazole 10% solution or vehicle, self-applied once daily for 48 weeks.[4] Studies were conducted according to international scientific/ethical standards and all participants and/or legal guardians provided informed consent. Bottles of study product (10 mL) were weighed upon dispensation at each study visit (every 4 weeks) and upon return at the following visit. Monthly medication use was calculated (mean daily use [g/day] x 30 days/month x density of efinaconazole 10% solution [mL/g]) and analyzed post hoc based on number of affected toenails, percent involvement of the target toenail, body mass index (BMI), and sex.

RESULTS

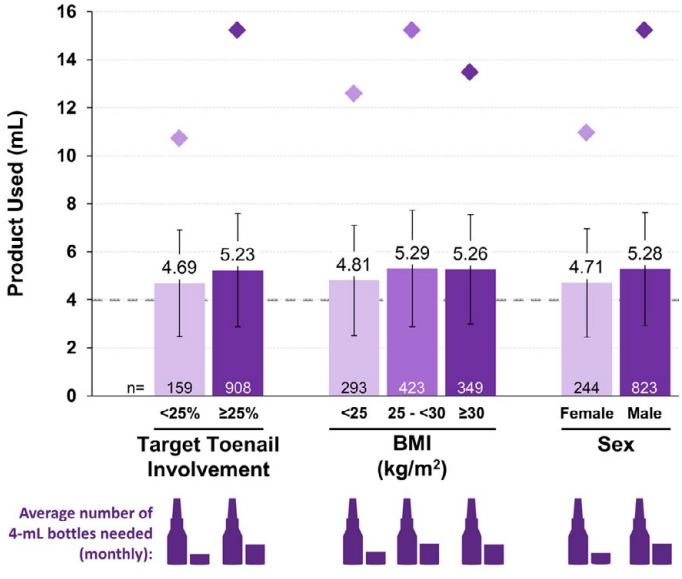
Efinaconazole-treated participants in both studies (n=656 and 580) had on average 3.7 to 3.8 affected toenails.[4] Among those with usage data (n=1067), over 55% had ≥4 affected toenails (Figure 1). For the 90% of participants with 2 to 6 affected nails, average medication use ranged from 4.39 to 6.36 mL/month, corresponding to 1.10 to 1.59 4 mL bottles/month; only the 10% of participants with one affected toenail used <4 mL of efinaconazole monthly. Additional subgroup analyses revealed no meaningful differences in efinaconazole usage based on target toenail involvement, BMI, or sex; average medication use was 4.69 to 5.29 mL/month, corresponding to

FIGURE 1. Calculated monthly usage of efinaconazole 10% topical solution by number of toenails treated.



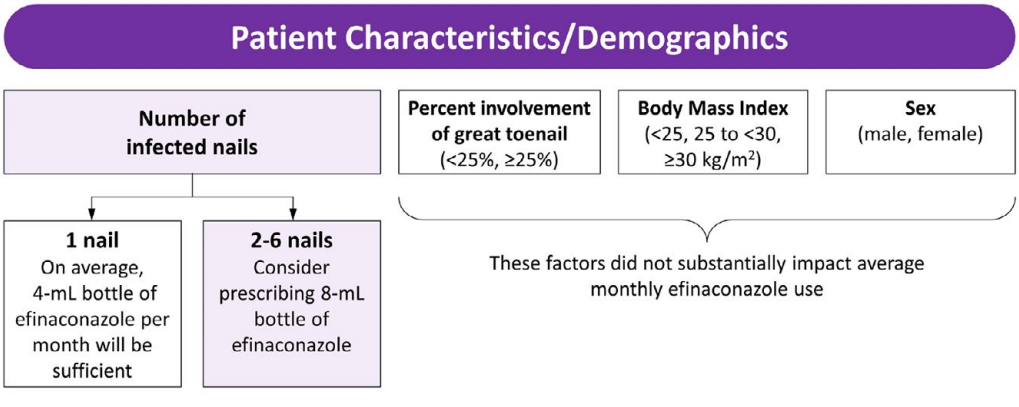
For study inclusion, all participants had at least one affected great toenail. Medication usage is presented as mean ± standard deviation. Diamonds indicate the estimated maximum monthly usage for each group. Dashed line indicates usage above which more than one 4-mL bottle would be needed per month.

FIGURE 2. Calculated monthly usage of efinaconazole 10% topical solution by target toenail involvement, BMI, and sex.



Medication usage is presented as mean ± standard deviation. Diamonds indicate the estimated maximum monthly usage for each group. Dashed line indicates usage above which more than one 4-mL bottle would be needed per month. BMI, body mass index.

FIGURE 3. The number of affected nails should be the major consideration when determining the amount of efinaconazole to prescribe per month.



1.17 to 1.32 4 mL bottles monthly (Figure 2). Because application instructions specify that the nail plate, toenail folds, toenail bed, hyponychium, and nail plate undersurface should be completely covered, regardless of the area of involvement, it was expected that medication usage might be similar for nails with different surface areas affected.[5]

DISCUSSION

In these clinical trials, participants were provided 10 mL of efinaconazole per month. In clinical practice, however, almost 90% of prescriptions for efinaconazole are for one 4 mL bottle monthly.[3] For patients with ≥2 affected toenails, a 4 mL bottle would likely be depleted in under a month, and after as few as 19 days with 6 affected nails, leaving treatment gaps until prescriptions are refilled. Because intermittent treatment may affect medication efficacy and increase the likelihood of relapse or reinfection,[1] patients with more than one nail involved might be more likely to achieve success with an 8 mL bottle of efinaconazole (Figure 3). Given that nail percent involvement, sex, and BMI do not affect medication usage, number of affected nails should be the major consideration when determining the monthly efinaconazole quantity to prescribe.

DISCLOSURES

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CASE REPORT

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A Case Series of TNF Inhibitor-Induced Psoriasis Successfully Treated With Upadacitinib

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ABSTRACT

Tumor Necrosis Factor-alpha inhibitors (TNF-i) are commonly used to treat immune-mediated diseases such as psoriasis, psoriatic arthritis (PsA), inflammatory bowel disease (IBD), spondyloarthritis (SpA) and rheumatoid arthritis (RA). However, paradoxical psoriasis induced by TNF-i has been described and is not uncommon, particularly with infliximab and etanercept. The presentation of TNF-i-induced psoriasis is most commonly plaque or palmoplantar morphology. Optimal treatment strategies for recalcitrant psoriatic disease are not well understood. In this case series, we report three patients with TNF-i-induced psoriasis who were treated with upadacitinib and experienced complete resolution of their psoriatic eruptions. The efficacy of Janus kinase inhibitors (JAK-i) is possibly explained by mechanisms involving uncontrolled production of type 1 IFNs as well as increases in IL-23 and T-helper 17 cells upstream of relevant JAK/STAT pathways. We also offer a proposed treatment algorithm that includes the use of JAK-i as a promising management option in patients with recalcitrant disease. However, larger studies are needed to confirm the efficacy and safety of JAK-i in this patient population.

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INTRODUCTION

Tumor Necrosis Factor-alpha inhibitors (TNF-i) treat and are FDA-approved for a wide spectrum of immune-mediated diseases including psoriasis, psoriatic arthritis (PsA), inflammatory bowel disease (IBD), spondyloarthritis (SpA) and rheumatoid arthritis (RA).[1] TNF-i-induced paradoxical psoriasis has been well described and is not uncommon given the frequent use of these agents, with a prevalence ranging from 0.6% to 5.3%.[2-10] Of the five existing approved TNF-i (adalimumab, infliximab, etanercept, certolizumab, golimumab), infliximab is associated with more than half of these cases (52-62%), followed by etanercept (12-29%).[2,11-13] Multiple morphologies may be seen, including plaque psoriasis, palmoplantar pustular psoriasis, guttate, and inverse psoriasis; the most common being plaque (15.8-50%) followed by palmoplantar (33.5-45%).[11-15] The mechanism of action remains unclear. It is hypothesized that blocking TNF-α allows increased and uncontrolled production of type 1 IFNs by plasmacytoid dendritic cells as well as an increase in IL-23 and T-helper 17 cells.[14,16,17] Both axes activate downstream JAK/STAT pathways implicated in disease pathogenesis.[22] Standard treatment of care, as detailed in a management algorithm by Li and Merola et al., is to either "treat through" while addressing psoriasis skin manifestations, switch the TNF-i therapy, or switch to a different class.[18] However, optimal treatment strategies for recalcitrant psoriatic disease are poorly understood. In this case series, we share the novel use of Janus kinase inhibitors (JAK-i) as promising agents in the management of patients with TNF-i-induced psoriasis as well as an up-to-date proposed treatment algorithm.

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CASE PRESENTATION

Case 1

A 57-year-old female with a history pertinent for remote pulmonary sarcoidosis, uveitis, psoriasis, and PsA presented with one year of a rash solely on her hands and feet. The rash first appeared a few weeks following the initiation of adalimumab for her PsA. On exam, the bilateral palms and soles were notable for pink to red plaques with an overlying silvery scale, clinically consistent with TNF-i-induced psoriasis with overlap features of eczematous dermatitis. Following discontinuation of adalimumab, the patient failed treatment with topical steroids, prednisone tapers, secukinumab, cyclosporine, infliximab, and most recently ixekizumab. Given the eczematous appearance of her eruption, inflammatory arthritis, no response to ixekizumab or other psoriasis-targeted treatments, and potential compatibility of JAK inhibitors with sarcoidosis, it was decided to trial upadacitinib 15 mg daily.[19] After 6 weeks, despite the persistence of her inflammatory arthritis the palmoplantar eruption and her baseline psoriasis had fully resolved.

Case 2

A 60-year-old female with a pertinent history of PsA presented with a rash solely on her palms and soles. The patient initially started etanercept 17 months prior to presentation and transitioned to adalimumab 10 prior to rash onset. On exam, the bilateral palms had thin well-demarcated pink scaly plaques as well as deep-seated pustules on the palms and soles, clinically consistent with TNF-i-induced palmoplantar pustular psoriasis. Following discontinuation of adalimumab, the patient failed treatment with topical steroids, prednisone tapers, phototherapy, and ixekizumab. Given the psoriatic plaques and concomitant inflammatory arthritis, the patient was started on upadacitinib 15 mg daily. After one month, there was marked improvement in the patient's palmoplantar eruption as well as control of her PsA (Figure 1).

Case 3

A 61-year-old female with a pertinent history of PsA presented with a rash on her soles, palms, and lower legs. The rash first appeared 7 years following initiation of adalimumab. On exam, there were pustules, erosions, scaling, and fissuring on the left palm and bilateral soles, as well as a few well-demarcated erythematous plaques on the bilateral lower legs, clinically consistent with palmoplantar pustulosis, likely TNF-i-induced. Following discontinuation of adalimumab, the patient failed treatment with topical steroids with calcipotriene, oral dapsone, and ustekinumab. We opted to trial upadacitinib 15 mg. After 3 months, her lesions cleared and her joint disease was well-controlled (Figure 1).

FIGURE 1. A collection of pictures displaying the marked improvement of recalcitrant TNF-i-induced palmoplantar psoriasis in patients before and after treatment with upadacitinib. The top four pictures represent case 2 and the bottom four pictures represent case 3. Pictures representing case 1 were unable to be obtained.

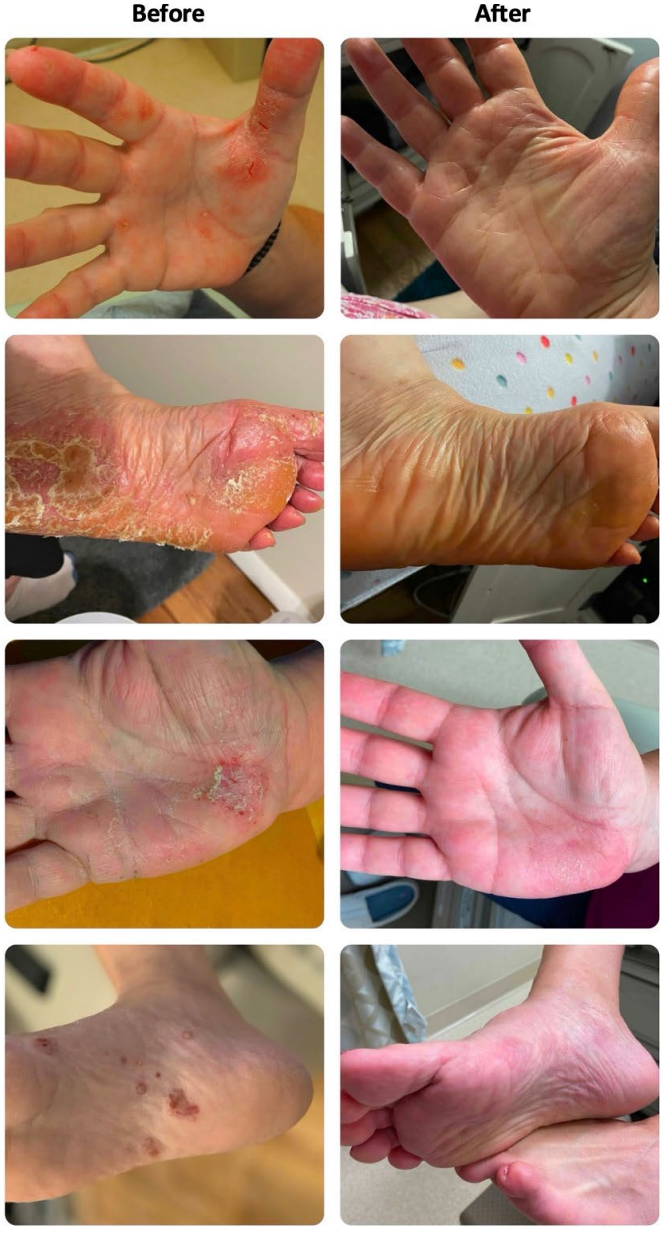

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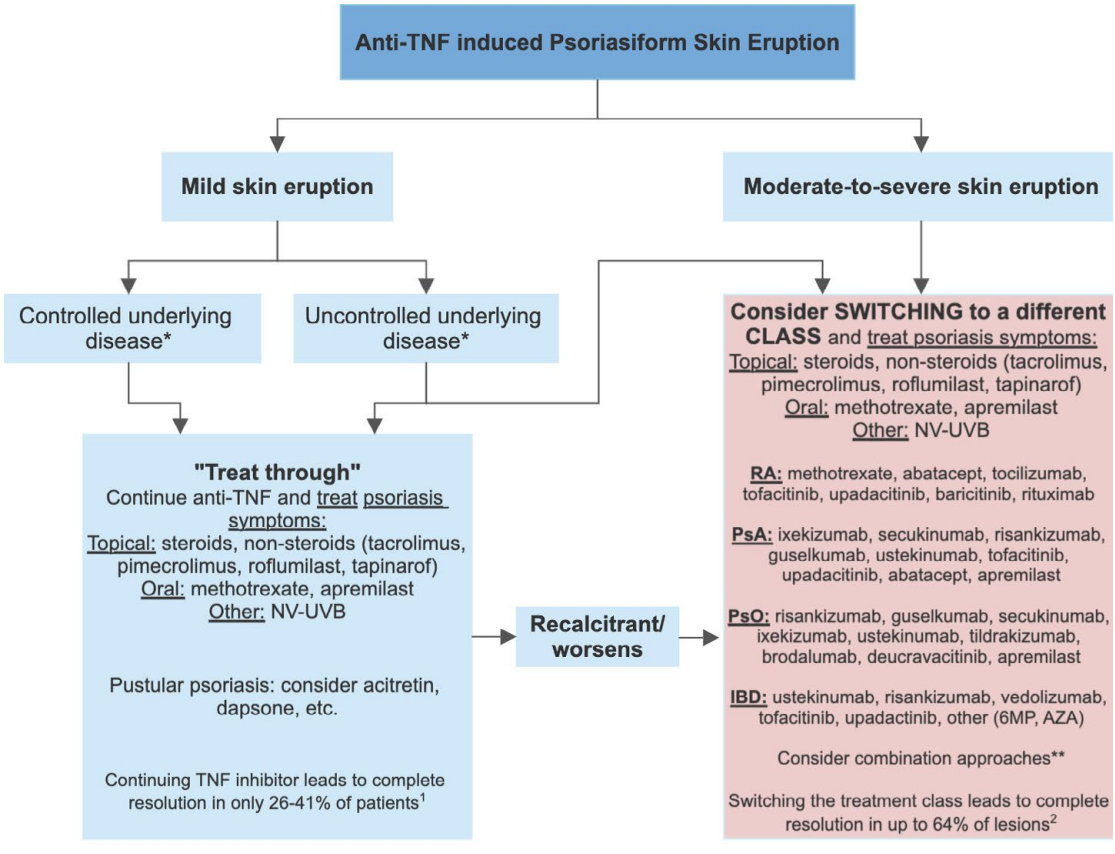
FIGURE 2. A proposed management approach for TNF-i-induced psoriasis found in data from the current literature as well as from a dermatology-rheumatology perspective (JFM) in treating such patients. Following an appropriate work-up for other etiologies, patients are stratified by severity and control of possible underlying disease (ie, RA, PsO, PsA, IBD). Patients with mild and controlled disease are recommended to "treat through," while patients with mild and uncontrolled disease or patients with recalcitrant/worsening disease can be considered to switch to a different class targeted to their underlying disease. Patients with moderate-to-severe disease are recommended to directly switch to a different class.



*Underlying disease: *RA* rheumatoid arthritis, *IBD* inflammatory bowel disease, *PsO* psoriasis, or *PsA* psoriatic arthritis. **Consider also cases in which anti-TNF therapy is required or favored (ie, uveitis, IBD) for combination therapy approaches (eg, anti-TNF + IL12/23 or IL23).

DISCUSSION

Therapeutic options for patients with TNF-i-induced psoriasis are sometimes limited by prior medication failures, underlying diseases, and co-morbidities, and some patients remain refractory to all agents.[18] There is a need for novel treatment options in such cases. JAK-i are small molecules that have proven their efficacy in PsA and plaque psoriasis in recent years, however, they have not been well-studied in TNF-i-induced psoriasis.[20] This case series presents evidence that upadacitinib, as a model of other JAK inhibitors, may be an effective option in patients with recalcitrant TNF-i-induced palmoplantar psoriasis with concomitant PsA or other conditions (ie, RA, IBD, etc).

Upadacitinib is a second-generation oral JAK1-selective inhibitor. It is approved for PsA, RA, ulcerative colitis, ankylosing spondylitis, and nonradiographic axial SpA in patients who have an inadequate response or intolerance to at least one TNF-i, as well as atopic dermatitis in patients inadequately controlled with other systemic therapies; however, it is not yet indicated for psoriasis.[21] This case series provides evidence that upadacitinib may treat TNF-i-induced psoriasis, however, the mechanism for this efficacy is unknown. One theory regarding the mechanism of TNF-i-induced psoriasis hypothesizes that blocking TNF-α leads to an uncontrolled upregulation of type 1 interferons.[19] IFN-α activates JAK1/TYK2, which activates STAT1/STAT2, therefore it is plausible that upadacitinib acts via blockage of this pathway.[22] A second theory implicates the IL-23/TH-17 axis in TNF-i-induced psoriasis. It is known that IL-23 activates JAK2/TYK2, which activates STAT3, in turn inducing and differentiating Th17 cells.[19] Accordingly, ustekinumab, an IL-12/23 antagonist, has shown efficacy for paradoxical anti-TNF psoriasis.[17] In contrast, upadacitinib may be involved in this axis via JAK1/JAK2 or JAK1/TYK2 signaling induced by IL-6.[22] Interestingly, several case reports have shown the efficacy of tocilizumab, an IL-6 antagonist, for palmoplantar pustular psoriasis (PPPP) triggered by TNF-i, and upadacitinib has been shown to potently inhibit IL-6, however, more research is required to define the role

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of IL-6 in PPPP.[23-26] Lastly, it is possible that upadacitinib acts via blockage of JAK1-dependent cytokines IL-2, IL-7, and IL-15, which sustain resident T cells at the site of inflammation.[27]

With regard to management, a proposed treatment algorithm by Li and Merola et al. recommends that patients with TNF-i-induced psoriasis be treated as follows: (1) patients with mild skin eruption and controlled underlying disease should be "treated through" and psoriasis symptoms managed with conventional psoriasis-specific therapy (eg, add topicals, methotrexate, dapsone, etc); (2) patients with mild skin eruption and uncontrolled underlying disease OR moderate-severe skin eruption and controlled underlying disease are recommended to switch to a different TNF-I and manage symptoms as above; (3) patients with moderate-severe skin eruption and uncontrolled underlying disease are recommended to switch to a different class and manage symptoms as above.1 However, in our up-to-date proposed treatment algorithm (Figure 2) we no longer recommend patients switch to a different TNF-i as complete resolution is limited to only 5% to 36.7% of cases, with a partial response in 18.4%.[2,11,12,14] Instead, we recommend patients with mild skin eruption and uncontrolled underlying disease, patients with a moderate-severe skin eruption, and patients with recalcitrant/worsening skin eruption switch directly to a different class as the rate of complete resolution increases to 64% and the alternative class options are increasingly safe, efficacious, and convenient.[2] For example, as shown in this case series, patients may benefit from the addition of JAK-i to this treatment algorithm given the mechanistic plausibility for its efficacy in treating psoriasis, including PPPP, as well as its potential for improved small molecule penetration of the palms and soles compared to that of monoclonal antibodies. Specifically, it may best serve a role as a suitable alternative class in patients with uncontrolled underlying diseases for which JAK-i are indicated.

CONCLUSION

To our knowledge, this is the first case series to describe the successful use of JAK-i in TNF-i-induced psoriasis. These observations are promising for the use of upadacitinib in such patients; however, multiple potential mechanisms implicating JAK-STAT pathways may support the use of other JAK-i as well, such as the TYK2 inhibitor, deucravacitinib. Our findings warrant the initiation of large, randomized, controlled studies of JAK-i in both treatment-naïve and treatment-refractory patients with TNF-i-induced psoriasis.

DISCLOSURES

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LETTERS TO THE EDITOR

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Teledermatology Platforms Usage and Barriers: A Cross-Sectional Analysis of United States-Based Dermatologists Pre- and Post-COVID-19

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ABSTRACT

Background: During the global COVID-19 pandemic, dermatologists increasingly adopted teledermatology to facilitate patient care.
Objective: To identify differences in teledermatology platform usage and functionality among dermatologists as a means of understanding the potential effect on virtual healthcare access.
Methods: Results from a 2021 cross-sectional pre-validated survey distributed to actively practicing United States dermatologists were analyzed based on timepoint when teledermatology was adopted relative to COVID-19, previous/currently used platforms, self-reported platform functionality, and barriers to teledermatology implementation. Analysis was performed using chi-square and odds ratios (OR) with 95% confidence intervals (95% CI) for categorical data and single-factor analysis of variance (ANOVA) with post-hoc Tukey-Kramer for continuous data. P<.05 was considered significant.
Results: Early adopters (EAs) trialed significantly more (2.3 vs 1.9, P=0.02) platforms than (post) COVID adopters (CAs) before choosing their current platform. More EAs reported using platforms capable of uploading images (P=.002), required a mobile application (P=.006), and allowed staff to join patient encounters (P<.001). While poor image quality was the most cited barrier to implementation, CAs and non-adaptors (NAs) were materially more likely to cite it as their largest barrier to teledermatology.
Limitations: The retrospective nature of the study and potential response bias.
Conclusion: Dermatologists' use of teledermatology materially correlates with their teledermatology-adoption timepoint, and future usage may be materially impacted by the end of the COVID-19 public health emergency. Future studies should aim at how implementation and barriers to teledermatology usage may impact access to care.

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INTRODUCTION

United States-based dermatologists adapted to the COVID-19 public health emergency in part by integrating teledermatology into their practices.[1,2] Pre-COVID-19, asynchronous or store-and-forward (SAF) teledermatology was a relatively cost-effective tool providing care to patients with minimal healthcare access.[3-5] Post-COVID-19, studies suggest that teledermatology usage materially shifted towards synchronous or live-interactive (LI)/video-based modalities.[6-13] This study aimed to identify differences between teledermatology-adoption timepoints (TAT) (relative to COVID-19) and associated teledermatology barriers to usage and platform characteristics.

METHODS

This study was exempt per Institutional Review Board (IRB) guidelines. A pre-validated anonymous survey was distributed via email to a proprietary purchased listserv of actively practicing US dermatologists. Completed results were stratified by TAT. Analysis was performed using chi-square, odds ratios (OR) with 95% confidence intervals (95% CI) for categorical data, t-tests for continuous data, and rank-based overlap (RBO) to compare ranked-ordered lists on a continuous scale from 0 (completely different) to 1 (identical) using Python 3.9.6.

RESULTS

Data from 338 practicing dermatologists were analyzed. The analysis regarding demographics and TAT is described in separate studies[12,13]; briefly, pre-COVID/early adopters (EA) were significantly more likely to have ≤10 years of experience (YoE) and be associated with academic medical-dermatology practices, while (post-) COVID adopters (CAs) were more likely to have ≥20 YoE and be associated with private medical-

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TABLE 1.

Top 5 teledermatology platforms Pre- and Post-COVID-19. Top 5 platforms that EAs and CAs of teledermatology have previously trialed compared with their current primary platform, using RBO to determine the degree of similarity between 0 (completely different) and 1 (identical).

EA (n, %)			CA (n, %)			*P*-value
# Platforms trialed, mean (SD)	2.3 (1.4)		1.9 (1.1)			0.02*
Trialed Platforms (n, %)	Current Platform (n, %)	Trialed v. Current RBO	Trialed Platforms (n, %)	Current Platform (n, %)	Trialed v. Current RBO	Current Platforms RBO
1. Doximity (29, 24.2%)	1. Epic MyChart (14, 18.2%)	0.26	1. Facetime (97, 27.2%)	1. Doxy.me (44, 18.2%)	0.8	0.33
2. Zoom (27, 22.5%)	2. EMA (10, 13.0%)		2. Doxy.me (73, 20.5%)	2. Facetime (43, 17.8%)		
3. Facetime (23, 19.2%)	3. Doxy.me (9, 11.7%)		3. Zoom (72, 20.2%)	3. Zoom (31, 12.8%)		
4. Epic MyChart (22, 18.3%)	4. Zoom (9, 11.7%)		4. Doximity (68, 19.1%)	4. Doximity (29, 12.0%)		
5. EMA (12, 10.0%)	5. Doximity (8, 10.4%)		5. EMA (50, 14.0%)	5. EMA (26, 10.7%)		

CA, (post) COVID adopter; EA, early adopter; RBO, rank-based overlap; SD, standard deviation.
*2-tailed t-test

Comparing the top 5 previously used with current-primary platforms, EAs' RBO is materially smaller than CAs' and suggests that CAs experimented with significantly fewer platforms than EAs (mean±SD 2.3±1.4 vs 1.9±1.1, *P*=0.02). The RBO comparing the top 5 current primary platforms between EAs and CAs is 0.33, suggesting a material difference in practice-integrated platforms (Table 1). Compared with CAs, proportionally more EAs reported using platforms that required a mobile application [62.0% v 45.3%; χ^2 (2,n=322)=10.10, *P*=.006], were capable of uploading images [63.3% v. 42.0%; χ^2 (2,n=322)=12.00, *P*=.002], and allowed staff to join ongoing patient encounters [57.0% vs 32.5%; χ^2 (2,n=322)=15.65, *P*<.001; Table 2]. There was no statistical difference based on platform compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations [χ^2 (2,n=322)=3.56, *P*=.17].

There was a significant relationship between TAT and the self-reported largest barrier to implementing teledermatology [χ^2 (12,n=338)=26.35, *P*=.01; Table 3]. While concerns regarding image quality were most cited across groups, compared with EAs non-adapters (NAs) were 7x (OR 7.77, 95% CI 2.26-26.7) and CAs were 1.58x (OR 1.58, 95% CI 0.91-2.76) more likely to cite poor image quality as their largest barrier to implementation.

DISCUSSION

We have previously demonstrated a significant increase in synchronous/LI teledermatology, especially among CAs[12,13]; reflected here by the self-reported popularity of video-based platforms. The RBO analysis demonstrates material heterogeneity between EAs and CAs post-COVID platform usage, suggesting that CAs (largely private dermatologists) are using teledermatology differently than their EA (largely Academic/Government-based) peers.[13] This is supported by

TABLE 2.

Self-reported teledermatology platform properties. Teledermatology platform properties stratified by when technology was adopted. There was a statistically significant relationship between timepoints of adoption and platform functionality. CAs were less likely to use platforms capable of uploading images, requiring an app to use, and allowing staff to join patient visits. There was no significant difference in HIPAA compliance between EAs and CAs.

	EA n (%)	CA n (%)	*P*-value (χ^2)
HIPAA compliant			
Yes	63 (79.7)	170 (70.0)	*P*=.17 χ^2 (2,n=322)=3.56
No	7 (8.9)	23 (9.5)	
Unsure	9 (11.4)	50 (20.6)	
Uploading Images			
Yes	50 (63.3)	102 (42.0)	*P*=.002 χ^2 (2,n=322)=12.00
No	20 (25.3)	80 (32.9)	
Unsure	9 (11.4)	61 (25.1)	
App required			
Yes	49 (62.0)	110 (45.3)	*P*=.006 χ^2 (2,n=322)=10.10
No	27 (34.2)	96 (39.5)	
Unsure	3 (3.8)	37 (15.2)	
Allows staff to join			
Yes	45 (57.0)	79 (32.5)	*P*<.001 χ^2 (2,n=322)=15.65
No	19 (24.1)	78 (32.1)	
Unsure	15 (19.0)	86 (35.4)	

CA, (post) COVID adopter; EA, early adopter; HIPAA, Health Insurance Portability and Accountability Act.

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TABLE 3.

Barriers to teledermatology implementation. Largest barrier to teledermatology usage stratified by when/if technology was adopted. There was a statistically significant relationship between timepoint of adoption and self-reported largest barrier. CAs and NAs were more likely to cite image quality as their largest barrier, while EAs reported their primary concern was reimbursement.

	EA n (%)	CA n (%)	NA n (%)	*P*-value (X^2)
None of the above, we are currently using telemedicine	22 (27.8)	65 (26.7)	0 (0.0)	*P*=.01 X^2 (12,n=338)=26.35
Patients are unable to use platforms/technology	20 (25.3)	56 (23.0)	2 (12.5)	
Staff are unable to use platforms/technology	2 (2.5)	4 (1.6)	1 (6.3)	
Image quality prevents accurate assessment	22 (27.8)	96 (39.5)	12 (75.0)	
Concerns about reimbursements for patient visits	11 (13.9)	18 (7.4)	0 (0.0)	
Concern with HIPAA compliance	0 (0.0)	3 (1.2)	0 (0.0)	
Financial concerns about investing in a platform	2 (2.5)	1 (0.4)	1 (6.3)	

CA, (post) COVID adopter; EA, early adopter; HIPAA, Health Insurance Portability and Accountability Act; NA non-adopter.

the fact that a greater percentage of EAs than CAs reported using platforms capable of asynchronous teledermatology (ie, uploading images), that allowed staff to join visits and required an "app" to use.

Image quality was highlighted as the greatest concern materially more often by CAs/NAs. Although our prior study indicated no material regional difference between EAs and CAs/NAs,[13] it is unclear how available mobile devices, mobile applications, and access to broadband internet play a role, especially among rural/lower socioeconomic patient populations with other barriers to healthcare access.[15] While asynchronous/SAF teledermatology can potentially partially mitigate these concerns, our previous study has found this method to be underused by ~50% of actively practicing US dermatologists.[13]

Of note, >30% of CAs reported using platforms without, at the time of writing, known integration with electronic medical records (EMRs), while 17.8% reported using Facetime as their current primary platform, which is not currently Health Insurance Portability and Accountability Act (HIPAA)-compliant. With the end of the COVID-19 public health emergency (May 11, 2023), covered healthcare providers have had until August 9, 2023, to transition to HIPAA-compliant platforms.[14] This may disproportionately affect private dermatologists and their ability to provide care to their patients.[1,5,13,16]

As CAs are disproportionately private dermatologists (a group that represents 80-90% of the current actively practicing US dermatologist workforce), it is important to understand the (evolving) role of technology in their practices.[5,16] With the end of the COVID-19 public health emergency, this may be an opportunity for CAs to expand their use of teledermatology, and adopt HIPAA-compliant platforms and additional modalities to care for all patient populations.

Limitations include retrospective study and response bias, with limited responses from NAs/rural dermatologists.

CONCLUSION

Our study demonstrates that teledermatology usage and implementation vary and correlate with when the technology was incorporated into US-based practices. Future studies should aim to investigate barriers to implementation, as well as how these barriers and teledermatology have impacted and may impact equitable access to dermatologic care.

DISCLOSURES

JWM has served as a Digital Health Fellow and an advisory board member for Doximity, Inc. RMC, MA, GHL, SP, and DSR have no relevant disclosures or conflicts of interest to declare.

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LETTERS TO THE EDITOR

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Tips, Trends, and Truths: A Study of Psoriasis Treatment Content on TikTok

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ABSTRACT

Introduction: With more than two billion downloads since its launch, TikTok is the fastest-growing video-sharing platform in the world. Many people turn to TikTok for dermatologic medical information. However, there is limited data about psoriasis and psoriasis treatment content on this social media platform.

Objective: To compare the viewer engagement, content quality, and viewer experience of psoriasis treatment TikTok videos between physicians and non-physicians.

Methods: We searched the terms "psoriasis" and "psoriasis treatment" on TikTok. Video characteristics were collected. Content quality was evaluated using DISCERN. Viewer experience was assessed using the AVA.

Results: Viewer engagement did not significantly differ between physicians and non-physician content creators (0.033±.005 vs 0.047±.001, P=0.066). Compared to non-physicians, physicians created videos of higher quality (DISCERN: 1.76±.058 vs 1.44±.032, P<0.001) and of greater viewer experience (AVA: 2.55±.183 vs 1.96±.081, P=0.001). However, there is room for improvement in terms of creating videos of higher quality by both physicians and non-physicians.

Conclusion: TikTok can be a powerful tool to promote health literacy and dispel misinformation. Dermatologists may consider focusing their efforts on creating comprehensive educational content and incorporating trending features to reach a wider audience.

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INTRODUCTION

Social media is a popular source of medical information.[1] Approximately 45% of individuals report that social media plays a role in their decision to seek medical care from a healthcare provider.[2] TikTok is a video-based application with more than two billion downloads since 2016, making it the fastest growing social media platform in the world.[1] A recent study found psoriasis to be among one of the most viewed dermatologic diseases on TikTok.[3] However, there is limited data about psoriasis treatment content on this social media platform. Given TikTok's increasing popularity, influence on health behaviors, and high viewership of psoriasis videos, it is necessary to characterize psoriasis content on this platform. The objective of this study is to compare the viewer engagement, quality, and viewer experience of TikTok videos relating to psoriasis and psoriasis treatment between physicians and non-physicians.

We conducted a cross-sectional analysis by performing a TikTok search of the terms *psoriasis* and *psoriasis treatment*. The top 120 videos that met the inclusion criteria were included in the analysis. Videos were included if they were related to psoriasis treatment, contained text or audio, and were in English. Videos included in the analysis were uploaded between March 28, 2020, and March 30, 2022. Viewer engagement was assessed using the following ratio: (number of comments + likes)/views. Content quality was evaluated utilizing the validated DISCERN instrument, a tool that analyzes consumer health information using a scale of one extensive shortcomings to five minimal shortcomings.[4] The Armstrong Viewer Assessment (AVA) assessed viewer experience using a scale of zero=poor to four=very good.[=] Content quality and viewer experience were evaluated by two independent raters. Two-tailed t-tests were used to compare mean DISCERN and AVA scores between physician and non-physician content creators. The threshold for significance was set at 0.05.

The top 120 psoriasis videos had 94,478,771 views, 4,433,402 comments, and 40,137 comments (Table 1). Videos were created by non-physicians (61.7%), physicians (21.7%), and private, skincare companies (16.7%; Table 1).

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TABLE 1.

Characteristics of Popular Psoriasis Content on TikTok

	No. of Videos (%)	Mean No. of likes	Mean No. of comments	Mean No. of views	Mean Viewer Engagement Ratio	Mean DISCERN (quality)	Mean AVA
Content Creator							
Individual - Non-Physician	74 (61.7)	49,280	422	554,698	.048±0.003	1.47±0.03	1.92±0.08
Individual - Physician	26 (21.7)	16,188	197	1,725,056	.033±0.005	1.76±0.05	2.55±0.18
Private Company	20 (16.7)	18,286	185	428,982	.041±0.007	1.31±0.03	2.10±0.19
Physician Subspecialty							
Dermatologist	23 (88.5)	18,187	218	1,945,434	.034±.006	1.74±.06	2.65±.19
Family Medicine	1 (3.9)	1,710	53	80,400	.021±NA	1.80±.NA	1.00±NA
Internal Medicine	1 (3.9)	817	44	20,700	.041±.NA	1.71±NA	2.00±NA
Podiatry	1 (3.9)	63	10	5,384	.013±.NA	2.25±NA	2.00±NA
Gender							
Female	80 (66.7)	50,206	423	627,409	.047±.003	1.45±.03	2.02±.09
Male	40 (33.3)	10,421	157	1,107,151	.038±.004	1.62±.04	2.22±.14
Video Type							
Anecdotal Experience	56 (46.7)	58108	500	1365952	.047±.004	1.41±.03	1.81±.08
Educational Content	37 (30.8)	6077	150	134719	.038±.004	1.77±.05	2.45±.17
Product Advertisement	27 (22.5)	35351	242	481514	.046±.007	1.35±.04	2.16±.15

NA; Not Applicable

Viewer engagement did not significantly differ between physicians and non-physician content creators (0.033±.005 vs 0.047±.001, *P*=0.066; Table 2). Compared to non-physicians, physicians created videos of higher quality (DISCERN: 1.76±.058 vs 1.44±.032, *P*<0.001) and greater viewer experience (AVA: 2.55±.183 vs 1.96±.081, *P*=0.001;Table 2). However, there is room for improvement in the creation of high quality videos by both physicians and non-physicians as indicated by a DISCERN score of 1-2.

As individuals continue to seek dermatologic health information on TikTok, high quality and accurate information must be available. Our findings suggest that the overall content quality could be improved by both physicians and non-physicians. Physicians may improve the quality of videos without sacrificing engagement by reviewing the risks and benefits of treatment, discussing mechanisms of action, and encouraging shared decision making. While this study did not assess accuracy, several videos claimed to provide a permanent solution to psoriasis. Dermatologists may combat misinformation by utilizing the "duet" feature on TikTok to directly respond to inaccuracies. Furthermore, with TikTok's recent extension of video limits to ten minutes, physician content creators can create thorough educational videos.

TABLE 2.

Video Characteristics Stratified by Physician vs. Non-Physician Professional Content Creators

	Physician (n=26)	Non-Physician (n=94)	*P*-value
Mean Viewer Engagement Ratio	.033±.005	.047 ±.003	0.066
Mean DISCERN	1.76±.058	1.44±.032	<0.001
Mean Armstrong Viewer Assessment	2.55±.183	1.96±.081	0.001

In addition to creating more comprehensive content, efforts should also be directed at reaching a wider audience. Although physicians shared videos of superior viewer experience compared to non-physicians, physicians only make up 21.7% of the content creators in the psoriasis space. Increasing the number of dermatologists on TikTok could be a promising initial step. However, it is also important for physicians to increase "virality" to expand viewership.[1] Physicians may do so by incorporating trending TikTok background songs, on-screen text, or wearing a white coat in their videos as these features were found to be included in top dermatologic educational content on TikTok.[1,6]

This study is limited by the scarcity of board-certified physicians on TikTok. Future research directions may focus on the efficacy of educational TikTok videos in increasing health literacy.

Given TikTok's increasing popularity, dermatologists should leverage the platform to deliver evidence-based dermatologic content to increase health literacy and dispel misinformation. Dermatologists should focus their efforts on increasing the quality of their videos by creating comprehensive educational

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content delivered in a short period of time and encouraging users to have an open dialogue with their physicians. Finally, dermatologists should incorporate trending features to reach a wider audience.

DISCLOSURES

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Topical Calcineurin Inhibitors in the Management of Chronic Pruritus in Older Adults: A Research Letter

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ABSTRACT

In this study, we aimed to analyze the literature to date on the utilization of topical calcineurin inhibitors in the management of pruritus among older adults, ages 65 and older. The 16 studies included in final analysis demonstrated that topical calcineurin inhibitors are well-tolerated across ages and are effective in treating a wide variety of chronic pruritic conditions. Collectively, these findings support that topical calcineurin inhibitors should be considered a safe, plausible option for managing age-associated itch.

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INTRODUCTION

Chronic itch is common among older adults, however, without overt serologic or histologic abnormalities, many geriatric patients have no discernible cause of their pruritus. In these cases, it is postulated that itching may be due to age-related immunologic and neuropathic pathophysiologic changes.[1] However, in the absence of a cohesive diagnosis, there is significant variability in the therapeutic strategies for managing itch in this population. This often results in undertreatment, exclusionary payer practices, and limited research efforts.

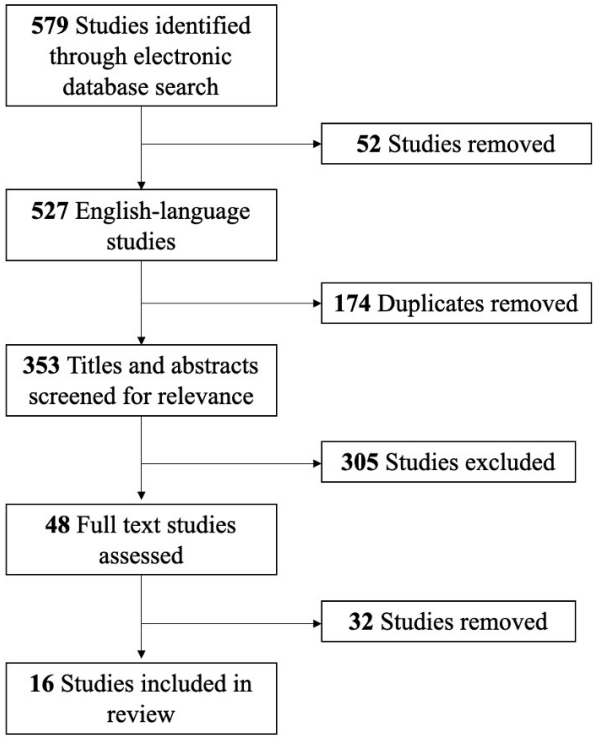
Topical calcineurin inhibitors (TCIs) are approved by the United States Food and Drug Administration for atopic dermatitis and have been reported to provide safe, rapid pruritus relief in these patients.[2] In addition to their anti-inflammatory effects, TCIs may also reduce itch by depleting pruritic neuropeptides in cutaneous nerve fibers,[3] and therefore, may serve as a therapeutic option for both inflammatory and neuropathic itch.[1]

Given the prevalence of itch among older adults and the anti-pruritic effects of TCIs, this study aims to evaluate the literature to date on the utilization of TCIs for pruritus management in older adults with the hopes of exploring another treatment option for age-associated itch.

MATERIALS AND METHODS

In May 2022, a scoping review of PubMed was conducted, limited to the English language, with search terms: 'calcineurin inhibitors', 'tacrolimus', 'pruritus', 'itch', 'elderly', 'older adult', and 'geriatric'. Studies were limited to those that included participants over the age of 65. The database search yielded a total of 579 articles, including 527 English-language studies.

FIGURE 1. Study selection methods.



Study selection flow diagram for the review of published studies on the use of topical calcineurin inhibitors in geriatric patients.

After removing 174 duplicate records and screening the remaining titles and abstracts for relevance, 48 full-text articles were reviewed (Figure 1).

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TABLE 1.

Studies Evaluating the Efficacy of Topical Calcineurin Inhibitors in the Management of Pruritic Conditions

Author	Diagnosis	Topical Therapy	Sample Size	Ages (years)	Itch Reduction	Medication-Related Adverse Effects
Ständer et al 2006[4]	Chronic pruritus, prurigo nodularis, anogenital pruritus	0.1% tacrolimus and 1.0% pimecrolimus	20	26-76	Mean reduction in itch of 67%	Burning (30%)
Ochi et al 2016[5]	Notalgia paresthetica	0.1% tacrolimus	7	Mean: 64.6	Reduction in itch intensity or frequency in 86% of patients	Burning (14%)
Patsatsi et al 2013[6]	Genital lichen sclerosis	Tacrolimus	46	Mean: 58.8	A significant decrease in itch (P=0.016)	None reported
Kelekci et al 2008[7]	Vulvar lichen simplex chronicus	1.0% pimecrolimus	12	44-65	A substantial decrease in pruritus at 1 (P<0.01) and 3 months (P<0.001)	Burning (33.3%)
Ucak et al 2013[8]	Pruritus ani	0.03% tacrolimus	32	18-66	Significant reduction in itching score at 4 (P=0.001), 6 (P=0.001), and 10 weeks (P=0.002)	Burning (12.5%)
Duque et al 2005[9]	Hemodialysis-related pruritus	0.1% tacrolimus	20	Mean: 59.6	No major difference in itch reduction between the tacrolimus and vehicle groups (P= 0.5).	Warmth/burning (67%)
Schulz et al 2007[10]	Asteatotic eczema	1.0% pimecrolimus	40	20-81	Pruritus severity was reduced by 65% (P=0.042)	None reported
Kim et al 2007[11]	Seborrheic dermatitis	1.0% pimecrolimus	20	22-79	Significant reduction in mean pruritus scores (P<0.001)	Burning/tingling (45%)
Acar et al 2010[12]	External auditory pruritus	1.0% pimecrolimus	43	24-69	Significant reduction in itch severity at 1 and 3 months (P<0.001)	Contact allergy (2.3%)
Kuypers et al 2004[13]	Uremic pruritus	0.1% tacrolimus	21	Mean: 61.6	Modified pruritis assessment score significantly reduced by 81.8% after 6 weeks of treatment	Tingling (19%), Stinging (4.8%), Rash (4.8%)
Weisshaar 2008[14]	Genital pruritus	1.0% pimecrolimus and 0.03% tacrolimus	2	67-73	Case 1: (1.0% pimecrolimus): Complete resolution of pruritus within 1 week through 3-month follow up Case 2: (0.03% tacrolimus): Complete resolution of pruritus within 2 weeks through 1-year follow up	None reported
Aguilar-Bernier et al 2005[15]	Primary biliary cirrhosis	0.1% tacrolimus	1	67	Complete resolution of pruritus and excoriations after 1 month of treatment without relapse at 6-month follow-up	None reported
Hanifin et al 2001[16]	Atopic dermatitis	0.03% and 0.1% tacrolimus	632	15-79	Significant reduction in pruritus score for both treatment groups (P<0.001)	No specific adverse events reported
Luger et al 2001[17]	Atopic dermatitis	0.6% and 1.0% pimecrolimus	130	18-71	Pimecrolimus 0.6% and 1.0% groups had a significant reduction in pruritus scores (P=0.001 and P=0.007)	Warmth/burning (43-49%)
Kaufmann et al 2006[18]	Atopic dermatitis	1.0% pimecrolimus	137	18-81	Significant improvement in pruritus (P=0.001)	Burning (3%)
Tan et al 2015[19]	Scrotal lichen simplex chronicus	0.1% tacrolimus	40	22-82	Significant reduction in mean itch score and itch frequency (P<0.0005)	Warmth or burning (30%)

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RESULTS

Among the 16 studies included in final analysis (Table 1), TCIs were used to treat various pruritic conditions, including chronic generalized pruritus. Only one study included exclusively patients over the age of 65 (n=2). Most studies (15/16) found that TCIs significantly improved pruritus. The most common adverse effect reported was transient application site burning, reported in 10/16 studies. There was a single report of a mild erythematous rash and one report of a contact allergy to TCIs, but there were no reports of serious infection or malignancy.

DISCUSSION

TCIs are generally well-tolerated and adverse effects are typically mild without increased concern of known side effects for older adults as compared younger populations. While a limited number of cases of lymphoma or skin cancer have been reported in patients receiving TCI therapy,[2] there is sparse evidence associating TCI use with malignancy.[20] When comparing this information to current treatment options for pruritus, TCIs avoid systemic immunosuppression, do not result in sedation, a potentially debilitating side effect for older adults, and are not associated with skin thinning.[21]

Still, data evaluating the efficacy of TCIs for pruritus in geriatric patients remains limited. This is unsurprising given the general underrepresentation of older adults in clinical trials.[22,23] Despite the paucity of primary literature, multiple articles highlight the use of TCIs as a plausible therapeutic option for pruritus in geriatric patients.[1,3,24] To our knowledge, this is the largest evaluation to date of its use in this neglected and underrepresented population. In conclusion, the summation of these studies helps providers and payers identify TCIs as a safe therapeutic option for age-associated itch.

DISCLOSURES

The authors have no conflict of interest to declare.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Implicit Bias and Clinical Decision Making in Psoriasis Management Among Dermatology Residents: A Feasibility Study

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Black and White individuals may not receive equal healthcare even when insurance status, income level, and access to health care are taken into account.[1] Despite psoriasis having an established standard of care, the black race is associated with a lower likelihood of receiving biologics among Medicare beneficiaries.[2] Implicit bias, which refers to subconscious beliefs that individuals have about other identity groups,[3] may perpetuate disparities by influencing physicians' clinical decision-making.[4] This IRB approved feasibility study assesses the association between implicit race bias, race-compliance stereotyping, and psoriasis patient management in dermatology residents.

A confidential online survey with a single, randomized vignette describing either a black or white 33-year-old male patient with severe plaque psoriasis was distributed to current US dermatology residents via the Association of Professors of Dermatology (APD) listserv from October 2021 to January 2022. Residents selected the best patient management option, rated their attitudes toward implicit bias using a Likert scale, and completed two Implicit Association Tests (IAT): Race and Race-Compliance.[5]

Data were analyzed using either Student t-tests or one-way ANOVA for normally distributed continuous variables when comparing two or more groups, and chi-square/Fisher exact tests for categorical variables, respectively; all tests were two-sided. The IAT d-scores range from -2 to +2, with positive d-score indicating implicit preference for white race relative to black race; a negative d-score indicates the converse.

Overall, 30 residents completed the survey (Table 1). Four dropped out before completing the Race IAT (n=26), and nine more dropped out before completing the Race-Compliance IAT (n=17). Residents assigned to either the white or black patient vignette were similar demographically (Table 1) and in their race and compliance IAT d-scores (Table 2).

Residents selected systemic, topical, and phototherapy at similar rates for both patient vignettes (P=0.99; Table 1). Though not statistically significant, biologics were chosen more often for the black patient (n=8, 50%) compared to the white patient (n=4, 28.6%, P=0.23; Table 1). Furthermore, Race IAT d-scores of residents assigned to the black patient show greater pro-white bias in residents who chose biologics (mean 0.32±0.25) compared to non-biologics (0.03±0.60, P=0.22) (Table 3). This difference is more pronounced when comparing the Race-Compliance IAT d-score between residents who chose biologics (0.23±0.31) versus non-biologics (-0.21±0.30) in the same group (P=0.06; Table 3).

Majority of residents agree that implicit bias may affect their management decisions (n=19, 63.3%), knowledge of their implicit biases may improve their clinical management (n=26, 86.7%), and formal training on implicit bias should be included in the residency curriculum (n=26, 86.7%; Table 1).

Our study demonstrated no statistically significant difference in dermatology residents' management of severe psoriasis between two different skin types. Additionally, residents were open to implicit bias education during residency training. Interestingly, biologics were chosen more often for the black patient compared to the white patient. This could be due to increased awareness of implicit bias and hypercorrection, perceived differences in disease severity from patient photos despite identical provided history, or study limitations: small sample size, risk of response and social desirability bias, and inability to determine response rate. Given the unexpected direction of implicit bias and associated clinical decision-making, as well as the limitations of vignette studies, future research in actual or simulated clinical settings could better advance our understanding of the role of implicit bias in clinical decision-making within dermatology.

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TABLE 1.

Comparing Residents' Demographics and Clinical Decisions by Assigned Vignette, and Perceptions of Implicit Bias Education and Impact

		Total N=30	White Vignette N=14	Black Vignette N=16	*P**
Year in Training, n (%)	PGY2	11 (36.7)	5 (35.7)	6 (37.5)	0.70
	PGY3	13 (43.3)	7 (50.0)	6 (37.5)	
	PGY4	6 (20.0)	2 (14.3)	4 (25.0)	
Residency Region, n (%)	Northeast	10 (33.3)	5 (35.7)	5 (31.3)	0.78
	South	1 (3.3)	0	1 (6.2)	
	Central	14 (46.7)	7 (50.0)	7 (43.8)	
	West	5 (16.7)	2 (14.3)	3 (18.7)	
Gender, n (%)	Female	14 (46.7)	5 (35.7)	9 (56.3)	0.26
	Male	16 (53.3)	9 (64.3)	7 (43.7)	
Latino/a/x, n (%)	No	26 (86.7)	13 (92.9)	13 (81.3)	0.55
	Yes	3 (10.0)	1 (7.1)	2 (12.5)	
	Unknown	1 (3.3)	0	1 (6.2)	
Race, n (%)	Non-Hispanic White	19 (63.4)	9 (64.3)	10 (62.5)	0.63
	Person of Color[a]	10 (33.3)	5 (35.7)	5 (31.3)	
	Unknown	1 (3.3)	0	1 (6.2)	
Therapeutic Route, n (%)	Systemic[b]	19 (63.3)	9 (64.3)	10 (62.5)	0.99
	Topical[c]	2 (6.7)	1 (7.1)	1 (6.2)	
	Phototherapy[d]	9 (30.0)	4 (28.6)	5 (31.3)	
Biologic Therapy, n (%)	Non-Biologic[e]	18 (60.0)	10 (71.4)	8 (50.0)	0.23
	Biologic[f]	12 (40.0)	4 (28.6)	8 (50.0)	
Q1: Management Decisions[g]	Disagree	8 (26.7)	--	--	--
	Neither Agree nor Disagree	3 (10.0)	--	--	
	Agree	19 (63.3)	--	--	
Q2: Knowledge[h]	Disagree	1 (3.3)	--	--	--
	Neither Agree nor Disagree	3 (10.0)	--	--	
	Agree	26 (86.7)	--	--	
Q3: Previous Training[i]	Disagree	3 (10.0)	--	--	--
	Neither Agree nor Disagree	2 (6.7)	--	--	
	Agree	25 (83.3)	--	--	
Q4: Residency Curriculum[j]	Disagree	0 (0)	--	--	--
	Neither Agree nor Disagree	4 (13.3)	--	--	
	Agree	26 (86.7)	--	--	

Footnote: **P*-values were generated using either one-way ANOVA or Student T-test by comparing scores across different groups.
[a]Person of Color consists of Asian (n=5), Multiracial (n=3), and Other (n=2)
[b]Systemic: methotrexate, acitretin, adalimumab, apremilast
[c]Topical: combination therapy with clobetasol and a topical vitamin D analogue
[d]Phototherapy: Narrowband UVB phototherapy
[e]Non-Biologic: combination therapy with clobetasol and a topical vitamin D analogue, Narrowband UVB phototherapy, methotrexate, acitretin, and apremilast
[f]Biologic: adalimumab
[g]Q1: Implicit (subconscious) bias about patients based on their race/ethnicity may affect the way I make management decisions.
[h]Q2: Knowledge of my implicit (subconscious) biases may help me improve my clinical management of patients.
[i]Q3: I previously had formal training on implicit (subconscious) bias in residency.
[j]Q4: Formal training on implicit (subconscious) bias should be included in the residency training curriculum.

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TABLE 2.

Comparing Race and Compliance IAT D-Scores Within Groups

		Race IAT			Compliant IAT		
		N (%)	D-Score mean (SD)	*P**	N (%)	D-Score mean (SD)	*P**
	Total	26 (100.0)	0.24 (0.45)		17 (100.0)	0.07 (0.29)	
Vignettes	White	10 (38.5)	0.33 (0.41)	0.38	7 (41.2)	0.08 (0.16)	0.81
	Black	16 (61.5)	0.17 (0.47)		10 (58.8)	0.05 (0.37)	
Year in Training	PGY2	10 (38.5)	0.22 (0.61)		5 (29.4)	0.25 (0.31)	
	PGY3	10 (38.5)	0.24 (0.39)	0.98	7 (41.2)	0.08 (0.25)	0.11
	PGY4	6 (23.0)	0.26 (0.24)		5 (29.4)	-0.14 (0.24)	
Residency Region	Northeast	10 (38.5)	0.39 (0.28)		6 (35.3)	0.15 (0.33)	
	South	1 (3.8)	0.23 (0)	0.53	0	--	0.6
	Central	10 (38.5)	0.08 (0.63)		6 (35.3)	-0.03 (0.37)	
	West	5 (19.2)	0.23 (0.23)		5 (29.4)	0.08 (0.10)	
Gender	Female	12 (46.2)	0.32 (0.23)	0.35	8 (47.1)	-0.03 (0.38)	0.25
	Male	14 (53.8)	0.16 (0.57)		9 (52.9)	0.15 (0.16)	
Race[a]	Non-Hispanic White	16 (64.0)	0.17 (0.51)	0.4	11 (64.7)	0.043 (0.35)	0.68
	Person of Color[b]	9 (36.0)	0.32 (0.34)		6 (35.3)	0.11 (0.15)	
Therapeutic Route	Systemic[c]	17 (65.4)	0.31 (0.26)		13 (76.5)	0.14 (0.25)	
	Topical[d]	2 (7.7)	0.51 (0.39)	0.16	0	--	0.07
	Phototherapy[e]	7 (26.9)	-0.031 (0.71)		4 (23.5)	-0.16 (0.33)	
Biologic Therapy	Non-Biologic[f]	15 (57.7)	0.16 (0.14)	0.32	9 (52.9)	-0.056 (0.25)	0.07
	Biologic[g]	11 (42.3)	0.34 (0.09)		8 (47.1)	0.20 (0.10)	

Footnote: **P*-values were generated using either one-way ANOVA or Student T-test by comparing scores across different groups.
[a]1 resident selected unknown race and was removed from this single analysis (N=25 instead of 26).
[b]Person of Color consists of Asian, Multiracial, and Other
[c]Systemic: methotrexate, acitretin, adalimumab, apremilast
[d]Topical: combination therapy with clobetasol and a topical vitamin D analogue
[e]Phototherapy: Narrowband UVB phototherapy
[f]Non-Biologic: combination therapy with clobetasol and a topical vitamin D analogue, Narrowband UVB phototherapy, methotrexate, acitretin, and apremilast
[g]Biologic: adalimumab

TABLE 3.

Comparing Race and Compliance IAT D-Scores for Different Therapies Stratified by Vignette

	Race IAT				Compliant IAT			
Type of Treatment	White Vignette		Black Vignette		White Vignette		Black Vignette	
Therapeutic Route	N (%)	D-Score mean (SD)	N (%)	D-Score mean (SD)	N (%)	D-Score mean (SD)	N (%)	D-Score mean (SD)
Systemic[a]	7 (70)	0.34 (0.30)	10 (62.5)	0.29 (0.24)	6 (85.7)	0.09 (0.18)	7 (70)	0.18 (0.31)
Topical[b]	1 (10)	0.78 (0)	1 (6.2)	0.23 (0.0)	0	--	0	--
Phototherapy[c]	2 (20)	0.09 (0.82)	5 (31.3)	-0.08 (0.76)	1 (14.3)	0.06 (0.0)	3 (30)	-0.24 (0.36)
*P**	--	0.44	--	0.38	--	0.9	--	0.17
Biologic Therapy	**N (%)**	**D-Score mean (SD)**	**N (%)**	**D-Score mean (SD)**	**N (%)**	**D-Score mean (SD)**	**N (%)**	**D-Score mean (SD)**
Non-Biologic[d]	7 (70)	0.31 (0.42)	8 (50.0)	0.03 (0.60)	5 (71.4)	0.07 (0.13)	4 (40.0)	-0.21 (0.30)
Biologic[e]	3 (30)	0.39 (0.48)	8 (50.0)	0.32 (0.25)	2 (28.6)	0.12 (0.29)	6 (60.0)	0.23 (0.31)
*P**	--	0.81	--	0.22	--	0.72	--	0.06

Footnote: **P*-values were generated using either one-way ANOVA or Student T-test by comparing scores across different groups.
[a]Systemic: methotrexate, acitretin, adalimumab, apremilast
[b]Topical: combination therapy with clobetasol and a topical vitamin D analogue
[c]Phototherapy: Narrowband UVB phototherapy
[d]Non-Biologic: combination therapy with clobetasol and a topical vitamin D analogue, Narrowband UVB phototherapy, methotrexate, acitretin, and apremilast
[e]Biologic: adalimumab

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DISCLOSURES

The authors have no conflicts of interest to declare.

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The Pediatric Dermatologist's View of Pediatric Vitiligo

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ABSTRACT

Background: No guidelines exist for pediatric vitiligo.
Objective: To identify practice patterns of pediatric dermatologists treating vitiligo.
Methods: A PeDRA survey was completed online by 56 pediatric dermatologists.
Results: Practitioners reported feeling most comfortable treating 13 to 17 years old and least comfortable treating infants. Quality of life was assessed by interview in 89.3%. Topical calcineurin inhibitors (TCI), topical corticosteroids (TCS), Narrowband UVB, coverup makeup, topical JAK inhibitors (tJAKi), and 308-nm laser were the leading vitiligo therapeutics chosen. 94.5% of practitioners reported experiencing frustration due to difficulties procuring therapies.
Conclusions: Pediatric vitiligo has notable effects on quality of life. Some therapeutic options exist which are preferred by pediatric dermatologists. There is a need for more data on therapeutics in infants and young children,

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To The Editor,

Few Surveyed practitioners provide medical intervention for vitiligo in the Netherlands.[1] In a recent United Kingdom qualitative patient survey, patients reported that their physicians had low awareness of the disease and available treatments, dismissing the disease as cosmetic.[2] There is evidence that in Saudi Arabia and India, there is a greater focus on therapy.[3,4] Little is known about pediatric dermatology practitioner attitudes and management of vitiligo.

A survey was designed by the Pediatric Dermatology Research Alliance (PeDRA) Skin of Color Focus Group investigators, reviewed by the PeDRA surveys committee, and received an exemption from the Mount Sinai Health Systems IRB.

Fifty-six of one hundred and seven eligible pediatric dermatologists completed the survey. Forty-four had been in practice for more than 5 years. Practitioners reported seeing an average of 8 pediatric and adolescent patients with vitiligo per month. The majority practiced in the US (n=45, 80.4%) and Mexico (n=6, 10.7%) and 48 were board-certified pediatric dermatologists; Providers surveyed reported feeling most comfortable treating older patients 13-17 (n=48, 85.7%), 5-8 (n=40, 71.4%), 2-4 years of age (n=18, 32.1%), less comfortable with toddlers and infants 13-23 (n=12, 21.4%), 7-12 (n=4, 7.1%), and 0-6 months (n=1, 1.7%) respectively. Quality of life (QoL) was assessed by interview (n=50, 89.3%), psychiatric screening (n=14, 25%), and QoL scores (n=11, 19.6%). Bloodwork was performed infrequently with full thyroid panels (n=38, 67.8%) and 25-OH vitamin D levels (n=27, 48.2%) being the most common labs (Table 1).

TABLE 1.

Demographics of Respondents	
Geographic Location	**n (%)**
United States	45 (80.4%)
Mexico	6 (10.7%)
Chile	1 (1.8%)
Costa Rica	1 (1.8%)
France	1 (1.8%)
Spain	1 (1.8%)
South Korea	1 (1.8%)
Bloodwork Performed	**n (%)**
Always Performed	13 (23.3%)
Usually Performed	12 (22.6%)
Sometimes Performed	11 (19.6%)
Rarely Performed	9 (16.1%)
Full Thyroid Panel	38 (67.8%)
25-OH Vitamin D	27 (48.2%)
Celiac	11 (19.6%)
Rheumatoid Factor	8 (14.3%)
Vitamin B12	8 (14.3%)
Zinc	5 (8.9%)
Copper	4 (7.1%)

Indicators of rapid color loss were thought to be ongoing color loss (n=49, 88%), acral location (n=33, 58.9%), greater than 25% depigmentation (n=32, 57.1%), and lesional poliosis (n=29, 51.7%). Greater than 50% color-loss (n=54, 96.4%), acral location (n=47, 83.9%), and prolonged disease course (n=42, 75%) were

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TABLE 2.

Therapeutic Choices for Vitiligo							
	<8-year-old with facial depigmentation <25% without eyelid localization	< 8-year-old with facial depigmentation <25% with eyelid localization	<8 years old with > or =25% depigmentation without eyelids	> 8-year-old with <25% BSA generalized depigmentation (trunk and extremities)	> 8-year-old with >25% BSA generalized depigmentation (trunk and extremities)	Segmental vitiligo localized to face	Segmental vitiligo localized to body
Topical calcineurin inhibitors	46 (82%)	52 (92.9%)	47 (81%)	29 (51.8%)	22 (39.3%)	46 (82.1%)	24 (42.9%)
Topical corticosteroids	29 (51.8%)	17 (30.3%)	30 (51.7%)	49 (87.5%)	39 (69.6%)	--	--
Class 1	5 (8.9%)	5 (8.9%)	5 (8.6%)	24 (42.8%)	16 (28.6%)	--	25 (44.6%)
Class 2	6 (10.7%)	2 (3.4%)	6 (10.3%)	12 (21.4%)	11 (19.6%)	--	10 (17.6%)
Class 3	9 (16.1%)	4 (6.8%)	9 (16.7%)	8 (14.2%)	7 (11.9%)	--	9 (16.1%)
Class 4	3 (5.3%)	4 (6.8%)	3 (5.2%)	5 (8.9%)	5 (8.5%)	--	4 (7.1%)
Class 5	6 (10.7%)	2 (3.4%)	5 (8.6%)	0 (0.0%)	0 (0.0%)	--	--
Narrowband UVB	5 (8.9%)	7 (11.9%)	7 (12.1%)	17 (30.4%)	31 (55.4%)	--	15 (26.8%)
Topical Jak inhibitors	5 (8.9%)	5 (8.9%)	6 (10.3%)	0 (0.0%)	5 (8.9%)	8 (14.3%)	5 (8.9%)
Coverup makeup	6 (10.7%)	8 (14.2%)	8 (13.8%)	0 (0.0%)	0 (0.0%)	--	--
Excimer laser	9 (16.1%)	5 (8.9%)	11 (19%)	8 (14.2%)	5 (8.9%)	14 (25%)	--
Oral Steroids	1 (1.8%)	0 (0.0%)	2 (3.4%)	0 (0.0%)	10 (17.9%)	--	--
Home Phototherapy	0 (0.0%)	0 (0.0%)	3 (5.2%)	5 (8.9%)	8 (14.3%)	--	--
Topical PUVA	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.4%)	2 (3.4%)	--	--

poor prognostic indicators in the opinion of survey participants. Topical calcineurin inhibitors (TCI), topical corticosteroids (TCS), Narrowband UVB, coverup makeup, topical JAK inhibitors (tJAKi), and 308-nm laser were the leading vitiligo therapeutics chosen (Table 2). Clinical photographs, measurement of lesion size (n=48 each, 85.7%), subjective patient-reported satisfaction (n=41, 73.2%), and percent re-pigmentation (n=34, 60.7%) were used most for disease monitoring. VASI scores (n=3, 5.3%), BSA (n=3, 5.3% and mobile device apps (n=1, 1.8%) were uncommonly used. Practitioners almost universally reported occasional to constant frustration in the care for pediatric vitiligo due to a lack of treatment options and insurance barriers (94.5%). Most (77.2%) reported always or often experiencing challenges in procuring appropriate therapies. Parental phobia of topical corticosteroid use in pediatric patients was noted to occur occasionally (n=29, 51.8%) to frequently (n=10, 17.8%).

TCI and TCS were favored for non-segmental and segmental vitiligo, with NB-UVB, excimer laser, tJAKi, and cosmetic cover-up being used consistently, but less frequently. Systemic agent usage was very limited. Barriers to the therapy of vitiligo identified by pediatric dermatologists include poor access to therapeutics, reduced comfort in treating children under 2 years of age, and parental anxiety. The publication of long-term safety data and an authoritative guideline to streamline diagnosis and treatment are warranted.

DISCLOSURES

Nanette Silverberg, MD has been a speaker and advisor for Astellas, and Incyte. Dr Schwartz and Mr Weingarten both report no conflicts of interest.

IRB: Pediatric Dermatology Research Alliance Approved IRB.

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NEWS, VIEWS, & REVIEWS

What's Old Is New: An Emerging Focus on Dermatoporosis

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INTRODUCTION

Defined by Kaya and Saurat in 2007, dermatoporosis is a chronic syndrome of excessive skin insufficiency/fragility.[1] This loss of the skin's mechanical strength is due to modifications of the extracellular matrix (ECM) and decreased viscoelasticity of the skin, primarily through the degradation of dermal collagen and elastic fibers and reduction of the glycosaminoglycan hyaluronate (HA) that stabilizes these fibers.[1] The most commonly diagnosed form is primary dermatoporosis, a result of chronological aging and chronic UV radiation exposure; secondary dermatoporosis is due to chronic topical or oral corticosteroid use. A limited number of studies from Europe have assessed the prevalence of dermatoporosis, with an estimated prevalence of 30.7–37.5% in patients 60 years and older, yet the prevalence is likely to increase as the aging population grows globally.[2,3]

Clinical Features of Dermatoporosis

Morphological features of dermatoporosis are skin atrophy, solar purpura, stellate pseudoscars, and superficial excoriations, particularly on sun-exposed sites (Figure 1).[4] The clinical staging of dermatoporosis considers clinical signs of skin fragility and skin thickness measured by ultrasonography (Table 1). Complications of dermatoporosis range from skin lacerations and delayed wound healing to deep dissecting hematomas that require surgical evacuation. Not simply a cosmetic concern, dermatoporosis truly impacts the morbidity and mortality of patients.[1]

Figure 1. (A) Dermatoporosis with pronounced skin atrophy and solar purpura, and a small laceration covered with a bandage. **(B)** Dermatoporosis following 11 months of topical treatment with daily application of calcipotriene 0.05% ointment and nightly application of tazarotene 0.045% lotion. Note improvement of skin atrophy and solar purpura, particularly on the forearms.

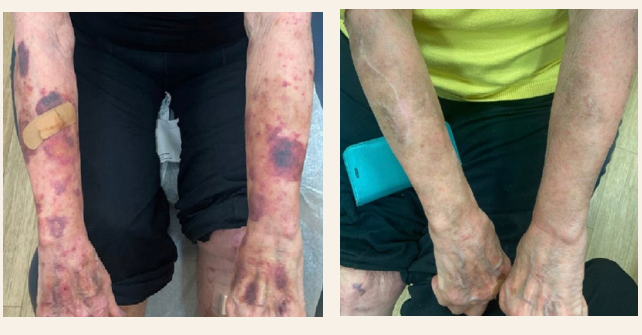

Table 1. Dermatoporosis Scoring System[4]

Clinical features	Absent	Present
Skin atrophy	0	1
Solar purpura	0	1
Stellate pseudoscars	0	1
Superficial excoriations	0	1
Small lacerations	0	2
Large lacerations	0	3
Superficial hematomas	0	4
Deep dissecting hematomas	0	5
Skin necrosis	0	6
Skin thickness (ultrasonography)	**Score**	
≤0.5 mm	3	
0.51–0.75 mm	2	
0.76–0.99 mm	1	
≥1 mm	0	
Score of dermatoporosis*	**Significance**	
0	No dermatoporosis	
1–7	Early stage	
8–9	Early intermediate stage	
10–12	Later intermediate	
13–16	Early advanced stage	
>16	Advanced stage	

*The global score of dermatoporosis is obtained by calculating the sum of all individual scores.

Pathophysiologic Mechanisms

HA and its cell surface receptor, CD44, are intricately linked to the pathogenesis of dermatoporosis, shown by the interaction of HA and CD44 to stimulate keratinocytes and the association of low levels of CD44 in dermatoporotic skin compared to young controls.[5,6] Moreover, levels of HA and expression of CD44 are known to decrease with age and following UVA and UVB exposure.[1,7] Histologically, dermatoporosis shows significant epidermal atrophy and a significantly increased number of cells in the epidermis positive for $p16^{Ink4a}$, a known biomarker of senescence.[8] Additional epidermal cellular markers of dermatoporosis include the preservation of Lrig1+ progenitor cells which inhibit the epidermal growth factor receptor, the decrease of Wnt signaling through loss of CD44 regulation, and the decreased expression of the calcium channel Orai-1 involved in keratinocyte proliferation.[8,9]

Treatment

Various topical and systemic therapies have been studied to treat dermatoporosis, including targeting the mechanistic pathways

discussed above, as well as supplementing with oral vitamin C and a bioflavonoid complex.[10,11] A mainstay of treatment is the application of topical retinoids as they upregulate HA and CD44 synthesis in mouse skin and reduce the signs of photoaging in clinical studies.[5,12,13] Moreover, the application of topical retinaldehyde plus intermediate-size hyaluronate fragments shows synergistic effects, with clinical improvement of purpura and skin thickness in addition to a significant reduction in $p16^{Ink4a}$-positive cells in the epidermis and dermis.[14–16]

Moreover, while vitamin D (VD) is a critical regulator of systemic calcium absorption and storage, it has essential functions in the skin. Notable effects of VD relevant to dermatoporosis include stimulating collagen synthesis, modulating the expression of genes contributing to epidermal development and maintenance, mitigating chronic inflammation associated with aging through anti-inflammatory effects, and providing cytoprotection in the setting of UV irradiation.[17] Given this relationship between VD and normal skin homeostasis, the use of VD analogs to treat dermatoporosis may be promising. The use of calcipotriene, a synthetic derivative of vitamin D3 (calcitriol), is well-established for the treatment of psoriasis through its inhibition of keratinocyte proliferation and induction of keratinocyte terminal differentiation.[18] Calcipotriene also improves wound healing through its promotion of keratinocyte migration and upregulation of human cathelicidin antimicrobial protein (hCAP18), a regulator of the innate immune response in the setting of tissue injury that promotes re-epithelialization and tissue repair.[19,20] Considering these results, focal supplementation of VD in the skin using an active analog such as calcipotriene may serve to reverse the dermatoporotic state, particularly in combination with a topical retinoid (Figure 2).

CONCLUSION

Dermatoporosis is a detrimental condition to the aging population and warrants continued study of its mechanisms and novel treatment options. While topical retinoids are well-known to effectively treat dermatoporosis, a vitamin D3 analog such as calcipotriene may be an additional, useful tool for treating and preventing this prevalent and deleterious skin disease.

Disclosure

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