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ORIGINAL ARTICLE

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Isotretinoin Does Not Increase the Risk of Inflammatory Bowel Disease: A TriNetX Retrospective Cohort Analysis

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ABSTRACT

Background: The increasing use of long-term, low-dose isotretinoin for acne has raised concerns about a potential association with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis.
Objective: To evaluate the association between isotretinoin therapy and the risk of IBD using a large real-world database.
Methods: We conducted a retrospective cohort study utilizing the TriNetX network. Patients with acne who received isotretinoin were compared to acne patients who were not exposed to isotretinoin. Propensity score matching (1:1) was performed to balance baseline characteristics. Patients were followed for 6 to 10 years post-exposure. Primary outcomes included incidence of IBD, Crohn's disease, and ulcerative colitis. Secondary outcomes included irritable bowel syndrome (IBS), fecal calprotectin elevation, and elevated lipid levels. Hazard ratios (HRs) were calculated using Cox proportional hazards models.
Results: Among 81,641 isotretinoin-exposed and 1,876,038 unexposed patients, 61,894 matched pairs were analyzed. Isotretinoin use was not associated with increased risk of IBD (HR: 0.88, 95% CI: 0.49–1.57) or ulcerative colitis (HR: 1.05, 95% CI: 0.78–1.41), and was associated with decreased risk of Crohn's disease (HR: 0.69, 95% CI: 0.51–0.94). IBS and fecal calprotectin elevation were not significantly different between groups. Lipid levels in the isotretinoin group were transiently elevated.
Conclusion: Long-term isotretinoin therapy does not increase the risk of IBD in acne patients.

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INTRODUCTION

Acne vulgaris is one of the most common chronic dermatologic conditions globally and often significantly affects quality of life. For moderate to severe and treatment-resistant acne, oral isotretinoin remains one of the most effective therapies.[1,2] Although isotretinoin is often used short-term, there is increasing interest in prolonged or repeated low-dose therapy and off-label applications for chronic dermatoses. These evolving use patterns have renewed concerns about the drug's long-term safety. A major concern that has been raised in the past was a potential association between isotretinoin use and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis.[3,6] Initial reports were based on case series or claims-based cohort studies, which lacked long-term follow-up, robust adjustment for confounders such as antibiotic exposure, or clinical detail.[5,6] More recent studies have questioned the validity of this association and even proposed a potential protective effect of isotretinoin.[7,10] However, findings remain inconsistent, and definitive conclusions are lacking. To address this question with greater clarity, we used the TriNetX network to conduct a large retrospective cohort study of acne patients with and without isotretinoin exposure. Our study differs from prior analyses in several ways. First, it utilizes real-world clinical data from multiple health systems and includes not only diagnostic codes, but laboratory values such as fecal calprotectin and low-density lipoprotein (LDL) levels. Unlike earlier studies based solely on administrative claims, our analysis included real-world laboratory data allowing for a more clinically meaningful assessment of intestinal inflammation and metabolic effects.

Second, we evaluated outcomes at 6-12 months, 5 years, and 10 years post-treatment, enabling a more comprehensive view of long-term risk. Finally, we used propensity score matching that controlled for relevant clinical covariates, including prior systemic antibiotic exposure which is a potential confounder that may have biased previous results.

We hypothesized that isotretinoin exposure would not be associated with increased incidence of IBD. We also evaluated irritable bowel syndrome (IBS) and fecal calprotectin to assess for subclinical gastrointestinal inflammation. IBS was included as a secondary outcome given that it can be an initial misdiagnosis in early IBD, and fecal calprotectin served as a validated biomarker of gut inflammation.[14] Together, these two outcomes served as ultra-sensitive markers for detecting underlying IBD.

Study Sample

We conducted a retrospective cohort study using the TriNetX Research Network, a global platform of de-identified electronic health records from over 100 healthcare organizations. Patients with a diagnosis of acne (ICD-10: L70) were identified and separated into two cohorts: those exposed to isotretinoin (RxNorm 197361) and those with no history of isotretinoin use. Long-term isotretinoin exposure was defined as having at least 6 months of therapy (≥6 prescriptions). The index date was the date of the first isotretinoin prescription for the exposed group and the date of acne diagnosis for the unexposed group. Patients were excluded if they had a prior documented diagnosis of IBD, IBS, prior fecal calprotectin testing, or hyperlipidemia requiring lipid-lowering treatment before the index date. Propensity score matching was performed to minimize confounding. Matching covariates included age, sex, race/ethnicity, BMI, smoking status, diabetes, and prior acne treatments such as systemic antibiotics and topical retinoids. This resulted in 61,894 matched patients in each cohort.

Outcomes

The primary outcomes were the presence of diagnosis codes for Crohn's disease (ICD-10 K50.x) or ulcerative colitis (ICD-10 K51.x) occurring after the index date. Secondary outcomes included new diagnoses of irritable bowel syndrome (ICD-10 K58.x) and elevated fecal calprotectin levels, which served as a marker of intestinal inflammation.

To assess metabolic side effects, we also evaluated new diagnoses of hyperlipidemia (ICD-10 E78.0) and laboratory results indicating elevated low-density lipoprotein (LDL) cholesterol levels >160 mg/dL and >180 mg/dL. All outcomes were evaluated at 6–12 months, 5 years, and 10 years post-index.

Statistical Analysis

Baseline characteristics between cohorts were assessed following matching. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of each outcome. Comparisons were made between isotretinoin-exposed and unexposed cohorts at each time point. All analyses were conducted using TriNetX's built-in analytic tools.

RESULTS

Baseline Characteristics

After matching, 61,894 isotretinoin-exposed patients were compared to 61,894 unexposed patients with acne. The cohorts were well-balanced across all matching variables. The mean age was approximately 22.5 years in both groups. Each cohort was approximately 55% female, and the racial/ethnic distribution was similar across groups. There were no significant differences in rates of smoking, diabetes, or prior systemic antibiotic or topical retinoid use. The only statistically significant difference was a slightly lower mean BMI in the isotretinoin group (24.6 vs 25), though this difference was not clinically meaningful. The distribution of patients across healthcare systems and follow-up duration was comparable between groups, ensuring sufficient power and long-term observation.

Ulcerative Colitis, Crohn's Disease, and Fecal Calprotectin

There was no significant difference in the incidence of ulcerative colitis between isotretinoin-exposed and unexposed patients (HR = 1.05, 95% CI: 0.78–1.41). Notably, Crohn's disease occurred less frequently in the isotretinoin group (HR = 0.69, 95% CI: 0.51–0.94), suggesting a potential protective effect. These outcomes remained stable at both the 5-year and 10-year timepoints.

Although isotretinoin-exposed patients had slightly higher rates of elevated fecal calprotectin (HR = 1.27, 95% CI: 0.91–1.78), the difference was not statistically significant. This biomarker of subclinical intestinal inflammation did not translate into increased IBD diagnoses, indicating that any inflammation present was not clinically consequential.

Irritable Bowel Syndrome

Rates of irritable bowel syndrome (IBS) were not significantly different between groups (HR = 0.93, 95% CI: 0.80–1.07). The inclusion of IBS as a secondary outcome reflects its potential role as an early diagnostic label for patients who later receive a diagnosis of IBD; however, no significant signal was detected.

Hyperlipidemia Diagnosis

Diagnoses of hyperlipidemia (ICD-10 E78.0) were more frequent among isotretinoin users during and shortly after treatment. Long-term follow-up showed no significant increase in new hyperlipidemia diagnoses between groups, reinforcing the short-lived nature of this effect.

LDL >160 and LDL >180

Direct laboratory measurements of cholesterol elevations were more common among isotretinoin-exposed patients at 5-year follow-up. Patients in this group were more likely to develop LDL levels >160 mg/dL and >180 mg/dL compared to the unexposed cohort. However, by 10-year follow-up, the difference in LDL elevations had resolved, with rates returning to levels comparable to the control group. These findings support the idea that isotretinoin-induced hyperlipidemia is transient and reversible.

TABLE 1.

Baseline Characteristics After Propensity Score Matching			
Characteristic	**Exposed Patients**	**Control Patients**	***P*-Value**
Demographics			
Age at Index (Mean ± SD)	22.4 ± 10.7	22.6 ± 10.9	0.1179
Female (%)	55%	55.80%	0.30
Male (%)	44.51%	43.73%	0.31
White (%)	65.03%	66.43%	0.06
Hispanic or Latino (%)	12.18%	11.94%	0.64
Asian (%)	7.8%	7.38%	0.32
Black or African American (%)	5.59%	5.17%	0.23
Diagnoses			
Hidradenitis Suppurativa (%)	2.33%	1.91%	0.07
Diabetes Mellitus (%)	1.99%	1.60%	0.06
Alcohol-Related Disorders (%)	0.94%	0.76%	0.19
Tobacco Use (%)	0.46%	0.36%	0.32
Medications			
Tetracyclines (%)	62.16%	62.08%	0.92
Tretinoin (%)	50.33%	51.07%	0.35
Clindamycin (%)	49.00%	49.26%	0.74
Corticosteroids for Systemic Use (%)	43.85%	43.42%	0.57
Adapalene (%)	20.43%	21.31%	0.16
BMI (Mean ± SD)	24.6 ± 5.81	25 ± 6.26	0.003

TABLE 2.

Six Months of Isotretinoin Therapy						
Condition	**Outcomes Over 5 Years**			**Outcomes Over 5-10 Years**		
	Number of Outcomes (Exposed)	**Number of Outcomes (Control)**	**Hazard Ratio (95% CI)**	**Number of Outcomes (Exposed)**	**Number of Outcomes (Control)**	**Hazard Ratio (95% CI)**
Ulcerative Colitis	20	14	1.16 (0.58, 2.31)	17	27	0.91 (0.49, 1.68)
Crohn's Disease	55	77	0.69 (0.49, 0.98)	<10	26	0.39 (0.17, 0.90)
All Inflammatory Bowel Disease	24	22	0.88 (0.49, 1.57)	20	46	0.63 (0.37, 1.07)
Calprotectin	90	57	1.27 (0.91, 1.78)	79	107	1.07 (0.80, 1.43)
LDL > 160 mg/dL	1178	315	3.55 (3.14,4.02)	95	132	1.11 (0.85,1.44)
LDL > 180 mg/dL	459	105	3.07 (3.29, 5.04)	44	64	1.04 (0.75, 1.45)
Irritable Bowel Syndrome	99	97	0.81 (0.61, 1.07)	111	157	1.01 (0.70, 1.52)
Hyperlipidemia	210	140	1.22 (0.98, 1.51)	216	258	1.27 (1.05, 1.52)

TABLE 3.

Twelve Months of Isotretinoin Therapy						
Condition	Outcomes Over 5 Years			Outcomes Over 5-10 Years		
	Number of Outcomes (Exposed)	Number of Outcomes (Control)	Hazard Ratio (95% CI)	Number of Outcomes (Exposed)	Number of Outcomes (Control)	Hazard Ratio (95% CI)
Ulcerative Colitis	23	22	0.84 (0.47, 1.51)	<10	<10	0.69 (0.24, 2.01)
Crohn's Disease	16	20	0.64 (0.33, 1.24)	<10	<10	0.45 (0.08, 2.50)
All Inflammatory Bowel Disease	208	248	0.65 (0.54, 0.78)	<10	<10	0.72 (0.26, 1.93)
Calprotectin	103	64	1.31 (0.96, 1.79)	24	19	1.15 (0.70, 1.89)
LDL > 160 mg/dL	285	56	4.35 (3.26,5.79)	26	27	0.99 (0.57,1.70)
LDL > 180 mg/dL	102	21	4.12 (2.12, 6.59)	16	15	1.06 (0.52, 2.15)
Irritable Bowel Syndrome	100	112	0.70 (0.54, 0.92)	33	24	1.33 (0.79, 2.26)
Hyperlipidemia	179	101	1.44 (1.03, 1.84)	71	38	1.87 (1.26, 2.77)

DISCUSSION

In this large retrospective cohort study, isotretinoin use was not associated with an increased risk of inflammatory bowel disease. Our analysis of over 120,000 matched acne patients across a decade of follow-up showed no significant association between isotretinoin and ulcerative colitis or overall IBD. Notably, isotretinoin use was associated with a lower risk of Crohn's disease, consistent with findings from prior large-scale studies that observed a similar signal.[11] These results reinforce the long-term gastrointestinal safety of isotretinoin, including in patients receiving extended or repeated courses of therapy. This study contributes novel insights to the ongoing debate around isotretinoin and IBD risk. Unlike earlier investigations that relied solely on insurance claims data, this analysis used real-world electronic health record data from multiple health systems incorporating both diagnostic and laboratory outcomes. In particular, we included fecal calprotectin, a noninvasive biomarker of intestinal inflammation, and LDL cholesterol, a key marker of isotretinoin-related metabolic effects. While some prior studies examined IBD incidence, most did not assess subclinical gut inflammation or track lab-confirmed metabolic changes over extended follow-up. Our ability to analyze these endpoints makes this study uniquely valuable in understanding isotretinoin's long-term risk profile.

Additionally, our design addressed an important confounder that may have biased earlier studies: prior antibiotic exposure. Because long-term antibiotic use for acne has been independently associated with IBD, we matched patients on this variable to isolate the effect of isotretinoin itself.[5,6] This strengthens our ability to attribute findings directly to isotretinoin and not to co-administered medications.

We also evaluated IBS as a secondary endpoint, given that it is often an early or alternative diagnosis in patients who later develop IBD.[14] Our finding of no increase in IBS among isotretinoin users further supports the absence of a gastrointestinal signal. Similarly, although fecal calprotectin elevations trended higher in the isotretinoin group, they were not statistically significant and did not correspond with IBD diagnoses, suggesting any observed inflammation was subclinical and transient.

As expected, we observed a temporary increase in serum LDL levels during isotretinoin treatment. This effect diminished after drug discontinuation. These results are consistent with earlier research showing that lipid elevations during isotretinoin therapy are reversible and not associated with long-term cardiovascular risk.[12]

Limitations of this study include its observational design and reliance on ICD-10 codes and laboratory data without individual chart validation. While propensity score matching reduced measured confounding, residual unmeasured bias is possible. For example, clinicians may be less likely to prescribe isotretinoin to patients with baseline gastrointestinal symptoms, which may have influenced our findings.

CONCLUSION

This large, multicenter cohort study found no evidence that isotretinoin increases the risk of inflammatory bowel disease using real-life laboratory data. Ulcerative colitis and overall IBD rates were not elevated among isotretinoin-exposed patients, and a significant reduction in Crohn's disease risk was observed. While mild laboratory elevations in fecal calprotectin and LDL cholesterol occurred during treatment, these changes were not sustained and did not correspond to clinical disease. These findings provide reassurance that isotretinoin is not a trigger for IBD and that its gastrointestinal safety profile is favorable. Continued laboratory monitoring during therapy remains appropriate, particularly for lipids, but long-term concerns about IBD risk appear unsupported.

DISCLOSURES

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ORIGINAL ARTICLE

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GLP-1 Receptor Agonists in Hidradenitis Suppurativa: A Novel Therapeutic Approach for Hidradenitis Suppurativa and Its Comorbidities

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder associated with many comorbidities, including obesity, diabetes, cardiovascular risk factors, mental health issues, and many more disorders. Current treatments including biologics, topicals, and surgical interventions often fall short in terms of patient satisfaction, demonstrating a need for additional innovative approaches that address HS-related comorbidities.

Objective: This review explores the novel application of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in HS treatment, particularly for patients with comorbid conditions such as metabolic syndrome, diabetes, and obesity. Emphasis is placed on combination therapy and the potential for GLP-1RAs to address both HS symptoms and associated comorbidities, with careful consideration of patient selection.

Methods: A review of emerging evidence and existing literature on GLP-1RAs and their applications for weight loss, metabolic regulation, and anti-inflammatory effects was conducted.

Findings: GLP-1RAs offer dual benefits for HS patients by modulating inflammatory pathways and addressing associated comorbid conditions. Case studies and preliminary data suggest that GLP-1RAs may reduce lesion severity, systemic inflammation, and morbidity, either as monotherapy or in conjunction with existing treatments. However, high-quality randomized controlled trials are indicated to confirm these findings.

Conclusion: GLP-1RAs represent a promising adjunctive or standalone treatment choice for those with HS and its related comorbidities. Further research is needed to establish their safety and efficacy in HS treatment.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition associated with significant physical, economic, and psychosocial burdens.[1] It is characterized by painful follicular occlusions, primarily at intertriginous locations, which can further manifest as nodules, abscesses, skin tunnels, and fibrosis.[2] HS is frequently associated with comorbidities such as obesity, diabetes, and metabolic syndrome[3], which can exacerbate systemic inflammation.[4] Despite the multitude of existing treatments for HS–including topicals, oral antibiotics, and biologics–many patients are dissatisfied with available therapies[5], underscoring the need for innovative treatments.

Glucagon-like peptide-1 Receptor Agonists (GLP-1RA) medications have emerged as a novel treatment opportunity for HS patients. Initially implemented as a type 2 diabetes mellitus (T2DM) medication, GLP-1RAs have demonstrated efficacy for weight loss and are used off-label for their systemic anti-inflammatory effects.[6] Preliminary studies have suggested that GLP-1RA may improve HS morbidity by reducing mechanical stress and systemic inflammation, while simultaneously addressing multiple comorbidities that often present with HS.[7]

The pathogenesis of HS is complex and not fully understood. Lesions generally begin with defective hair follicle maturation, resulting in occlusion and rupture. This leads to exaggerated proliferation of both keratinocytes and the immune system, with neutrophilic and lymphocytic predominance. HS is strongly associated with immune abnormalities, oxidative damage,[8] and elevated cytokine pathways, including tumor necrosis factor-alpha (TNF-α), interleukin-17A (IL-17A), interleukin-17F (IL-17F), interleukin-1 beta (IL-1β), interleukin-23 (IL-23), and interleukin-26 (IL-26).[2,7]

HS has been associated with a host of comorbid conditions that may impact treatment outcomes, worsening both HS morbidity and overall patient health. These conditions include, but are not limited to[9]:

- Depression and anxiety
- Smoking and substance use disorder
- Polycystic ovary syndrome (PCOS)
- Obesity, dyslipidemia, and metabolic syndrome
- Diabetes mellitus and hypertension
- Cardiovascular disease
- Inflammatory bowel disease (IBD)
- Spondyloarthritis
- Sexual dysfunction

Existing Treatments for HS

HS treatment requires a multifaceted approach, targeting both local and systemic aspects of the disease.

Despite the options in Table 1,[10] up to 45% of patients report dissatisfaction with existing treatments.[5] For example, the first-line biologic agents such as adalimumab (TNF-α inhibitor) and secukinumab (IL-17A inhibitor) have shown efficacy, but are associated with significant limitations, including patient dissatisfaction and infection risks.[10] Additionally, these therapies do not address the common concurrent conditions that often present with HS. This highlights the need for innovative approaches that also target associated comorbidities.

Mechanism of GLP-1RAs and Emerging Evidence for HS

Glucagon-like peptide 1 (GLP-1) is an endogenous peptide hormone that acts on L-cells lining the ileum and colon and is primarily known for its role in glucose metabolism. Postprandially, GLP-1 enhances β-cell proliferation, suppresses glucagon, and slows gastric emptying.[11] Beyond metabolic effects, GLP1-RAs exhibit systemic anti-inflammatory activity by modulating the Nuclear factor kappa B (NF-κB) pathway, TNF-α, IL-6, and IL-1β.[6,7,8,12,13]

For refractory HS cases, GLP-1RAs provide unique advantages by targeting oxidative stress—a key component of HS pathology that is not addressed by biologics. Elevated ischemia-modified albumin (IMA) levels in patients with severe HS emphasize the role of oxidative damage,[8] which GLP-1RAs can alleviate by stabilizing NF-κB inhibitors.[6]

Preliminary evidence suggests that these mechanisms may benefit HS patients, given that HS is often characterized by systemic inflammation.[14] Case studies and retrospective analyses of liraglutide, semaglutide, and tirzepatide have reported reduced lesion count, systemic inflammation, and patient-reported flares.[15,16,17] These preliminary findings suggest GLP-1RAs as a promising adjunctive or standalone therapy for HS, though large-scale randomized controlled trials are needed to confirm these findings.

Details of Common HS Comorbidities and the Potential Role of GLP-1RAs

In addition to their use for T2DM and promising preliminary results in HS treatment, GLP-1RAs have many systemic effects that can be applied toward other contributing and comorbid conditions that exist in patients with HS.

Obesity

Obesity exacerbates HS through mechanisms including systemic inflammation and mechanical stress placed on lesions.[7] Patients who are overweight typically have larger

TABLE 1.

Current Treatment Options for Hidradenitis Suppurativa. This table provides an overview of existing treatment modalities for hidradenitis suppurativa, including topical, systemic, and surgical approaches.

Treatment Type	Treatment	Description
Topical and Localized Therapies	Topical Clindamycin	Reduces bacterial load and has anti-inflammatory properties.
	Resorcinol	A keratolytic agent.
	Intralesional Corticosteroids	Reduces localized inflammation and lesion size.
Systemic Therapies	Oral Antibiotics	Tetracyclines (e.g., doxycycline) and rifampin-clindamycin combinations.
	Adalimumab	A TNF-α inhibitor.
	Secukinumab	An IL-17A inhibitor.
	Bimekizumab	Newest FDA approved biologic, inhibits both IL-17A and IL-17F.
Surgical Interventions	Deroofing	Opens and drains sinus tracts, reducing lesion recurrence.
	Excision	Removes affected tissue, however, can lead to scarring and recurrence rate approaches 100%.
	CO2 Laser	Used for lesion excision.

TABLE 2.

FDA-Approved GLP-1 Receptor Agonists for Weight Loss. This table outlines the effectiveness of liraglutide, semaglutide, and tirzepatide in weight management and their implications for HS treatment.

Medication	Study Results
Liraglutide	In a 56-week study, patients receiving liraglutide achieved significant weight loss compared to placebo, with 63.2% losing at least 5% of their body weight and 33.1% losing over 10% (P<0.001).
Semaglutide	In a 68-week trial, participants receiving semaglutide experienced significant weight loss (–14.9% vs –2.4% with placebo, P<0.001), with 86.4% achieving ≥5% weight loss and 50.5% achieving ≥15% weight loss.
Tirzepatide	Tirzepatide, the most recently approved, has dual-agonist properties, agonising both GIPR and GLP-1R. This has been shown to enhance insulin secretion, reduce blood glucose, and promote greater weight loss through synergistic effects on hypothalamic neurons involved in appetite regulation. One three year long study displayed the effects in weight loss. At 176 weeks, tirzepatide led to significant dose-dependent weight loss (–12.3% to –19.7% vs –1.3% with placebo, P<0.001) and reduced the incidence of type 2 diabetes (1.3% vs 13.3%, P<0.001).

intertriginous folds, contributing to the mechanical stress on lesions.[18] Excess adipose tissue and insulin resistance have also been linked to chronic systemic inflammation due to metabolic dysregulation, resulting in exacerbation of HS due to its highly inflammatory nature. A recent cross-sectional study showed a poorer metabolic profile, higher central adiposity, and a higher prevalence of metabolic syndrome in those with HS.[4] Considering these factors, Patients who lose excess fat have been shown to have better clinical outcomes, with a reduction in both HS severity and subsequent remission.[18]

The current FDA-approved GLP-1 RAs indicated for weight loss include liraglutide and semaglutide, as well as dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor (GIPR) agonist tirzepatide.[20] These agents are associated with significant weight loss. Liraglutide specifically has been shown to reduce HS lesion severity by modulating key inflammatory pathways and contributing to overall weight reduction.[19] Study details are displayed in Table 2.[21,22,20,23,24]

Cardiovascular Risk Factors

HS is associated with increased cardiovascular risk due to its associations with obesity, smoking, hypertriglyceridemia, and diabetes. A systematic review comparing 6,174 HS patients with 24,993 controls revealed significant associations with obesity (OR 3.45), smoking (OR 4.34 for active smokers, OR 6.34 for former smokers), hypertriglyceridemia (OR 1.67), and diabetes (OR 2.85).[25,26]

GLP-1RAs have been shown to reduce cardiovascular risk factors through various systemic mechanisms, including reducing atherosclerotic events, reducing inflammation, lowering blood pressure, weight loss, lipid modulation, and improving cardio-renal health.[27] Specifically, liraglutide, semaglutide, and tirzepatide have all been shown to reduce cardiometabolic risk factors.[28,29,30]

Depression

HS has significant mental health impacts, and several studies have linked HS with depression. Senthilnathan et al. found that 33% of those with HS also had major depressive disorder, and also found no correlation between HS severity and depression severity, suggesting that even those who struggle with mild disease may suffer from mental health impacts. Similarly, several systematic reviews and meta-analyses further confirm this association, with depression prevalence in HS patients ranging from 16.9% to 26.5%, which is much higher than in populations without HS.[31]

Emerging studies have suggested that GLP-1RAs may reduce symptoms of depression, the mechanism of which is theorized to be a reduction in inflammation and improved brain insulin signaling. Chen et al performed a review of six studies comprising 2,076 patients total, and found that those on GLP-1RAs had lower depression rating scale scores compared to the controls, with liraglutide producing the most significant effect. Further robust clinical studies are needed, however, given the small sample size and to establish causation.[32]

Polycystic Ovarian Syndrome (PCOS)

Polycystic Ovarian Syndrome (PCOS) is a common endocrine disorder in women characterized by hormonal imbalance, insulin resistance, and chronic inflammation, all of which contribute to metabolic and reproductive complications. Its complex pathogenesis involves genetic and environmental factors, including geography, diet, socioeconomic status, and pollutants.[33] PCOS is strongly associated with HS, and one cross-sectional study of 22,990 HS patients found a 9.0% prevalence of PCOS, compared to 2.9% in those without HS (P<0.0001). HS patients were 2.14 times more likely to have PCOS, highlighting the need for screening in those with androgen excess.[34]

GLP-1RAs have emerged as a promising treatment for the metabolic complications of PCOS, improving insulin resistance, obesity, and dyslipidemia. GLP1-RAs offer additional benefits compared to the traditional PCOS therapies, such as metformin, as they promote weight loss, appetite regulation, and improved glucose metabolism. GLP-1RAs have demonstrated BMI reduction, reduced androgen levels, and added improvements in cardiovascular health in PCOS patients.[35] Given that both

HS and PCOS exhibit associations with metabolic dysfunction, GLP-1RAs may represent a novel therapeutic option for both conditions, addressing their shared inflammatory and insulin-resistant pathophysiology.

Type 2 Diabetes Mellitus (T2DM)

Type 2 Diabetes Mellitus (T2DM) is a condition characterized by an initial resistance of the pancreatic B-cells to the actions of insulin, with eventual loss of B-cells and loss of endogenous insulin production.[36] DM, specifically T2DM, is a common comorbidity in HS, with a prevalence of 20.2% among HS patients. HS patients, especially those with advanced versions of the condition (Hurley stage III), face a significantly higher risk of developing DM, with a 5.3-fold greater likelihood than those with milder HS.[37]

GLP1RAs are a first-line treatment for T2DM, and have been since 2005. They modulate T2DM by stimulating endogenous insulin secretion, suppressing glucagon, and delaying gastric emptying, all of which also promote weight loss. They can also reduce inflammation and cardiovascular risk factors. By improving insulin sensitivity, promoting weight loss, improving cardiovascular risk factors, and reducing pro-inflammatory cytokines, GLP-1 RAs may help alleviate both T2DM and HS symptoms; however, more robust studies are needed.[38]

Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a burdensome gastrointestinal condition characterized by chronic inflammation and lesions throughout the bowel. It has a strong immune basis, genetic influences, and environmental triggers. IBD can be subclassified into either Crohn's disease (CD) or Ulcerative Colitis (UC), with CD involving transmural inflammation of the ileum and colon with "skip lesions", and UC involving the epithelium of the entire rectum.[39]

HS is strongly associated with IBD. A meta-analysis of eight studies, including over 93,000 patients found a significant association between hidradenitis suppurativa (HS) and inflammatory bowel disease (IBD). Two case-control studies and a cohort study further supported this association, showing a 5.6-fold increased risk of IBD in HS patients.[40]

HS and IBD share genetic susceptibility, immune dysregulation, and altered microbiota. Both conditions also involve elevated inflammatory cytokines such as TNF-α, interleukin-1β, and interleukin-6, and respond to TNF inhibitors,[41] therefore, making their pathogenesis quite similar and suggesting that GLP1-RAs may be effective in treating both.

Spondyloarthritis (SpA)

Spondyloarthritis (SpA) is an umbrella term for a group of inflammatory rheumatic diseases, including axial spondyloarthritis, psoriatic arthritis, reactive arthritis, arthritis associated with chronic inflammatory bowel disease, and undifferentiated spondyloarthritis. Its pathogenesis is closely tied to overproduction of inflammatory cytokines such as TNFα, IL-17A, IL-23, IL-6, IL-1 beta, and IFN-gamma.[42,43]

SpA exhibits a powerful association with HS and has been shown to be an independent risk factor for the development of the disease. One cross-sectional study investigated the prevalence of SpA in patients with HS compared to healthy controls. Results found that 28.2% of HS patients were diagnosed with SpA, compared to 2.6% of controls, showing an 11-fold increased risk of SpA in HS patients.[44]

GLP1-RAs may be indicated as a novel treatment for SpA given their anti-inflammatory properties, specifically targeting proinflammatory cytokines, including TNF-α, IL-6, and IL-1β.[12] Given the strong association between SpA and HS, and the shared inflammatory pathways between these conditions, further investigation may position GLP-1RAs for the treatment of SpA in HS.

GLP-1RAs Risks

While GLP-1RAs are generally safe, the patient selection process must consider certain contraindications. Studies of GLP-1RA effects on mice have demonstrated C-cell hyperplasia and calcitonin release, suggesting medullary thyroid cancer risk;[45] however, this has not been reproduced in any human studies. Gastrointestinal issues such as pancreatitis, gastroparesis, and bowel obstruction have also been associated with GLP-1RAs.[46] These side effects are rare, however, and the most common side effects are nausea, vomiting, diarrhea, and constipation, as described in Table 3.[47,21,22,24]

TABLE 3.

Common Adverse Effects of FDA-Approved GLP-1RAs This table summarizes the most common side effects of GLP-1 receptor agonists, primarily gastrointestinal symptoms, with rare but serious risks.

Medication	Side Effects
Liraglutide	The most common adverse events were mild to moderate nausea and diarrhea, with serious events occurring in 6.2% of the liraglutide group versus 5.0% of the placebo group.
Semaglutide	Gastrointestinal side effects such as nausea and diarrhea led to a higher discontinuation rate (4.5% vs 0.8% with placebo).
Tirzepatide	Most adverse events were mild-to-moderate gastrointestinal issues occurring during the initial dose-escalation phase, with no new safety concerns identified.

Combination Therapy

Rationale for Synergistic Treatment

Biologics (adalimumab, secukinumab, or bimekizumab) are currently considered the standard treatment for refractory HS,[10] but do not target oxidative stress, which has been shown to be a key contributor to HS pathogenesis.[8] Some HS patients fail to achieve satisfactory control of their disease even after trying the existing treatment modalities,[5] suggesting a need for novel treatment options.

GLP-1RAs may complement biologics by targeting systemic inflammation and metabolic dysfunction, thus addressing HS from multiple angles. The modulation of cytokine pathways from biologics[10] in combination with the systematic reduction in inflammation resulting from GLP-1RAs[6] may work in tandem to address multiple mechanisms responsible for the pathogenesis of HS.

Emerging case studies and observational data suggest potential benefits of combining GLP-1RAs with biologics. A case report of a patient with severe HS, who initially saw some improvement with the biologic infliximab, was started on concurrent tirzepatide. After 8 months, robust improvements in HS abscess size, nodule counts, and overall quality of life were observed.[17] This underscores the possibility of combining these medication classes for a more comprehensive approach for treating HS; however, more rigorous clinical trials are needed to address efficacy and safety profiles.

Designing Combination Therapy Protocols

For patients tolerating biologics, GLP-1RAs may enhance outcomes. In patients with more severe HS, initiating both therapies concurrently could provide more comprehensive symptom relief.

For patients unable to tolerate biologics, a standalone approach with GLP-1s may be possible.

This may also be an effective approach for patients with mild HS and one or more co-existing conditions that may be addressed with novel GLP-1 therapy. This may be more cost-effective and a way to reduce polypharmacy.[48]

Practical Implications

Clinical Integration

To integrate GLP-1RAs into HS management, dermatologists must collaborate with endocrinologists and primary care physicians to address patient comorbidities comprehensively. Multidisciplinary care models are essential for optimizing patient outcomes.[49]

All patients should have regular follow-up and be monitored, with strategies such as regular assessments of weight, HS severity (eg, International Hidradenitis Suppurativa Severity Score System [IHS4]),[50] and other metabolic parameters to monitor existing comorbidities.

Cost and Accessibility

The high cost of GLP-1RAs is a barrier to access. GLP-1 RAs, while typically covered by insurance plans when used for T2DM, are not covered by marketplace insurances or Medicare when prescribed for weight loss or other off-label uses.[51]

However, in March 2024, Medicare announced that Part D plans cover Semaglutide for overweight patients or those with cardiovascular disease, even if they do not have established T2DM.[52] This is a significant step toward increasing accessibility for HS patients and other established off-label indications.

Challenges and Future Directions

- Lack of rigorous clinical studies investigating GLP-1 efficacy and safety as a sole treatment for HS.
- The lack of large-scale clinical trials evaluating the safety and efficacy of GLP-1RAs in conjunction with biologics for HS treatment.[17]
- Further studies are needed to establish the relationship between comorbidities and HS, specifically to establish causation.

Hidradenitis suppurativa is a complex and multifactorial condition associated with multiple comorbidities such as obesity, diabetes, cardiovascular complications, and more. Its multifactorial nature often makes it difficult to treat. While existing therapies address many of the mitigating factors of HS, they fail to address contributors such as mechanical stress from excess body weight, oxidative stress, and metabolic factors.

GLP-1RAs are a promising novel treatment for HS and the comorbidities that it often presents with. These medications modulate systemic inflammation, oxidative stress, and promote weight loss with improved glycemic control. Addressing these pathways not only modulates HS lesions, but may also address the multiple comorbid conditions associated with HS.

Preliminary studies and case reports have suggested that GLP-1RAs can improve HS severity, and potentially work in tandem with biologics such as infliximab to address HS pathogenesis from multiple pathways. GLP-1RAs may even be able to work as a standalone option for those unable to tolerate biologics, or those who have concurrent conditions that can be treated with GLP-1s and who want to avoid polypharmacy.

Preliminary evidence for the use of GLP-1RAs in the treatment of HS appears promising, though barriers such as high cost and limited clinical trial data remain. Further large-scale research is still needed to establish their safety and efficacy in the context

of HS treatment. As further evidence is discovered, GLP-1RAs may eventually become a useful tool in the arsenal of primary care providers and dermatologists in their multidisciplinary approach for HS and its contributing comorbid conditions.

DISCLOSURES

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ORIGINAL ARTICLE

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Evaluating the Risk of Atherosclerotic Cardiovascular Disease in Inflammatory Skin Disease: Insights From a TriNetX Cohort Study

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ABSTRACT

Objective: Recognizing the risk of atherosclerotic cardiovascular disease (ASCVD) in patients is crucial in clinical practice. Recent studies suggest an association between inflammatory skin diseases and ASCVD. This study evaluates ASCVD risk in inflammatory skin disease patients using a standardized assessment model.

Methods: We used the TriNetX platform to analyze 10-year ASCVD risk in inflammatory skin conditions. Propensity score-matched (PSM) cohorts adjusted for confounders. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression.

Results: Inflammatory skin diseases were associated with elevated ASCVD risk. Hidradenitis suppurativa showed the strongest association (HR 1.32; 95% CI: 1.17–1.48). Elevated risks were also noted for psoriasis (HR 1.21; 95% CI: 1.14–1.28) and atopic dermatitis (HR 1.15; 95% CI: 1.04–1.26). These risks were lower than in diabetes mellitus (HR 2.57; 95% CI: 2.52–2.63).

Conclusion: Patients with hidradenitis suppurativa, psoriasis, and atopic dermatitis exhibit increased ASCVD risk. While lower than in diabetes mellitus, findings highlight the role of dermatologists in ASCVD risk identification and management.

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide and demands early identification and tailored risk reduction strategies.[1] Randomized controlled trials have established the efficacy of certain medication classes, such as statins, in reducing ASCVD events irrespective of baseline lipid values.[2] These findings have driven a shift in prescribing practices, emphasizing the importance of personalized risk stratification and management for primary event prevention.[3]

Assessing an individual's risk for ASCVD involves a comprehensive assessment of multiple comorbid conditions, with the goal of tailoring therapies to reduce their risk.[4] A risk calculator, such as the one provided by the American Heart Association, is often used to estimate a patient's ASCVD risk over the course of 10 years, incorporating variables such as age, gender, and the presence of diabetes or hypertension as major components.[5] Based on the results, targeted risk reduction interventions, including the prescription of specific medications, are implemented to mitigate the risk of primary ASCVD events.[6] To expand on these findings, we conducted a multicenter retrospective cohort study using the TriNetX Research Network to evaluate the risk of ASCVD events among patients with inflammatory skin conditions. Our study was designed based on established ASCVD risk calculators, controlling for comorbidities such as diabetes mellitus, tobacco use, and hypertension, while estimating 10-year ASCVD risk.[7] Propensity score matching was employed to account for these comorbidities. We hypothesized that certain inflammatory skin diseases may independently elevate ASCVD risk, irrespective of comorbidities.

We compared outcomes between a cohort of patients with inflammatory skin conditions and a cohort of healthy individuals. To contextualize the ASCVD risk associated with inflammatory skin conditions, we performed a sensitivity

analysis. This analysis compared a cohort of patients with diabetes mellitus or hypertension—conditions with a well-documented association with increased ASCVD risk—to the same healthy cohort. Additionally, we evaluated the risk of ASCVD in a non-inflammatory skin condition, melanocytic nevi, to further validate our model.

Study Sample

This retrospective cohort study utilized data from the TriNetX Research Network, a national federated network of de-identified electronic health records (EHRs) from over 92 participating healthcare organizations and over 100 million patient charts covering diverse healthcare regions and settings from 2003 to 2024. To identify patients, TriNetX utilizes the International Classification of Diseases, Tenth Revision (ICD-10), Current Procedural Terminology (CPT), RxNorm, and Anatomical Therapeutic Chemical (ATC) codes. In our primary analysis, we identified an exposed cohort consisting of patients aged 50 who were diagnosed with hidradenitis suppurativa (ICD-10: L73.2), psoriasis (ICD-10: L40.0), or atopic dermatitis (ICD-10: L20.9).

A control cohort was established, consisting of patients aged 50 who received an ICD-10 code for a medical examination without an abnormal finding (ICD-10 code: Z00.00). Patients with a documented low-density lipoprotein >180 mg/dL, suggesting familial hyperlipidemia, were excluded. Additionally, patients identified as part of a research study (ICD-10 code: Z00.6) were excluded.

To provide additional context, we conducted supplementary analyses comparing well-known high ASCVD risk conditions, such as diabetes mellitus and hypertension, to the control cohort. We also included a comparison with a condition without a known ASCVD association, melanocytic nevi, against the control cohort.

Measures

The charts of patients in the exposed and control cohorts were analyzed for differences in the risk of ASCVD events. These outcomes included the development of ischemic heart disease (ICD-10: I20-I25), ischemic cerebrovascular accident (ICD-10: I63), and atherosclerosis (ICD-10: I70). Patients with outcomes occurring before the index date were excluded. Additional sensitivity analyses were conducted to evaluate the development of each ASCVD event independently. An additional cohort of diabetic patients was also analyzed for the risk of ASCVD in order to offer a comparator to a disease with a well-known risk of ASCVD.

Statistical Analysis

Propensity score matching (PSM) was applied to both the exposed and control cohorts to minimize the effect of confounding variables and ensure comparability. The matching was performed using a 1:1 greedy nearest neighbor algorithm, based on the presence of certain demographic, diagnostic, and prescription data as referenced in Table 1. The index date for the exposed cohort was defined as the point in time when the patient was diagnosed with an inflammatory skin disease. For the control cohort, the index date was set as the point in time when the patient's chart received the diagnosis code for an examination without abnormal findings (ICD-10 Z00.00). The analysis time window began one day after the index date and extended up to a 10-year period. This duration was selected to align with the standard practice of expressing ASCVD risk estimates over 10-year intervals. Since ASCVD calculators do not incorporate a lag period, our model also excluded this feature. Cox proportional hazards regression models were applied, calculating hazard ratios (HRs) and 95% confidence intervals (CIs).[8] Censoring was applied to patients who were lost to follow-up or did not experience the outcomes of interest by the end of the study. All calculations and statistical analyses were performed using the TriNetX platform.

RESULTS

Demographics

Our analyses included well-matched cohorts for psoriasis, hidradenitis suppurativa, and atopic dermatitis, ensuring demographic consistency. The hidradenitis suppurativa cohort included 5,576 patients in both the exposed and control groups, with females predominating at 70.75% in both groups. Smoking prevalence was higher in this cohort than in others, at 26% in the hidradenitis suppurativa cohort versus 26% in the control cohort. The psoriasis cohort included 32,640 patients in both the exposed and control groups, demonstrating well-balanced gender distribution and comorbidities, with minor variations in obesity prevalence. The atopic dermatitis cohort consisted of 9,797 patients in both groups, with a lower prevalence of comorbid conditions such as diabetes and hypertension. The melanocytic nevi cohort included 47,754 patients in both the exposed and control groups. Females predominated, representing 59.03% of both the exposed and control cohorts. The remainder of the demographics, medications, and diagnoses were well balanced in this study. These results demonstrate strong demographic and clinical matching, ensuring reliable comparisons and minimizing confounding biases.

Risk of ASCVD Event With Diagnosis of Diabetes Mellitus or Hypertension

To establish a baseline comparison for our model, we analyzed patients with diabetes mellitus or hypertension in comparison to a healthy cohort. Patients with diabetes mellitus exhibited significantly higher rates of ASCVD events than healthy controls, with an HR of 2.57 (95% CI: 2.52–2.63). Similarly, patients with hypertension were significantly associated with ASCVD, though the effect was less pronounced, with an HR of 1.90 (95% CI: 1.87–1.93).

TABLE 1.

Baseline Patient Characteristics

Patients aged 50 years old (ICD-10)	Type 2 diabetes mellitus (E11)	Encounter for general examination without complaint (Z00)	*P* value	Hypertension (I10)	Encounter for general examination without complaint (Z00)	*P* value	Hidradenitis suppurativa (L73.2)	Encounter for general examination without complaint (Z00)	*P* value
n= before PSM	440,356	510,782		769,362	514,456		5,691	605,409	
n= after PSM	263,249	263,249		462,108	462,108		5,576	5,576	
Male %	1.00	47.25	<0.001	44.19	44.40	0.04	25.19	25.19	1.00
Female %	1.00	48.61	<0.0001	51.14	51.18	0.75	70.75	70.75	1.00
Black or African American %	1.00	15.50	<0.0001	12.78	12.8	0.80	32.38	32.37	0.98
Hispanic or Latino	9.89	10.47	<0.0001	6.33	6.35	0.68	6.85	6.83	0.97
Asian %	5.49	4.95	<0.0001	5.72	5.50	<0.0001	1.22	1.22	1.00
Antilipemic Agents	17.24	16.19	<0.0001	5.94	6.11	0.0007	28.17	28.19	0.98
Aspirin	5.46	4.86	<0.0001	2.82	2.78	0.24	20.15	20.14	0.97
Essential Hypertension (I10)	38.36	38.80	0.0009	13.75	13.72	0.61	45.05	45.05	1.00
Diabetes (E08-E13)	100	0	<0.0001	4.82	4.72	0.01	27.81	27.81	1.00
Nicotine Dependence (F17.200)	4.58	4.96	<0.0001	2.55	2.59	0.14	26.86	26.88	0.98
Tobacco Use Disorder (Z72.0)	2.26	2.43	<0.0001	1.10	1.13	0.19	11.65	11.65	0.97

Patients aged 50 years old (ICD-10)	Psoriasis L40.0	Encounter for general examination without complaint (Z00)	*P* value	Atopic Dermatitis (L20)	Encounter for general examination without complaint (Z00)	*P* value	Melanocytic Nevi (D22)	Encounter for general examination without complaint (Z00)	*P* value
n= before PSM	34,206	614,141		10,325	605,409		48,460	600,756	
n= after PSM	32,640	32,640		9,797	9,797		47,754	47,745	
Male %	44.47	44.48	0.98	34.97	34.94	<0.002	36.86	36.86	0.98
Female %	51.91	51.91	0.98	59.94	59.94	<0.0001	59.03	59.03	0.99
Black or African American %	4.95	4.95	1.00	18.97	18.97	<0.0001	2.14	2.14	1.00
Hispanic or Latino	6.53	6.52	0.93	6.31	6.31	1.00	3.36	3.36	0.98
Asian %	4.82	4.81	0.95	9.74	9.74	1.00	1.72	1.72	1.00
Antilipemic Agents	20.37	20.36	0.96	18.52	18.52	1.00	6.23	6.23	0.98
Aspirin	12.95	12.96	0.98	12.30	12.30	1.00	3.35	3.35	0.98
Essential Hypertension (I10)	30.82	30.72	0.98	31.10	31.10	1.00	9.90	9.90	1.00
Diabetes (E08-E13)	13.68	13.69	0.96	12.50	12.50	1.00	3.02	3.02	1.00
Nicotine Dependence (F17.200)	10.72	1.73	0.97	10.20	10.20	1.00	1.79	1.79	0.98
Tobacco Use Disorder (Z72.0)	3.87	3.86	0.91	3.70	3.70	1.00	0.72	0.71	0.93

TABLE 2.
ASCVD Risk After Dermatology Diagnosis

Diagnosis	ICD-10 Code	Mean follow up (days)	All ASCVD[a]			Ischemic Heart Disease[b]			Ischemic CVA[c]			Atherosclerosis[d]		
			Exposed Number of Outcomes	Control Number of outcomes	HR (95% CI)	Exposed Number of Outcomes	Control Number of outcomes	HR (95% CI)	Exposed Number of Outcomes	Control Number of Outcomes	HR (95% CI)	Exposed Number of Outcomes	Control Number of Outcomes	HR (95% CI)
Type 2 Diabetes Mellitus	E11	1,276	30,801	13,388	2.57 (2.52,2.63)	25,137	10,609	2.58 (2.52,2.63)	7,502	2,135	3.47 (3.31,3.64)	9,876	2,855	3.43 (3.29,3.58)
Hypertension	I10	1,227	47,718	27,259	1.90 (1.87,1.93)	39.311	21,837	1.90 (1.87,1.94)	11,200	4,933	2.21 (2.14,2.29)	13,829	6,723	1.98 (1.98,2.04)
Hidradenitis suppurativa	L73.2	1,204	630	548	1.32 (1.17,1.48)	420	375	1.24 (1.08,1.43)	108	112	1.04 (0.80,1.36)	210	111	2.09 (1.66,2.64)
Psoriasis	L40	1,304	2455	2,067	1.21 (1.14,1.28)	2,037	1,646	1.26 (1.18,1.34)	422	367	1.14 (0.99,1.31)	669	531	1.26 (1.26,1.41)
Atopic Dermatitis	L20	1,230	873	790	1.15 (1.04,1.26)	484	506	0.96 (0.84,1.08)	122	115	1.06 (0.82,1.37)	159	131	1.22 (0.97,1.54)
Melanocytic Nevi	D22	1,451	2,031	2,516	1.00 (0.94,1.06)	1,685	2,033	1.03 (0.96,1.10)	299	415	0.90 (0.77,1.05)	439	539	1.02 (0.90,1.16)

To protect patient privacy, Trinetx rounded numbers up to 10 when needed.
[a]ICD-10: I20-125, I70, I63; [b]ICD-10: I20-125; [c]ICD-10: I63; [d]ICD-10: I70

Sub-analyses of the diabetes cohort revealed consistently elevated risks across all outcomes, including ischemic heart disease (HR 2.58; 95% CI: 2.52–2.63), ischemic cerebrovascular accidents (HR 3.43; 95% CI: 3.31–3.64), and atherosclerosis (HR 3.43; 95% CI: 3.29–3.58). For perspective, a 50-year-old female with diabetes mellitus, but without hypertension or tobacco use, would have an estimated 10-year ASCVD risk of 2.1% according to the American Heart Association ASCVD Risk Calculator.

Risk of ASCVD Event With a Diagnosis of Hidradenitis Suppurativa

The risk of all ASCVD events was elevated after a diagnosis of hidradenitis suppurativa with an HR of 1.32 (95% CI: 1.17,1.48). Among the ASCVD events, the highest risk was for atherosclerosis, with an HR of 2.09 (95% CI: 1.66,2.64). The risk for heart disease was also elevated with an HR of 1.24 (95% CI: 1.08,1.43). The risk for ischemic cerebral vascular accident was also slightly elevated but did not achieve statistical significance with an HR of 1.04 (95% CI: 0.80,1.36).

Risk of ASCVD Event With Diagnosis of Psoriasis

The overall risk of ASCVD following a diagnosis of psoriasis was elevated, with an HR of 1.21 (95% CI: 1.14,1.28). A similar trend was observed for ischemic heart disease (HR 1.26; 95% CI: 1.18,1.34) and atherosclerosis (HR 1.26; 95% CI: 1.26,1.41).

Risk of ASCVD Event With Diagnosis of Atopic Dermatitis

The overall risk of ASCVD after a diagnosis of atopic dermatitis was mildly elevated, with an HR of 1.15 (95% CI: 1.04,1.26). Sub-analyses examining specific diseases, including ischemic heart disease, ischemic cerebrovascular accidents, and atherosclerosis, showed elevated HRs but did not reach statistical significance.

Risk of ASCVD Event With Diagnosis of Melanocytic Nevi

The risk of ASCVD was evaluated in a cohort of patients with melanocytic nevi to provide a comparison with a non-inflammatory skin condition. The overall risk of ASCVD was not elevated, with an HR of 1.00 (95% CI: 0.94,1.06). Similarly, no significant elevation was observed in the risk of ischemic heart disease (HR 1.68; 95% CI: 0.96,1.06), ischemic cerebrovascular accidents (HR 0.90,; 95% CI: 0.77,1.05), or atherosclerosis (HR 1.02; 95% CI: 0.90,1.16).

DISCUSSION

Our study found that patients with inflammatory skin conditions have an increased risk of ASCVD. Notably, individuals with hidradenitis suppurativa demonstrated a significantly elevated ASCVD risk relative to the control group. Similarly, an increased ASCVD risk was observed in patients with atopic dermatitis and psoriasis, aligning with findings from prior studies.[8] These findings suggest an elevated risk for ASCVD with common inflammatory skin conditions, although this risk is not as high as other common medical conditions, such as diabetes or hypertension.

Recent studies have highlighted an increased risk of ASCVD associated with inflammatory skin conditions. For example, a cross-sectional study demonstrated an elevated cardiovascular disease risk in patients with such conditions.[9] However, this study was limited by its single-center design did not account for some common inflammatory skin conditions, such as hidradenitis suppurativa, and did not offer a comparison to common medical conditions.

Our analysis takes a different methodological approach to provide more comprehensive insights by incorporating comparisons to standardized risk calculators. For instance, using the ASCVD risk calculator, a 50-year-old diabetic with characteristics similar to our study population is estimated to have a 10-year ASCVD risk score of 2.1%. This corresponded to an HR of 2.57 (95% CI: 2.52,2.63) in our model. Based on our findings, we can deduce that patients with inflammatory skin conditions may have an ASCVD risk higher than the general population but lower than that of diabetic patients. These results not only align with the prevailing hypothesis in existing literature that inflammatory skin conditions are associated with an elevated risk of ASCVD but also provide additional valuable context.

Chronic inflammatory skin conditions commonly managed by dermatologists are closely linked to systemic inflammation.[10] The mechanisms underlying systemic inflammation in these dermatologic conditions are well documented and mediated by specific cytokines. For instance, interleukin (IL)-4 and IL-13 play central roles in atopic dermatitis, while IL-17 is pivotal in psoriasis.[11] Additionally, C-reactive protein has been implicated in hidradenitis suppurativa, which is another inflammatory protein closely tied to cardiovascular health.[12] These inflammatory pathways contribute to endothelial dysfunction, a key factor in the pathogenesis of atherosclerosis.[13]

These findings highlight the important role dermatologists can play in identifying and addressing ASCVD risk factors. Recognizing cardiovascular risk within the scope of dermatology practice provides an additional opportunity for physicians to identify high-risk patients and facilitate potentially life-saving interventions.

A key strength of this study lies in the use of the ASCVD risk assessment model, which facilitates comparisons against a standardized framework and enhances confidence in the findings. Additionally, the large sample size, spanning multiple medical centers and regions, adds robustness to the conclusions. The application of PSM further strengthens the study by minimizing confounding factors and balancing demographic and clinical characteristics—such as age, gender, and race—between the exposed and control cohorts. This rigorous methodological approach enhances both the validity and reliability of the results.

While the study has notable strengths, it also has several limitations. As a database cohort study, it identifies associations rather than establishing causations, underscoring the need for further investigation. Biases inherent in observational research may have influenced the observed associations. Another limitation involves the complexities of temporal associations between the diagnosis of an inflammatory skin condition and the onset of ASCVD events. For example, an ASCVD event occurring within a week of diagnosis may not indicate causation due to the insufficient time frame to establish a causal relationship. Conversely, individuals with inflammatory skin conditions often exhibit pre-existing systemic inflammation, which predisposes them to cardiovascular diseases well before their clinical diagnosis. The systemic effects of these conditions likely predate the formal diagnosis, as the diagnosis date does not necessarily correspond to the onset of the disease. Finally, these findings may have limited generalizability outside the TriNetX network. Prospective studies are required to rigorously evaluate both short and long-term outcomes.

CONCLUSION

Patients with inflammatory skin conditions, including hidradenitis suppurativa and atopic dermatitis, have an elevated risk for ASCVD. These findings underscore the importance of recognizing inflammatory skin conditions as markers of systemic inflammation, highlighting the need for cardiovascular risk assessments and early interventions to mitigate ASCVD events.

DISCLOSURES

The authors have no conflicts to disclose. No funding has been received for this article. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the US Department of Veterans Affairs.

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ORIGINAL ARTICLE

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Clindamycin Phosphate 1.2%/Adapalene 0.15%/ Benzoyl Peroxide 3.1% Gel for Moderate-to-Severe Acne: A Pooled Analysis by Age

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*Ortho Dermatologics is a division of Bausch Health US, LLC

ABSTRACT

Background: Acne pathophysiology and presentation may differ between pediatric/adolescent/young adult (9-24 years) and adult (≥25 years) patients. Fixed-dose clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel demonstrated superior efficacy to vehicle and component dyads with good safety/tolerability in 3 clinical trials of acne. This post hoc analysis evaluated the efficacy/safety of CAB in pediatric/adolescent/young adult ("younger") vs adult participants.

Methods: In one phase 2 (NCT03170388) and two phase 3 (NCT04214652, NCT04214639) trials, participants aged ≥9 years with moderate-to-severe acne were randomized to once-daily CAB or vehicle gel. Pooled data were analyzed for participants grouped by age: younger (9-24 years; n=515) and adult (≥25 years; n=142). Endpoints included the percentage of participants achieving treatment success (≥2-grade reduction from baseline in Evaluator's Global Severity Score and clear/almost clear skin) and least squares mean percent change from baseline in inflammatory/noninflammatory lesions at week 12. Treatment-emergent adverse events (TEAEs) were evaluated throughout.

Results: At week 12, approximately half of CAB-treated participants in both age groups achieved treatment success (9-24: 50.6%; ≥25: 49.0%) vs less than one-fourth with vehicle (15.7%; 20.6%; $P<0.01$, both). Across groups, CAB yielded >70% reductions in inflammatory/noninflammatory lesions vs 45% to 62% with vehicle ($P\leq0.001$, all). For all endpoints, CAB efficacy was similar across age groups. Most TEAEs with CAB were of mild-to-moderate severity, and there were no age-related trends in safety/tolerability.

Conclusions: Fixed-dose, triple-combination CAB gel was efficacious and well tolerated in participants with moderate-to-severe acne, regardless of age. Approximately half of the participants achieved clear/almost clear skin, with >70% reductions in lesion counts.

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INTRODUCTION

Acne vulgaris is one of the most common skin disorders, with an estimated global prevalence of >9% across all ages.[1] In part because onset is often associated with puberty-related hormonal changes, acne has been considered a condition of adolescence, affecting an estimated 85% of teenagers and young adults.[2,3] However, not only is there a trend toward earlier onset of acne in preadolescence, but acne can also persist beyond adolescence and well into adulthood.[4-8] Previous studies have demonstrated age-related differences in clinical presentation and severity of acne and its impact on quality of life (QoL).[5] For example, while acne generally presents as a more severe disease in adolescents compared with adults, it has a greater negative effect on QoL in female adults vs adolescents.[4,5] Therefore, a better understanding of how age might impact treatment efficacy, QoL, and safety outcomes is important.

Pathogenesis of acne vulgaris involves abnormal keratinization, increased sebum production and inflammation, and follicular

proliferation of *Cutibacterium acnes*.[9,10] Combining more than one active ingredient to target multiple acne pathophysiological pathways may improve efficacy. Current American Academy of Dermatology guidelines for management of mild to severe acne in patients aged ≥9 years recommend combination topical treatments, with strong recommendations for the antimicrobial benzoyl peroxide (BPO), retinoids, and/or antibiotics.[6] Combinations containing BPO and an antibiotic can reduce the risk of antibiotic resistance.[6] Furthermore, fixed-dose combination treatments have the potential to improve treatment efficacy over separate applications of multiple ingredients,[11] and may also confer the additional benefit of improved convenience and adherence by simplifying the treatment regimen.[3,11-14]

Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% polymeric mesh gel (CAB; Cabtreo®; Ortho Dermatologics, Bridgewater, NJ) is the only fixed-dose, triple-combination product approved by the US Food and Drug Administration for treatment of acne, and is indicated for use in patients 12 years of age and older.[15] In a 12-week, randomized, double-blind phase 2 trial of participants aged ≥9 years with moderate to severe acne, CAB gel demonstrated superior efficacy to both vehicle and component dyads, with favorable safety and tolerability.[16] Furthermore, two similarly designed, phase 3 trials showed that CAB gel was generally well-tolerated and led to a significantly greater percentage of patients achieving treatment success, as well as significantly greater reductions in inflammatory and noninflammatory lesions compared with vehicle.[11,17]

For this post hoc analysis, data from the phase 2 and two phase 3 trials were pooled to evaluate the efficacy and safety of CAB gel in participants divided into two age groups: 9 to 24 years and ≥25 years; the older age cutoff was chosen as acne in patients ≥25 years is typically considered adult acne.[4,5]

MATERIALS AND METHODS

Study Design and Participants

This pooled post hoc analysis included data from one phase 2 (NCT03170388) and two identical phase 3 (NCT04214639; NCT04214652) multicenter, double-blind, 12-week trials.[11,16,17] Briefly, eligible participants were aged ≥9 years with moderate to severe acne (Evaluator's Global Severity Score [EGSS] of 3 or 4), ≥30 to ≤100 inflammatory (eg, pustules, papules, and nodules) and ≥35 to ≤150 noninflammatory (closed and open comedones) facial lesions, and ≤2 facial nodules at screening. Participants were randomized 2:1 (phase 3 trials) or 1:1 (phase 2 trial) to once-daily CAB gel or vehicle gel. The phase 2 trial also included component dyad gel treatment arms; results from these treatments are not reported here. CeraVe® (L'Oreal, New York, NY) hydrating cleanser and moisturizing lotion were provided as needed for optimal cleaning and moisturizing of the skin. Sunscreen was also provided as needed.

All three trials followed principles of Good Clinical Practice and the Declaration of Helsinki. Trial protocols were approved by the relevant independent ethics committees or institutional review boards at all investigational sites. Written informed consent was provided by all participants or their legal guardians.

Assessments

Efficacy evaluations included treatment success, defined as the percentage of participants achieving ≥2-grade reduction from baseline in EGSS and a score of 0 (clear) or 1 (almost clear), as well as inflammatory and noninflammatory lesion counts. Assessments were performed at baseline and weeks 2, 4, 8, and 12.

QoL was assessed at baseline and week 12 via the Acne-Specific QoL (Acne-QoL) questionnaire. Four domains are covered by this 19-item questionnaire: acne symptoms, role-emotional, self-perception (5 questions each), and role-social (4 questions). All Acne-QoL questions were scored from 0 (extremely) to 6 (not at all), with increases from baseline indicating improvement.[18]

At all post-screening visits, investigator assessments of cutaneous safety (scaling, erythema, hypopigmentation, hyperpigmentation) and participant assessments of tolerability (itching, burning, stinging) were scored using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Treatment-emergent adverse events (TEAEs) were monitored throughout the study.

Statistical Analysis

Data were pooled for participants grouped by age: 9 to 24 years (pediatric/adolescent/young adult participants, hereafter referred to as the younger subgroup) or ≥25 years (the adult subgroup). The intent-to-treat (ITT) population included all randomized participants who received the study drug. The safety population comprised all randomized participants who used the study drug at least once.

Treatment success was analyzed using Firth's penalized likelihood logistic regression test with a factor of treatment (CAB vs vehicle) or age group (younger vs adult). Percent changes from baseline in inflammatory and noninflammatory lesion counts were analyzed using analysis of covariance (ANCOVA) with a factor of treatment group or age and baseline lesion count as a covariate. If significant skewness was observed, data were rank-transformed prior to ANCOVA. Missing values were imputed using the Markov Chain Monte Carlo method. Acne-QoL domain scores of 0 to 6 were transformed to 1 to 7 prior to ANCOVA with a factor of treatment group or age and covariate of baseline domain score; no imputation of missing values was performed. SAS® version 9.4 or later (SAS Institute; Cary, NC) was used to perform all statistical analyses. Statistical significance was based on two-tailed tests of the null hypothesis resulting in $P \leq 0.05$.

Cutaneous safety and tolerability assessments and treatment compliance, defined as participants missing no more than 5 consecutive days of dosing and applying 80% to 120% of expected applications, were summarized using descriptive statistics. TEAEs were recorded and classified using Medical Dictionary for Regulatory Activities terminology. Imputations were not made for missing safety data.

RESULTS

Participant Demographics and Baseline Characteristics

The ITT population comprised 657 participants (9-24 years, n=515; ≥25 years, n=142). Participant demographics and baseline clinical characteristics are presented in Table 1. The majority of participants were female, with a greater percentage in the adult vs younger subgroup (85.2% vs 53.2%), and most self-identified as White. Most participants (>87%) had moderate acne at baseline (EGSS=3). A higher percentage of participants in the younger subgroup was male vs the adult subgroup (46.8% vs 14.8%), and more participants in the adult subgroup self-identified as Black (27.5% vs 12.6%) or Asian (10.6% vs 7.4%). At baseline, mean noninflammatory lesion counts were higher in the younger subgroup (51.6 vs 43.7). Treatment compliance was high (>90%) in both age groups.

Efficacy

At week 12, approximately half of CAB-treated participants in both age groups achieved treatment success vs less than one-quarter with vehicle (P<0.01, both; Figure 1). Significant differences in treatment success were achieved with CAB treatment vs vehicle as early as week 4 for the younger subgroup (9.8% vs 2.5%, P<0.01) and week 8 for the adult subgroup (30.1% vs 9.4%, P<0.05). The only significant difference between CAB-treated participants across the two age groups was at week 8, with greater treatment success rates in the adult vs younger participants (30.1% vs 19.2%; P<0.05).

Both age groups had >70% reductions from baseline at week 12 in lesion counts with CAB vs 45% to 62% with vehicle (P≤0.001; Figure 2). Inflammatory and noninflammatory lesion reductions were also significantly greater with CAB than vehicle as early as week 2 in the younger subgroup and week 4 in the adult subgroup (P<0.05, both). No significant differences in lesion reductions between the CAB-treated younger and adult subgroups were observed at any time point. Representative images depicting acne improvement in CAB-treated participants in both age groups are shown in Figure 3.

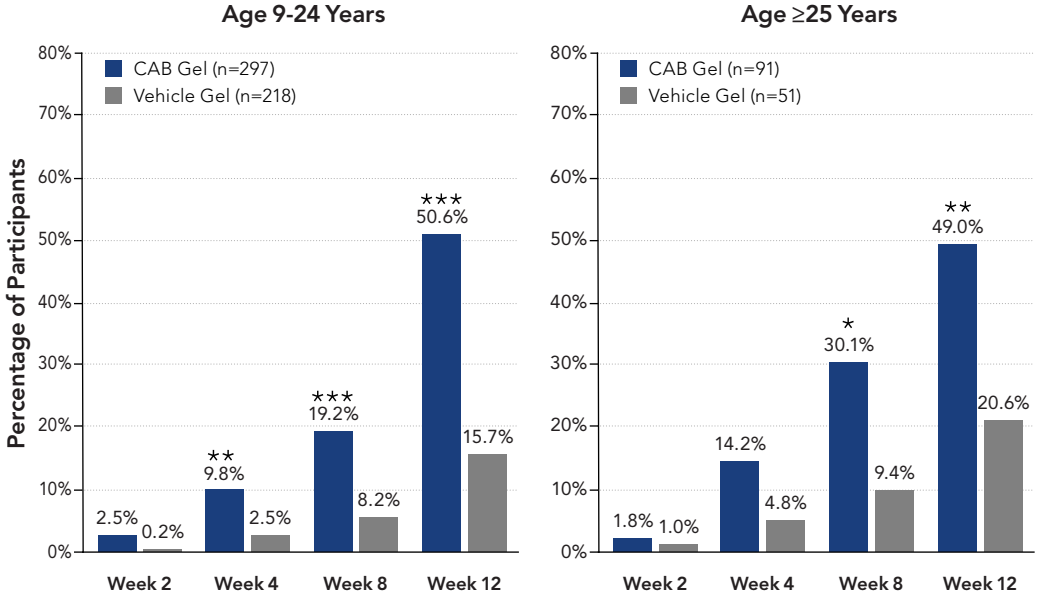
TABLE 1.

Participant Demographics and Baseline Characteristics (ITT Population, Pooled)

	Age 9-24 years		Age ≥25 years	
	CAB gel (n=297)	Vehicle gel (n=218)	CAB gel (n=91)	Vehicle gel (n=51)
Age, mean (SD), y	16.7 (3.2)	17.2 (3.2)	31.1 (5.3)	32.1 (6.1)
Age, median (range), y	16 (10-24)	17 (11-24)	29 (25-48)	30 (25-47)
Sex, female, n (%)	159 (53.5)	115 (52.8)	79 (86.8)	42 (82.4)
Ethnicity, Hispanic/Latino, n (%)	66 (22.2)	49 (22.5)	24 (26.4)	8 (15.7)
Race, n (%)				
White	218 (73.4)	164 (75.2)	49 (53.8)	29 (56.9)
Black or African American	41 (13.8)	24 (11.0)	23 (25.3)	16 (31.4)
Asian	21 (7.1)	17 (7.8)	10 (11.0)	5 (9.8)
Other[a]	17 (5.7)	13 (6.0)	9 (9.9)	1 (2.0)
Inflammatory lesion count, mean (SD)	38.2 (10.4)	38.8 (9.8)	36.0 (5.7)	34.0 (4.7)
Noninflammatory lesion count, mean (SD)	52.3 (20.1)	50.6 (18.3)	43.8 (9.5)	43.6 (11.0)
Evaluator's Global Severity Score, n (%)				
3 – Moderate	260 (87.5)	192 (88.1)	80 (87.9)	50 (98.0)
4 – Severe	37 (12.5)	26 (11.9)	11 (12.1)	1 (2.0)

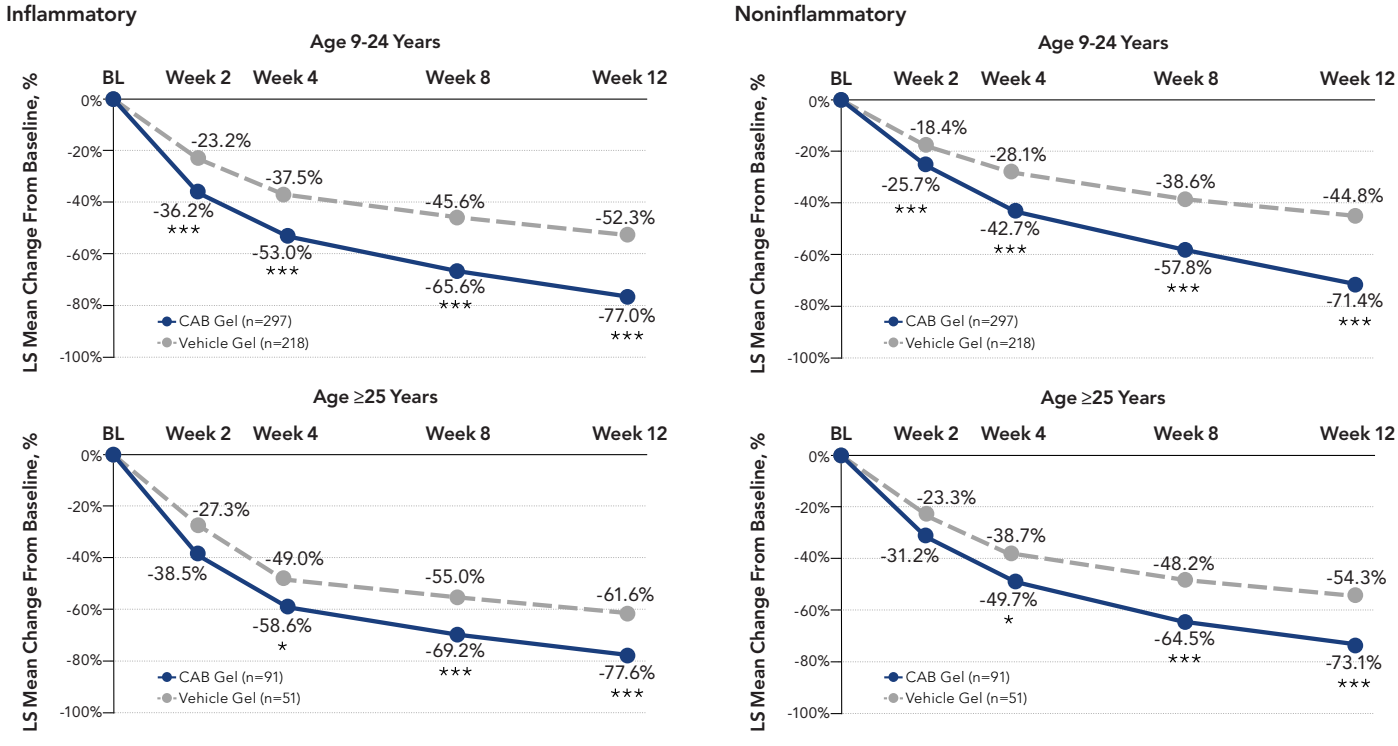
[a]American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Multiple/Not Reported/Unknown.
CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; ITT, intent to treat; SD, standard deviation.

FIGURE 1. Treatment success[a] through week 12 by age (ITT population, pooled participants).



*P<0.05, **P<0.01, ***P≤0.001 vs vehicle. [a]Defined as ≥2-grade reduction from baseline in Evaluator's Global Severity Score and a score of 0 (clear) or 1 (almost clear). There were no significant differences between active treatment age groups except at week 8 (P<0.05). Values have been adjusted for multiple imputation (MCMC).
CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; ITT, intent to treat; MCMC, Markov Chain Monte Carlo.

FIGURE 2. Acne lesion reductions by age and visit (ITT population, pooled).



*P<0.05, **P<0.01, ***P≤0.001 vs vehicle. Values have been adjusted for multiple imputation (MCMC).
CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; ITT, intent to treat; LS, least squares; MCMC, Markov Chain Monte Carlo.

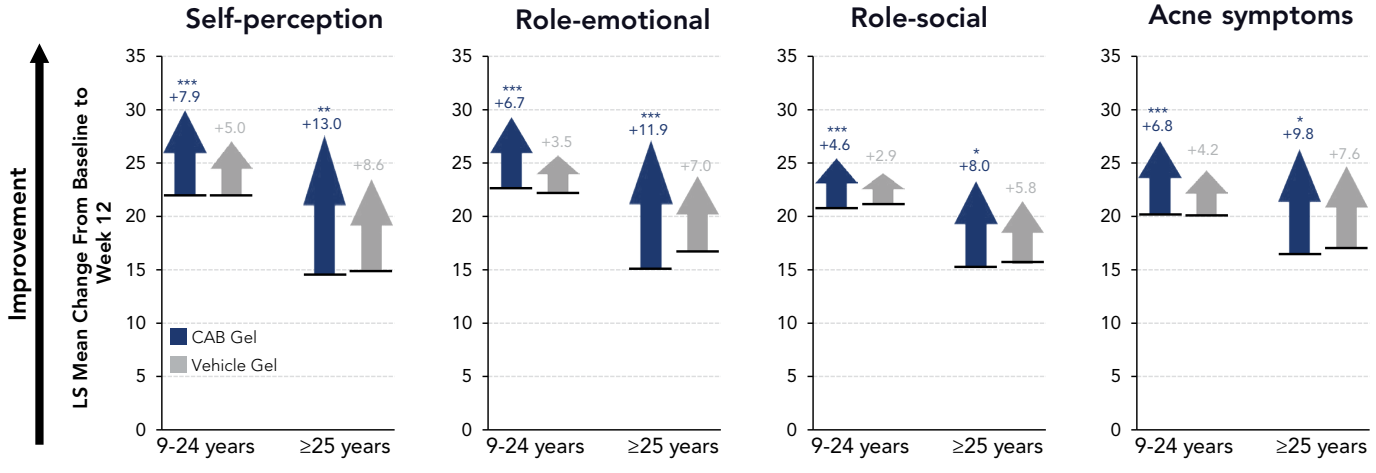
FIGURE 3. Acne improvements with CAB gel in participants aged 9 to 24 and ≥25 years.



Individual results may vary. Photographic images © 2025. Courtesy of Ortho Dermatologics trial investigators. Part of this figure was previously published in Stein Gold LS et al, 2023.[17]

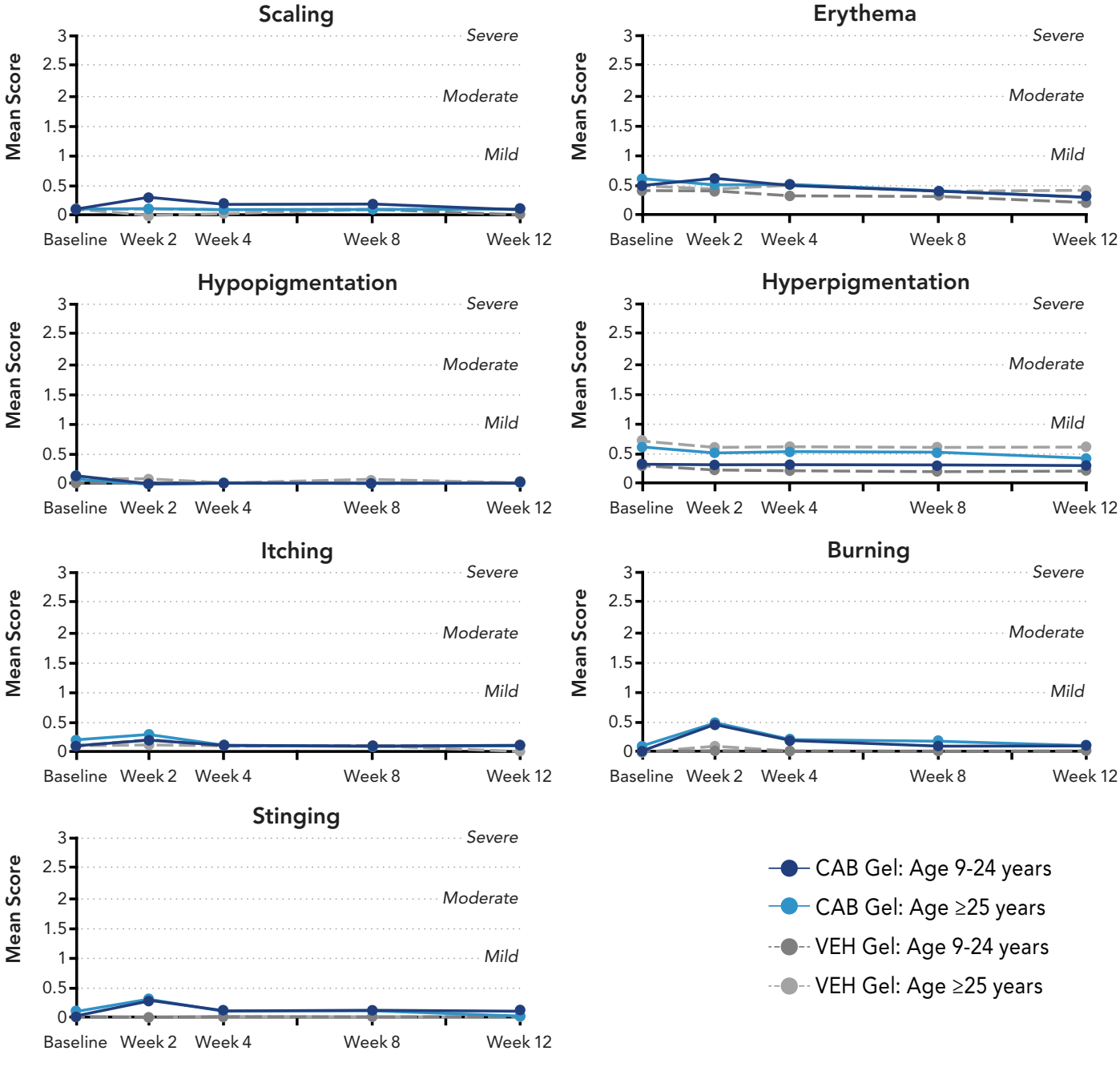
CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; EGSS, Evaluator's Global Severity Score (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe); IL, inflammatory lesions; NIL, noninflammatory lesions.

FIGURE 4. Acne-QoL improvements by age at week 12 (ITT population, pooled).



*P<0.05, **P<0.01, **P<0.001 vs vehicle
Age 9 to 24 years: baseline CAB n=297, vehicle n=217; week 12 CAB n=264, vehicle n=190.
Age ≥25 years: baseline CAB n=91, vehicle n=51; week 12 CAB n=76, vehicle n=48.
No imputation for missing values.
Acne-QoL, Acne-Specific Quality of Life questionnaire; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; ITT, intent to treat; LS, least squares.

FIGURE 5. Cutaneous safety and tolerability by age and visit (safety population, pooled).



Assessments were graded on a 4-point scale (0=none; 1=mild; 2=moderate; 3=severe).
Age 9 to 24 years baseline: CAB n=293, vehicle n=216; week 12: CAB n=264, vehicle n=191[a] or 192[b].
Age ≥25 years baseline: CAB n=90, vehicle n=21; week 12: CAB 75[a] or 76[b], vehicle n=48.
[a]For scaling, erythema, hypopigmentation, and hyperpigmentation.
[b]For itching, burning, and stinging.
CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.

TABLE 2.

Summary of Adverse Events Through Week 12 (Safety Population, Pooled)

Participants, n (%)	Age 9-24 years		Age ≥25 years	
	CAB gel (n=293)	Vehicle gel (n=216)	CAB gel (n=90)	Vehicle gel (n=51)
Reporting any TEAEs	93 (31.7)	30 (13.9)	24 (26.7)	2 (3.9)
Related to study drug	56 (19.1)	3 (1.4)	20 (22.2)	1 (2.0)
Reporting any serious AEs	1 (0.3)[a]	0	0	0
Discontinued drug or study due to AE	8 (2.7)	2 (0.9)	3 (3.3)	0
Severity of TEAEs				
Mild	54 (18.4)	17 (7.9)	12 (13.3)	2 (3.9)
Moderate	35 (11.9)	12 (5.6)	6 (6.7)	0
Severe	4 (1.4)	1 (0.5)	6 (6.7)	0
Most common treatment-related TEAEs[b]				
AS pain	33 (11.3)	2 (0.9)	9 (10.0)	0
AS dryness	11 (3.8)	0	5 (5.6)	0
AS exfoliation	7 (2.4)	1 (0.5)	2 (2.2)	0
AS irritation	6 (2.0)	0	2 (2.2)	0
Xerosis	0	0	3 (3.3)	1 (2.0)
AS erythema	2 (0.7)	0	3 (3.3)	0
AS pruritus	2 (0.7)	0	3 (3.3)	0
Erythema	2 (0.7)	0	2 (2.2)	0

[a]Sickle cell anemia with crisis; not considered related to the study drug and no study discontinuation.
[b]Reported in ≥2% participants in any treatment group.
AE, adverse event; AS, application site; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Improvements from baseline in Acne-QoL scores at week 12 were significantly greater with CAB vs vehicle across all four domains for both age groups ($P<0.05$, all; Figure 4). Although improvements were generally numerically greater in the adult subgroup, there were no significant differences between the two age groups.

Safety and Tolerability

Rates of TEAEs with CAB treatment were slightly lower in the adult subgroup (Table 2). Most TEAEs were of mild or moderate severity in both age groups. Sickle cell anemia crisis was the only serious AE; it was not considered related to treatment and did not lead to study or drug discontinuation. The most common CAB treatment-related TEAEs in both age groups were application site pain and dryness. Rates of discontinuation due to AEs were low and similar among younger (2.7%) and adult (3.3%) CAB-treated participants.

For all participants, the mean scores for cutaneous safety and tolerability assessments with CAB treatment were ≤0.8 (1=mild) at all visits (Figure 5). Transient increases were observed for scaling, itching, burning, and stinging at week 2, began to decrease by week 4, and resolved back to or near baseline values by week 12. These increases were similar between the age groups. The mean value of the worst (highest) cutaneous safety/tolerability score at any time post-baseline was <1 in both age groups (data not shown). Overall, no notable age-related trends in safety or tolerability were observed.

DISCUSSION

Acne is considered a condition of adolescence; however, adults, especially women, can experience late onset or chronic recurrent acne, and the negative impact on QoL can be worse in adults than in adolescents.[5] In this pooled, post hoc analysis of 3 clinical trials, triple-combination, fixed-dose CAB gel was well tolerated and had significantly greater efficacy than vehicle over 12 weeks in both younger (pediatric/adolescent/young adult) and adult participants with moderate to severe acne. Notably, the older age group was comprised predominantly of females, demonstrating the efficacy of CAB in this challenging-to-treat population. No age-related trends in efficacy, safety, or tolerability were observed, suggesting that CAB is a valuable treatment option for patients of all ages.

Approximately half of all participants who received CAB achieved treatment success by week 12, vs less than a quarter with vehicle gel, regardless of age group. Furthermore, >70% reductions in inflammatory and noninflammatory lesions were observed with CAB; these improvements are in line with those seen in the overall populations from the phase 2 and phase 3 trials.[11,16,17] In the present analyses, improvements following CAB treatment were rapid, as significantly more participants achieved treatment success by week 4 in the younger subgroup and by week 8 in the adult subgroup vs vehicle gel. Similarly, significantly greater reductions in both inflammatory and noninflammatory lesions with CAB vs vehicle were achieved as early as week 2 for the younger subgroup and by week 4 for the adult subgroup. These rapid improvements may be a strong motivator for treatment adherence, especially in younger patients who often have lower adherence rates.[19,20]

When compared with other 12-week acne clinical trials of topical, fixed-dose dual-combinations containing clindamycin/BPO or adapalene/BPO, CAB demonstrated greater lesion reductions in the present pooled analyses. For the adult subgroup, mean lesion reductions with CAB were greater compared with other clinical studies of dyad-treated adult female participants (inflammatory: CAB, 77.6%; dyads, 64.6-73.0% [mean or median]; noninflammatory: CAB, 73.1%; dyads, 51.0-70.0%).[21-24] For the younger subgroup, comparisons to other fixed-dose combinations are more challenging as many studies had an upper age limit around 18 years. However, compared with one study of clindamycin phosphate 1.2%/BPO 2.5% in female patients aged <25 years, lesion reductions with CAB in younger patients in the present analyses were greater (inflammatory: CAB, 77.0% vs 69.3% [median]; noninflammatory: CAB, 71.4% vs 49.6%).[24] It should be noted that these age-grouped studies were conducted only in female patients, and as such there is a notable paucity of data on topical combination treatment in adolescent and adult males. Another caveat to these comparisons is that these are not head-to-head studies, and patient populations and designs may differ.

Acne can have lasting adverse effects on QoL largely because of its visible nature. Social life, self-esteem, and body image are negatively impacted, and acne is linked to higher unemployment rates, suicidal ideation, and increased rates of comorbidities such as depression and anxiety.[25-28] Effects of acne on emotional, psychological, and social aspects of QoL can be worse in adults than adolescents.[5] This is reflected in baseline Acne-QoL scores in the present analyses: mean domain scores were lower (worse) at baseline in the adult group compared with the younger group (range: 14.6-17.1 vs 20.1-22.6). While scores for all 4 domains were significantly improved with CAB vs vehicle in the younger and adult groups ($P \leq 0.05$, both), increases were numerically smaller among younger participants (4.6-7.9) compared with adult participants (8.0-13.0), though this was likely due to their higher baseline scores.

One concern regarding combination therapies is the potential for increased TEAEs with each additional active ingredient. Application site irritation and other tolerability concerns are commonly associated with topical acne treatments; these are of particular concern in pediatric patients as they are more likely to experience irritation.[29] In this analysis, CAB was generally safe and well tolerated in both younger and adult participants. In both age groups, TEAE rates with CAB treatment (9-24 years: 31.7%; ≥25 years: 26.7%) were consistent with the overall phase 2 and phase 3 trial populations (24.6%-36.2%),[16,17] and rates of cutaneous irritation were low (≈2%). CAB's unique polymeric gel vehicle with micronized BPO and adapalene was designed to provide even delivery over the skin and better absorption, which may contribute to a favorable tolerability profile.[16,17] Additionally, the anti-inflammatory properties of clindamycin and the moisturizing agents in CAB may mitigate irritation associated with BPO and adapalene.[9,30-32]

Limitations of these pooled analyses include the limited treatment duration (12 weeks) and the likelihood that treatment adherence is higher in clinical trials vs real-world settings. Moreover, this pooled study does not account for variations in acne presentation or associated sequelae across skin type, sex, and other demographic factors, thus limiting the generalization of these findings. Finally, these trials were not powered to detect statistical differences between subgroups.

CONCLUSION

Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1% polymeric mesh gel—the only approved triple-combination, fixed-dose, topical acne treatment—was efficacious, safe, and well tolerated in participants with moderate to severe acne, regardless of age. Approximately half of the younger (pediatric/adolescent/young adult) and adult CAB-treated participants achieved clear/almost clear skin, with >70% reductions in lesion counts after 12 weeks. No age-related trends in efficacy or tolerability were observed, suggesting that the innovative CAB gel (indicated for use in patients aged ≥12 years[15]) is a valuable treatment option for patients of all ages.

DISCLOSURES

Leon H. Kircik has served as a consultant, speaker, advisor or an investigator for Allergan, Almirall, EPI Health, Galderma, Novartis, Ortho Dermatologics, and Sun Pharma. Julie C. Harper has received honoraria from Almirall, Cutera, Galderma, LaRoche-Posay, Ortho Dermatologics, and Sun Pharma. Hilary Baldwin has served as advisor, investigator, and on speaker's bureaus for Almirall, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharma. Lawrence F. Eichenfield has received honoraria for consulting services from AbbVie, Amgen, Arcutis, BMS, Dermata, Dermira, Dermavant, Eli Lilly, Forte Pharma, Galderma, Incyte, Johnson & Johnson, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and Ortho Dermatologics; and received study support (to institution)

from AbbVie, Amgen, Bausch Health, Dermata, Dermira, Eli Lilly, Galderma, Incyte, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme. Emil A. Tanghetti has served as speaker for Eli Lilly, Novartis, Ortho Dermatologics, Sun Pharma, Galderma, AbbVie, and Dermira; served as a consultant/clinical studies for Hologic, Ortho Dermatologics, and Galderma; and is a stockholder for Accure. Emmy Graber has served as a consultant/advisor, research investigator, and/or speaker for Digital Diagnostics, Almirall, Cutera, Hovione, Keratin Biosciences, La Roche Posay, Lipidor AB, Ortho Dermatologics, Sebacia, SolGel, Verrica, and WebMD. Heather C. Woolery-Lloyd is a shareholder for Somabella Laboratories, LLC, and has served as a speaker for Aclaris and Ortho Dermatologics, a consultant for Ortho Dermatologics, and has received grants/research funding from Aclaris, Allergan, Endo, Eirion, Galderma, Golge, LEO Pharma, Nestle, and Pfizer. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Zoe D. Draelos received funding from Ortho Dermatologics.

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ORIGINAL ARTICLE

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Clinical Evaluation of Thiamidol-Containing Formulations for the Visual Management of Facial Hyperpigmentation

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ABSTRACT

Background: Cutaneous hyperpigmentation, which includes melasma, post-inflammatory hyperpigmentation, and solar lentigines, significantly impacts patients' quality of life. The overproduction of melanin is mediated by activation of the skin enzyme tyrosinase, leading to excess melanin deposition in the skin. Thiamidol (isobutylamido thiazolyl resorcinol) formulations have been previously shown to be effective in reducing the cutaneous pigmentation associated with this human skin enzyme.

Methods: A randomized study was performed with 90 subjects clinically presenting with facial hyperpigmentation (Thiamidol serum n=43; Thiamidol regimen n=47) as measured by colorimeter and individual typology angle (ITA^0) to assess the efficacy of a Thiamidol-based serum (2X daily application; morning/night) or a Thiamidol-based regimen (day lotion with SPF 30 + serum in morning; night cream + serum at night) for 12 weeks with a 6-week regression period.

Results: A significant visible reduction in facial hyperpigmentation, assessed by increases in L* and ITA° values, along with an increase in skin radiance and shine, were observed as early as week 2, with continued improvement through week 12 in both the treatment groups relative to baseline. At week 12, changes in radiance and shine were trending toward enhancement in the regimen group compared with the serum group.

Discussion: This study demonstrates the clinical effectiveness of Thiamidol-containing formulations in the visible improvement of facial hyperpigmentation and in overall skin radiance and shine.

Conclusion: These data support the use of Thiamidol-containing formulations as part of the overall management strategy for individuals affected by facial hyperpigmentation.

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INTRODUCTION

Pigmentary disorders, including melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, axillary hyperpigmentation, periorbital hyperpigmentation, and vitiligo, are some of the most commonly reported dermatological skin disorders, which significantly impact patients' quality of life.[1,2] In a recent survey of 48,000 individuals from 34 countries covering all continents, 50% of the subjects (average age 44 years) reported having at least one pigmentary disorder, with more women (59%) affected.[1] Amongst these disorders, hyperpigmentation-associated skin disorders, primarily melasma, PIH, and solar lentigo, accounted for the majority of the self-reported conditions.[1] Furthermore, in individuals with skin of color (SOC), particularly those with African, Asian, or Hispanic heritage, the incidence of reported PIH far exceeded that of the general population (15% vs ~1%).[1]

Hyperpigmentation is mediated by the overstimulation of the melanin production pathways in melanocytes, resulting in the deposition of excess melanin in the skin.[3,4] The key rate-limiting step in these complex pathways centers on the conversion of Tyrosine to L-Dopa, via the catalyzing enzyme tyrosinase, with eventual generation of the melanin end products eumelanin and pheomelanin.[5]

Recently, isobutylamido thiazolyl resorcinol (Thiamidol) has been identified from a library of 50,000 compounds as the most effective inhibitor of human tyrosinase with activity (half-maximal inhibition concentration, IC_{50} = 1.1 mmol/L). This far exceeds that of common anti-pigmentation ingredients, including hydroquinone and kojic acid,[6] making it a suitable ingredient for inclusion in over-the-counter (OTC) anti-pigmentation products.

Previous studies have demonstrated the reduction of hyperpigmentation mediated by melasma, post-inflammatory hyperpigmentation (acne-, UV-B-, and laser-induced), and solar lentigo via treatment with various Thiamidol-based formulations, both in a single product and in multi-product regimen protocols in both randomized controlled trials (RCTs) and real-world settings.[7-17] The objective of this research was to investigate the clinical efficacy of a novel cosmetic Thiamidol-containing serum and Thiamidol-containing regimen (day lotion with SPF 30, serum, and night cream) for the visible management of facial hyperpigmentation.

MATERIALS AND METHODS

Trial Design

This randomized study was conducted between August 2024 and January 2025 in a study center (Dermico, Broomall, Pennsylvania, USA). In the 12-week treatment phase, the subjects returned at weeks 2, 4, 8, and 12 for assessment and at week 18 after a 6-week treatment discontinuation (regression phase).

The study was conducted following International Conference on Harmonization Good Clinical Practice (ICH E6 (R2) GCP) guidelines, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Prior to initiation of the study, the protocol, informed consent form, and product information were submitted and approved by the Sterling Investigational Review Board. Subject anonymity in the study documentation was maintained by coded entry.

Study Population and Treatment

Eligible for the trial were healthy male and female subjects aged 18 to 65 years with Fitzpatrick skin types (FST) I to VI, who had individual typology angles (ITA°) ranging from +65° to -31° and with an ITA° differences of >5 ITA units on their facial skin between the area of interest (AOI) and surrounding skin sites (SSS) as determined at the pre-study visit, who had used SPF-containing products in the past, who were able to read, understand, and sign the informed consent form (ICF), and who were willing and able to follow all study requirements and restrictions.

For 12 weeks, the subjects allocated to the Thiamidol-serum group applied twice daily (morning and night) on their face the Thiamidol-containing serum. Subjects were instructed to apply a standard SPF lotion to their face at least once in the morning after serum application. Subjects were allowed to apply SPF lotion up to 4 times daily as needed, with a minimum of 2 hours between applications. The subjects allocated to the Thiamidol-regimen group applied twice daily (morning and night) on their face the Thiamidol-containing serum followed by the Thiamidol-containing day lotion with SPF30 in the morning and the Thiamidol-containing night cream at night. Subjects were allowed to apply standard SPF lotion to their face as needed at least 2 hours after the day of lotion application.

Subjects were asked to stop the use of all topical products (lotions, creams, serums, sunscreens, etc.) on their face for the 3 days prior to the start of the study and until the completion of week 12. Subjects were allowed to continue using non-medicated and non-brightening facial cleansers. Subjects were asked to avoid sun exposure for over 15 minutes, including artificial sun, during the 3 days prior to the start of the study and for the duration of the study. Subjects had to refrain from any activities that would increase body temperature or induce sweating during the 2 hours before their first 2 visits. Subjects could not be taking and be willing to not take any anti-inflammatory medications starting 48 hours prior to their appointments.

Assessments

The primary outcome of the study was the evaluation of the hyperpigmentation-reducing effect of the Thiamidol-serum or Thiamidol-regimen (serum, day lotion with SPF 30, and night cream) through skin pigmentation measurements (L*Mean and ITA°), radiance, and shine at baseline, week 2, week 4, week 8, week 12, and post-regression phase (week 18). Briefly, visible, cross-polarized (X-Pol), parallel-polarized (P-Pol), and UV fluorescence clinical images were acquired for each time point using a Visia-CR system (Canfield, Parsippany, NJ). X-Pol and P-Pol images were used to quantify skin tone, shine, and radiance. A standardized region of interest from each facial image was translated pixel by pixel from the native RGB values into the L*a*b* color space, then analyzed in terms of its image histogram parameters. Individual Topology Angle (ITA) was calculated from L* and b* values using the equation ITA = [arctan(L*-50)/b*)] *180/π. The mean of the L* value and ITA value were used to represent skin lightening, while a partial least squares regression model was employed to quantify perceived shine and radiance as a balance of skin surface and subsurface reflection components.[21,22]

Statistical Analysis

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

RESULTS

Study Demographics

Between August 2024 and January 2025, 90 male and female subjects (n = 89 females; n = 1 male) between 18 and 64 years (mean: 50.61 + 10.83 years), with Fitzpatrick Skin Types

TABLE 1.

Study Demographics				
Characteristic	**Thiamidol-serum group (n=43)**		**Thiamidol-regimen group (n=47)**	
Gender	**M**	**F**	**M**	**F**
	1	**42**	**0**	**47**
Age, years + SD	27	51.59 (+ 9.71)	N/A	50.15 (+ 11.48)
Phototype, n				
FST I	0	2	N/A	3
FST II	0	13	N/A	13
FST III	0	15	N/A	14
FST IV	0	5	N/A	2
FST V	0	11	N/A	12
FST VI	1	1	N/A	3

FST, Fitzpatrick skin type; SD, standard deviation.

(FSTs) I-VI (FST I = 5; FST II = 26; FST III = 29; FST IV = 7; FST V = 23; FST VI = 4), and ITA° ranging from +65° to -31° with ITA° differences of >5 ITA units on their facial skin between and area of interest (AOI) and surrounding skin sites (SSS) as determined at their pre-study visit (PSV) were enrolled, of whom 43 were randomized to the Thiamidol-serum group and 47 were randomized to the Thiamidol-regimen group. The randomized subjects' demographics were balanced among the 2 treatment groups (Table 1).

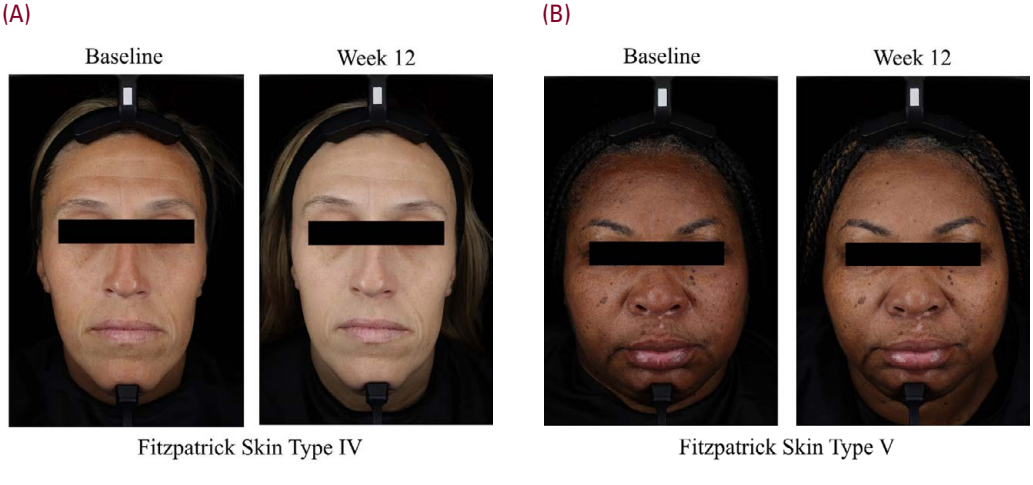
Efficacy, Clinical Photography

Clinical photographs demonstrated visible improvement of facial hyperpigmentation in subjects from both groups, Thiamidol-serum group (Figure 1) and Thiamidol-regimen group (Figure 2), and in multiple FSTs, including FST IV (Figure 1A) and FST V (Figure 1B) for the Thiamidol-serum groups and FST III (Figure 2A) and FST V (Figure 2B) for the Thiamidol-regimen group. Visible improvements of facial hyperpigmentation were observed in subjects from all FSTs included in both groups (full data not shown).

Efficacy, Skin Lightening (L*Mean, ITA°)

Two methods were used to measure the efficacy (skin lightening) of the Thiamidol-serum and Thiamidol-regimen treated subjects, L*Mean and ITA°. L*Mean uses a 3-dimensional color model (CIELAB Color Space), to objectively measure the lightness or darkness of skin on a scale of 0 (pure black/darkest) to 100 (pure white/lightness), with increases in L*Mean after anti-pigmentation treatment demonstrating overall skin lightening.[18,19] ITA° is an objective measure of skin color and

FIGURE 1. Representative clinical photography of subjects. Improvement in facial hyperpigmentation following treatment with Thiamidol formulated serum (12 weeks). (A) FST IV subject; (B) FST V subject.

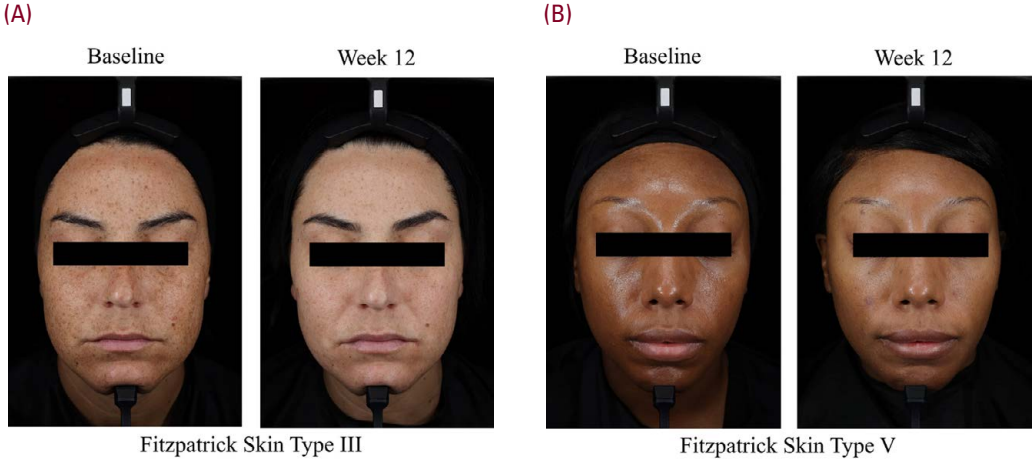


FST, Fitzpatrick skin type.

overall skin pigmentation and is derived from both lightness of skin (L*Mean) and the yellow and blue color of skin.[20] Statistically significant (P<0.05) increases in L*Mean were observed as early as week 2 relative to baseline for both the Thiamidol-serum and Thiamidol-regimen groups, with continued increases in skin lightening measured (L*M) through week 12 (Figure 3). Skin lightening was maintained through the end of the study (week 18), which included a 6-week regression phase (no application of product) (Figure 3).

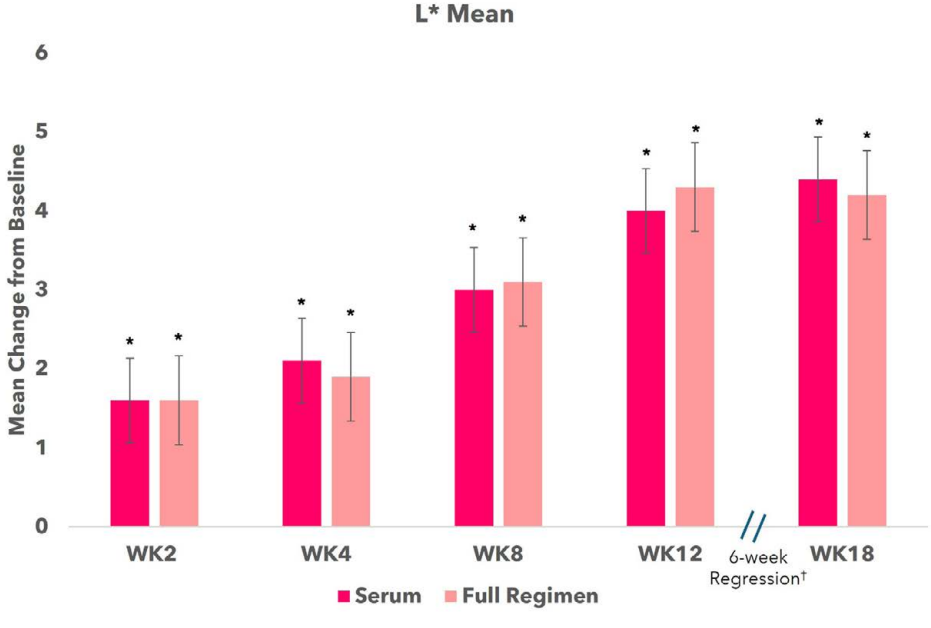
Similar to L*Mean, a statistically significant (P<0.05) increase in ITA° mean was measured relative to baseline as early as week 2, with an ~4 mean ITA unit increase in both the Thiamidol-serum and Thiamidol-regimen groups, with continued increases observed through week 12 (Thiamidol-serum = Mean 11.3 ITA units increase; Thiamidol-regimen = Mean 11.8 ITA units) and sustained efficacy through week 18 (6 week regression phase) (Figure 4).

FIGURE 2. Representative clinical photography of subjects. Improvement in facial hyperpigmentation following treatment with Thiamidol formulated full regimen (serum, day lotion, and night cream) (12 weeks). (A) FST III subject; (B) FST V subject.



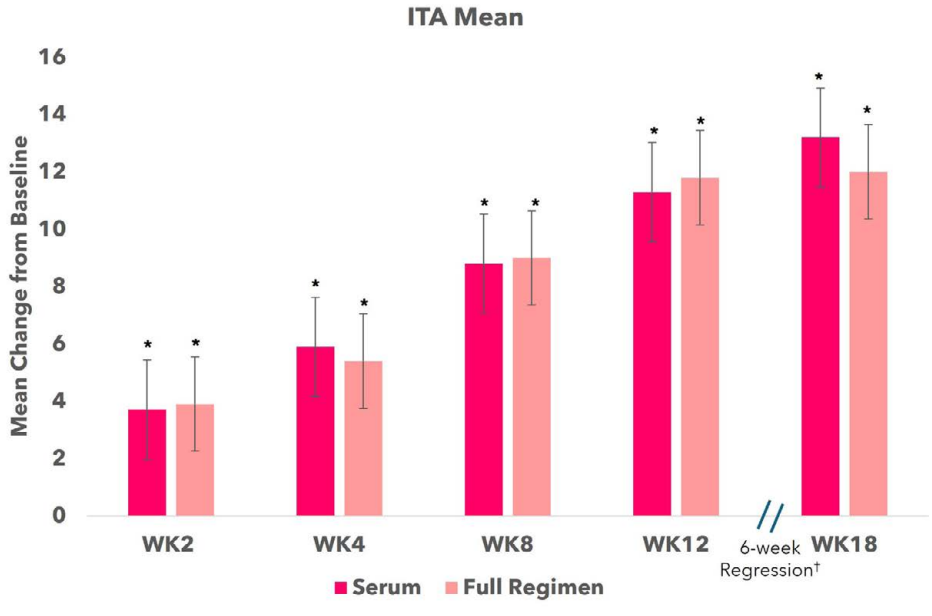
FST, Fitzpatrick skin type.

FIGURE 3. L* Mean (skin lightness) following treatment with Thiamidol formulated serum or Thiamidol formulated full product regimen (serum, day lotion, and night cream) compared with baseline at all time points assessed.



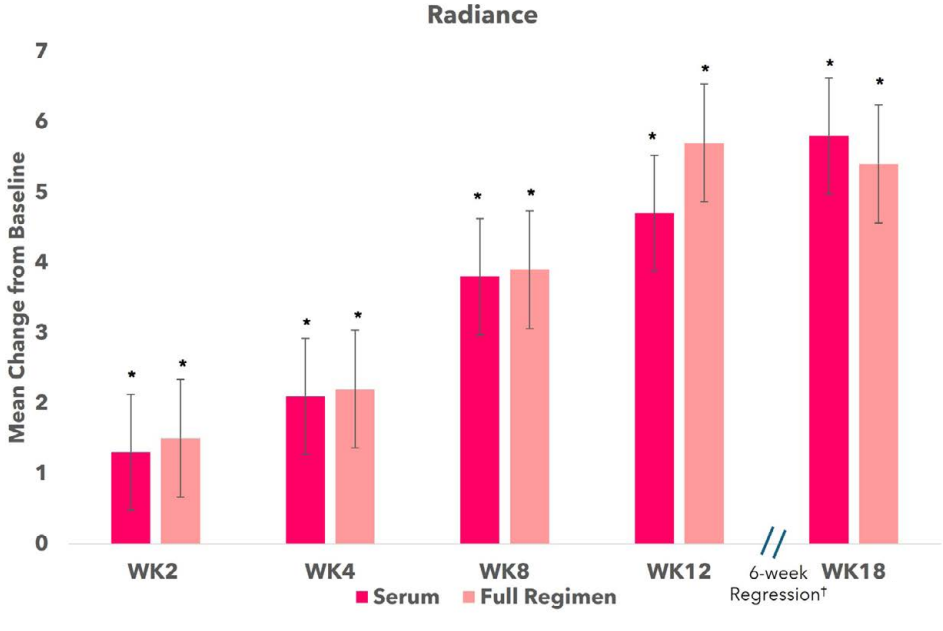
Significant differences between treatment groups and baseline as indicated (*P<0.05).
†Subjects did not use any Thiamidol products during regression phase.

FIGURE 4. Mean Individual Typology Angle (ITA°) following treatment with Thiamidol formulated serum or thiamidol formulated full product regimen (serum, day lotion, and night cream) compared with baseline at all time points assessed.



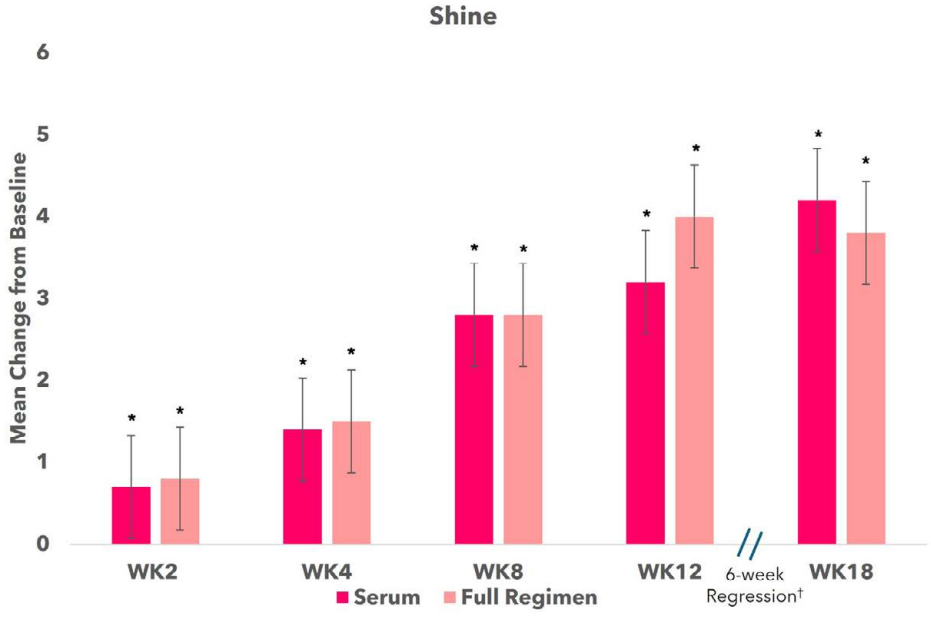
Significant differences compared with baseline as indicated (*P<0.05).
†Subjects did not use any Thiamidol products during regression phase.

FIGURE 5. Mean radiance measured following treatment with Thiamidol formulated serum or Thiamidol formulated full product regimen (serum, day lotion, and night cream) compared with baseline at all time points assessed.



Significant differences compared with baseline as indicated (*P<0.05).
†Subjects did not use any Thiamidol products during regression phase.

FIGURE 6. Mean shine measured following treatment with Thiamidol formulated serum or Thiamidol formulated full product regimen (serum, day lotion, and night cream) compared with baseline all time points assessed.



Significant differences compared with baseline as indicated (*P<0.05).
†Subjects did not use any Thiamidol products during regression phase.

Efficacy, Radiance, and Shine

Efforts to better evaluate the efficacy of anti-pigmentation products beyond skin lightening have expanded into the objective quantitative measurement of skin's radiance and shine. Both skin radiance and shine center on the skin's interaction with light, more specifically, the amount of light reflected at the skin surface and resulting optical characteristics of skin, giving the appearance of younger, brighter, glossier, even-toned skin.[21,22] Subject's full-face images were captured using a Visia-CR imaging system, with subsequent measurement and quantitation of radiance and shine.

On hyperpigmented skin, both radiance and shine improved statistically significantly (P<0.05) compared with baseline in both the Thiamidol-serum and Thiamidol-regimen groups starting at week 2 and increasing at every time point through week 12, and maintained through the 6-week regression phase, week 18 (Figures 5 and 6). While not reaching statistical significance, changes in radiance and shine trended in favor of the Thiamidol-regimen group compared with the Thiamidol-serum group at week 12 (Figures 5 and 6).

DISCUSSION

Pigmentary disorders, particularly those associated with hyperpigmentation (eg, melasma, PIH, solar lentigines, etc.), remain one of the most common dermatologic diagnoses, especially in individuals with skin of color (SOC).[23-25] The prevalence of PIH, melasma, and solar lentigo has been reported to be as high as 15%, 50%, and 90%, respectively.[4,26,27]

Hyperpigmentation occurs when excess melanin is deposited in the skin, most commonly due to overstimulation of melanin synthesis within the melanocyte.[4,28,29] The key rate-limiting step in this complex pathway centers on the conversion of the amino acid tyrosine to L-Dopa, mediated by the cellular enzyme, tyrosinase, leading to a cascade of reactions culminating with the production of the 2 melanin products, eumelanin (brown/black pigment) and pheomelanin (light red-yellow pigment).[5,30]

Therapeutic approaches to treat hyperpigmentation center on agents that reduce melanin synthesis or enhance dispersion and removal of melanin once formed.[24,31] The removal of 2% hydroquinone from the market, following the passing of the CARES Act of September 2023, created a critical gap in over-the-counter anti-pigmentation options, particularly for patients with access to care issues.[24,31] Recently, isobutylamido thiazolyl resorcinol (Thiamidol) has been identified as an effective inhibitor of human tyrosinase and melanin production, with an IC50 = 1.1 mmol/L and near 100% inhibition of human tyrosinase at 10 mmol/L, as compared with 4-butylresorcinol's IC_{50} = 21 mmol/L and hydroquinone's IC_{50} > 4000 mmol/L.[6] Thiamidol-based formulations have been studied in multiple clinical studies worldwide targeting hyperpigmentation associated with mild-to-severe melasma, acne-induced PIH, laser-induced PIH, and solar lentigines in both randomized controlled, vehicle-controlled, head-to-head, combination/adjunctive treatment, and real-world studies.[6,7,10,12-17]

Based on these studies, a randomized study was conducted to investigate the clinical efficacy of a novel cosmetic Thiamidol-containing serum and a Thiamidol-containing regimen consisting of a Thiamidol-containing day lotion with SPF 30, the Thiamidol-containing serum, and a Thiamidol-containing night cream for the visible management of facial hyperpigmentation as assessed by various objective assays (colorimetric and photographic image analysis), including L*Mean, ITA°, Radiance, and Shine. While other investigators have included L*Mean and ITA° as part of the clinical assessment of Thiamidol-containing formulation, this is the first reported study to include Radiance and Shine as key endpoints objectively measured, rather than subjectively by the investigator or patient questionnaire.

In this study, changes in hyperpigmentation as measured by 2 objective skin lightening measurements (L*Mean and ITA°) were observed as early as week 2 posttreatment initiation in both the Thiamidol-serum and Thiamidol-regimen groups compared with baseline levels. This improvement continued to increase at each assessment time point (week 4, week 8) through the end of the treatment phase of the study (week 12), with skin lightening maintained through the 6-week regression phase (no treatment), suggesting sustained inhibition of tyrosinase activity and melanin production, with enhancement of prolonged sustainment of melanin inhibition trending in favor of the Thiamidol-serum group compared with the Thiamidol-regiment group (statistical significance not reached), which warrants longer term studies to evaluate further.

It should be noted that Thiamidol mediated inhibition of melanin synthesis is reversible, with viability of human cultured melanocytes post treatment as demonstrated by Mann et al.[6] The increases in ITA° observed in this study are consistent with data reported by Roggenkamp et al, for subjects using a similar regimen of Thiamidol-containing products (day lotion with SPF, serum, and night cream) for 24 weeks for treatment of moderate-to-severe melasma.[13] Additionally, the observed increases in L*Mean are consistent with those reported by Vachiramon et al following twice-daily application of a Thiamidol-containing formulation for treatment of laser-induced PIH for 8 weeks.[16]

While reduction of melanin deposition in skin is the key attribute for any anti-pigmentation therapeutic, efforts to address the overall skin's appearance, including commercially appealing attributes like radiance and shine are highly desirable.[32] The visual perception of skin's radiance and shine is mediated by interactions of light and skin resulting in surface and subsurface reflections yielding what consumers commonly describe as "an internal glow".[21,22,32] Efforts to improve overall skin appearance by improving radiance and shine, in addition to reducing hyperpigmentation, could lend to overall patient satisfaction with skin appearance and patient adherence.

To evaluate the impact of treatment with both the Thiamidol-serum and Thiamidol-regimen, radiance and shine were measured at weeks 2, 4, 8, 12, and after the 6-week regression period (week 18). Subject photographs were taken using a Visia-CR imaging system, and images were graded for radiance and shine according to methods developed by Matsubara et al.[21,22] Increases in both parameters (relative to baseline) were observed starting at week 2, increasing at each time point through week 12 with sustainment through the 6-week regression period. Changes in radiance and shine trended to enhancement in the Thiamidol-regimen group compared with the Thiamidol-serum group at 12; however, statistical significance was not achieved. Additional studies beyond 12 weeks would be beneficial to evaluate any additional benefits of the full treatment regimen compared with serum alone on the improvement of skin radiance and shine. The increases in both of these parameters over time suggest that reduction of hyperpigmentation by Thiamidol-containing products/regimen treatment may result in optical characteristics of the skin, yielding a perception of brighter, more radiant skin.

This study has several strengths, including the inclusion of varied skin types representing the general population dealing with hyperpigmentation, spanning FST I to VI. Additionally, the inclusion of both a Thiamidol regimen and a Thiamidol-serum-alone group is in accordance with real-world settings in which individuals often using an array of treatment products for the management of hyperpigmentation or lean towards serums alone to complement their overall skin health regimen. Lastly, the inclusion of the 2-objective measure of optical reflection of skin resulting in the visual perception of radiance and shine is a novel approach to assessing anti-pigmentation products and treatment approaches. Limitations of the study are the monocentric study approach, relatively low number of patients, and lack of a vehicle control group, which should be addressed in future studies.

CONCLUSION

This study demonstrates the clinical effectiveness of Thiamidol-containing formulations in the visible improvement of facial hyperpigmentation and in overall skin radiance and shine. Use of the Thiamidol containing either the serum twice daily or the full regimen (day lotion with SPF 30, serum, and night cream) resulted in a significant visible improvement of facial hyperpigmentation as early as week 2, while use of the full regimen trended towards enhanced efficacy of radiance and shine. Therefore, these data support the use of Thiamidol-containing formulations as part of the overall management strategy for individuals affected by facial hyperpigmentation.

DISCLOSURES

SRD has served as an investigator and/or consultant for multiple entities in the past, including Beiersdorf. He has also held multiple leadership positions in organized medicine. EL has

served as an investigator, speaker, advisor, and/or consultant for AbbVie, Almirall, Amgen, Arcutis, Bausch, Beiersdorf, Bristol-Myers Squibb, Cassiopeia, Cellceutix, Dermavant, Eli Lilly, Galderma, GSK, Incyte, Kenvue, LEO, L'Oreal, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi, Sun Pharma, Takeda, UCB Pharma, and Vyne. NE has served as an investigator for Pfizer and as a speaker and/or advisory board member for AbbVie, Allergan, Avita, Beiersdorf, Canfield, Dior, Galderma, Incyte, Janssen, L'Oreal, La Roche-Posay, Lilly, McGraw-Hill, Medscape, Pfizer, Sanofi, Takeda, and VisualDx. She has also received royalties from McGraw-Hill and has stock options in VisualDx. CF is an investigator affiliated with Novartis. Additionally, she serves as a consultant or advisor for Galderma, Sun Pharma, Avita, Procter & Gamble, Regeneron, Aerolase, Benev, L'Oreal, La Mer, Avene, Kenvue, Bristol Myers Squibb, Nutrafol, Acclaro, Beiersdorf, Primus, Johnson & Johnson, Crown Aesthetics, and AbbVie. PG has served as an investigator and/or consultant for Allergan, BOD Clinuvel, Clinuvel, Incyte, Johnson & Johnson, L'Oreal, Merck, Pfizer, SkinBetterScience, and Versicolor Technologies.

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ORIGINAL ARTICLE

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Disparities in Hidradenitis Suppurativa Clinical Trials: An Updated Review of ClinicalTrials.gov From 2020 to 2024

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ABSTRACT

Background: There is a notable lack of diversity in dermatologic studies, even concerning conditions that are known to have a higher prevalence in the skin of color (SOC) population, such as hidradenitis suppurativa (HS). This study updates the current literature on SOC representation in dermatology by analyzing the demographics and locations of HS clinical trials from 2020 to 2024, during which there were significant advancements in therapeutics.

Methods: A search of the term "hidradenitis suppurativa" was conducted on the ClinicalTrials.gov website for trials initiated between June 2020 and December 2024.

Results: Five clinical trials totaling 411 participants were included. Caucasian/White participants (n=281, 68.4%) comprised the majority, followed by African American/Black (n=93, 22.6%) participants. In comparison to HS trials from 2008 to 2020, the 5 recent trials between 2020 and 2024 demonstrated a significant (P<0.001) increase (14.9% vs 22.6%, respectively) in the percentage of Black participants. Most US clinical trial sites (n=38, 59.3%) were located in cities with moderate (12.6-49.9%) to high (>50%) Black populations.

Conclusions: The increase in the proportion of Black participants in HS clinical trials from 2008–2020 to 2020–2024 demonstrates a promising outlook for improved representation in HS clinical trials. Nonetheless, an underrepresentation of Black participants in HS clinical trials continues to persist, highlighting the necessity for continued efforts in the inclusion of SOC individuals in clinical research.

J Drugs Dermatol. 2025;24(12):1203-1207. doi:10.36849/JDD.9066R1

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic skin disease characterized by debilitating symptoms associated with the highest comorbidity burden and lowest quality of life among dermatologic conditions.[1] HS largely affects the African American (AA)/Black population, with epidemiology studies demonstrating the highest prevalence in Black populations.[2] In the United States (US), Black patients with HS have been shown to have a higher disease burden, manifesting as higher disease severity, healthcare utilization, and number of surgeries compared to other racial groups.[3] Despite this, there are notable disparities in the enrollment of Black participants in HS clinical trials. A study by Okeke et al. analyzing demographics of HS trials from 2008 to 2020 found that Black participants made up a minority (14.9%) of the participants.4 Since 2020, significant therapeutic advancements, notably FDA approvals of secukinumab, an interleukin-17A (IL-17A) inhibitor, and bimekizumab, a monoclonal antibody targeting IL-17A and IL-17F, have emerged.[5,6] This study updates the current literature on Black patient representation in HS clinical trials with the advent of multiple biologic therapies and explores possible barriers to inclusion.

MATERIALS AND METHODS

A search for "hidradenitis suppurativa" was conducted on ClinicalTrials.gov for clinical trials with a start date between June 1, 2020, and December 1, 2024. Trials were included if they reported at least one of the following: race, ethnicity, or Fitzpatrick skin type (FST), and if they had at least one US location. In total, 5 trials were included. Trials were excluded if they lacked sufficient demographic data or if they were ongoing.

Patient characteristics (sex, race, ethnicity, Hurley stage) and trial characteristics (intervention type, phase, location) were collected from each trial. Data was retrieved using both ClinicalTrials.gov and PubMed by utilizing the NCT number, trial title, or authors' names to locate the corresponding articles. Black population densities at trial sites were categorized as "very low" (0.0-0.9% of population), "low" (1-12.5%), "moderate" (12.6-49.9%), or "high" (>50%) as defined by Okeke et al.[4] Race categories

included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black, White, Multiracial, and Unknown/Not reported.

The proportion of Black participants was compared to White participants using a Chi-squared test of independence. A one-sample Chi-squared test (α level = 0.05) was also used to compare the proportion of Black subjects first to the calculated expected rates of enrollment using prevalence rates, then to the previously reported rates in HS trials from 2008 to 2020.[4] The expected proportion of Black subjects with HS (32.6%) was determined using previously reported race-specific prevalence rates by Garg et al.[7] All statistical analyses were conducted on IBM SPSS Statistics Version 29.0.2.0 and specified a priori.

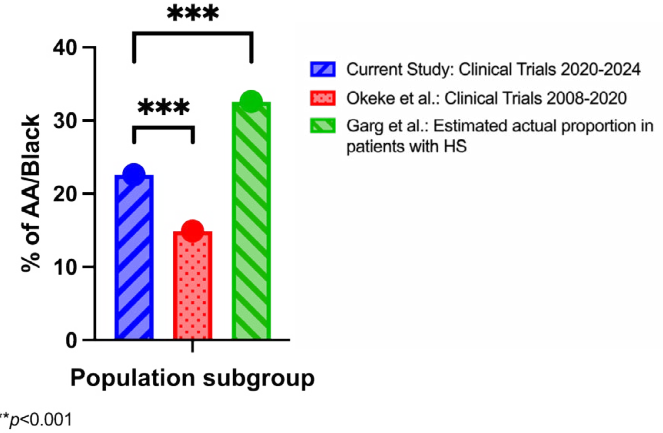
RESULTS

Five clinical trials with a total of 411 participants met the inclusion criteria. White participants comprised the majority of the trials (n=281, 68.4%), followed by Black (n=93, 22.6%), Asian (n=20, 4.9%), Other/Unknown (n=10, 2.4%), multiracial (n=4, 1%), American Indian or Alaskan Native (n=2, 0.5%), and Native Hawaiian/Other Pacific Islander (n=1, 0.2%). The difference in proportion between the White and Black participants was significant (P<0.001). No trials reported FST data.

The majority of the US clinical trial sites (n=38, 59.3%) were located in cities with moderate to high Black populations, while the minority (n=26, 40.7%) were located in areas with very low to low Black populations (Table 1).

There was a significant increase in the proportion of Black participants in HS trials from 2008–2020 to 2020–2024 (14.9% vs 22.6%, P<0.001; Figure 1).[4] Overall, however, Black participants were significantly underrepresented compared to the expected proportion of Black patients with HS in the US (P<0.001, Figure 1).

FIGURE 1. Comparison of the proportion of Black individuals in HS clinical trials from 2020 to 2024, HS clinical trials from 2008 to 2020[4] and HS population data.[7]



***p<0.001

AA: African American

DISCUSSION

Our findings show that Black participant enrollment in HS clinical trials has increased since 2020, reflecting some progress in skin of color (SOC) representation. However, Black subjects continue to be significantly underrepresented relative to the disease prevalence in this population. White participants were enrolled at three times the rate of Black participants, despite HS being twice as prevalent in Black individuals.[1] These findings align with general trends seen in clinical trial research, where the majority of prior published studies on HS have been on largely White cohorts.[8] As Black patients have higher rates of comorbidities (including cardiovascular disease, diabetes, hypertension, and obesity), they face a higher risk for severe and chronic HS symptoms compared to White patients.[8,9] Furthermore, Black patients with HS tend to present with significantly higher Hurley stage of disease and greater outpatient visit rates compared to their White counterparts.[10,11,12] They are also more likely to experience significant delays in diagnosis and reduced access to dermatologic care compared to White and Hispanic patients.[13]

Barriers to Enrollment

The underrepresentation of minority groups in clinical trials is multifaceted, influenced by multiple systemic, interpersonal, and individual-level barriers. At the systemic level, structural barriers to participation include geographic accessibility and restrictive exclusion criteria that may disproportionately impact certain populations.[4,14] Our findings show that more than half (59.3%) of the 64 HS trial locations across the US were in areas with moderate to high Black populations (≥12.6%), an increase from 49% in trials conducted from 2008-2020.[4] This shift may have contributed to the overall rise in Black participant enrollment. However, other systemic barriers, such as exclusion criteria, may still disfavor SOC participant enrollment.[14] For example, exclusion criteria such as prior biologic medication use (in two trials), presence of more than 20 draining fistulas (in two trials), or opioid use for HS-related pain during the study could disproportionately exclude Black patients, who tend to have a more severe disease presentation. Additionally, Black patients have been found to be prescribed biologic therapy at higher rates than patients of other races for conditions such as asthma, potentially further limiting their eligibility.[15] Other exclusion criteria, such as a known history of HIV, Hepatitis B, or Hepatitis C (in one trial), may impact certain racial groups more than others. A report published by the US Department of Health and Human Services Office of Minority Health in 2022 demonstrated that Black patients have higher rates of Hepatitis B and are over seven times more likely to be diagnosed with HIV compared to White patients.[16] Lastly, the exclusion of participants with uncontrolled depression or suicidal thoughts (in one trial), may be another potential barrier for SOC patient participation, as major depression and its risk factors are more prevalent among Black and Hispanic patients.[17] While some exclusions are necessary to minimize the effect of confounding variables on

TABLE 1.

Hidradenitis Suppurativa Clinical Trials 2020-2024: Locations, Participant Characteristics, and Demographics of US Trial Locations

Clinical Trial Sponsor, Year Completed, (NCT #)	University of Miami, 2022 (NCT04648631)	Boehringer Ingelheim, 2022 (NCT04762277)	Eli Lilly and Company, 2022 (NCT04493502)	AbbVie, 2022 (NCT04430855)	Incyte Corporation, 2023 (NCT04476043)
Intervention type, Intervention, Phase	Device, Antibiofilm surfactant wound gel, Phase N/A	Drug, Spesolimab, Phase 2	Drug, LY3041658, Phase 2	Drug, Upadacitinib, Phase 2	Drug, Povorcitinib, Phase 2
Total Study Locations, n	15[a]	25[b,c]	20[d,e]	26[f,g]	40[h,i]
HS participants, n	15	52	67	68	209
Sex, n (%)					
Female	13 (86.7%)	31(59.6%)	47 (70.1%)	53 (77.9%)	158 (75.6%)
Male	2 (13.3%)	21 (40.4%)	20 (29.9%)	15 (22.1%)	51 (24.4%)
Ethnicity, n (%)					
Hispanic or Latino	N/A	2 (3.8%)	13 (19.4%)	14 (20.6%)	28 (13.4%)
Not Hispanic or Latino	N/A	44 (84.6%)	50 (74.6%)	54 (79.4%)	179 (85.6%)
Other/Unknown	N/A	6 (11.5%)	4 (6%)	0 (0%)	2 (1%)
Race, n (%)					
American Indian or Alaskan Native	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	1 (0.5%)
Asian	1 (6.7%)	6 (11.5%)	1 (1.5%)	6 (8.8%)	6 (2.9%)
Native Hawaiian	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)
Black or AA	2 (13.3%)	4 (7.7%)	17 (25.4%)	19 (27.9%)	51 (24.4%)
White or Caucasian	12 (80%)	35 (67.4%)	46 (68.6%)	41 (60.3%)	147 (70.3%)
Multiracial	0 (0%)	0 (0%)	3 (4.5%)	1 (1.5%)	0 (0%)
Other/Unknown	0 (0%)	6 (11.5%)	0 (0%)	0 (0%)	4 (1.9%)
Hurley Stage, n (%)					
Hurley Stage I	N/A	N/A	N/A	1 (1.5)	N/A
Hurley Stage II	N/A	N/A	N/A	35 (51.4%)	N/A
Hurley Stage III	N/A	N/A	N/A	32 (47.1%)	N/A
# of Clinical Trial Locations in US Cities, Grouped by AA/Black Population Level, n (%)					
Very Low[j]	0 (0%)	1 (20%)	1 (6.7%)	0 (0%)	2 (8%)
Low[k]	0 (0%)	1 (20%)	5 (33.3%)	6 (33.3%)	10 (40%)
Moderate[l]	1 (100%)	3 (60%)	9 (60%)	12 (66.7%)	11 (44%)
High[m]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)

US, United States, HS, hidradenitis suppurativa, AA, African American
[a]Miami, FL
[b]Non-US Countries: Australia, Belgium, Canada, Czechia, France, Germany, Italy, Netherlands, Norway, Poland, Spain
[c]US Cities: Los Angeles, CA, Indianapolis, IN, Rochester, MN, Oklahoma City, OK, Pittsburgh, PA
[d]Non-US Country: Australia
[e]US Cities: Rogers, AR, Fountain Valley, CA, Los Angeles, CA, Hollywood, FL, Miami, FL, Tampa, FL, Marietta, GA, Sandy Springs, GA, Beverly, MA, Boston, MA, Saint Louis, MO, Portsmouth, NH, Durham, NC, Cincinnati, OH, Cleveland, OH
[f]Non-US Countries: Canada, Japan, Puerto Rico
[g]US Cities: Phoenix, AZ, Little Rock, AR, San Diego, CA, Boca Raton, FL, Miami, FL, Tampa, FL, Skokie, IL Indianapolis, IN, Boston, MA, Saint Louis, MO, East Windsor, NJ, Durham, NC, Cleveland, OH, Tulsa, OK, Pittsburgh, PA, Charleston, SC, Houston, TX, Spokane, WA
[h]Non-US Countries: Canada, France, Germany, Poland, Spain
[i]US Cities: Hoover, AL, Gilbert, AZ, Phoenix, AZ, Fountain Valley, CA, Fremont, CA, Huntington Beach, CA, Newbury Park, CA Sacramento, CA, Cromwell, CT, Coral Gables, FL, Miami, FL, Tampa, FL, Tampa, FL (2nd location), Atlanta, GA, West Lafayette, IN, Baton Rouge, LA, New Orleans, LA, Boston, MA, Fort Gratiot, MI, Saint Louis, MO, the Bronx, NY, Chapel Hill, NC, Winston-Salem, NC, Hershey, PA, Bellaire, TX
[j]Cities with 0.0-0.9% AA/Black population
[k]Cities with 1-12.5% AA/Black population
[l]Cities with 12.6-49.9% AA/Black population
[m]Cities with >50% AA/Black population

TABLE 2.

Summary of Participant Characteristics and Locations of Hidradenitis Suppurativa Clinical Trials	
Total Clinical Trials (# of participants)	**5 (411)**
Trials that Reported Sex (# of participants)	5 (411)
Sex	# of Participants (%)
Female	302 (73.5%)
Male	109 (26.5%)
Trials that Reported Ethnicity (# of participants)	3 (344)
Ethnicity	# of Participants (%)
Hispanic or Latino	55 (16%)
Not Hispanic or Latino	283 (82.3%)
Other/Unknown	6 (1.7%)
Trials that Reported Race (# of participants)	5 (411)
Race	# of Participants (%)
American Indian or Alaskan Native	2 (0.5%)
Asian	20 (4.9%)
Native Hawaiian/Other Pacific Islander	1 (0.2%)
AA/Black	93 (22.6%)
Caucasian/White	281 (68.4%)
Multiracial	4 (1%)
Other/Unknown	10 (2.4%)
Trials that Reported FST (# of participants)	0 (0)
Trials that Reported Hurley Stage (# of participants)	2 (89)
Hurley Stage	# of Participants (%)
Hurley Stage 1	1 (1.5%)
Hurley Stage 2	35 (51.5%)
Hurley Stage 3	32 (47.1%)
# of Clinical Trial Locations in US Cities, Grouped by AA/Black Population Level	# of Trial Sites (%)
Very Low AA/Black Populationa	4 (6.3%)
Low AA/Black Populationb	22 (34.4%)
Moderate AA/Black Populationc	36 (56.2%)
High AA/Black Populationd	2 (3.1%)

FST, Fitzpatrick Skin Type, AA, African American
[a]Cities with 0.0-0.9% AA/Black population
[b]Cities with 1-12.5% AA/Black population
[c]Cities with 12.6-49.9% AA/Black population
[d]Cities with >50% AA/Black population

the study and to prevent undue risks in immunocompromised populations, awareness of their potential impact on enrollment is important.

At the interpersonal level, implicit bias by the investigators or referring clinicians may further contribute to trial disparities.[18] A retrospective study by Case et al found significant differences in the probability of a patient receiving screening for cardiovascular clinical trials. In their study, White patients were nearly twice as likely as Black patients to be screened for cardiovascular clinical trials (18.9%, vs 9.3%). At the individual level, barriers may include discomfort with or distrust of the clinical trials process, communication issues, perceived harm, and time/resource constraints.[19]

Additionally, systemic and interpersonal barriers seen specifically in HS patients from minority groups included longer time to first consultation, longer time to diagnosis, and a greater

likelihood of misdiagnosis, which may limit trial participation.[20] Within dermatology, minority groups also face unequal access to healthcare, potentially lowering exposure to clinical trial opportunities.[21] Identifying and eliminating such barriers to enrollment through improved patient education and increased provider awareness of bias is necessary for equitable SOC representation in HS research.

Importance of Representation

Inclusion of representative populations in clinical trial research is particularly crucial for HS, given the disproportionate impact of the disease in Black patients. Differences in disease severity, time to diagnosis, comorbidities, and outcomes underscore the importance of enrolling a diverse population of patients for clinical trials. Particularly in the age of new therapies such as biologics, it is vital to ensure that populations with a high disease prevalence and disease burden are included to ensure the safety and efficacy of the new drugs in these populations, as responses to treatment may differ based on background and associated comorbidities. Lastly, increasing diversity in trials may help to increase trust in the healthcare system, which is a critical factor in treatment adherence and outcomes, and may help improve disparities in HS patients.[22,23]

Limitations/Strengths

This study is primarily limited by its four-year timespan, leading to fewer trials compared to Okeke et al's study, which included trials spanning over a decade.[4] As such, the smaller scope of our study introduces a risk for increased variability, skewing, and an over- or under-estimation of the effects or the sizes of the groups. Additionally, eligible studies were identified using ClinicalTrials.gov as the sole database, potentially omitting relevant clinical trials. A key strength of this study is the use of race-specific prevalence rates of HS, which are not always available for many dermatologic conditions. Using race-specific prevalence rates offers a more accurate representation of the demographics of the disease. An additional strength of this study is the cross-referencing of PubMed done to obtain data for the identified clinical trials, potentially mitigating the effects of reporting bias as prior studies have shown that the majority of clinical trials do not publish results or link associated articles on ClinicalTrials.gov.[24]

CONCLUSION

The overall 7.7% increase in the proportion of Black participants in HS clinical trials since 2020 demonstrates a promising outlook for SOC representation in HS clinical trials. Nonetheless, there remains an overall disparity between the enrollment of Black and White HS participants, despite the higher prevalence and severity of this disease in the former population. There is a need for continued efforts to address underrepresentation and ensure equitable inclusion of individuals with SOC in future HS clinical trial research.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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The Current Landscape of Treatment of Warts

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ABSTRACT

Warts have bothered people since the early Greek and Roman empires.[5] For centuries, people have studied causes of and treatments for these irritating tumors. In recent history, treatments have stagnated. Warts are caused by non-enveloped, circular, double-stranded DNA human papillomavirus (HPV).[6] Most infections are subclinical, but clinically relevant disease ranges from warts to invasive carcinoma.[6] Two-thirds of warts resolve spontaneously within 2 years, meaning that the stakes for treatments are high.[4] Successful therapies need to have high resolution, few side effects, and act fast. The lack of radical antiviral HPV treatment represents a significant care gap. Although common warts are generally due to low-risk HPV strains, coinfection with higher-risk variants is not uncommon.

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INTRODUCTION

What Are Warts?

Warts are papillomas arising from HPV infection of epidermal or mucosal cells. Histologically, warts demonstrate epidermal hyperplasia, parakeratosis, koilocytosis, and papillomatosis. Reasons for treatment include pain, functional impairment, transmission risk, and cosmetic embarrassment.[18] Presenting patients may represent an infected population, so measures inhibiting spread, such as socks covering affected feet, are beneficial.[4] There are several types of skin/cutaneous and submucosal warts. Cutaneous warts can be further subdivided. Verruca vulgaris (Figure 1), or common warts, often appear as hyperkeratotic papules and plaques.[4] Plantar warts (Figures 2, 5)

FIGURE 1. Common wart (verruca vulgaris) on the finger.



FIGURE 2. Mosaic plantar wart on the plantar aspect of the foot.



FIGURE 5. Multiple plantar warts on the foot. Note disruption of skin markings by HPV infection that are helpful to differentiate from callous or corn.



are thick, painful hyperkeratotic plaques, often beneath pressure points on the plantar aspect of the foot.[4] They look similar to corns, but corns do not exhibit pinpoint bleeding upon paring, and preserve skin markings.[4] Periungual warts (Figure 6) are found around or under the nail beds, particularly in people who bite their nails.[4] Finally, planar warts (Figure 4) appear as flat-topped papules, particularly on women's faces or legs.

FIGURE 6. Periungual and Subungual wart.

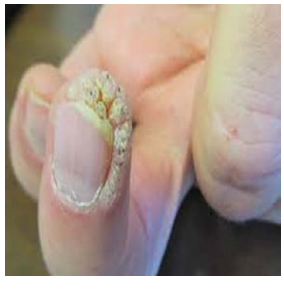


FIGURE 4. Multiple flat warts on the face.



FIGURE 3. Filiform wart on the nostril.



Thrombosed capillaries are characteristic of warts (the "seeds") but are absent in facial and planar warts and thus are not diagnostic.[4] Warts are clinically diagnosed, but it is important to remain open-minded and biopsy if the diagnosis is uncertain. Large hyperkeratotic warts and warts treated with podophyllotoxin can mimic squamous cell carcinoma.[4]

Who Is At Risk?

Warts are uncommon in infancy but more common throughout childhood. After the second decade, the incidence again decreases. Risk factors include affected contacts, nail biting, walking barefoot, and immunosuppression.

When to Escalate Treatment?

Primary care providers often treat cutaneous warts. Those with large or numerous warts, immunocompromised status, diagnostic uncertainty, or lesions resistant to treatment for over three months should be referred to dermatology.[4]

MATERIALS AND METHODS

A literature review of *Archives of Dermatology* and the *Journal of the American Academy of Dermatology* (JAAD) was undertaken. To continue a detailed search, other resources, such as PubMed at the US National Library of Medicine (PubMed) and the Journal of the American Medical Association (JAMA), were analyzed. Keywords include 'HPV,' 'warts,' 'treatment,' 5-FU, and 'bleomycin.' Relevant findings are discussed below.

RESULTS

The reviewed articles agree that more studies are needed to evaluate effective treatments for warts.

DISCUSSION

Topical Treatments

Topical treatments ablate warts or stimulate an immune response. A large advantage is self-administration, but this makes compliance and proper application paramount.

Salicylic acid is one of the most popular compounds available by prescription or over-the-counter (OTC) at concentrations between 5 and 40%.[3,19] It softens the hyperkeratotic epidermis and is suitable for all cutaneous lesions. For optimal results, the excess keratin should be removed and the area soaked in warm water.[3] Salicylic acid significantly increases wart clearance but may be more effective on the hands.[14] Advantages of salicylic acid include low cost and easy accessibility. Disadvantages include requiring several weeks of daily use and irritation, especially on the face.

Silver nitrate is a form of chemical cautery used twice weekly.[3] It is available as a 0.5% OTC lotion, a 20-50% OTC solution, or prescribed at 95%, and is often associated with potassium nitrate.[3] The clearance rate is between 43 and 63.3% but it must be applied carefully to prevent post-treatment scars.[3]

Topical trichloroacetic acid (TCA) is a chemical cauterization applied clinically at 80 to 90% concentrations with 70 to 80% clearance and 36% recurrence.[6] Adverse effects include pain, burning, ulceration, and crusting.[6] Care must be taken to avoid normal tissue during application.

Imiquimod binds membranous TLR7, activating dendritic cells, macrophages, and keratinocytes to release type 1 interferons and enhance cell-mediated cytolytic activity.[6] It may have difficulty penetrating thickened epidermis, decreasing the efficacy for non-genital warts.[3] It comes in different concentrations, each with its own application regimen. One study applied 5% imiquimod cream either nightly or thrice weekly for up to 16 weeks.[24] Those who reported full clearance only experienced 15% recurrence. Patients with residual lesions underwent surgical excision and experienced 20% recurrence, compared to 65% after surgery alone.[24] The 5% cream is applied thrice weekly for up to 16 weeks. 3.75% cream is applied daily for up to 8 weeks. Imiquimod may induce immunologic memory to prevent future warts.[24] Disadvantages include systemic effects and patient noncompliance during complicated regimens.[6]

Cidofovir is an antiviral nucleotide analog that inhibits DNA polymerase to block viral DNA synthesis and replication, inducing apoptosis in infected cells.[6,23] It has favorable outcomes in children and transplant patients with recalcitrant warts. A case study discussed treatment with cidofovir diluted 1:3 with normal saline, followed by 1:4 for an additional 3 injections, with no warts after four months.[23] Adverse effects include pain, pruritus, dermatitis, and rarely erosions or ulcerations.[6]

TABLE 1.

A Summary of the Current Treatments for Warts

Treatment	Efficacy	Disadvantages	Recurrence
1. Salicylic acid	64%[5]	- long duration - stinging, soreness[5] - cellulitis[5]	--
2. Imiquimod	30-89%[4]	- systemic side effects[5] - compliance[6]	15-20%[24]
3. Cidofovir	50-65%[6]	- pain[6] - pruritis[6] - dermatitis[6] - erosions/ulcerations[6] - one report of acute on chronic renal failure[6]	--
4. Podophyllotoxin	45-77%[6]	- burning[6] - redness[6] - pain[6] - itching[6] - swelling[6] - enteritis[6] - bone marrow suppression[6] - neurological deficits[6]	38%[6]
5. Duct tape	85%[4]	- no advantage over placebo[14]	--
6. Cryotherapy	29.7-88%[3,5,6]	- pain[5] - vascular/dermal damage - does not treat subclinical lesions[6]	25-40%[6]
7. Heat therapy	46-79.2%[25]	--	
8. Surgical Excision	35-72%[6]	- scarring - viral spread - does not treat subclinical lesions	19-29%[6]
9. Photodynamic Therapy	73-98.2%[3,5]	- bloating - stinging	3.6%[6]
10. Candida Immunotherapy	50-88.6% + acitretin: 66.7%[15] + PPD: 70.6%[12]	- edema - flu-like symptoms - induration - purple digit syndrome	--
11. Purified Protein Derivative	32.1-61.1%	- fever[18] - transient edema[18]	9%[12]
12. Diphencyprone	60%[4]	- unsuitable for children[4] - severe blistering[4] - eczema[4] - mutagen[3]	--
13. Vitamin D3	60%[21]	--	--
14. HPV vaccine (bi)	30-81.8%[1,22]	- erythema[22] - transient edema[22] - pruritis[1] - fatigue[1] - flu-like symptoms[22]	--
15. HPV vaccine (quad)	90%22	- erythema[22] - edema[22] - flu-like symptoms[22]	--
16. MMR vaccine	63-81%[18]	- flu-like symptoms[18]	6%[18]
17. 5-FU	30-66.7%[2,3]	- pain - hemorrhagic bullae - hyperpigmentation	--
18. Bleomycin	16-94%[4]	- extensive necrosis	--
19. Cimetidine	84.3%[5]	- GI upset[5]	- 7.2%[5]
20. isotretinoin	39.6%[6]	- contraindicated in pregnancy[6]	9.5%[6]
21. Digoxin + Furosemide	28%	--	--
22. Laser therapy	23-64%[4,6]	- scarring - viral spread[6] - burning[17] - hyperpigmentation[17] - flu-like symptoms[17]	77%[6] - increased risk in smokers[5]
23. Antiretroviral treatments	N/A	- no proven effecacy[8]	--
24. Zinc sulfate	11-78.1% [3, 16, 26]	- pain[16] - dyspigmentation[16] - flu-like symptoms[16]	--
25. silver nitrate	43-63.3%[3]	- scarring[3]	--
26. Topical TCA	70-80%[6]	- ulceration[6] - crusting[6]	36%[6]

Podophyllotoxin, purified extract of the podophyllum plant, binds to cellular microtubules and inhibits mitosis, inducing necrosis.[6] It is applied twice daily for three consecutive days per week for up to four weeks, with 45 to 77% clearance.[6] Erosion development indicates successful necrosis.[6] Adverse effects include enteritis, bone marrow suppression, and neurological deficits due to excessive absorbtion.[6] Others include burning, redness, pain, pruritus, and swelling.[6]

One study found 85% clearance using duct tape, a treatment low in cost and pain.[4] Duct tape is applied and removed after 6 days, stimulating the immune system through local irritation.[3] There has been no reported advantage over a placebo.[14]

Destructive Treatments

Cryotherapy, the most common in-office treatment, is first-line therapy. Warts and a surrounding rim of normal tissue are frozen with liquid nitrogen at -196°C, causing direct destruction and secondary inflammation.[3,4] It clears 29.7-88% of warts within three sessions with 25 to 40% recurrence.[3,5,6] There is no significant difference in results between 2, 3, and 4-week intervals.[14] However, aggressive treatment is more effective than gentle therapy, despite increasing adverse effects.[1,4] One study comparing cryotherapy with topical treatments found that cryotherapy is beneficial for warts on the hands but not the feet. Another study comparing cryotherapy with a placebo found no benefit of cryotherapy.[4] A study comparing cryotherapy to immunotherapy found that cryotherapy cleared 20% of warts, versus 50% following immunotherapy.[13] This suggests that cryotherapy may be an outdated treatment. Disadvantages of cryotherapy include procedural pain, no treatment of subclinical lesions, and possible permanent dermal and vascular damage, causing scarring, especially in patients with dark skin.[3,5] Cryotherapy requires multiple visits, possibly decreasing patient compliance. Cryotherapy causes vasoconstriction beyond the active cooling time.[9] While not an outright adverse effect, it can be detrimental when combined with other vasoconstrictive agents.

Curettage and cautery, although previously popular, are not currently in favor. Other surgical methods include shaving, scissor excision, and electrocautery. These are associated with 35 to 72% clearance, but 19 to 29% recurrence, possibly caused by untreated subclinical lesions, since one cannot 'cut out' a virus.[6] The main advantages are immediate results, especially for large, obstructive lesions, and tissue for histopathological examination.[4] Disadvantages include bleeding, pain, longer healing time, and possible aerosolized spread of virions.[6] Electrocautery is contraindicated in patients with pacemakers and may cause scarring.

Immunomodulatory Treatments

As the innate immune system fights viruses, stimulating it could facilitate wart clearance. *Candida*, mumps, and trichophyton antigens have been injected into warts for this purpose, showing promising efficacy and low recurrence rates compared to traditional options.[11,16] It does not require treatment of individual lesions, but induces a systemic response.[13] The trauma of injection alone may be sufficient for a response.[18]

Photodynamic therapy involves applying topical aminolevulinic acid (AVA) followed by blue light. AVA is internalized and converted to phytotoxic protophyrin IX by UV light.[4,6] This allows for targeted phototoxicity, facilitated by production of oxygen and free radicals that selectively destroy warts, and immune cell infiltration, with 73 to 98.2% clearance.[3,5,6]

Candida yeast injection produces a localized immune response with greater than 50% efficacy.[9] It is injected monthly into one representative wart, often the largest.[20] Per a retrospective chart review, patients who experienced lesion regression received higher doses over more sessions.[20] One study compared *Candida* injections at different concentrations and 2% zinc sulfate injections, all injected intralesionally. In the group that received 1/100 *Candida* antigen, 88.6% experienced complete resolution. With 1/1000 *Candida* antigen, 74.3% experienced a complete response.[16] One study compared *Candida* antigen with traditional treatments, showing 50% and 48% clearance, respectively. There were more adverse effects following traditional treatment, including hypertrophic scarring in 9% compared to none following *Candida* antigen.The most common side effects of *Candida* antigen are transient edema, induration, and flu-like symptoms.[13] In a study injecting 0.3 mL of *Candida albicans* intralesionally, 87% developed temporary edema.[26] A rare outcome is purple digit syndrome, presenting with edema, severe pain, and purple hue of the affected finger.[10] It can be treated with prednisone.[9,10] A case study reported an adverse reaction to the second dose of *Candida* antigen, indicating that minimal initial reaction does not predict future reactions.[10]

Bleomycin, an antimitotic chemotherapy, inhibits DNA synthesis by blocking thymidine incorporation and causes inflammation.[3,4] Studies on the benefit of intralesional bleomycin have been inconsistent, with clearance ranging from 16% to 94%.[4,14]

Zinc stimulates leukocytes and natural killer cells.[16] One study compared zinc sulfate at 10 mg/kg to a placebo. After 1 month, 59.3% experienced complete resolution of their warts, and those that did not continued treatment for another month.[26] After the second month, a total of 78.1% experienced complete resolution. Another study found 11% resolution using topical zinc sulfate.[3] Treating intralesionally with 2% zinc sulfate showed 68.6% resolution.[16] Zinc is associated with pain, dyspigmentation and flu-like symptoms.[16]

Purified protein derivative is suitable for pregnant patients. A study compared intralesional *Candida* antigen versus intralesional tuberculin to treat recalcitrant genital warts. 0.1 mL every 2 weeks was injected into the largest wart for 5 sessions or until complete clearance.[11] The *Candida* group observed 41.3% clearance, and the tuberculin group 32.1% clearance, with no statistically significant difference.[11] Another study injected untreated/recalcitrant warts with 0.05 mL of PPD with 76% clearance.[18] The risk of recurrence is about 9%.[12]

Diphencyprone is applied in increasing concentrations to elicit a type IV hypersensitivity reaction. This treatment results in 60% clearance, depending on the patient's immune status.[4] It is a mutagen, and its precursors may cross-react with other chemicals, decreasing its safety.[3]

Vitamin D3 injections may facilitate healing through immune stimulation.[21] One study injected 0.1 mL/cm^2 Vitamin D3 below the wart.[21] Resolution began within 7 to 10 days with wart shedding within 4 to 6 weeks.

Local hyperthermia acts as immunoadjuvant therapy in treating warts.[25] Hyperthermia increases the proliferation of natural killer cells, cytokines, and increases membrane permeability, treating local and subclinical warts.[25] A case study found that 11 sessions resolved treated and non-treated lesions in treatment-resistant warts.[25]

Many immunotherapies stimulate different pathways of the immune system, thus combining immunotherapies may increase efficacy. One study compared alternating intralesional PPD and *Candida* antigen versus either agent alone.[12] With PPD only, there was 61.1% clearance. *Candida* antigen only had 36.8% clearance. Alternating treatments resulted in 70.6% clearance.[12] The researchers postulated that this results from a synergistic interaction.[12] Another study compared combined acitretin and *Candida* antigen versus either one alone.[15] Administering acitretin or *Candida* antigen alone resulted in 38.9% and 33.3% clearance, respectively. When combined, there was 66.7% clearance.[15] The combination of the *Candida* antigen stimulating T_H1 helper cytokines and acitretin modulation of epithelial cell proliferation increases the immune response, clearing near and distant lesions.[15]

One study treated recalcitrant warts with HPV vaccination. Of the three available vaccines, the bivalent and the quadrivalent have been successful treatments. One study administered the bivalent vaccine intralesionally (63.6% clearance) and intramuscularly (81.8% clearance).[1] The bivalent vaccine contains an AS04 that stimulates a TLR4 agonist, directly stimulating APCs and causing immune responses and long-lasting antibodies.[1] In another study, the quadrivalent vaccine resulted in higher resolution (90%) than the bivalent (30%).[22] This outcome was unexpected, as although the quadrivalent vaccine has more antigenic load, the immunologic responses to the bivalent are more robust.[22] HPV vaccination has few adverse effects, usually limited to transient erythema and edema.[13] It also induces long-term immunity and produces cross-reactive antibodies.[22]

The MMR vaccine also stimulates an immune response against HPV.[18] In one study, 75% of patients who received 0.5 mL of the vaccine biweekly experienced resolution of their warts.[18] Other studies reported clearance rates of 63 to 81%.[18] The most reported adverse effect is flu-like symptoms.[18]

Fluorouracil's deoxyribonucleotide and folate cofactor bind to thymidylate synthase, forming a covalently bound ternary complex. Cases have reportedly administered the needle-free injection of fluorouracil to treat warts, with two patients experiencing complete resolution and no recurrence after 6 months. The advantage of this administration is high-speed liquid flow allowing an even and controlled medication distribution. Available literature describes 30 to 66% clearance rates, but this treatment requires further study.[2,3] 5-FU is cost efficient and has fewer adverse effects than medications such as bleomycin, but is not FDA approved to treat warts, and carries some severe side effects, including hemorrhagic bullae and hyperpigmentation.[6]

Systemic Treatments

Systemic treatments for warts are promising, but confirming efficacy is difficult due to the spontaneous resolution rate.[4] The most common agent is cimetidine, which enhances mitogen-induced lymphocyte proliferation and inhibits suppressor T-cell function through histamine type-2 antagonism for 84.3% clearance.[3] Although it has been used to treat recurrent warts with relatively good results, studies have shown limited efficacy.[3] Interferon binds to cell membranes to induce enzymes, enhance macrophage phagocytosis, and augments T lymphocyte cytotoxicity. One study found the recurrence rate of local interferon to be statistically insignificant.[6]

Isotretinoin has retinoid and immunomodulatory activity, is an effector of epithelial differentiation and proliferation, and may downregulate HPV transcription. Although this treatment only shows 39.6% clearance, it also has only 9.5% recurrence.[6] Isotretinoin is absolutely contraindicated in pregnancy.

Miscellaneous Treatments

One study compared intralesional combined digoxin and furosemide versus intralesional 5-FU on recalcitrant plantar warts.[2] Both treatments block cellular K+ influx, required for DNA replication. Combined digoxin and furosemide was less effective (28%) than 5-FU, *Candida* antigen (60%), and vitamin D3 (48%). Despite differences in clearance, each group was associated with reduction in warts compared to saline.[2]

Laser treatments are proposed physician-administered treatment. The main disadvantages are varying efficacy, high price, and inaccessibility. They should be considered in immunosuppressed patients with refractory lesions or as adjunctive therapy, such as to prepare the skin for additional therapies. CO2 uses infrared light to non-selectively vaporize lesions. The laser destroys the wart, then destroys layers of virally infected cells.[5] CO2 lasers show less efficacy than salicylic acid and cryotherapy. A significant disadvantage is the clearance rate of 23-52% with 77% recurrence.[6] Adverse effects include 18% incidence of scarring. Pulsed dye lasers emit photons between 585 and 595 nm.[17] It destroys the dilated superficial capillaries supporting the warts and may destroy the virus itself due to HPV's sensitivity to heat.17 When PDL was compared to SA and CO2 laser, a study found a 3x increased risk of recurrence with the latter two. Adverse effects include burning pain, hyperpigmentation, and flu-like symptoms.[17]

There have been reports of wart regression upon starting antiretroviral treatment in patients with HIV. Studies have not demonstrated antiretroviral treatment directly impacting the HPV lesions, but rather the antiretroviral therapy aiding in the status of the patient's immune system, allowing clearance of the lesions. This is further demonstrated in a vignette that demonstrated an association between increasing CD4 count and resolution of warts. They also discovered that patients with CD4 cell counts <0.135*10^3/uL before starting antiretroviral treatment will have persistent warts despite rising CD4 cell counts.[8] Although this does not describe a new treatment, it confirms the importance of cell-mediated immunity.

Folk Treatments

As warts developed, folk remedies followed. Some may seem outlandish but demonstrate a rudimentary understanding of viral wart transmission, such as "passing" warts to another person, animal, or object.[7] Other remedies included rubbing a large snail on the wart before hanging it on a thorn, or having a bush cricket bite off the warts.[7] These demonstrate the same difficulty in determining coincidences between treatment and spontaneous resolution of the warts, making it difficult to prove a treatment's efficacy.

CONCLUSION

The treatments offered for warts now have not been updated in decades.[5] This is exacerbated by warts' likelihood to resolve on their own. Many folk treatments demonstrated basic understanding of the transmissibility of warts, but others showed that clearance of warts is often coincidencidental.[7] One study injected saline into warts, representing a 'spontaneous resolution group', with 8.6% clearance.[12] There is currently no antiviral treatment for HPV, meaning that treatments do not address the base cause. There are many new treatments being explored, but the consensus between researchers and clinicians is that more study is needed to confirm their efficacy and safety. While these treatments seem promising in case reports and small studies, we remain in need of larger, randomized controlled trials to ensure that we are not again falling victim to coincidence between new treatment and spontaneous resolution of warts.

DISCLOSURES

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ORIGINAL ARTICLE

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Report From the 2024 International Dermatology Outcome Measures (IDEOM) Annual Meeting

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ABSTRACT

Background: International Dermatology Outcome Measures (IDEOM) is a nonprofit organization committed to advancing the development and accessibility of evidence-based, consensus-driven outcome measures in dermatology. This mission is supported by a diverse group of stakeholders who collaborate to improve the research and treatment of dermatologic disease.

Summary: The 2024 IDEOM Annual Meeting was held on April 5-6, 2024. During the event, work groups in psoriatic disease, hidradenitis suppurativa, geriatric dermatology, connective tissue disease, vitiligo, itch, actinic keratosis, acne, and cutaneous T-cell lymphoma discussed research progress and conducted breakout sessions. This report summarizes each workgroup's updates.

Key Messages: This report outlines the key research advancements made by each IDEOM workgroup at the 2024 IDEOM Annual Meeting.

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INTRODUCTION

International Dermatology Outcome Measures (IDEOM) is a nonprofit organization dedicated to developing validated patient-reported outcome measures PROMs (patient-reported outcome measures) for dermatologic research and clinical practice. IDEOM comprises a diverse group of stakeholders, including patients, physicians, government agencies, industry professionals, nonprofits, and researchers. IDEOM's PROMs are freely available.

Annually, IDEOM stakeholders convene in work groups to assess progress, share study results, and plan future research. Work groups focus on psoriatic disease, hidradenitis suppurativa (HS), geriatric dermatology, connective tissue disease (CTD), vitiligo, itch, actinic keratosis (AK), acne, and cutaneous T-cell lymphoma (CTCL). This report highlights the advancements presented by the work groups during the 2024 IDEOM Annual Meeting.

Early Detection of Psoriatic Arthritis in Argentina

Silvia Fernández Barrio, the founder of the Asociación Civil para el Enfermo de Psoriasis (AEPSO), highlighted the success of initiatives in Argentina designed to improve the detection of psoriatic arthritis (PsA). AEPSO, Argentina's pioneering psoriasis (PsO) patient organization, partnered with the Sociedad Argentina de Psoriasis (SOARPSO) and the Sociedad Argentina de Reumatología (SAR) to develop a PsA symptom checker for community risk assessment. This initiative also facilitated community access to local psoriatic disease specialists through a comprehensive digital map detailing provider locations, contact information, and appointment availability. The effort saw the voluntary participation of 192 dermatologists and rheumatologists from all 24 provinces of Argentina.

Silvia also highlighted the AEPSO Truck initiative, funded by Novartis, which travels across Argentina providing free medical appointments and using ultrasound for PsA diagnosis. In Bahía Blanca, the AEPSO Truck offered 147 free appointments, benefiting over 80 PsO patients and 18 PsA patients, with a PsA diagnosis rate of 22.5% among those screened.

Provisional IDEOM Definition of Contextual Factors: Suggestion for an Adolpment of the OMERACT Consensus-Based Operational Definition

Dr Robin Christensen, member of the Outcome Measures in Rheumatology (OMERACT) organization and co-chair of the Contextual Factors Working Group, proposed that IDEOM adopt the OMERACT consensus-based definition of contextual factors (CFs) for use in dermatology. This approach, known as "adolpment," was introduced by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group to enable clinical recommendations across fields. The OMERACT Filter 2.0[1] defines CFs as variables that, while not outcomes of the study, must be identified and quantified to interpret study results.

The OMERACT CFs Working Group developed an operational definition and guidance for handling CFs in clinical trials. A Delphi survey established consensus on three CF types: effect-modifying (alter treatment effects), outcome-influencing (independently impact outcomes), and measurement-affecting (influence outcome validity/reliability).[2] Dr Christensen emphasized that this framework could guide CF implementation in dermatology and encouraged continued discussion at IDEOM.

WORKGROUP UPDATES

Psoriatic Disease

Screening and Treating to Target for Psoriatic Arthritis using the PEST and PsAID-12 Instruments

Dr Alice Gottlieb and Dr Hassan Hamade presented an ongoing quality improvement initiative at Mount Sinai that aims to optimize PsA care by facilitating screening, assessment, and referral processes. Dr Gottlieb emphasized that timely intervention in PsA is crucial to reducing the risk of permanent disability.

The Psoriasis Epidemiology Screening Tool (PEST) and the Psoriatic Arthritis Impact of Disease 12-item questionnaire (PsAID-12) are incorporated into the electronic medical records of 26 dermatology clinics. Those with a PEST score ≥3 or a preexisting PsA diagnosis subsequently complete the PsAID-12. PsAID-12 score >4 indicates an unacceptable PsA symptom state,[3] necessitating treatment modification or referral.

Preliminary results showcased this framework's feasibility in a real-world clinical setting. The project is ongoing, with plans to further educate providers on the utility of this approach.

Treatment Satisfaction

Dr April Armstrong discussed how patients' perceptions of their medications directly influence their willingness to take them and, consequently, treatment satisfaction and outcomes. The DermSat-7 is a tool designed to measure treatment satisfaction, with questions on three main domains: effectiveness, convenience, and overall satisfaction.[4] The effectiveness domain reflects a treatment's impact on the skin condition and appearance, while the convenience domain includes storage, preparation, ease of use, and treatment frequency. Dr Armstrong noted that in a multicenter, cross-sectional pilot study of PsO patients, the DermSat-7 showed strong validity, reliability, and consistency.

Dr Armstrong also introduced the DermSat-11 study, actively recruiting with the National Psoriasis Foundation (NPF). The DermSat-11 now includes a domain for adverse effects (AEs) covering undesired skin signs, symptoms, and AEs in other organs, alongside domains for effectiveness, convenience, and overall satisfaction.

Patient Preference for Treatment Delivery

Dr Armstrong moderated a breakout session to explore patient preferences for PsO treatment delivery methods, assuming comparable safety and efficacy. Nearly 30 participants, including patients and non-patient stakeholders, were surveyed. 45.5% of patients had experienced PsO with body coverage over 10% and most had used topical treatments, with many trying oral medications, injectables, and phototherapy. Both groups preferred injectable medications over oral and topical treatments, prioritizing treatment effectiveness, side effects, cost, and convenience. The session concluded that less frequent injectables were preferred, with plans to verify these findings in a larger, more diverse group.

Further Validation of the IDEOM Musculoskeletal (MSK)-Q for Psoriatic Disease

Dr Joseph F. Merola and Dr Lourdes Perez-Chada presented on the IDEOM Musculoskeletal Questionnaire (IDEOM MSK-Q), an instrument designed to assess MSK symptoms and their impact on health-related quality of life (HRQoL) in PsO. Dr Merola discussed IDEOM's development of a core domain set (CDS) for PsO trials, emphasizing the limitations of measuring PsA symptoms in clinical studies.

To examine the validity of the IDEOM MSK-Q across diverse populations, a cross-sectional analysis was conducted using data from the Cohort for Psoriasis and Psoriatic Arthritis *Registry* (COPPAR) study at Brigham and Women's Hospital. This study includes adults with PsO and/or PsA and collects data every six months, including physical assessments and patient-reported outcomes.

Results included 245 patients, with 47.9% at minimal disease activity and 80% scoring PsAID ≤ 4. Statistical analysis demonstrated strong construct validity and known groups validity, with significant differences observed based on disease activity and PsA status.

Establishing a Standardized Global Assessment Measure

Dr Merola led a consensus exercise to establish a standardized global assessment measure for disease activity in PsO clinical trials. Participants preferred static assessments, investigator terminology, and a 5-point scale to reduce complexity. While views varied on endorsing a single Investigator Global Assessment (IGA), there was agreement that standardization would aid cross-study comparisons. Limitations of current IGAs, including scoring inconsistencies and lesion averaging, were noted.

Hidradenitis Suppurativa

Biomarkers

Dr Saakshi Khattri presented a recent study exploring the potential of tape strips as a non-invasive alternative to skin biopsies for identifying HS biomarkers.[5] The study received support through a grant from IDEOM.

Tape strips were collected from 22 adult HS patients and 22 healthy controls and compared with traditional skin biopsies. Critical biomarkers typically found in HS skin biopsies, including tumor necrosis factor (TNF) and interleukin-17 (IL-17), were successfully identified in tape strips. These biomarkers were upregulated in lesional and non-lesional skin of HS patients compared to controls, with the highest levels in lesional skin. There was a strong positive correlation between TNF levels in tape strips and previously published skin biopsy data, with similar patterns for IL-17. Additionally, tape strip biomarkers correlated with the International Hidradenitis Suppurativa Severity Score System (IHS4), linking disease severity with identified biomarkers. The findings suggest that tape strips can effectively substitute for skin biopsies, reducing patient discomfort and risk.

Telehealth

Dr Tarannum Jaleel and Dr Winston Liu presented updates on developing a standardized return visit assessment form for telehealth use. During Phase 1, the workgroup conducted numerous Delphi rounds to achieve consensus, defined as 70% agreement, on included items. 16 items were included, with Phase 2 focused on refining item wording and constructs.

Next steps include finalizing the assessment's format. Phase 3 will pretest the draft to evaluate length, feasibility, clarity, and feedback on item relevance and cultural adaptations. Phase 4 will field test the questionnaire without supervision, collect feedback via a debriefing questionnaire, and translate as needed.

Refining the Telehealth Instrument

Dr Jaleel led a breakout session focused on refining the telehealth questionnaire. Based on feedback from patient participants, the questionnaire was deemed clear and comprehensive. Participants expressed a strong desire to continue using the questionnaire.

Suggestions were made to include symptoms such as sleep disturbance and fatigue, and to address risk factors and triggers more explicitly. Next steps include securing funding for validation, recruiting clinicians for a pilot study, and creating a virtual platform.

Musculoskeletal Symptoms in HS and Potential Value of the IDEOM MSK-Q

Ariana Zhang discussed the often-overlooked link between HS and inflammatory arthritis.[6] The IDEOM MSK-Q is being evaluated for its potential use in HS patients to measure symptom severity and screen for inflammatory arthritis. Preliminary content validity exercises at the IDEOM 2023 annual meeting showed promising results among HS stakeholders. Future efforts will further evaluate the validity of the IDEOM MSK-Q for use in HS.

Assessing Musculoskeletal Burden in HS Patients using the IDEOM MSK-Q in Clinical Practice

Gretchen Ball presented a quality improvement study at Mount Sinai using the IDEOM MSK-Q to evaluate MSK symptoms and impact in HS patients. Over eight months, 62 patients completed the IDEOM MSK-Q and showed a high prevalence of MSK symptoms and impact on HRQoL. Twenty-six patients completed the survey at a second time point with a mean follow-up of 89 days. Preliminary data indicate that the IDEOM MSK-Q may be responsive to the addition of immunomodulatory treatment, reflecting the tool's potential in monitoring HS treatment outcomes.

Relevance and Comprehensiveness of the IDEOM MSK-Q in the HS patient population

The HS Workgroup held a breakout session to assess the IDEOM MSK-Q's relevance and comprehensiveness for HS patients. Three focus groups were conducted, one with patients and two with non-patient stakeholders. In the patient group, open-ended questions explored experiences with MSK symptoms (Box 1). Non-patient participants reviewed the questionnaire and discussed its relevance, missing content, and clarity. To foster stakeholder "buy-in," at least five content experts contributed their perspectives. Sessions were facilitated by trained researchers and audio-recorded, with transcripts coded under two themes (relevance and comprehensiveness) in NVivo 11.0 by two independent reviewers (SR, GDB).

BOX 1. Open-Ended Questions Presented to Patient Stakeholders During the Focus Group Discussion

Have you noticed any discomfort, pain, or difficulty with your joints? For example, do you ever feel stiffness, swelling, or have trouble moving certain joints? If so, can you explain your experience?

How does having joint problems affect your life?

Can you share your experiences with fatigue and how it impacts your daily life?

Is there anything related to MSK symptoms that we did not discuss?

Eighteen stakeholders participated in the breakout session. Arianna Zhang reported that participants in the patient group (n=9) resonated with the questionnaire items and suggested no additional domains (Table 1). Gretchen Ball and Audrey Hao reported that the non-patient stakeholder groups endorsed the questionnaire's relevance but raised concerns about comprehensiveness (Table 2). Suggested improvements include separating questions for joint and back pain, renaming "Pain" to "Musculoskeletal Pain," clarifying the meaning of "last seven days", simplifying jargon like "musculoskeletal," and acknowledging patients' struggle to determine the source of their pain.

The session affirmed the IDEOM MSK-Q's relevance for HS and highlighted refinements to improve clarity, guiding future validation to better capture MSK symptom burden.

Geriatric Dermatology

Dr Daniel Butler shared updates from the Geriatric Dermatology Workgroup, which met in early 2024 to set two main goals: promoting stakeholder inclusivity and refining tools to better serve the geriatric population. The workgroup posed three key questions: (1) How are older adults omitted from current systems, particularly in outcome measurements; (2) What unique outcomes are crucial for geriatric dermatology patients; (3) In which diseases is age a unique risk factor or modifier?

CTD

Dr Merola discussed the inadequacy of systemic lupus erythematosus (SLE) measures to fully inform cutaneous lupus erythematosus (CLE) outcomes. He stressed the need for CLE-specific studies and the appropriate application of CLE outcome

TABLE 1.

Mapping of Patient-Reported Concept to the IDEOM MSK-Q Items

IDEOM MSK-Q Item	Patient-Reported Quote Relevant to IDEOM MSK-Q Item	Frequency
Pain	"The minute I stop and sit, my hips, back, and elbows are killing me." – *HS patient*	14
Joint swelling	"Look at my ankle… It's swollen. And it's only that one, right? … Extreme pain…. inflamed. And then five days later, nothing. I walk perfectly and it's completely fine. And then it'll go again." – *HS patient*	4
Joint stiffness	"I can't sit for long periods of time. And when I get up, everything is so stiff between the muscles and joints. And I didn't know it was related to HS. So it's comforting to know that it's not just my body aging quicker than that it's supposed to." – *HS patient*	4
Work and/or school activities	"I'd say probably eight years ago, I started telling my dermatologist who treats my HS that my hands hurt all the time… I work on a computer for a living… what do I do? Stop working?" – HS patient	5
Family, social, and/or leisure activities	"Social interaction, you gave up… I'm disabled" – *HS patient*	4
Physical activities	"I have a constant pain in my ankle where it swells… my ankle is constantly swollen and it makes it very difficult for me to walk. I walk with a limp when it flares really badly." – *HS patient*	7
Sleep	" …Rubbing my feet together when I go to bed because my feet start to ache… and then my knees start to hurt. Then I'm rubbing the knees… Trying to find the right position and then staying in that position and then making it worse 'cause you had to stay in that position and stay asleep, and then you wake up and you're like, 'Ow.'" – *HS patient*	2
Emotional state	"I struggle to get out of bed, and that can impact how I feel about going to work… because I'm like, 'Oh, God. Is it that time - I've got to get up? Have I got to go through this again?' It can impact… your day and walking distances. I wanna get up. I wanna walk. I wanna lose weight. I wanna go swimming. I wanna do these things. But if I'm in pain, it's very hard to motivate yourself when you're in constant pain because of joints." – *HS patient*	7
Endorsing fatigue	"I'm not good… I'm just constantly tired. Everything's tired. Your eyelashes are tired. The tips of your nails are tired… everything hurts and it's tired and low energy" – *HS patient*	4

TABLE 2.

Focus Groups at the 2024 IDEOM Annual Meeting		
Identified Themes, Codes and Subcodes	**Relevant Quote**	**Frequency**
COMPREHENSIVENESS: Missing Items		
"Not applicable" option for Question 4 (Impact on work and/or school) and Question 5 (Impact on family, social, and/or leisure activities)	"When I ask [patients] about either work or school or… family, social, leisure, sometimes they reply, 'I just don't do that.' Like, they don't work or go to school and there's no 'none of the above' options… same with family, social, leisure, they'll be like, 'Oh, I just stay at home anyway'… they don't feel like they have a place to put that." – *nonpatient stakeholder*	1
Isolating back pain	"Should we [list] back separately, which is important, and also a difference between with and without movement." – *nonpatient stakeholder*	1
Joint pain related to movement		
Impact on sexual activity	"There isn't anything about… sexual or intimacy impact… it's such an important question. Especially for HS." – *nonpatient stakeholder*	1
Trauma or recent surgery	"In terms of symptoms, intensity, impact, or fatigue, is there any concept we're missing? I like what you brought up… this non-related pain or other events… Maybe trauma or recent surgery." – *nonpatient stakeholder*	1
Pain medication utilization in the past 7 days	"One question that could be interesting is, in the past week, how much have you needed to use NSAIDs?" – *nonpatient stakeholder*	2
COMPREHENSIVENESS: Contextual factors to consider		
Severity of HS	*"Would there be interest in assessing whether patients with… greater severity of HS … have greater joint symptoms?"* – *nonpatient stakeholder*	1
Current treatments for MSK symptoms	"What about treatments not on here? If someone's taking nonsteroidals… or opioids from the emergency room."– *nonpatient stakeholder*	1
Patient familiarity with MSK symptom language	"I think people with inflammatory arthritis, in general, have seen a rheumatologist. HS patients normally haven't." – *nonpatient stakeholder*	1

measures. He presented independent work around a working core domain and core outcome measures set, which was further endorsed at the ICCLE meeting in Japan.[7] He shared information about an instrument he independently developed (the CLA-IGA and its revision, the CLA-IGA-R) to meet regulatory demands for an outcome measure in late-phase clinical trials. This instrument would ideally complement the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), has the potential for use in low disease activity, and has recently completed a validation/reliability study.[8] The IDEOM CTD Workgroup is also collaborating with OMERACT to establish a formal CDS for CLE.

Vitiligo

Dr Nanette Silverberg highlighted a new comprehensive model encompassing core and secondary domains to assess treatment-related outcomes in vitiligo. The core domains focus on systematically assessing the extent of depigmentation, understanding patient goals, and evaluating post-treatment outcomes while incorporating tools for shared decision-making between clinicians and patients. The workgroup is collecting data to validate their model and construct a database for retrospective analysis.

Refining the Domain Model

During the breakout session, the Vitiligo workgroup refined its model, moving some domains to the CF list. They emphasized the importance of anxiety and depression scales as experimental domains and streamlined core domains to include Wood lamp assessment, depigmentation extent and location, stigma, and HRQoL. In the voting session, most participants supported including questions on weekly treatment time and extra time for daily coverage (makeup/clothing).

Itch

Dr Brian Kim provided an overview of the Itch Workgroup's objective: to overcome barriers to recognizing chronic pruritic disorders as distinct disease entities and to develop pathways for FDA-approved treatments.

Dr Sonja Ständer initiated a consensus conference to redefine itch and stressed that chronic pruritus should be recognized as both a symptom and a disease. This dual recognition is crucial for justifying therapeutic approaches. During this meeting, 31 different definitions of itch were proposed. Two definitions are under discussion as of December 2023: one defining itch as a sensation and the other as a disease (Version 0.5).

Defining Itch

During the breakout session, two definitions of itch were presented. The new definition described pruritus as a negative sensation of the skin and/or mucous membranes, commonly eliciting a need to scratch, and that can vary in extent, location, severity, chronicity, and impact on HRQoL. The older definition described itch as an unpleasant sensation that elicits the desire or reflex to scratch. In voting, 60% preferred the new definition; 40% favored the old.

Actinic Keratosis

Dr Daniel Siegel and Dr Yvonne Nong updated on the actinic keratosis (AK) Workgroup's progress. The Brooklyn VA received IRB approval for its 2-question patient satisfaction survey, now in its pilot phase. The survey asks patients if they would repeat their AK treatment and, if not, why (eg, cosmetic concerns, pain, cost, or convenience), and if they would be willing to undergo the treatment 2-4 yearly. Preliminary results showed all five participants were willing to repeat photodynamic therapy, with four willing to do it 2-4 times yearly.

Dr Nong discussed the need to revisit the 12-item AK questionnaire. Next steps include ongoing data collection at the Brooklyn VA, Mount Sinai, and other sites, and refining the 12-question survey to reduce fatigue.

AK Prevention

During the AK Workgroup breakout session, participants discussed strategies to modify patient behavior to prevent AKs and squamous cell carcinoma (SCC), focusing on patients' lack of awareness of their condition. They discussed improving treatment assessment and proposed two key questions to measure understanding of treatment's preventive benefits.

Acne

Dr John Barbieri focused on six core outcome domains identified by The Acne Core Outcomes Research Network (ACORN): HRQoL, treatment satisfaction, scars/dark marks extent, long-term acne control, appearance satisfaction, and signs/symptoms. He highlighted inconsistencies in PROMs in acne and rosacea trials. ACORN's recent COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) review found Acne-Q and CompAQ have sufficient evidence for content validity in acne studies. No measures for dyspigmentation were found, prompting development efforts for a PROM. The DermSat-7 had sufficient measurement properties to evaluate treatment satisfaction.[9] The group has also developed and validated a single-item ACORN patient global assessment.[10] Although an original Delphi exercise did not reach consensus on how to assess signs/symptoms in acne patients, ACORN prefers lesion counts and IGA, aligning with regulatory recommendations.

Cutaneous T-Cell Lymphoma

Dr Michi Shinohara and Dr Cecilia Larocca discussed redefining CDS for Cutaneous T-Cell Lymphoma (CTCL) to include all domains, not just HRQoL. The project has been renamed "CDS Generation for CTCL (MF/SS)" with plans for protocol modification.

The work completed thus far will be renamed "Defining Core Concepts for HRQoL for CTCL," with the goal of item generation for HRQoL in CTCL. The protocol for this project has been registered with PROSPERO and consists a systematic literature review (SLR) on HRQoL in patients with mycosis fungoides/Sézary syndrome, a Health Care Provider Survey, and a qualitative study regarding HRQoL domains for patients underrepresented in CTCL literature. Preliminary SLR data show physical function concepts are most represented, while treatment burden and socioeconomic factors are least represented. The qualitative study enrolled 10 participants at the time of presentation and is under review for content saturation and inclusion of a diverse participant profile. The next step is to finalize HRQoL item bank generation for an e-Delphi activity.

CONCLUSION

The IDEOM Annual Meeting continues to offer a distinct forum where stakeholders from various medical specialties combine their unique perspectives to advance outcome measure research in dermatology. The concerted efforts of the IDEOM work groups have led to significant strides in PROM development for dermatologic conditions.

DISCLOSURES

SR, GDB, AJZ, CA, AH, HH, GMH, YN, WWL, CL, SFB, AE, JL report no disclosures.

JSB has served as a consultant for Honeydew Care and Sanofi Pasteur. SK is an employee of Mount Sinai and a consultant for AbbVie, Eli Lilly, Janssen, and Novartis. She is on the speaker bureau for UCB, Janssen, Lilly, Regeneron, and AbbVie. She receives research funding from AbbVie, Pfizer, Incyte, and Takeda. TJ received funds from UCB, NIH, Skin of Color Society, Dermatology Foundation; Consultation: Novartis and Eli Lilly; Investigator for UCB, Eli Lilly, AbbVie, and Eli Lilly. Received support for attending meetings and/or travel: Skin Color Society, and IDEOM; Received payment or honoraria for lectures, speaker, and presentation: Peer View; Received support for attending meetings/travel: Skin Color Society; Leadership or fiduciary role: Skin Color Society. BSK has served as a consultant to AbbVie, AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Incyte, Lilly, and Pfizer and as a member of advisory boards for Cara Therapeutics, Regeneron, and Sanofi; in addition, he is a shareholder in Locus Biosciences and Recens Medical, and he is on the scientific advisory boards for Granular Therapeutics, ABRAX Japan, and Recens Medical. MS has received research funding from Kyowa Kirin. DB has served as a speaker for Galderma and Leo and a consultant for Sanofi, Leo, and True Botanicals. DS has served as a consultant to Biofrontera.

NBS is a consultant, investigator, or speaker for Alphyn, Avita, Incyte, Pfizer, Regeneron-Sanofi, and Verrica. RC has no financial conflicts of interest. However, RC is a founding member of the OMERACT Technical Advisory Group and the Strategic Advisory Group, which could be perceived as an intellectual conflict of interest. VS has worked as a consultant for the following companies: Abbvie, Alpine Immune Sciences, Alumis, Amgen Corporation, Ampel Biosolutions, AstraZeneca, Bayer, Blackrock, BMS, Boehringer Ingelheim, Celltrion, Citryll Contura, Cullinan, Fortress Biotech, Genentech / Roche, GSK, Inmedix,

Janssen, Kiniksa, Lilly, Novartis, Omeros, Pfizer, R-Pharm, RAPT, Regeneron, Samsung, Sandoz, Sanofi, Scipher, Setpoint, Sobi, Spherix, Synact, Takeda, and Urica AWA has served as a research investigator, scientific advisor, or speaker for AbbVie, Amgen, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Mindera, Nimbus, Novartis, Ortho, Sun, Dermavant, Dermira, Sanofi, Takeda, Organon, Regeneron, Pfizer and Ventyx. LPC has received consulting fees from Takeda and Bristol-Myers Squibb. She has also received honoraria for Bristol-Myers Squibb educational activities and participation on the advisory board. JFM is a consultant and/or investigator for Amgen, Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, AbbVie, Dermavant, Eli Lilly, Incyte, Moonlake, Novartis, Janssen, UCB, Sanofi-Regeneron, Sun Pharma, Biogen, Pfizer, and Leo Pharma. ABG has received honoraria as an advisory board member and consultant for Amgen, AnaptysBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Eli Lilly, Highlights Therapeutics, Janssen, Novartis, Sanofi, Teva, UCB, and Xbiotech (stock options for RA).

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Impact of Low-Dose Oral Minocycline (DFD-29) on Skin, Gastrointestinal, and Vaginal Microflora in Healthy Adults

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ABSTRACT

Background: DFD-29 (minocycline hydrochloride extended-release capsules, 40 mg) has shown significant therapeutic benefit vs placebo and doxycycline in treating moderate-to-severe rosacea. However, the impact of its use on skin, vaginal, and gastrointestinal microbiota is unknown.

Methods: In this multicenter, randomized, double-blind, placebo-controlled trial, 60 healthy adults were randomized in a 2:1 ratio to receive either DFD-29 (40 mg) orally or a matching placebo once daily for 16 weeks. Microbiological samples were collected from the skin (forehead), vagina, and stool at baseline and weeks 4, 8, and 16 to evaluate changes in normal microbiota species (via culture and 16S rRNA sequencing), in the MIC90 of selected colonized microbial species, and in opportunistic microbiota with DFD-29 vs placebo. Safety was evaluated via analysis of adverse events, vital signs, and laboratory tests.

Results: Thirty-eight adults assigned to DFD-29 and 19 adults assigned to placebo were included in the microbiota evaluable population. There were no significant differences detected in the abundance of microbial species in the skin, stool, or vagina from baseline to week 16 between the DFD-29 and placebo groups. No significant differences were detected in resistance to minocycline between DFD-29 and placebo. There were also no significant differences in the presence of opportunistic microbiota at any time point. No significant safety issues were reported.

Conclusion: Administration of DFD-29 for 16 weeks had no detectable effects on skin, GI tract, or vaginal microflora and was well tolerated in healthy adults, reinforcing its potential as a therapeutic option in moderate-to-severe rosacea.

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INTRODUCTION

Rosacea is a chronic inflammatory facial skin disease that affects 5% to 10% of the population and can adversely affect quality of life.[1,2] Common signs and symptoms of rosacea include skin erythema, the development of erythematous papules and pustules, flushing, telangiectasia, phymatous changes, and ocular manifestations.[3,4] While its pathogenesis is not fully understood, it is believed to be multifaceted and involves immune and inflammatory dysregulation, neurovascular dysregulation, microbiome dysbiosis, and genetics.[5-10] Systemic antibiotics, such as minocycline and doxycycline, are frequently used to control rosacea symptoms.

Minocycline is a chemically modified, second-generation, broad-spectrum tetracycline that effectively targets a wide range of Gram-positive and Gram-negative bacteria and atypical organisms,[11] preventing bacterial growth by inhibiting protein synthesis.[12] It also exhibits potent anti-inflammatory properties.[11]

A low-dose formulation of minocycline hydrochloride (HCl), DFD-29, has shown superior therapeutic benefit vs placebo and doxycycline in treating rosacea and has recently been approved for this indication by the US Food and Drug Administration under the brand name of Emrosi™ (minocycline hydrochloride).[13-15] However, the impact of DFD-29 on skin, gastrointestinal (GI), and vaginal microbiota is unknown. This study evaluated whether treatment with DFD-29 results in shifts in the normal microbiota of the skin, GI tract, or vagina, the development of resistance to minocycline, and the appearance of or increase in opportunistic microbiota (yeast or opportunistic bacteria).

MATERIALS AND METHODS

This multicenter, randomized, double-blinded, placebo-controlled, parallel-group Phase 1 trial (NCT05597462) compared the impact of DFD-29 (minocycline hydrochloride extended-release capsules; Emrosi, Journey Medical Corporation) and matching placebo on skin, GI, or vaginal microflora in 60 healthy adults (30 males and 30 females) aged 18 to 65 years (Figure 1). The study was conducted between September 28, 2022, and February 24, 2023, at 2 sites in El Paso, Texas, and Las Cruces, New Mexico. Both studies followed Good Clinical Practice, US local laws and regulations, and the Declaration of Helsinki. Institutional review boards at each study center approved the protocol and consent forms, and written informed consent was obtained from all participants.

Subjects were eligible for the trial if they were aged ≥18 and ≤65 years, agreed to avoid using another antibiotic during the 16-week treatment period, were not pregnant or lactating, agreed to use an acceptable method of birth control (women of childbearing potential and all male subjects), and were in good health and free from any clinically significant disease that may have interfered with the evaluation of microbiota or the administration or absorption of study drugs.

Individuals were excluded if they had a history of vaginitis within 3 months of randomization; had used systemic non-tetracycline antibiotics within 6 weeks or systemic tetracycline antibiotics within 3 months; had been treated with systemic retinoids or therapeutic vitamin A supplements within 180 days; or used topical retinoids, antibiotics, corticosteroids, anti-mycotic agents, azelaic acid, or ivermectin on the face within 30 days; or were unable or unwilling to provide fecal/stool samples or self-collect vaginal swabs.

Subjects were randomly assigned in a 2:1 ratio to DFD-29 40 mg or matching placebo capsules once daily orally for 16 weeks (113 days). Randomization was stratified by gender, so that approximately an equal number of male and female subjects were enrolled within each treatment group, using a randomization schedule generated by an independent statistician. The study consisted of a screening period (day -30 to day -1) and a treatment period (day 1 to day 113) and included 5 visits.

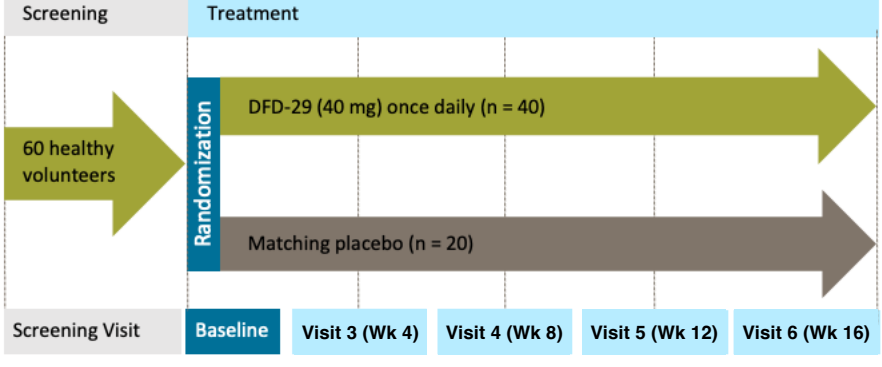
Subjects were instructed to take oral DFD-29 or a placebo once daily at a fixed time of day (preferably in the morning after an overnight fast) with 240 mL (1 glass) of water and were advised to avoid consuming substances that could potentially interfere with minocycline absorption 1.5 hours before to 3.0 hours after taking the study drug. Both DFD-29 and matching placebo capsules were provided by Dr. Reddy's Laboratories Ltd, in Telangana, India. All investigators, study staff, and sponsor staff were blinded to study drugs until study closure.

At each visit, microbiologic assessments of skin swabs, stool samples, and vaginal swabs were performed to evaluate the impact of DFD-29 or placebo on the microbiome of the skin, GI tract (through the stool), and the vagina. Trained staff collected skin swab samples from 5 different forehead regions using 3 swabs designated for bacterial 16S rRNA taxonomic identification and 2 swabs designated for microbial culture. Subjects collected stool samples within 4 hours of each scheduled visit. Female subjects were instructed to self-collect vaginal samples at a private location at the study site by inserting and briefly swirling 5 swabs from different interior regions of the vaginal surface, starting with the deepest region.

Swabs were then placed into culture media tubes (Cary-Blair collection tubes) for shipment within 12 hours to the central laboratory (Ecco Labs). Samples were then sowed and incubated for 48 hours in standardized culture media, and pathogenic microbial agents and normal culturable microflora were identified.

The minimum inhibitory concentration (MIC) against minocycline in the isolated strains was determined using the Epsilometer (E-Test).[16] The 2022 Clinical and Laboratory Standards Institute (CLSI) M100 database was then used to generate a list of species sensitive to minocycline based on the MIC categorization of sensitivity. The minocycline MIC_{90} was determined using

FIGURE 1. Study design.



Wk; week.

a gradient diffusion method specified in the CLSI guidelines. Sensitive (S) species included those with MIC_{90} of ≤4 µg/mL; species with indeterminant sensitivity (I) had a MIC_{90} of 4.1 to 15.9 µg/mL, and resistant species (R) had a minocycline MIC_{90} of ≥16 µg/mL. The top 10% most frequent organisms at baseline were analyzed.

To complete the microbial gene analysis, the pooled swabs for bacterial 16S rRNA taxonomic identification were placed into Norgen Biotek DNA collection and preservation tubes, frozen at -70 °C within 12 hours, and shipped under dry ice to the central laboratory (Creative Biogen) in batches for long-chain 16S sequencing.

The primary outcome of the study was the shift in culturable levels of microbial species colonized from skin, the GI tract, and vaginal swabs from baseline to week 16 in the DFD-29 group compared to the placebo group. Changes in the expression levels of the predominant microbial operational taxonomic units (OTUs) detected from 16S ribosomal RNA (rRNA) gene analysis at each site from baseline to week 16 in the DFD-29 the placebo group were the supportive analysis. Target sequences were amplified by polymerase chain reaction, and their products were purified, quantified, and homogenized to generate SMRT bell libraries. Qualified libraries were processed for sequencing on the PacBio Sequel platform and converted into circular consensus sequencing (CCS) files by SMRTlink. Effective CCS were clustered into OTUs/amplicon sequence variants (ASVs) and processed following feature analysis.

The Shannon Diversity Index was computed for all samples to determine the abundance and distribution of abundance of microbial species at each site. Changes in antibiotic resistance (MIC_{90}) and appearance of opportunistic microbiota (Candida albicans or bacteria) from baseline to week 16 in the DFD-29 group vs placebo were also evaluated. Safety was assessed by evaluation of adverse events (AEs) at each visit.

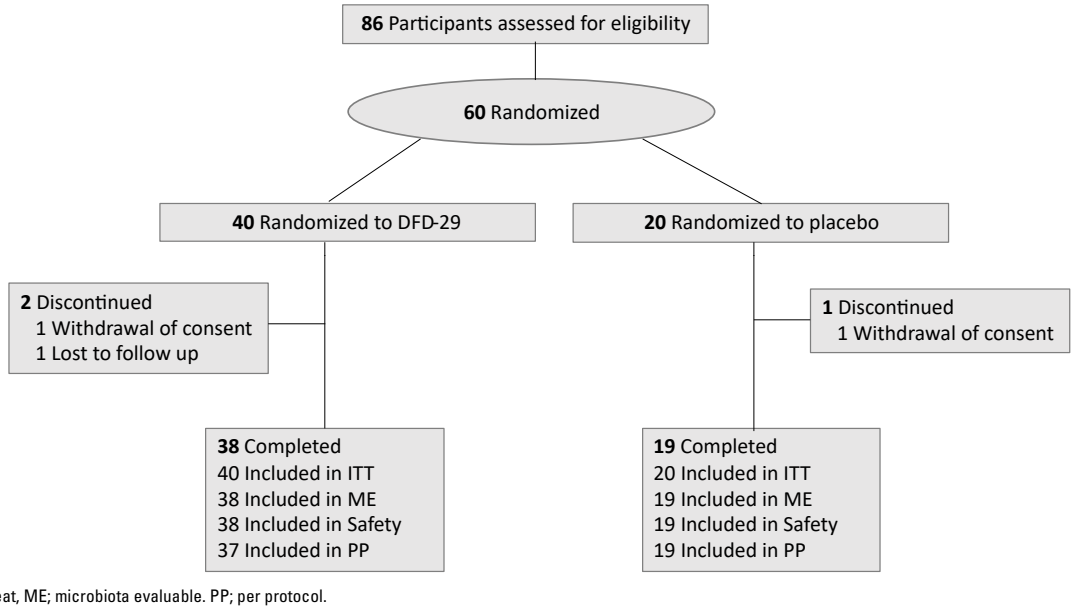
No formal statistical sample size estimation was performed for this Phase 1 study. The Safety population included all randomized subjects who had received at least one dose of study medication and had at least one post-baseline safety assessment. The ITT population included all randomized subjects. The microbiota evaluable (ME) population, the primary population for microbiologic assessments, included all intention-to-treat (ITT) subjects who provided microbiology samples for skin, stool, or vagina at both baseline and week 16.

Changes in the percentage of subjects with cultured microbiota at each site were evaluated using descriptive statistics. Treatment groups were compared at weeks 4, 8, and 16 using Fisher's exact tests. Comparisons in changes in the relative abundance of microorganisms, Shannon Diversity Indices, and MIC values were summarized by site and calculated using Wilcoxon rank sum tests. Microbiota species appearing at week 16 and not baseline were considered opportunistic based on growth density and if they were from a genus known in the literature to be opportunistic or pathogenic. The proportions of subjects with at least 1 opportunistic microbiota that met the above criteria were assessed and compared between groups using Fisher's exact tests.

RESULTS

Among 86 subjects screened, 60 were randomized, and 57 completed the study (Figure 2). Thirty-eight adults assigned to DFD-29 and 19 adults assigned to placebo were included in the

FIGURE 2. Subject disposition.



ITT; intention-to-treat, ME; microbiota evaluable. PP; per protocol.

ME population. Demographic and baseline characteristics of the study subjects were comparable between the groups (Table 1). The mean age of the subjects was 43.4 years (11.9 SD). All subjects were White, 50.9% were female (n = 29), and 94.7% (n = 54) were Hispanic or Latino. Mean BMI was 30.8 kg/m^2 (6.5 SD).

Table 2 presents the number and proportion of individuals with the 10% most prevalent microorganisms grown from the swabs or fecal samples after use of either DFD-29 or placebo. There was no clinically relevant impact on levels of cultured microbiota across the skin, gastrointestinal tract, or vagina with DFD-29 treatment when compared to placebo at baseline, week 4, week 8, or week 16. Although a high degree of variability was noted in the cultured microbiota from individual subjects over the treatment period, no individual subject showed a clinically meaningful increase or decrease in any microbial species.

MIC_{90} values for minocycline in the DFD-29 and placebo groups were similar in pre-identified microbiota over time (Table 3). Among subjects with the identified genera at baseline, changes in resistance patterns did not differ between the DFD-29 and placebo groups. There was no evidence that MIC_{90} values at any of the body sites indicated a change from minocycline sensitivity to minocycline resistance.

Figure 3 shows the number of subjects who had at least 1 cultured opportunistic microorganism present at baseline and at week 16. Only *Staphylococcus* and *Enterococcus faecalis* is were identified as preselected candidates for opportunism. The number of subjects with these bacteria was low, and no subject had heavy culture growth at any time. A few cultures from the skin and vagina had growth of *Candida* spp at baseline, but the number of these subjects was similar between groups and did not increase at week 16 in either group. There was no indication that pathogenic growth resulted in AEs or in physical signs or symptoms.

The top 10 most relatively abundant OTU/family/genus identified at baseline by 16S rRNA sequencing by body region in the supportive OTU analysis are summarized in Table 4. While there were variable changes in the relative abundance of OTUs between treatments from baseline to 16 weeks, these differences were not clinically meaningful. Although statistically significant differences in the abundance of *Lactobacillus*, *Streptococcus*, and *Prevotella* species from vaginal swabs at week 16 were seen in the DFD-29 and placebo groups, these changes were not associated with any shifts in the cultured microbiota and did not result in any clinical signs or symptoms. For the supportive analysis of microbial diversity, changes in the Shannon Diversity Index from baseline to week 16 were neither clinically relevant nor statistically significant for any of the identified genera.

Overall, 3 subjects (5.3%) had at least 1 treatment-emergent AE (TEAE), including 2 subjects (5.3%) in the DFD-29 group and 1 (5.3%) in the placebo group. The two TEAEs in the DFD-29 group were UTIs, diagnosed in two female subjects based on the presence of red blood cells in the urine. There were no clinical signs or symptoms of UTI, and cultures were not performed to confirm UTI. One subject in the placebo group reported a headache. No severe TEAEs were reported, and no TEAEs led to treatment discontinuation.

TABLE 1.

Demographics and baseline characteristics*			
Characteristic	**DFD-29 (n = 38)**	**Placebo (n = 19)**	**Total (N = 57)**
Age, y			
Mean (SD)	42.4 (11.9)	45.3 (12.0)	43.4 (11.9)
Median (range)	41.0 (20-64)	48.0 (24-63)	42.0 (20-64)
Sex, n (%)			
Male	18 (47.4)	10 (52.6)	28 (49.1)
Female	20 (52.6)	9 (47.4)	29 (50.9)
Race, n (%)			
White	38 (100.0)	19 (100.0)	57 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	36 (94.7)	18 (94.7)	54 (94.7)
Not Hispanic or Latino	2 (5.3)	1 (5.3)	3 (5.3)
Mean BMI, kg/m^2 (SD)	29.7 (6.0)	33.1 (7.1)	30.8 (6.5)

*Safety population.
BMI; body mass index, SD; standard deviation.

TABLE 2.

Presence of Culturable Microbiota in ME population. Data Presented as n (%).

Normal (culturable) flora	Assessment	DFD-29 (n = 38)	Placebo (n = 19)	*P* value
Skin				
Coagulase-negative *Staphylococcus*	Baseline	16 (42.1)	3 (15.8)	0.518
	Week 16	19 (50.0)	12 (63.2)	
Propionibacterium acnes	Baseline	10 (26.3)	4 (21.1)	0.372
	Week 16	4 (10.5)	4 (21.1)	
Staphylococcus epidermidis	Baseline	8 (21.1)	4 (21.1)	1.000
	Week 16	0 (0)	0 (0)	
Staphylococcus hominis	Baseline	3 (7.9)	3 (15.8)	1.000
	Week 16	0 (0)	0 (0)	
Viridans group *Streptococcus spp*	Baseline	6 (15.8)	4 (21.1)	1.000
	Week 16	2 (5.3)	0 (0)	
Stool				
Citrobacter freundii	Baseline	8 (21.1)	1 (5.3)	0.028
	Week 16	2 (5.3)	4 (21.1)	
Coagulase-negative *Staphylococcus*	Baseline	2 (5.3)	6 (31.6)	0.274
	Week 16	4 (10.5)	0 (0)	
Enterobacter aerogenes	Baseline	11 (28.9)	3 (15.8)	0.433
	Week 16	4 (10.5)	5 (26.3)	
Enterobacter cloacae	Baseline	6 (15.8)	2 (10.5)	1.000
	Week 16	0 (0)	0 (0)	
Enterococcus spp	Baseline	22 (57.9)	9 (47.4)	0.537
	Week 16	26 (68.4)	15 (78.9)	
Escherichia coli	Baseline	34 (89.5)	18 (94.7)	1.000
	Week 16	35 (92.1)	18 (94.7)	
Klebsiella oxytoca	Baseline	8 (21.1)	0	0.158
	Week 16	3 (7.9)	4 (21.1)	
Klebsiella pneumoniae	Baseline	15 (39.5)	9 (47.4)	0.512
	Week 16	12 (31.6)	4 (21.1)	
Proteus mirabilis	Baseline	10 (26.3)	4 (21.1)	1.000
	Week 16	5 (13.2)	3 (15.8)	
Pseudomonas aeruginosa	Baseline	6 (15.8)	3 (15.8)	0.495
	Week 16	11 (28.9)	7 (36.8)	
Vagina*				
Escherichia coli	Baseline	13 (34.2)	7 (36.8)	0.686
	Week 16	10 (26.3)	3 (15.8)	
Lactobacillus spp	Baseline	11 (28.9)	5 (26.3)	0.250
	Week 16	9 (23.7)	2 (10.5)	
	Baseline	10 (26.3)	2 (10.5)	
Coagulase-negative *Staphylococcus*	Week 16	11 (28.9)	4 (21.1)	1.000
Corynebacterium spp	Baseline	7 (18.4)	2 (10.5)	1.000
	Week 16	3 (7.9)	1 (5.3)	
Enterococcus spp	Baseline	6 (15.8)	3 (15.8)	0.153
	Week 16	15 (39.5)	9 (47.4)	
Klebsiella pneumoniae	Baseline	6 (15.8)	3 (15.8)	1.000
	Week 16	3 (7.9)	1 (5.3)	

*Percentages are calculated based on the total population and not the number of subjects who underwent vaginal assessments (n = 20 for DFD-29 and n = 9 for placebo).

TABLE 3.

Change in MIC_{90} to Minocycline Values From Baseline to Week 16 in Cultivated Microbiota*

	DFD-29 (n = 38)		Placebo (n = 19)		*P* value
	n	Mean change in MIC (SD)	n	Mean change in MIC (SD)	
Skin					
Coagulase-negative *Staphylococcus*	8	0.71 (4.22)	2	2.49 (0.93)	0.695
Propionibacterium acnes	2	2.55 (0.43)	1	1.94 (0.00)	0.540
Staphylococcus aureus	0[a]	0	1	-8.40 (0.00)	N/A
Stool					
Enterobacter aerogenes	0[a]	0	1	3.00 (0.00)	N/A
Enterococcus spp	15	-17.4 (21.6)	7	-1.57 (4.69)	0.091
Escherichia coli	31	-1.55 (5.51)	17	-6.78 (16.6)	0.605
Klebsiella pneumoniae	7	-3.01 (7.84)	7	-0.98 (2.74)	0.925
Vagina					
Coagulase-negative *Staphylococcus*	6	-17.4 (23.6)	0[a]	0	N/A
Corynebacterium spp	1	0	0[a]	0	N/A
Escherichia coli	6	-2.17 (5.43)	6	-7.63 (4.02)	0.245
Lactobacillus spp	3	1.04 (0.57)	0[a]	0	N/A

*Data from the ME population are presented.
MIC_{90}, minimal inhibitory concentration for minocycline; SD, standard deviation.

FIGURE 3. Subjects with opportunistic organisms present at week 16 but not present at baseline in the ME population. No significant between-group differences were observed.

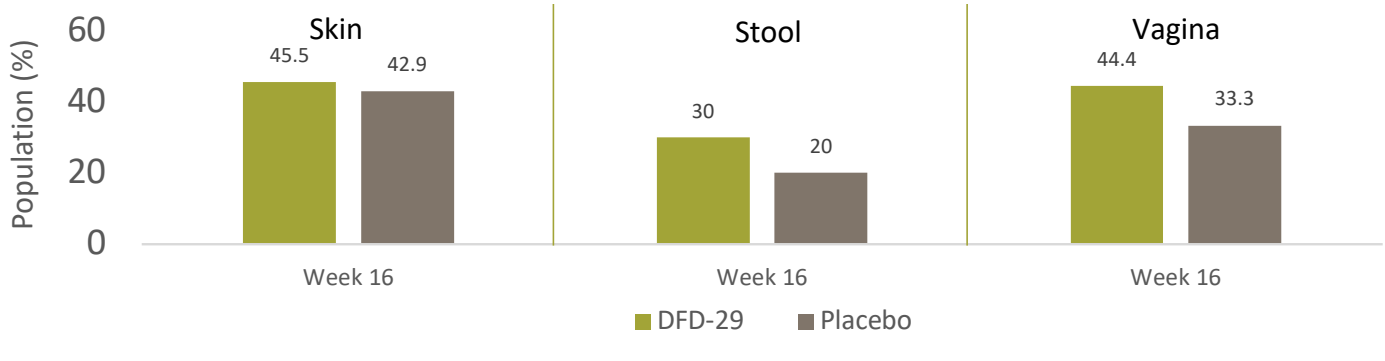


TABLE 4.

Taxonomic Microbiome Summary of Mean Changes (SD) in Abundance Values in the ME Population.

Genus	DFD-29 (n = 38)				Placebo (n = 17)				*P* value
	n	Baseline	Week 16	Change	n	Baseline	Week 16	Change	
Skin									
Prevotella 9	38	0.144 (0.199)	0.144 (0.207)	0.00 (0.148)	17	0.176 (0.207)	0.120 (0.233)	-0.057 (0.208)	0.299
Escherichia shigella	38	0.018 (0.037)	0.008 (0.023)	-0.010 (0.041)	17	0.043 (0.136)	0.018 (0.050)	-0.024 (0.134)	0.669
Bacteroides	38	0.241 (0.146)	0.307 (0.204)	0.067 (0.141)	17	0.227 (0.172)	0.252 (0.172)	0.025 (0.143)	0.367
Faecalibacterium	38	0.111 (0.092)	0.065 (0.046)	-0.045 (0.091)	17	0.088 (0.050)	0.085 (0.069)	-0.002 (0.084)	0.295
Ruminococcus gnavus group	38	0.011 (0.061)	0.005 (0.012)	-0.006 (0.058)	17	0.005 (0.011)	0.002 (0.005)	-0.003 (0.008)	0.337
Fusobacterium	38	0.021 (0.069)	0.018 (0.069)	-0.003 (0.089)	17	0.009 (0.034)	0.000 (0.000)	-0.009 (0.034)	0.834
Akkermansia	38	0.028 (0.065)	0.028 (0.093)	0.000 (0.117)	17	0.035 (0.058)	0.036 (0.097)	0.000 (0.113)	0.935
Prevotella	38	0.004 (0.010)	0.016 (0.071)	0.013 (0.070)	17	0.019 (0.052)	0.043 (0.134)	0.024 (0.122)	0.978
Klebsiella	27	0.012 (0.038)	0.001 (0.003)	-0.012 (0.038)	11	0.007 (0.012)	0.001 (0.001)	-0.006 (0.011)	0.628
Megamonas	11	0.001 (0.004)	0.001 (0.004)	0.000 (0.000)	6	0.025 (0.059)	0.016 (0.039)	-0.009 (0.020)	0.378
Stool									
Lactobacillus	38	0.315 (0.258)	0.028 (0.062)	-0.287 (0.270)	18	0.269 (0.237)	0.020 (0.036)	-0.250 (0.247)	0.630
Akkermansia	38	0.004 (0.005)	0.006 (0.018)	0.002 (0.020)	18	0.030 (0.108)	0.006 (0.016)	-0.024 (0.110)	0.951
Muribaculaceae unclassified	38	0.035 (0.042)	0.074 (0.054)	0.039 (0.068)	18	0.044 (0.060)	0.066 (0.057)	0.022 (0.088)	0.415
Prevotella	38	0.089 (0.062)	0.006 (0.012)	-0.083 (0.063)	18	0.088 (0.066)	0.030 (0.068)	-0.058 (0.106)	0.425
Gardnerella	38	0.040 (0.043)	0.005 (0.015)	-0.035 (0.047)	18	0.041 (0.054)	0.002 (0.003)	-0.039 (0.054)	0.605
Bacteroides	38	0.017 (0.032)	0.069 (0.075)	0.052 (0.084)	18	0.012 (0.009)	0.084 (0.058)	0.072 (0.056)	0.069
Dialister	38	0.018 (0.027)	0.003 (0.010)	-0.014 (0.025)	18	0.018 (0.026)	0.010 (0.029)	-0.008 (0.041)	0.732
Megasphaera	24	0.024 (0.022)	0.001 (0.001)	-0.023 (0.022)	13	0.018 (0.024)	0.002 (0.003)	-0.016 (0.025)	0.067
Lachnospiraceae NK4A136 group	38	0.010 (0.013)	0.030 (0.019)	0.020 (0.022)	18	0.012 (0.022)	0.027 (0.019)	0.015 (0.027)	0.630
Unclassified bacteria	34	0.012 (0.017)	0.002 (0.004)	-0.010 (0.018)	14	0.016 (0.027)	0.002 (0.003)	-0.014 (0.027)	0.725
Vagina									
Lactobacillus	19	0.497 (0.310)	0.290 (0.0386)	-0.208 (0.326)	8	0.367 (0.274)	0.523 (0.404)	0.155 (0.230)	0.007
Streptococcus	19	0.008 (0.014)	0.039 (0.134)	0.031 (0.124)	8	0.121 (0.305)	0.002 (0.002)	-0.120 (0.305)	0.002
Prevotella	19	0.149 (0.108)	0.180 (0.170)	0.031 (0.167)	8	0.132 (0.075)	0.049 (0.090)	-0.083 (0.150)	0.024
Haemophilus	19	0.015 (0.057)	0.013 (0.055)	-0.002 (0.005)	8	0.012 (0.025)	0.000 (0.000)	-0.012 (0.025)	0.506
Gardnerella	19	0.060 (0.067)	0.063 (0.115)	0.003 (0.094)	8	0.040 (0.041)	0.030 (0.059)	-0.010 (0.082)	0.474
Akkermansia	19	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	8	0.037 (0.077)	0.001 (0.002)	-0.037 (0.078)	0.107
Campylobacter	19	0.022 (0.048)	0.030 (0.061)	0.008 (0.028)	8	0.012 (0.015)	0.019 (0.047)	0.007 (0.054)	0.094
Sneathia	19	0.024 (0.045)	0.024 (0.066)	-0.001 (0.065)	7	0.011 (0.015)	0.000 (0.001)	-0.011 (0.016)	1.000
Fastidiosipila	19	0.028 (0.044)	0.006 (0.016)	-0.022 (0.039)	8	0.021 (0.036)	0.001 (0.002)	-0.020 (0.037)	0.770
Bacteroides	19	0.006 (0.017)	0.014 (0.051)	0.008 (0.051)	8	0.045 (0.062)	0.042 (0.064)	-0.003 (0.108)	0.811

SD, standard deviation

DISCUSSION

Systemic antibiotics are a mainstay for the treatment of moderate-to-severe rosacea.[17,18] Theoretically, the use of such broad-spectrum antibiotics for long durations could exert selective pressure on microorganisms, which could lead to resistance. The use of broad-spectrum antibiotics could impact the composition, diversity, and equilibrium of the microbiota, with the potential to lead to long-term dysbiosis if used at higher antimicrobial doses.[19,20]

For years, a modified-release formulation of doxycycline (40 mg once daily) has been the only oral tetracycline FDA-approved for the treatment of inflammatory lesions of rosacea.[21] However, oral minocycline has been used off-label to treat this condition for years, usually at a dose of 100 mg/day.[11,22]

DFD-29 provides the lowest approved dose of minocycline and a systemic minocycline exposure far lower than that seen with antimicrobial doses of minocycline. A previous pharmacokinetic study of DFD-29 reported a steady state C_{max} of ~300 ng/mL, which is significantly lower than the known MIC of 1000 ng/mL for minocycline.[15]

The results from this study confirm these findings and indicate that administration of DFD-29 for 16 weeks had no detectable effects on microbiota in the skin, GI tract, or vagina. DFD-29 was not associated with the development of resistance to minocycline in the microbiota at any site studied. DFD-29 also showed no significant increase in the frequency of opportunistic bacteria during or after treatment and had no clinically meaningful impact on the relative levels of bacterial OTUs as determined by 16S rRNA sequencing. Overall, use of DFD-29 for 16 weeks was generally safe and well tolerated in healthy adults.

There are few data on the impact of lower doses of minocycline or doxycycline on GI, skin, or vaginal microflora, although doxycycline 40 mg is considered a subantimicrobial dose.[23,24] A small trial of 4 women receiving 100 mg oral minocycline reported a 1.4-fold reduction in the mean relative abundance of *Cutibacterium acnes* in the skin microbiota at week 4 of treatment.[25] Decreases in the relative abundance of *Cutibacterium, Corynebacterium, Prevotella, Lactobacillus*, and *Porphyromonas* were also observed.

In contrast, increases in the relative abundance of *Streptococcus, Chryseobacterium, Finegoldia, Pseudomonas, Erwinia, Actinobacillus*, and *Micrococcus* were seen with minocycline, demonstrating that higher doses of oral minocycline can alter the skin's microbiome. Similarly, another study evaluating the effects of 100 mg oral minocycline given twice daily in 8 patients with acne reported significant changes in gut and skin microbiota following 4 weeks of treatment, including reductions in *Lactobacillus salivarius* (P=0.001), *Bifidobacterium adolescentis* (P=0.002), *Bifidobacterium pseudolongum* (P=0.010), and *Bifidobacterium breve* (P=0.042) in the gut, increases in *Bifidobacterium longum* (P=0.028) and *Leuconostoc mesenteroides* (P=0.029) in the skin, and reductions in *Staphylococcus epidermidis* (P=0.009) and *Prevotella nigrescens* (P=0.028) in the skin.[26]

Results from the present study support evidence from randomized, double-blind, placebo- and active-controlled studies of DFD-29 indicating its efficacy and tolerability in the treatment of moderate-to-severe rosacea.[14,15] In two recent phase 3 trials, DFD-29 (40 mg/d) demonstrated superior efficacy in the proportion of subjects achieving Investigator's Global Assessment (IGA) success vs placebo and doxycycline 40 mg/d. DFD-29 also showed superior efficacy in reducing inflammatory lesions vs both comparators and improved Clinician's Erythema Assessment vs placebo.[14] This sub-antimicrobial formulation of minocycline, with its superior efficacy vs doxycycline 40 mg/d, may provide significant advantages in rosacea management.[15]

In the current study, DFD-29 had no significant impact on the microbiota of the skin, GI, or vaginal tract and thus may be suitable for longer-term use compared to standard doses of minocycline. The results from this study are particularly clinically relevant given its use of the latest available microbiological techniques to assess the impact on normal and pathogenic microorganisms.

CONCLUSION

In conclusion, administration of DFD-29 for 16 weeks had no detectable effects on microbiota in the skin, GI tract, or vagina. Overall, the use of DFD-29 for 16 weeks was generally safe and well tolerated in healthy adults and may offer a useful option for patients with moderate-to-severe rosacea.

DISCLOSURES

Richard L. Gallo MD PhD is a consultant for Journey Medical Corporation. Hilary Baldwin MD is a consultant for and has received honoraria from Almirall, Arcutis, Beiersdorf, Cutera, Dermavant, Galderma, Journey, Kenvue, La Roche-Posay, l'Oreal, Nutrafol, Ortho, Sun, and Tarsus. Julie Harper MD is a consultant for and has received honoraria from Almirall, Arcutis, Beiersdorf, Bioderma, Bubble, Cutera, Galderma, Journey Medical Corporation, L'Oreal, Nutrafol, Ortho, and Sun. Srinivas Sidgiddi MD is an employee of Journey Medical Corporation. Neal Bhatia MD reports grants and/or research funding from AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Boehringer Ingelheim, Dr. Reddy's Laboratories, DUSA Pharmaceuticals, Inc., LEO Pharma US, Mindera, Nutrafol, Pfizer, Sanofi/Regeneron, Soligenix, Sun Pharmaceutical Industries, Verrica Pharmaceuticals, and Zerigo Health, and personal fees from Almirall, Beiersdorf, Biofrontera AG, Castle Biosciences, Dermavant Sciences, Ferndale Laboratories, Galderma Laboratories, ISDIN, Johnson and Johnson Consumer Products Company, La Roche-Posay Laboratorie Pharmaceutique, Ortho Dermatologics, Practical Dermatology,

Sanofi/Regeneron, and Sun Pharmaceutical Industries. John A. McLane PhD is an employee of Catawba Research and reports no other conflicts of interest.

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ORIGINAL ARTICLE

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More Than Skin Clearance: Connecting Brodalumab's Mechanism of Action to Patient Outcomes in Psoriasis

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ABSTRACT

Psoriasis has profound negative impacts on quality of life (QOL), including stigmatization, discrimination, occupational challenges, and mental health concerns, which are correlated with disease severity. Effective, long-term symptom control can dramatically improve the psychological and social outcomes for patients with psoriasis, though certain mechanisms of action of biologic therapies may contribute to reduced or diminished efficacy, need for treatment switching, and reduced QOL. Brodalumab is the only approved biologic indicated for moderate-to-severe plaque psoriasis that binds to interleukin-17 (IL-17) receptor A rather than targets specific IL-17 cytokines, which may contribute to its high clinical efficacy among patients who have lost responses to other biologic therapies and may also lead to sustained improvements in QOL. In biologic-experienced and biologic-naive patients, brodalumab has demonstrated optimal efficacy and improvements in QOL in both clinical trials and real-world studies, including improvements over other biologic therapies. This has the potential to dramatically improve the mental and social burdens faced by patients with moderate-to-severe psoriasis.

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INTRODUCTION

Moderate-to-severe psoriasis is associated with substantial burden, including increased depression and anxiety and reduced quality of life (QOL).[1] Skin clearance with biologic therapies is associated with improved QOL; however, psoriatic disease may fail to respond to certain agents, leading to a lack of efficacy and disease recurrence and contributing to a frustrating cycle of treatment switching.[2,3] Differences in the mechanism of action (MOA) of available therapies may result in various response rates and durability of responses, which lead to differential impact on QOL.[3,4]

Brodalumab is a fully human monoclonal antibody antagonist of the human interleukin-17 receptor A (IL-17RA) that is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.[5] Unlike other biologics that target specific IL-17 cytokines, brodalumab is the only approved biologic for psoriasis that binds IL-17RA, blocking signaling from multiple IL-17 family members, including IL-17A, IL-17C, IL-17E, IL-17F, and IL-17A/F.[4] This comprehensive receptor-level blockade may contribute to brodalumab's clinical efficacy in patients after failed treatment with other targeted therapies, including IL-17 cytokine inhibitors, and may lead to improvements in QOL.[6]

This narrative review examines the humanistic burden of psoriasis, evaluating how complete and sustained skin clearance affects psychosocial outcomes and QOL, with a focus on brodalumab's unique MOA and its ability to improve dermatological and mental health outcomes, even in patients who have experienced prior biologic treatment failure. A graphical summary of this review is shown in Figure 1.

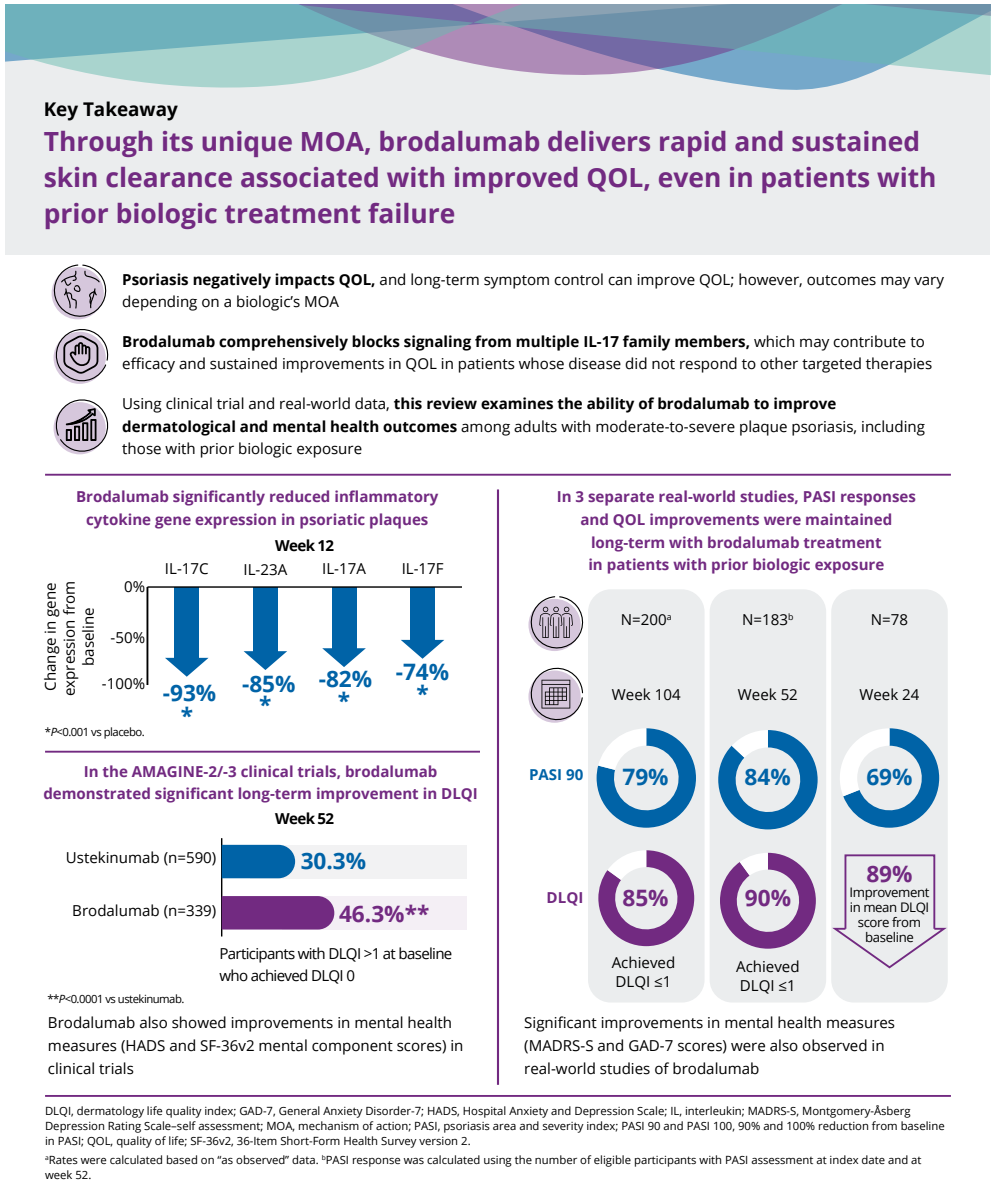
Patient Burden Associated With Psoriasis and Treatment Nonresponse

Disease Burden

Psoriasis has a profound negative impact on patients, from stigmatization to occupational challenges and mental health concerns.[7] A survey of 514 patients with psoriasis showed that perceived stigmatization was experienced by 73% of patients.[8] Stigmatization was associated with higher impact on daily life; lower education; higher disease visibility, severity, and duration; and higher levels of social inhibition.[8]

Additionally, psoriasis is associated with poor mental health outcomes, including depression, anxiety, suicidality, obsessive-compulsive behavior, somatization, and interpersonal sensitivity.[1,9,10] Rates of depression can reach 34% among patients with psoriasis[10] and are higher in men than women experiencing severe psoriasis and in younger vs older patients

FIGURE 1. Graphical summary.



DLQI, dermatology life quality index; GAD-7, General Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; IL, interleukin; MADRS-S, Montgomery-Åsberg Depression Rating Scale–self assessment; MOA, mechanism of action; PASI, psoriasis area and severity index; PASI 90 and PASI 100, 90% and 100% reduction from baseline in PASI; QOL, quality of life; SF-36v2, 36-Item Short-Form Health Survey version 2.

[a]Rates were calculated based on "as observed" data. [b]PASI response was calculated using the number of eligible participants with PASI assessment at index date and at week 52.

with mild and severe psoriasis.[11] Furthermore, patients with psoriasis are significantly more likely to have suicidal ideation or attempt suicide than patients with melanoma and allergic dermatological conditions.[12]

Because psoriasis affects mental health, patient-reported outcome measures (PROMs) have been increasingly incorporated in clinical studies.[13,14] The dermatology life quality index (DLQI) is a 10-item questionnaire that evaluates patient perception of their dermatology-specific health-related QOL, with scores ranging from 0 to 30 (0-5 = mild, 6-10 = moderate, and 11-30 = severe).[13] However, there are inherent limitations to PROMs, including the potential for item bias, which may be influenced by demographics,[13] and underestimation of disease severity in patients who respond "not relevant" to >1 item[15]; therefore, additional validation tools may be needed.

Psoriasis may also negatively impact relationships and finances, contributing to stress that may exacerbate inflammation and disease.[7] In a global survey of 8338 patients with moderate-to-severe psoriasis, 84% of respondents had experienced discrimination and/or humiliation in their daily lives.[16] Negative social interactions, such as being asked whether they are contagious and being stared at in public, were experienced by 45% and 40% of respondents, respectively.[16] Furthermore, 54% of respondents believed that their disease had impacted their professional lives; of these respondents, 38% and 30% stated that they lost productivity owing to itching and pain, respectively, and 11% had to quit a job because of psoriasis.[16]

Disease and Treatment Burden Within the Treatment Landscape

Patient QOL and disease severity demonstrate a clear relationship, with treatment success rates impacting PROMs.[1,17]

Participants with moderate-to-severe psoriasis in a prospective study who did not achieve 75% improvement in psoriasis area and severity index score (PASI 75) after 16 weeks of treatment with systemic therapy were 4 times as likely to experience a negative impact on QOL than those who achieved PASI 75 (odds ratio 4.2; *P*=0.012).[1] Worsening of mean DLQI scores was also observed in participants with worsening or no improvement in body surface area at 6 months after systemic therapy initiation from the CorEvitas Psoriasis Registry (n=2620).[17]

Recently, therapeutic targets have evolved with the increased effectiveness of novel therapeutics.[18] Although PASI 75 has been used as a primary endpoint in most clinical trials, PASI 90 and PASI 100 are increasingly recognized as more clinically meaningful responses, particularly for severe psoriasis.[18] Importantly, reduction in PASI correlates with improved DLQI,[18] and patient satisfaction increases almost linearly from PASI 50 to PASI 90.[19] Economic modeling demonstrates that PASI 90 and PASI 100 achievements provide greater social value and lower economic impact compared with PASI 75.[20] Therefore, outcome measures should reflect recent therapeutic advancements.[18]

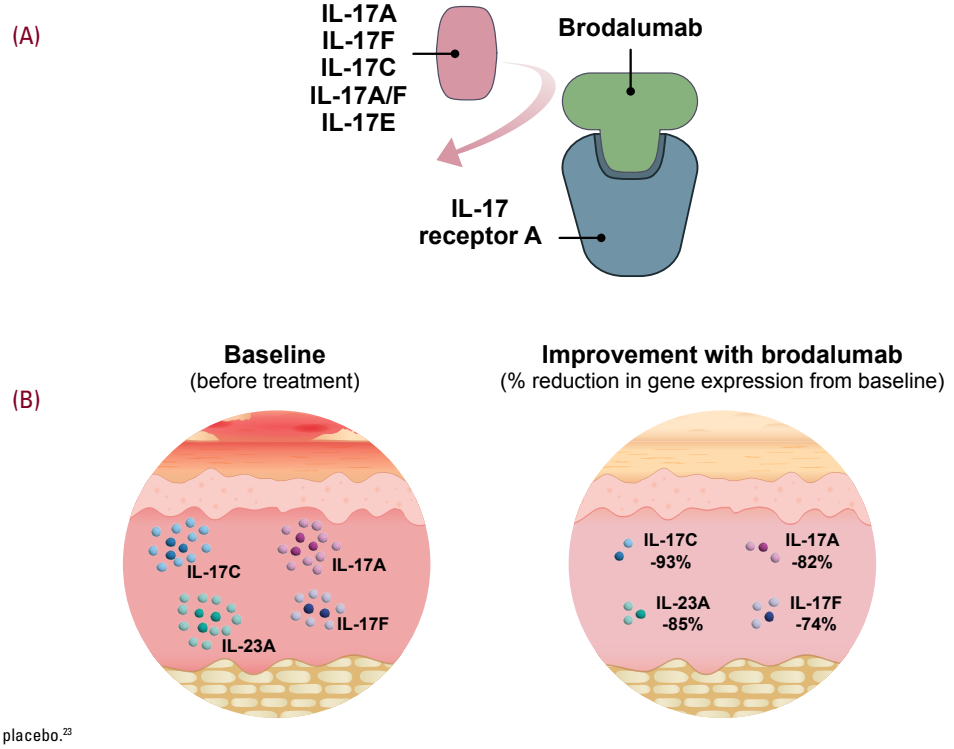
Biologic therapies have had a positive effect on patient outcomes, although treatment durability remains a critical consideration. An analysis of 7490 patients enrolled in the Psoriasis Longitudinal Assessment and Registry reported that biologics (etanercept, adalimumab, infliximab, and ustekinumab) were associated with a decreased risk of depression compared with other agents (methotrexate, cyclosporine, systemic corticosteroids, fumarates, mycophenolate mofetil, and oral retinoids; hazard ratio, 0.76; 95% confidence interval, 0.59-0.98).[21] However, some patients experience inadequate response or diminishing response over time; this nonresponse is associated with greater disease severity and negative impacts on QOL,[4] highlighting the need for additional therapeutic options.

Together, these psychological and social outcomes highlight the importance of long-term skin clearance.

Mechanism of Action of Brodalumab

Biologic nonresponse requires a switch in therapy, ideally to a drug with a different MOA to increase the likelihood of treatment response.[6] Due to its unique MOA, brodalumab may be an effective option after failure of first-line treatments, including anti–IL-17 agents.[6] Unlike other biologic agents that target specific cytokines such as IL-17A (secukinumab and ixekizumab) or IL17A and IL-17F (bimekizumab),[4,22] brodalumab blocks the IL-17 RA itself, thereby preventing signaling from multiple IL-17 family members, including IL-17A, IL-17C, IL-17E, IL-17F, and IL-17A/F (Figure 2A).[5,23] In addition to direct blockade of IL-17 family members, treatment with brodalumab 210 mg has been shown to reduce gene expression of *IL-17C, IL-17A, IL-17F*, and *IL-23A* by at least 74% in lesional skin (Figure 2B).[23] IL-17C, reported to be expressed at levels 125-fold higher than IL-17A in psoriatic

FIGURE 2. (A) Brodalumab targets IL-17 signaling at the receptor level.[5] (B) Brodalumab significantly reduces inflammatory cytokine gene expression from baseline in psoriatic plaques at 12 weeks.



IL, interleukin. *P<0.001 vs placebo.[23]

lesions, functions as a key inflammation amplifier through a positive feedback loop with IL-17–producing T cells and keratinocytes[24]; thus, IL-17C inhibition by brodalumab may be a critical factor underlying its efficacy in patients with prior anti–IL-17A therapy failure. Therefore, the unique MOA of brodalumab may translate into meaningful clinical and patient-reported outcomes, particularly in patients who have experienced nonresponse with other biologics.[6]

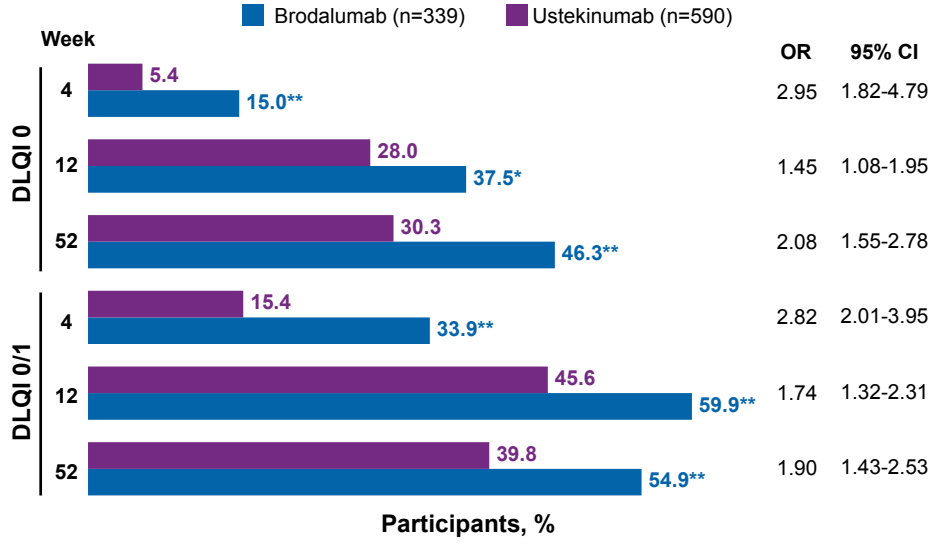
Impact of Brodalumab Treatment on QOL in Biologic-Experienced Patients

Clinical Trials

Patients with prior biologic treatment failure experienced durable improvements in skin clearance and QOL measures with brodalumab treatment. In the phase 3 AMAGINE-2/-3 clinical trials, brodalumab demonstrated superior clinical efficacy and improvements in QOL compared with ustekinumab.[25-27] A greater proportion of the participants with prior biologic failure had improvements in skin clearance and PROMs with brodalumab vs ustekinumab, including PASI 90 (63% vs 36%; $P \leq 0.001$), PASI 100 (32% vs 11%; $P \leq 0.003$), DLQI 0/1 (56% vs 40%), and a psoriasis symptom inventory (PSI) of ≤8 (57% vs 48%) at week 12.[26] PSI measures the severity of 8 signs and symptoms of psoriasis on a 5-point scale ranging from 0 (not at all) to 4 (very severe); total scores range from 0 to 32.[26] Furthermore, participants who experienced inadequate response to ustekinumab (defined as a single static physician's global assessment [sPGA] score ≥3 or persistent sPGA score of 2 over ≥4 weeks) could switch to brodalumab or continue ustekinumab at week 16.[27] Greater improvements in DLQI (69.1% vs 61.1%) and PSI (55.6% vs 33.6%), as well as higher PASI 90 and PASI 100 response rates, were also observed at week 52 in participants who switched to brodalumab compared with those who continued ustekinumab after inadequate response.[27] In a pooled analysis of AMAGINE-2/-3 data through 52 weeks, brodalumab 210 mg every 2 weeks (Q2W; n=339) was associated with significantly greater reduction in DLQI from baseline compared with ustekinumab (n=590).[28] Among participants with DLQI >1 at baseline, a substantially greater proportion of participants treated with brodalumab achieved a DLQI of 0 or ≤1 at weeks 4 and 12 vs those treated with ustekinumab, and these reductions were sustained through week 52 (Figure 3).[28] Furthermore, open-label extension studies found that >90% of participants treated with brodalumab who showed improvements in DLQI by week 12 maintained those improvements through week 120.[29]

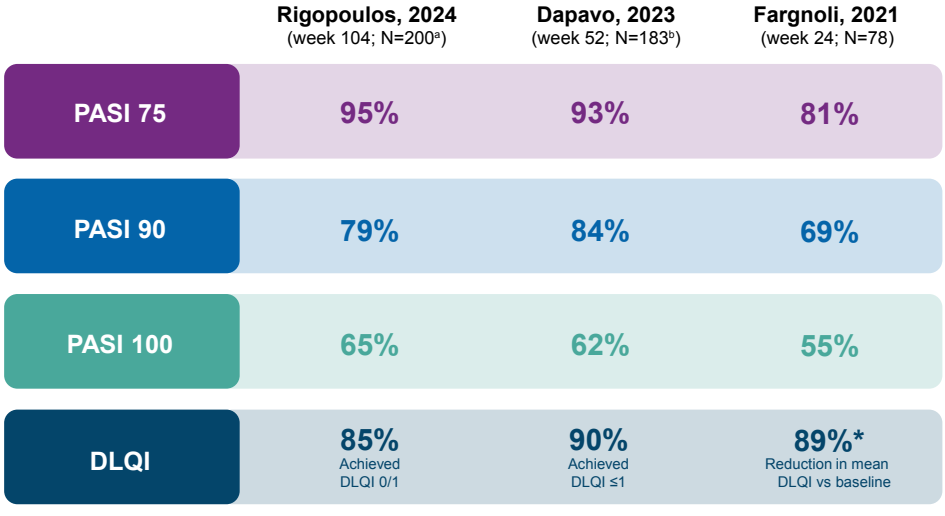
To evaluate the cumulative treatment benefit of brodalumab, an area-under-the-curve analysis was performed using pooled data from brodalumab phase 3 trials, capturing the rapidity and durability of PASI responses.[30] In pooled analyses of AMAGINE-2/-3, brodalumab was associated with a significantly greater cumulative benefit through 52 weeks vs ustekinumab in participants achieving PASI 100 and PASI 90 ($P<0.0001$), with 69% added benefit in participants achieving PASI 100 and 42% added benefit in those achieving PASI 90. Median time to PASI 100 was shorter with brodalumab vs ustekinumab (14 vs 44 weeks, respectively) and achieved as early as 2 to 4 weeks. At the end of the maintenance phase, 90.1% and 76.7% of participants who had achieved PASI 100 with brodalumab and ustekinumab, respectively, sustained PASI 100 responses. Across AMAGINE-1/-2/-3, PASI response level strongly correlated with achievement of DLQI 0/1 ($P<0.0001$), with 83.5% of PASI 100 responders achieving DLQI 0/1.

FIGURE 3. Proportion of participants in the AMAGINE-2/-3 trials with DLQI >1 at baseline who achieved DLQI 0 or 0/1 with brodalumab vs ustekinumab at weeks 4, 12, and 52.[28]



CI, confidence interval; DLQI, dermatology life quality index; OR, odds ratio. *$P<0.05$ vs ustekinumab. **$P<0.0001$ vs ustekinumab.

FIGURE 4. PASI response rates and DLQI improvement in participants with prior biologic experience treated with brodalumab in real-world studies.[33-35]



DLQI, dermatology life quality index; PASI, psoriasis area and severity index. [a]Rates were calculated based on "as observed" data. [b]PASI response and DLQI ≤1 rates were calculated using the number of eligible participants with PASI assessment at the index date and at week 52, and with DLQI assessment at week 52, respectively. *P<0.0001 vs baseline.

In a prospective phase 3 trial, participants receiving brodalumab showed significant improvement in model-based Hospital Anxiety and Depression Scale (HADS) scores and reduced severity of anxiety compared with those receiving placebo at week 12.[31] These changes were shown to be durable because the Medical Outcomes Study 36-Item Short-Form Health Survey version 2 mental component scores increased by week 12 of brodalumab treatment and remained higher than baseline average in an open-label extension study through week 120.[29]

Collectively, data from clinical trials demonstrated significant improvements in PROMs with brodalumab treatment vs ustekinumab, suggesting brodalumab's mechanism of targeting IL-17 RA provides meaningful clinical advantages.

Real-World Studies

The ability of brodalumab to achieve skin clearance and improve QOL, including in biologic-experienced patients, has also been demonstrated in open-label and real-world studies.

An open-label, phase 4 study of brodalumab in participants with prior tumor necrosis factor α (TNF-α) inhibition failure showed significant improvements in PASI score (8.7 to 2.5; P<0.0001) and DLQI score (10.1 to 4.1; P=0.004) after 12 weeks.[32] Similarly, several studies demonstrated long-term maintenance of PASI responses and DLQI improvements with brodalumab, including in participants with prior biologic exposure (Figure 4).[33-35] In a study of 200 participants who were initiating or switching to brodalumab, "as observed" data showed that 85% and 65% of participants achieved DLQI 0/1 and PASI 100 at week 104, respectively.[33] In a study of 183 participants, 38% of whom received biologic therapy before brodalumab initiation, 90% and 62% of participants achieved a DLQI score of ≤1 and PASI 100 at week 52, respectively.[34] A retrospective study of 78 participants, 23% of whom had IL-17A therapy failure, showed significant reductions in mean DLQI and significant improvement in PASI scores from baseline at week 24 (P<0.0001 for both).[35]

Mental health improvement was also reported in the open-label phase 4 study, including improvements in the Montgomery-Åsberg Depression Rating Scale–self assessment (7.1 to 3.8; P=0.0007) after 12 weeks of brodalumab treatment.[32] Nominal reductions were also observed in HADS-A (anxiety) and HADS-D (depression).[32] Additionally, in a Japanese study of 73 participants with psoriasis receiving brodalumab (ProLOGUE), median General Anxiety Disorder-7 (GAD-7) scores significantly decreased from baseline (6.5) to week 12 (1.0, P=0.002) and week 48 (0.5, P=0.005) in those with a baseline GAD-7 score of ≥5.[36]

In studies comparing numerous biologics for psoriasis (including TNF-α, IL-12/-23, IL-23, and IL-17 inhibitors), brodalumab demonstrated comparable or superior skin clearance, with corresponding increases in QOL. In a cross-sectional study of 40 participants treated with IL-17 inhibitors (secukinumab and ixekizumab), IL-17RA inhibitor (brodalumab), or IL-23 inhibitors (guselkumab and risankizumab), brodalumab and risankizumab were the top-ranked drugs in terms of self-reported QOL.[37] When compared with IL-17 inhibitors (ixekizumab and secukinumab), brodalumab was associated with the greatest reduction in PASI scores, lowest DLQI scores, and the highest rates of DLQI scores

<1 after ≥12 weeks of treatment.[37] Additionally, the rapidity of brodalumab's 210 mg onset of action was demonstrated in systematic reviews.[38,39] In a review encompassing brodalumab, ixekizumab, secukinumab, guselkumab, tildrakizumab, and risankizumab, brodalumab 210 mg was associated with the shortest weighted mean time to 25% and 50% of participants achieving PASI 90 (3.5 and 6.2 weeks, respectively) and 25% achieving PASI 100 (6.9 weeks).[38] Overall, IL-17 inhibitors such as brodalumab and ixekizumab demonstrated a more rapid onset of action compared with IL-23 inhibitors. Findings from another systematic review support faster onset of action of IL-17 inhibitors vs IL-23 inhibitors, with brodalumab and ixekizumab having the most rapid treatment effects at week 2.[39] Brodalumab and ixekizumab were also reported to have the greatest effect on DLQI at week 12. Another retrospective study showed significantly higher rates of PASI 90 (66%) at the earliest time point (week 16) with brodalumab compared with 5 IL-23 and IL-17A inhibitors (P<0.001).[40] Because high levels of skin clearance correlate with improved PROMs,[9] the rapid effect of brodalumab may alleviate patient burden and dissatisfaction quicker than other therapies.

Despite its benefits, brodalumab has been utilized less in the United States compared with the European Union.[41] In the United States, brodalumab carries a boxed warning in the prescribing information regarding suicidal ideation and behavior and, unlike in the European Union, is only available under a Risk Evaluation and Mitigation Strategy (REMS); however, no causal relationship has ever been established.[42] Six years of pharmacovigilance data were collected from 5138 patients in the United States with an estimated exposure of 6900 patient-years. There were 58 documented cases of depression (1.13 events/100 patients); 4 cases (7%) were deemed related to brodalumab, and all occurred before the 4-year pharmacovigilance report. One suicide attempt was reported in year 3, but no completed suicides have been reported throughout the 6 years. Recently, a panel of dermatology experts initiated a call to action regarding the REMS program for brodalumab.[43] Based on worldwide postmarketing data, the panel determined that the risk of suicidality for brodalumab was comparable to that of other biologics and that brodalumab has been incorrectly associated with suicidality.

CONCLUSION

Moderate-to-severe psoriasis is associated with substantial clinical and humanistic burden. Improvements in skin clearance have been associated with improved QOL, though some biologics may lack durability. By targeting IL-17RA, brodalumab provides long-lasting skin clearance and improved QOL, including in patients with prior biologic failure, potentially leading to substantial improvements in mental and social burden. Future studies evaluating depression and other psychological comorbidities in patients who have experienced prior biologic nonresponse are warranted to characterize the patient burden of treatment switching.

DISCLOSURES

JK has served as a consultant or speaker for AbbVie, Amgen, EPI, Janssen, LEO Pharma, Lilly, Novartis, Ortho Dermatologics, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Sun Pharma. GH is or has served as an investigator for Athenex, Boehringer Ingelheim, Bond Avillion, Bristol Myers Squibb, Celgene, Janssen, Lilly, MC2, Novartis, PellePharm, Pfizer, and UCB; and is a consultant, advisor, or speaker for AbbVie, Boehringer Ingelheim, Dermtech, Incyte, Janssen, LEO Pharma, Lilly, Ortho Dermatologics, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Sun Pharma, and UCB. ML is an employee of Mount Sinai; has received research funds from AbbVie, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Clexio, Dermavant Sciences, Incyte, Inozyme, Johnson & Johnson, Lilly, Pfizer, Sanofi-Regeneron, and UCB; and is a consultant for Aikium, Almirall, AltruBio, Amgen, Apogee, Arcutis, AstraZeneca, Atomwise, Avotres, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Celltrion, CorEvitas, Dermavant Sciences, Dermsquared, Evommune, Facilitation of International Dermatology Education, Forte Biosciences, Galderma, Genentech, Incyte, LEO Pharma, Mayne Pharma, Meiji Seika Pharma, Mindera, Mirum Pharmaceuticals, Okura, Pfizer, Revolo, Sanofi-Regeneron, Seanergy, Strata, Sun Pharma, Takeda, Trevi, and Verrica. AJ is an employee of Bausch Health Companies Inc.

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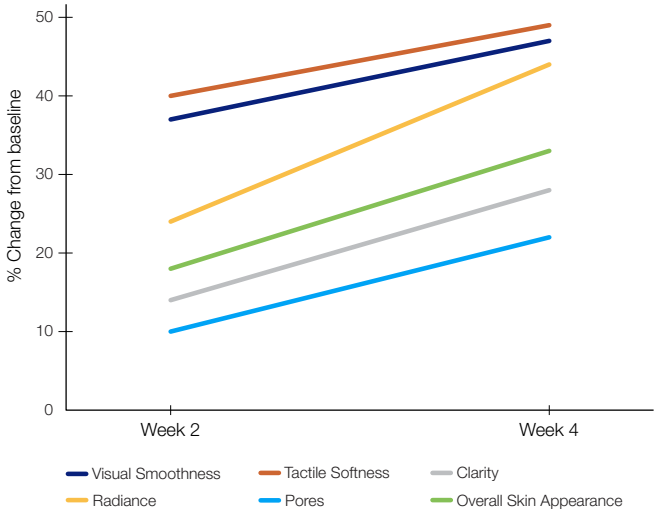
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ORIGINAL ARTICLE

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Skin Improvements in Acne Vulgaris Patients Using Gel-Matrix Moisturizer as a Complement to Topical Treatments

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ABSTRACT

Background: A novel gel-matrix moisturizer was designed to 1) deliver immediate, long-lasting hydration benefits in a lightweight, non-greasy, noncomedogenic formula that is suitable for use on dry, oily, acne-prone, and sensitive skin; 2) reduce acne-related and acne medication–induced skin irritation and dryness; and 3) improve quality of life (QoL), when used as an adjunctive moisturizer by patients with acne using topical treatments.

Objective: To assess the biological effects of the gel-matrix moisturizer on key epidermal proteins of skin barrier function, and clinical improvements in skin attributes and tolerability in adults with acne undergoing topical treatment.

Methods: Preclinical and clinical studies evaluated the tolerability of the gel-matrix moisturizer and its effects on filaggrin and aquaporin-3 protein levels (markers of barrier function), skin texture, appearance, and QoL in the study population.

Results: In skin explant studies, the gel-matrix moisturizer demonstrated significant increases in levels of filaggrin (+36%) and aquaporin-3 (+102%) versus untreated controls (both $P<0.05$). Clinically, at week 4 compared with baseline, the gel-matrix moisturizer demonstrated significant improvements in visual skin smoothness, roughness, clarity, radiance, pore issues, and overall skin appearance (all $P<0.01$), as well as significant decreases in skin itching ($P<0.01$) and tightness ($P<0.002$). Patients with acne also using topical over the counter and prescription treatments reported significant improvements in QoL at week 4 ($P<0.001$).

Conclusion: The gel-matrix moisturizer improved barrier function and skin attributes without exacerbating acne symptoms, offering suitable topical moisturization when used as an adjunctive moisturizer with acne treatments.

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INTRODUCTION

With an estimated prevalence of 9.4% globally, acne vulgaris (hereafter referred to as acne) is one of the most common cutaneous diseases worldwide, with one of the highest disease burdens of disease.[1] Mechanistically speaking, acne is a complex, multifactorial skin condition associated with reduced levels of filaggrin[2] and aquaporin-3[3] proteins, impaired barrier function,[4] and increased transepidermal water loss (TEWL),[5] which can lead to skin dryness, sensitivity, and irritation.[4] Furthermore, prescription and over-the-counter (OTC) actives commonly used to treat and prevent acne, such as retinoids and benzoyl peroxide, help accelerate skin cell turnover and suppress sebum production via keratolytic, comedolytic, sebostatic, and/or bactericidal mechanisms of action,[6,7] thereby causing skin dryness and irritation[4,6] and affecting patients' compliance with treatment.[8,9] Moreover, harsh cleansers formulated with traditional small-monomer surfactant micelles can also cause skin dryness and irritation by washing away essential natural moisturizing factor (NMF) compounds naturally present in the skin. A lightweight moisturizer that provides long-lasting skin hydration without a greasy residue is an ideal adjunctive product for acne patients who may have excess sebum but also suffer from acne-related dryness and irritation.[4,10]

Stratum corneum (SC) moisture levels are critical for enzymatic processes involved in surface desquamation,[11-14] which help maintain proper barrier function. Low SC moisture content can inhibit the desquamation process, causing non-viable skin cells to accumulate and clog pores, which leads to the formation of acne lesions.[15,16] SC corneocytes contain various hygroscopic molecules (e.g., amino acids, urea, saccharides, and electrolytes) that comprise the NMF and efficiently bind water to support moisture retention and barrier function.[17-19] Epidermal proteins such as filaggrin and aquaporin-3 play a critical role in sustaining SC hydration and barrier integrity.[20-24] Through enzymatic metabolism, for example, filaggrin breaks down into free amino acids that constitute a significant proportion of the NMF residing in the SC corneocytes.[20-22,24] Moreover, filaggrin deficiency has been associated with increased TEWL[2,20-22,24] and acne.[2] Aquaporin-3 supports the transport of water molecules (among others) from the deeper epidermal layers to the surface SC layer, and deficiency has been shown to decrease the SC's water-holding capacity (capacitance).[3,25,26]

For individuals with acne, a topical moisturizer that improves skin hydration and treatment tolerability without exacerbating acne symptoms could also improve compliance with topical acne treatments. Such a moisturizer should not clog pores or cause accumulation of lipids or excess sebum at the interface between lesional and non-lesional skin areas. It should also be non-irritating and gentle enough for daily use in combination with topical acne treatments. A novel topical gel-matrix moisturizer was designed to deliver immediate and sustained hydration benefits in a lightweight, non-greasy, non-comedogenic formula that is suitable for use on dry, oily, acne-prone, and sensitive skin. The gel-matrix moisturizer contains amino acids, electrolytes, and other NMF compounds that bind water on and within the SC; low levels of emollients and occlusives to help mitigate TEWL without clogging pores; and biomimetic fatty acid esters that help improve skin hydration (based on capacitance measurements)[27] while stabilizing the emulsion formula.

Summarized herein are the findings of preclinical studies of the gel-matrix moisturizer that evaluated its biological skin effects, as well as clinical studies of skin attributes, skin tolerability, and experience following complementary use in individuals with topically treated acne.

MATERIALS AND METHODS

The Gel-Matrix Moisturizer's Effects on Markers of Barrier Function in Preclinical Studies

Skin biopsies were treated with the gel-matrix moisturizer once daily for 3 to 6 days or left untreated (controls). The samples were then collected and processed for histological examination via immunohistochemistry, using anti-filaggrin (Santa Cruz #sc-66192) and anti-aquaporin-3 (Sigma-Aldrich #HPA014924) antibodies per the manufacturer's instructions.

Clinical Benefits of the Gel-Matrix Moisturizer in Patients With Acne Undergoing Topical Treatment

A single-center, monadic, 4-week study evaluated tolerability and efficacy of the gel-matrix moisturizer when used once daily (or twice daily if desired) as directed for 4 weeks on the face and neck of adults (20–43 years of age) with acne undergoing daily treatment with prescription and/or OTC treatment (Table 1). Although standardizing the amount of gel-matrix moisturizer used daily by the study participants might improve statistical sensitivity, the application regimen of once or twice daily was selected to reflect real-world use of moisturizers and is thus clinically relevant. Eligible acne treatments included (but were not limited to) benzoyl peroxide, retinoids (eg, adapalene, tretinoin, tazarotene), topical antibiotics, topical dapsone, and Epiduo [Galderma Laboratories LP, Fort Worth, TX]). Use of oral isotretinoin (Accutane; Journey Medical Corporation, Scottsdale, AZ) was prohibited.

Investigator grading of tolerability (i.e., erythema/redness, rash/irritation, peeling/flaking, surface roughness, and dryness) and efficacy (i.e., visual smoothness, tactile softness, clarity, radiance, pores, and overall skin appearance), as well as participant grading of tolerability (i.e., stinging, burning, itching, tightness, redness, peeling/flaking, roughness to the touch, dryness, and overall sensitivity) and efficacy (i.e., issues with smoothness, softness, clarity, radiance, pores, and overall skin appearance) were performed at baseline, week 2, and week 4, based on a 5-point ordinal scale: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe.

At week 4, study participants completed a questionnaire regarding the gel-matrix moisturizer's attributes and aesthetics. At baseline and week 4, the participants also completed the Acne Quality of Life Index (AQoLI) questionnaire, in which 21 items were organized into 3 domains (mood, psyche, and social), each consisting of 7 items. Each domain score was obtained by summing scores for the corresponding 7 items and subtracting it from 49 (maximum score possible). The total AQoLI score was derived by summing the score of all 21 items and subtracting it from 147. A greater score represented a worse quality of life.

Digital images of each participant's face were taken at baseline and week 4, using a VISIA-CR 4.3 imaging system (Canfield, Parsippany, NJ, USA) under standard lighting conditions.

Data from patients who received treatment and had ≥1 post-baseline evaluation (i.e., the intent-to-treat [ITT] population) were included in statistical testing. The mean change from baseline was estimated at post-baseline timepoints for applicable parameters. The null hypothesis (mean change from baseline = 0) was tested using a Wilcoxon signed-rank test for applicable parameters.

RESULTS

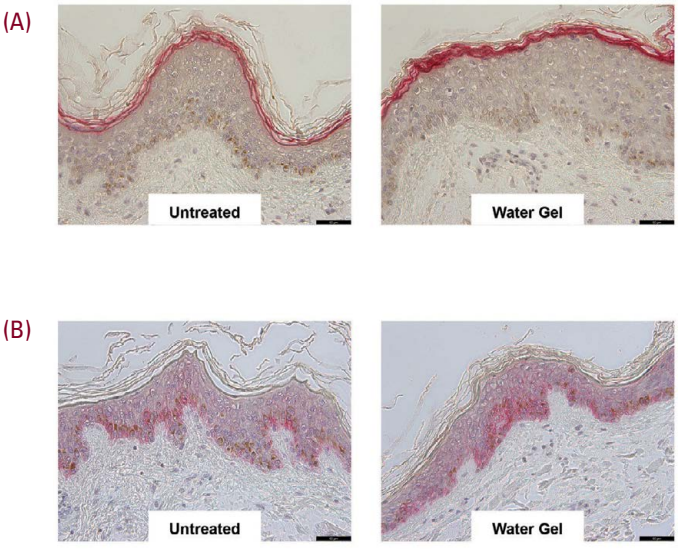
Preclinical Findings - The Gel-Matrix Moisturizer Upregulated Proteins Relevant to Skin Barrier Function

After a 3-day treatment, the gel-matrix moisturizer significantly increased the levels of filaggrin by +36%, compared with untreated controls (P<0.05; Figure 1A). After a 6-day treatment, the gel-matrix moisturizer significantly increased the levels of aquaporin-3 by +102%, compared with untreated controls (P<0.05; Figure 1B).

Clinical Findings - The Gel-Matrix Moisturizer Provides Sustained Benefits in Patients With Acne Undergoing Topical Treatment

Thirty-two subjects were enrolled; all completed the study and constituted the ITT/per protocol population. No adverse events were reported throughout the 4-week study.

FIGURE 1. The gel-matrix moisturizer (Water Gel) induced increases of (A) filaggrin and (B) aquaporin-3 proteins in human skin explants treated with the gel-matrix moisturizer for 3 and 6 days, respectively. Bar, 50 µm.



Per investigator grading of the gel-matrix moisturizer's tolerability in patients with topically treated acne, no statistically significant changes in signs of clinical irritation (i.e., erythema/redness, rash/irritation, peeling/flaking, surface roughness, and dryness) were observed at week 4, compared with baseline (Table 2). In fact, numerical improvements from baseline in erythema/redness, surface roughness, and dryness (≥66.7%) were observed at week 4 (Table 2).

Per investigator grading of the gel-matrix moisturizer's efficacy, statistically significant improvements from baseline in visual smoothness, tactile softness, clarity, radiance (all $P<0.001$), pores ($P=0.008$), and overall skin appearance ($P<0.001$) were observed at week 2 (10.0%–40.0%) and at week 4 (22.5%–49.6%) ($P\leq0.001$ for all; Figure 2A).

Patient assessment of tolerability was consistent with the investigators' findings; no statistically significant increases in stinging, burning, itching, tightness, redness, peeling/flaking, surface roughness, dryness, and overall sensitivity were observed at week 4, compared with baseline (Table 2). In fact, statistically significant improvements from baseline in itching, tightness, redness, peeling/flaking, surface roughness, dryness, and overall sensitivity ranged from 61.1% to 95.7% at week 4 ($P\leq0.002$ for all; Table 2).

Patient assessment of efficacy was also consistent with the investigators' findings; statistically significant improvements from baseline in skin smoothness, softness, clarity, radiance, pores, and overall skin appearance were reported by patients at week 2 (25.3%-37.8%) and week 4 (49.5%–66.2%) ($P<0.001$ for all; Figure 2B).

TABLE 1.

Demographics and Baseline Characteristics. Participants of the single-center, 4-week clinical study. Of 32 individuals enrolled, 32 constituted the per protocol population and were analyzed.

Parameter	N=32
Female, n (%)	28 (87.5)
Mean age, y	31.2
Min, Max	20, 43
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	32 (100)
Race, n (%)	
Black or African American	11 (34.4)
White or Caucasian	20 (62.5)
Multiracial	1 (3.1)
Fitzpatrick skin type, n (%)	
I	7 (21.9)
II	13 (40.6)
III	0
IV	0
V	7 (21.9)
VI	5 (15.6)
Acne treatment, n (%)	
Prescription (ie, retinoids, topical antibiotics, topical dapsone, or Epiduo)	18 (56.3)
OTC (ie, benzoyl peroxide, salicylic acid)	18 (56.3)

OTC, over-the-counter.

All (10) product attributes self-evaluated in this population of patients (N=32) were rated favorable at week 4 by a statistically significantly higher proportion of patients ($P<0.001$), compared with the proportion of patients who rated them as neutral or unfavorable. Notably, the study participants indicated that the product left their skin feeling hydrated (100%; n=32); felt gentle on their skin (100%; n=32); helped soothe their skin (n=27, 84.4%); was easily incorporated into their daily acne treatment routine (100%; n=32); improved their ability to tolerate their acne treatment products (81.3%; n=26); and helped them stay compliant with their acne treatment routine (90.6%; n=29).

In addition, statistically significant improvements from baseline in AQoLI were reported at week 4 in all 3 domains. Specifically, at least three-quarters of respondents reported improvements in the mood (75.0%; n=24), psyche (84.4%; n=27), and social (87.5%; n=28) domains, as well as in their total score (87.5%; n=28) ($P<0.001$ for all; Figure 3).

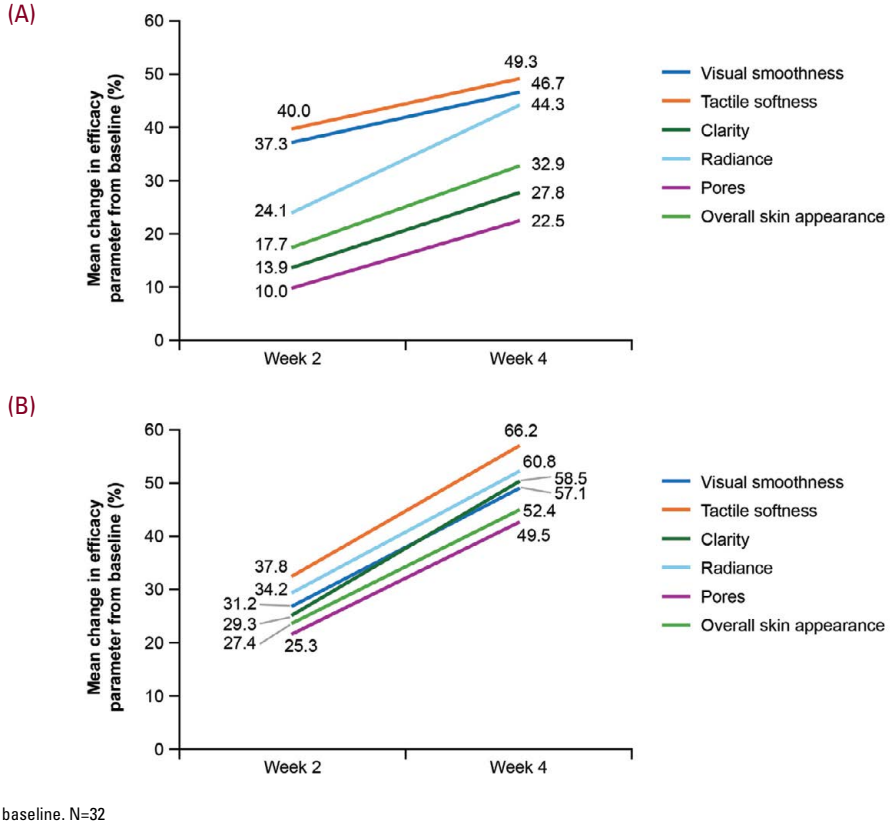
TABLE 2.

Investigator and Patient Grading. Tolerability of the gel-matrix moisturizer in patients with acne undergoing topical treatment with prescription or over-the counter products, per the 5-point ordinal scale.

Tolerability	Baseline Mean (SD)	Week 2, Mean (SD)	Week 4, Mean (SD)	Participants whose score improved at 4 weeks, %	Mean CFB at 4 weeks, %	*P*-Value
Investigator						
Erythema/redness	0.16 (0.37)	0.13 (0.34)	0.03 (0.18)	12.5	80.0	0.125
Rash/irritation	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0	--	--
Peeling/flaking	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0	--	--
Surface roughness	0.03 (0.18)	0.03 (0.18)	0.00 (0.00)	3.1	100	1.00
Dryness	0.09 (0.30)	0.03 (0.18)	0.03 (0.18)	6.3	66.7	0.500
Patient						
Stinging	0.25 (0.51)	0.13 (0.34)	0.06 (0.35)	18.8	75.0	0.109
Burning	0.13 (0.34)	0.06 (0.25)	0.13 (0.49)	12.5	0	0.813
Itching	0.72 (0.89)	0.34 (0.55)	0.03 (0.18)	46.9	95.7	<0.001
Tightness	0.75 (0.92)	0.41 (0.50)	0.22 (0.42)	43.8	70.8	0.002
Redness	1.13 (0.98)	0.63 (0.55)	0.44 (0.62)	56.3	61.1	<0.001
Peeling/flaking	0.97 (1.06)	0.47 (0.76)	0.16 (0.37)	53.1	83.9	<0.001
Surface roughness	1.25 (0.95)	0.84 (0.77)	0.44 (0.72)	62.5	65.0	<0.001
Dryness	1.81 (1.09)	1.06 (0.98)	0.47 (0.62)	75.0	74.1	<0.001
Overall sensitivity	1.81 (1.26)	0.91 (0.64)	0.44 (0.56)	75.0	75.9	<0.001

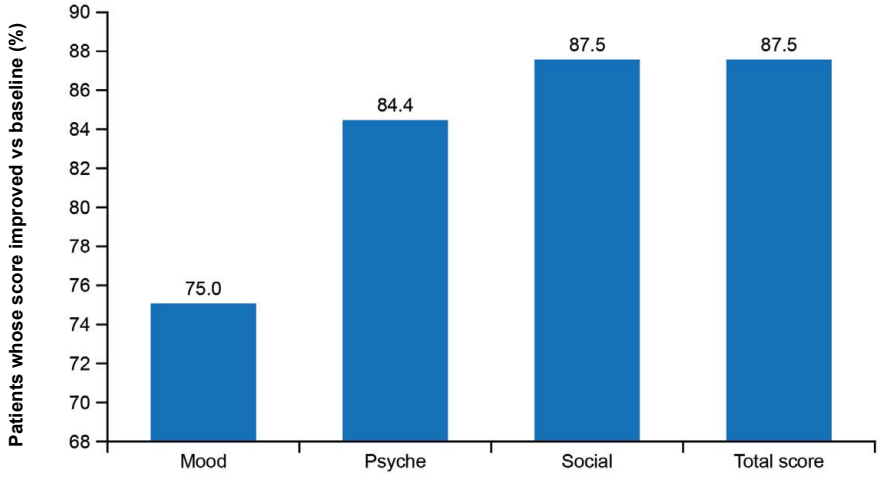
Lower values indicate improvement.
CFB, change from baseline; SD, standard deviation.

FIGURE 2. (A) Investigator and (B) patient assessment of efficacy of the gel-matrix moisturizer on acne, per the 5-point ordinal scale.



P<0.05 for all changes from baseline. N=32

FIGURE 3. Proportion of patients with acne whose Acne Quality of Life Index increased after using the gel-matrix moisturizer once daily for 4 weeks, compared with baseline.



P<0.001 for all vs baseline.

FIGURE 4. Images of the cheek of a representative study participant with topically treated acne, taken under standard lighting conditions before and after use of the gel-matrix moisturizer once daily for 4 weeks.



Consistent with the above findings, images of a representative patient with acne undergoing treatment with Epiduo showed visibly improved skin after use of the gel-matrix moisturizer once daily for 4 weeks, compared with baseline (Figure 4).

DISCUSSION

The use of the gel-matrix moisturizer demonstrated significant increases in epidermal proteins critical for proper skin barrier function and hydration. These evaluations of biological skin effects were confirmed through clinical assessments of skin hydration improvement. With validated SC hydration benefits, the gel-matrix moisturizer further demonstrated clinical benefits through once daily application in combination with topical acne treatment. Patients showed significant improvements in several visible and tactile skin attributes (e.g., hydration, smoothness, softness, and overall appearance), skin tolerability, and overall quality of life. It is also noteworthy that patients' self-assessments of the gel-matrix moisturizer's attributes (eg, lightweight, quick absorption, and non-greasy) were highly favorable, highlighting the perceived benefits that can help drive usage among the target patient populations. Per the AQoLI scores, use of the study product increased acne treatment adherence.

The overall experience with the gel-matrix moisturizer used daily as a complementary product was thus highly favorable, based on several parameters. These findings are clinically relevant, as acne can have negative effects on facial aesthetics, self-esteem, and social interactions, which in turn can lead to anxiety and depression.[4,28]

Compliance with acne treatment can be low. In reviewing the literature of the past 5 years for articles on adherence with treatment in patients with acne, 15% to 64.4% of study participants were found to have low or poor adherence.[29-32] One study reported adverse effects of skin burning, stinging, redness, and dryness as reasons for non-adherence to topical acne treatment in 12% of patients.[30] The soothing effect of the gel-matrix moisturizer on the skin and its ability to significantly reduce dryness and redness (among others) together support the use of the gel-matrix moisturizer to improve compliance with acne treatment, and suggest that daily use of the gel-matrix moisturizer provides benefits that can improve adherence to acne treatment in affected patients. Additional studies designed to compare adherence to acne treatment with or without the gel-matrix moisturizer are needed.

Previous studies have also reported the benefits of adding other moisturizers to acne treatment. A 4-week, randomized, controlled study of patients with acne (N=100) found that adherence to treatment was significantly higher when once-daily adapalene topical treatment was used after pretreatment with a heparinoid-containing moisturizer (100%), compared with adapfalene alone (70%).[33] Moreover, use of the adjunctive moisturizer reduced the incidence of patient-reported symptoms.[33] Per other randomized, controlled studies of patients with acne, once-daily use of a ceramide-based[10] or ceramide/niacinamide-based[34] moisturizer along with topical acne treatment (adapalene/benzoyl peroxide gel)[10,34] was beneficial in reducing facial dryness,[10] erythema,[10] scaling,[10] irritation,[34] and acne lesions (inflammatory and non-inflammatory),[34] and in improving barrier function,[10] without compromising efficacy of the acne treatment. With its improvement in barrier function (as evidenced by increased filaggrin and aquaporin-3), the gel-matrix moisturizer would be expected to provide similar clinical benefits. Future studies designed to refine the understanding of the gel-matrix moisturizer's benefits when used as a complementary product to topical acne treatment should also compare its effects to those of a dermatologist-recommended moisturizer (OTC or prescription).

CONCLUSION

Overall, this research demonstrates that daily use of the gel-matrix moisturizer as a complementary product to topical acne treatment was well tolerated; easily incorporated in the daily acne treatment routine; effective in reducing irritation; and statistically effective in improving key markers of skin barrier function, cosmetic appearance of the skin, and quality of life of affected patients. Moreover, these improvements made it easier for the study patients to be compliant with their daily topical acne treatment. Collectively, this information supports the use of the gel-matrix moisturizer as a topical product of choice to improve and maintain skin barrier health in individuals with acne.

DISCLOSURES

ZD has received a research grant from Kenvue Inc. KTB, EZ, W-HL, RP, DM, and JMB are/were employees of Kenvue Brands LLC (formerly Johnson & Johnson Consumer Inc.).

Funding Information

This study was supported by Kenvue Brands LLC (Formerly Johnson & Johnson Consumer Inc.).

Ethics Statement

The protocol of each clinical study was reviewed and approved by Advarra Institutional Review Board (Columbia, MD) or Sterling Institutional Review Board (Atlanta, GA) before study initiation. Each study participant provided written informed consent before undergoing any study-related procedures/assessments.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

ACKNOWLEDGMENT

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

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



GUEST
Dr. Alexandra Golant

Available now at JDDonline.com/podcast

ARCUTIS BIOTHERAPEUTICS

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

An Open-Label, Single-Center Proof of Concept Study Evaluating the Efficacy and Safety of Tirzepatide for Moderate to Severe Hidradenitis Suppurativa

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory disease associated with obesity and metabolic dysregulation. Current therapies yield variable benefits and do not target metabolic drivers. Tirzepatide, a dual GLP-1/GIP receptor agonist, induces weight loss and exerts anti-inflammatory effects, offering a potential novel approach for the treatment of HS.

Objectives: To evaluate the efficacy and safety of tirzepatide in adults with moderate-to-severe HS.

Methods: In this open-label, single-center, single-arm proof-of-concept study, 20 adults with moderate-to-severe HS (Physician's Global Assessment ≥3; BMI ≥27) received once-weekly tirzepatide, titrated to maximum tolerated dose, for 24 weeks, followed by an 8-week washout. The primary endpoint was Hidradenitis Suppurativa Clinical Response (HiSCR) at week 24. Secondary endpoints included changes in PGA, Dermatology Life Quality Index (DLQI), pain visual analog scale (VAS), and Hospital Anxiety and Depression Scale (HADS). Analyses were conducted using an intention-to-treat approach.

Results: At week 24, 16 of 20 participants (80.0%; $P<0.00001$) achieved HiSCR. Improvements were also observed in DLQI, VAS, and PGA scores, with some benefits persisting through week 32. Treatment was well tolerated, with high adherence and favorable metabolic effects.

Limitations: Single-center, open-label design, modest sample size.

Conclusions: Tirzepatide demonstrated promising efficacy and tolerability in patients with moderate-to-severe HS and obesity. Larger randomized trials are warranted to confirm efficacy, durability, and safety.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder of the pilosebaceous unit, characterized by deep, tender, purulent cystic lesions found primarily in intertriginous areas. HS is tightly related to obesity, dyslipidemia, and type 2 diabetes mellitus (T2DM) due to its chronic state of inflammation. Adipose tissue secretes adipokines, like leptin, resistin, and visfatin, which are highly active molecules, both metabolically and immunologically. There is also suppression of adiponectin, which is anti-inflammatory.[1,2] Current therapies for HS, including adalimumab, secukinumab, bimekizumab, oral and topical antibiotics, and anti-inflammatory agents, fail to address one of the root causes, the metabolic and inflammatory burden, which could be an important driver of the disease.

Glucagon-like-peptide-1 receptor agonists (GLP-1 Ra) are synthetic polypeptides that mimic the endogenous activity of glucagon-like-peptide-1 (GLP-1). Semaglutide, dulaglutide, and liraglutide are GLP-1 Ra approved for both obesity and diabetes mellitus. Tirzepatide, however, the newer generation GLP-1 Ra, has dual activity, stimulating both GLP-1 and GIP, making it even more efficacious. They have a long duration of action and effectively lower blood glucose, body weight, and body fat percentage, amongst other effects, making them now one of the front-line therapies for T2DM, dyslipidemia, and obesity. GLP-1 receptor agonists foster an anti-inflammatory state by reducing adipose tissue, body weight, and pro-inflammatory adipokines.

Several case reports are suggesting the efficacy of GLP-1 Ras in HS.[3-4] Herein, we propose that tirzepatide represents a novel therapeutic avenue for the treatment of HS, a debilitating disease for which currently approved treatments results have been variable.

MATERIALS AND METHODS

This was an open-label, single-center, single-arm proof-of-concept study of 20 adults with a treatment period of 24 weeks followed by an 8-week washout. Eligible participants were adults with moderate-to-severe hidradenitis suppurativa, defined as a Physician's Global Assessment (PGA) score ≥3 and a body mass index (BMI) ≥27. All patients received once-weekly tirzepatide, escalated per protocol to a maximum tolerated dose over 24 weeks. Nominal visits were baseline (week 0) and weeks 4, 8, 12, 16, 20, 24, and 32 (off-drug durability). Laboratory assessments were obtained at baseline and week 24. Participants were evaluated weekly. The primary endpoint was achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) at week 24. Secondary endpoints included changes in PGA, Modified Sartorius score, Dermatology Life Quality Index (DLQI), pain visual analog scale (VAS), and Hospital Anxiety and Depression Scale (HADS). Efficacy analyses were conducted using an intention-to-treat (ITT) approach, with sensitivity analyses and confidence intervals reported. The study was approved by an institutional review board, and all participants provided written informed consent.

RESULTS

This open-label, single-center, single-arm study provided proof-of-concept evidence that once-weekly tirzepatide improved disease activity in adults with moderate to severe HS. In our cohort (N=20), the sex distribution was 14 females (70%) and 6 males (30%). Mean start weight was 254.9 ± 50.8 lbs (95% CI: 232.6–277.2). HiSCR is a binary endpoint, meaning a patient is considered a HiSCR responder if they achieve ≥50% reduction in the total number of abscesses and inflammatory nodules (AN count) AND no increase in the number of abscesses and draining fistulas. At week 24, 16/20 participants met HiSCR (80.0%, exact 95% CI 56.3–94.3; P<0.00001) (Figure 1). One of the participants gave consent to include clinical pictures as seen in Figures 4 to 5.

Longitudinal analyses demonstrated early and sustained improvements across clinical and patient-reported outcomes seen as the secondary endpoints. The baseline inflammatory burden median AN was 5 (mean ± SD: 7.2 ± 2.9). AN count reductions reached statistical significance beginning at week 12 (P=0.005), with robust significance from week 16 through week 32 (all P<0.001). Mean DLQI scores improved significantly from week 12 onward (DLQI 15.7 ± 5.4, 95% CI: 13.3–18.1) (P<0.001 at weeks 20–32) (Figure 2). VAS pain scores showed the earliest response, with significant improvement by week 8 (P<0.00625), and continued reductions through week 32 (Δ = –6.7, 95% CI –7.7 to –5.7; P<0.001) (Figure 3). Screening HADS scores were low on average (anxiety 0.11 ± 0.32; depression 0.42 ± 0.96; n = 19), which was not statistically significant.

Weight loss was substantial (–43.7 lbs, 95% CI –50.2 to –37.2; P<0.001 at week 32). Directionally, greater weight loss was aligned with lower AN counts; however, regression models adjusting for baseline severity indicated no independent effect of weight change on lesion reduction.

FIGURE 1. Hidradenitis Suppurativa Clinical Response (HiSCR50): Primary endpoint result.

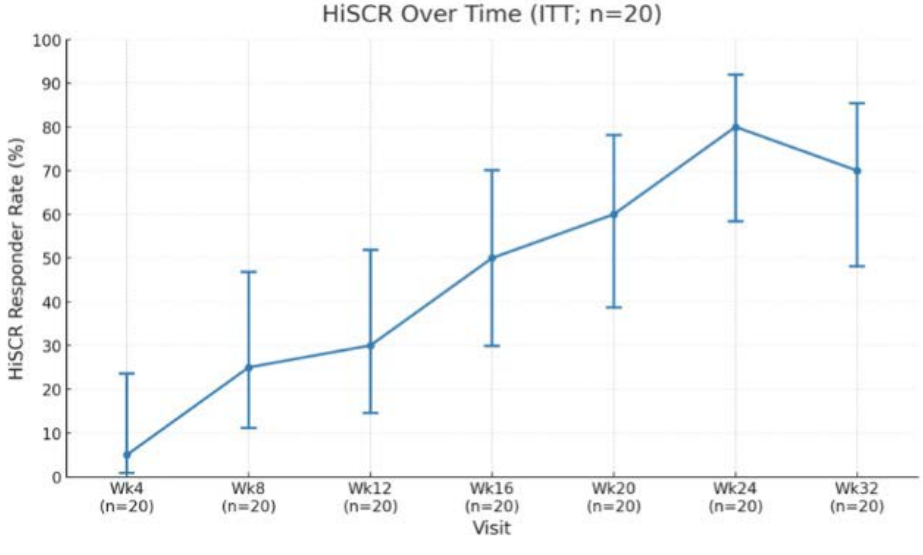
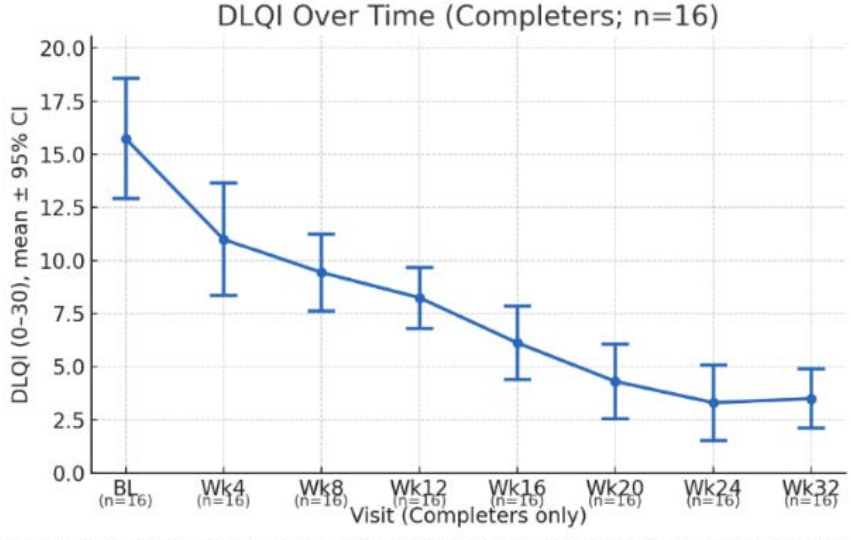
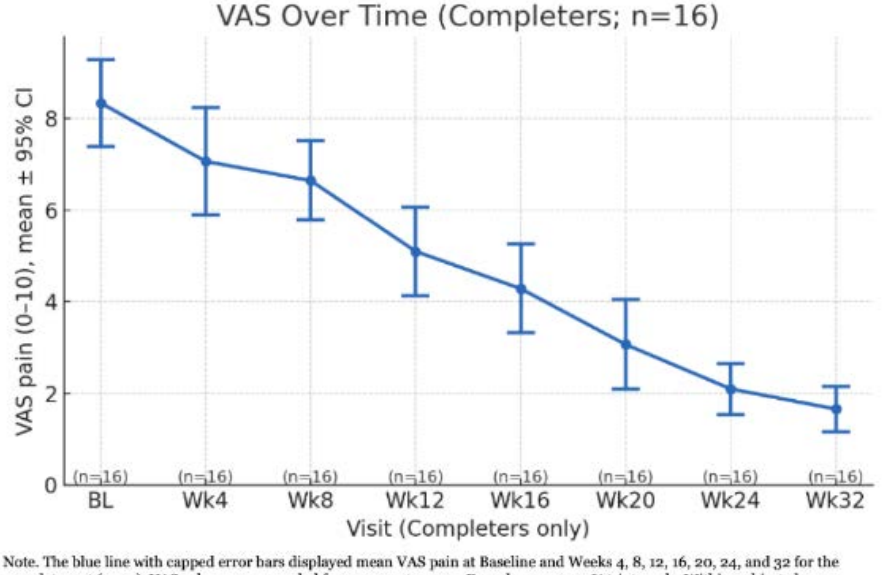


FIGURE 2. Dermatology Life Quality Index (DLQI) over time.



Note. Mean DLQI at Baseline and Weeks 4, 8, 12, 16, 20, 24, and 32 for the completer set (n=16). Error bars were 95% t-intervals. Within-subject change was evaluated using paired t-tests vs Baseline with Bonferroni correction ($\alpha = 0.00625$). The first significant reduction occurred at Week 12, with improvements sustained through Weeks 16–32 (Weeks 20–32, $P < 0.001$).

FIGURE 3. Pain Visual Analog Score (VAS) over time.



Note. The blue line with capped error bars displayed mean VAS pain at Baseline and Weeks 4, 8, 12, 16, 20, 24, and 32 for the completer set (n=14). VAS values were rescaled from 0–100 to 0–10. Error bars were 95% t-intervals. Within-subject change was evaluated using paired t-tests vs Baseline with Bonferroni correction ($\alpha = 0.00625$). The first significant reduction occurred at Week 8; Weeks 12–32 were highly significant (all $P < 0.001$).

FIGURE 4. Baseline: multiple erythematous to violaceous subcutaneous nodules and indurated plaques, several with overlying follicular openings and sinus tract formation. Double-headed and open comedones are visible. There is surrounding postinflammatory hyperpigmentation and scarring with fibrotic bands.



FIGURE 5. Week 24 marked reduction in active inflammation. Previously indurated nodules have flattened, with residual postinflammatory hyperpigmentation and fibrotic scarring. No new abscesses or draining sinus tracts are evident. Subtle erythema persists in areas of prior activity, but overall disease burden is significantly diminished.



While significant improvements were observed in AN counts, DLQI, and VAS pain, changes in HADS scores were not statistically significant. This likely reflects the low baseline levels of anxiety and depression within our cohort, leaving little room for measurable improvement. Importantly, the absence of significant change in HADS does not diminish the broader clinical and quality-of-life benefits demonstrated, but instead underscores that patients in this trial were not entering with substantial psychiatric comorbidity. Future studies including patients with higher baseline psychosocial burden may better clarify the potential effects of tirzepatide on mood and mental health outcomes in HS.

Laboratory Assessments

High-sensitivity C-reactive protein (hsCRP) decreased significantly from baseline to week 7, with a mean reduction of ~1.3 mg/L (~29%, *P*=0.0026), consistent with reduced systemic inflammation. The rest of the laboratory monitoring demonstrated modest changes across hematologic and biochemical parameters. Most values remained within normal clinical ranges and did not show statistically significant differences over the study interval.

Safety Analysis

Over the 32 weeks of the study, only one treatment-related adverse event was reported, which was constipation (5%). Nausea, diarrhea, vomiting, and other GI symptoms are recognized and expected adverse reactions of GLP-1 receptor agonists per the tirzepatide package insert and were therefore not categorized as treatment-emergent adverse events (TEAEs) in this study.

Four patients discontinued (two for lack of efficacy, one for protocol deviation, one lost to follow-up). Laboratory assessments demonstrated modest but statistically significant reductions in several hematologic parameters (WBC, platelets, eosinophils) and select serum chemistry measures (BUN, creatinine, bilirubin, electrolytes), while hemoglobin A1c remained stable. Most values remained within normal clinical ranges and did not prompt intervention.

Statistical Analysis

Efficacy analyses were conducted in the intent-to-treat (ITT) population, with sensitivity analyses (non-responder imputation, multiple imputation, per-protocol, and rescue-as-failure scenarios) performed for the primary endpoint. Longitudinal within-subject changes in AN count, DLQI, and VAS pain were assessed using paired t-tests at each visit vs baseline with Bonferroni correction (α=0.00625). Paired pre-/post comparisons were also performed for laboratory parameters, including CBC, serum chemistry, glycemic indices, and hsCRP. Exploratory analyses examined correlations between weight loss and AN reduction using both change-score regression and ANCOVA models. Figures display mean ± 95% confidence intervals, with observed cases specified.

DISCUSSION

In this open-label, single-center study, weekly tirzepatide achieved a HiSCR response in 80% of adults with moderate to severe HS and obesity, accompanied by improvements in pain and quality of life. These findings are striking, given the baseline severity of disease, and reinforce the hypothesis that metabolic interventions may play a disease-modifying role in HS.

GLP-1 is an incretin hormone secreted by intestinal L-cells after meals that enhances insulin release and suppresses inappropriate

glucagon secretion. It also delays gastric emptying, blunts the postprandial glucose spike, slows the absorption of nutrients, and decreases ectopic fat through weight loss. Besides its effect on the gastrointestinal system itself, it also acts on the central nervous system (CNS), specifically on the hypothalamic satiety center, promoting satiety and reducing appetite, leading to sustained weight loss.[5] These medications play an anti-inflammatory role in patients by decreasing macrophage infiltration in adipose tissue, lowering IL-6 and TNF-α, and increasing adiponectin, an anti-inflammatory cytokine.[4]

Despite their recent surge in visibility, GLP-1 RAs have been established therapeutic agents for over a decade (Table 3). Liraglutide, approved in 2010, is a daily injection available as Victoza® for TD2M and as Saxenda® for obesity. Dulaglutide, marketed as Trulicity® is a weekly injection approved for the treatment of T2DM, since 2014. Semaglutide, marketed as Ozempic® for T2DM and Wegovy® for weight loss, is a weekly injection that was approved in 2017, and its oral version Rybelsus® has been approved as a daily pill for T2DM since 2019. Their more recent use for weight loss and glycemic control has shown "incidental" findings of improved psoriasis, HS, and acanthosis nigricans (AN).[5,6,7]

Semaglutide is structurally modified for higher albumin binding, prolonging its half-life, making it more efficacious for weight loss and glycemic control than liraglutide, as well as the benefit of its weekly vs daily dosing. Tirzepatide, however, is a dual glucose-dependent insulinotropic polypeptide (gip) and GLP-1 Ra. GIP enhances insulin secretion, improves insulin sensitivity, enhances adipose tissue energy handling, and acts in synergy with GLP-1. This makes tirzepatide more effective in weight loss and greater reductions in HbA1C and body weight than the other GLP-1 Ras, like semaglutide, as evidenced in the SURPASS head-to-head trials.3 In SURPASS-2, tirzepatide at a 15 mg dose, produced a mean weight loss of around 25 lbs compared with 13 lbs for semaglutide 1 mg, and an HbA1C reduction of –2.3% vs –1.9% respectively. Tirzepatide´s half-life is approximately 5 days, allowing once-weekly subcutaneous administration. A phase 2b trial also showed that tirzepatide patients had a significant reduction in HbA1C.[3]

There are ongoing trials at the moment for HS, focused on biologics and small molecules, aiming to decrease inflammatory cytokines; however, research indicates that, regardless of treatment, lifestyle changes, especially weight loss and tobacco cessation, significantly decrease the severity and prolong flare-free periods.[1] It has been clear for decades that obesity and metabolic disturbances are risk factors for HS, and their severity may be correlated with the extent of the disease.

The robust clinical responses observed with tirzepatide suggest that interrupting systemic inflammatory loops can translate into meaningful dermatologic benefit. GLP-1 receptor agonists exert effects beyond weight loss: preclinical studies demonstrate that they reduce macrophage infiltration into adipose tissue, suppress NF-κB signaling, and lower circulating IL-6 and TNF-α.[4] Tirzepatide, as a dual GLP-1/GIP agonist, may further enhance these effects by promoting insulin sensitivity and restoring metabolic homeostasis.[3,4] Notably, the clinical improvements in HiSCR, DLQI, and pain occurred within 24 weeks, suggesting a relatively rapid effect of metabolic modulation. The persistence of benefit at week 32, after drug discontinuation, raises the intriguing possibility of durable disease modification – potentially by rebalancing the inflammatory adipokines and restoring adipose immune homeostasis.

The significant reduction in hsCRP further supports the systemic anti-inflammatory effect of tirzepatide, complementing the clinical improvements observed in AN count, pain, and quality of life. This biomarker change is biologically consistent with GLP-1/GIP–mediated modulation of adipose inflammation and suggests a broader immunometabolic impact beyond local HS lesion control.

Anecdotal Observations

One participant with type 2 diabetes mellitus remained on metformin throughout the study. Another participant with polycystic ovary syndrome (PCOS) and longstanding amenorrhea experienced resumption of menses at week 16 after a 5-year absence, accompanied by improvement in acanthosis nigricans; notably, this patient also reported being able to return to the gym due to marked improvement in overall well-being. Additionally, one participant with type 2 diabetes was able to continue tirzepatide therapy under the care of her primary physician following study completion.

Strengths and Limitations

This was a designed study to investigate tirzepatide, an incretin with a dual mechanism of action (GLP-1 and GIP receptor agonist) in HS, distinguishing it from prior reports involving other GLP-1 receptor agonists and providing a unique therapeutic profile that may enhance both metabolic and inflammatory outcomes. The study included 20 patients with strong adherence, supported in part by the motivation due to the weight loss observed. Consistent follow-up provided an opportunity to note incidental findings, such as improvement in acanthosis nigricans alongside decreased body weight. This proof-of-concept trial is limited by its open-label, single-arm design, modest sample size, and single-center scope, which restricts the generalizability of the findings. It should be noted that the amount of weight loss was not an independent predictor of improvement. Nonetheless, the magnitude of effect and its alignment with emerging pathophysiology support further investigations including large scale, randomized, controlled trials.

CONCLUSION

In patients with HS who are overweight and obese, drugs that target GLP-1 and GIP may be a viable option. Clearly, phase 3 studies with larger cohorts will be required to determine the value of this new approach.

DISCLOSURES

Dr. Francisco Kerdel has served as a speaker for Eli Lilly, Janssen, AbbVie, Pfizer, Celgene, Novartis, Ortho, UCB, Leo, Menlo, Sanofi, Regeneron, Sun, Brickell, Incyte, Aristea, Acelyrin, and Rapt Therapeutics. He has received research support from Eli Lilly, X-Biotech, Janssen, AbbVie, Pfizer, Celgene, Novartis, Ortho, UCB, Leo, Regeneron, Sun, Brickell, Incyte, Aristea, Acelyrin, and Rapt Therapeutics, and has served on advisory boards for X-Biotech, AbbVie, Celgene, Novartis, Ortho, UCB, Leo, Menlo, Regeneron, Brickell, Incyte, Aristea, Acelyrin, and RaptTherapeutics. Alan Villacampa was previously employed by Eli Lilly as a medical science liaison.

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CASE REPORT

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Resolution of Lichen Simplex Chronicus With Nemolizumab: A Case Report

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ABSTRACT

Introduction: Lichen simplex chronicus is a debilitating condition characterized by lichenified skin secondary to intractable itch. Lichen simplex chronicus is challenging to treat, with current treatment options, such as topical calcineurin inhibitors, gabapentinoids, and dupilumab, commonly being ineffective, leaving patients with worsening symptoms and poor quality of life.

Case Presentation: We report a case of lichen simplex chronicus in the setting of neuropathic pruritus successfully treated with nemolizumab in a 52-year-old woman. The patient did not report any side effects but reported significant improvement in quality of life.

Conclusion: Lichen simplex chronicus has a significant impairment on quality of life, as it has been linked to anxiety, depression, and poor sleep, underscoring the importance of proper disease management. Current treatment regimens for lichen simplex chronicus are often ineffective. Our observation suggests that nemolizumab may be effective in managing lichen simplex chronicus; larger studies are warranted to confirm these findings.

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INTRODUCTION

Lichen simplex chronicus (LSC) is a debilitating chronic itch condition, affecting up to 12% of the population, severely impacting patients' quality of life. It is characterized by lichenified skin secondary to intractable itch. Frequent scratching is an impetus for skin barrier disruption, leading to a pro-inflammatory state, sensory dysfunction, and an activated itch-scratch cycle, further perpetuating the condition. The pathogenesis of LSC is unclear. It is thought to be a non-histaminergic process mediated by pruritogen binding to G-protein coupled receptors or ion channels, particularly transient receptor potential channels, which may be an essential component in interleukin 31 (IL-31)-mediated itch.[1] Lichen simplex chronicus remains challenging to treat, with current options including topical calcineurin inhibitors, topical steroids, gabapentinoids, antidepressants, and dupilumab.[1] Here, we report the resolution of lichen simplex chronicus, previously refractory to a multitude of treatments, with nemolizumab.

Report of a Case

A 52-year-old woman presented with an 8-year history of pruritus of the labia majora, which she described as burning and localized. The patient had a past medical history of hyperlipidemia, polycystic ovarian syndrome, prediabetes, atopic dermatitis, and, notably, an L4-L5 disc bulge secondary to a car accident 9 years prior. The patient had difficulty at work due to the constant itch she was experiencing, as well as her poor sleep. The pruritus was refractory to intralesional triamcinolone injections, a compounded ketamine, amitriptyline, and lidocaine (KAL) formulation, silver sulfadiazine cream, and pramoxine hydrochloride lotion. She did not tolerate gabapentin or pregabalin. Clobetasol and halobetasol did provide symptom relief but were discontinued due to the risk of atrophy from chronic use. The patient's physical exam is shown in Figure 1.

She was diagnosed with LSC in the setting of neuropathic pruritus secondary to bulging L4-5 discs. She was started on nemolizumab, which provided the patient with immediate relief. She received an initial loading dose of 60 mg injected subcutaneously, followed by 30 mg injections every 4 weeks. Just prior to receiving nemolizumab, the patient described the

FIGURE 1. Lichen simplex chronicus in the setting of neuropathic itch of the labia majora.



Lichenified pink to violaceous plaques with excoriations and hyperpigmentation on the bilateral labia majora.

itch as a 10 of 10, and 2 weeks after the injection, the patient described the itch as a 4/10. Two months after receiving her first injection, after receiving 4 total injections, the patient described the itch as a 0 of 10, and she was very happy with the results, improving her sleep and quality of life. The patient did not report any side effects.

DISCUSSION

Nemolizumab is an IL-31 receptor alpha antagonist,[2] currently FDA approved for the treatment of atopic dermatitis and prurigo nodularis.[3] Treatment of prurigo nodularis with nemolizumab reduces itch intensity and sleep disturbance as early as week 4 of treatment,[2] which is similar to our case. The role of IL-31 in LSC has not been fully elucidated; however, it is known that IL-31 receptor A is expressed on epithelial and neuronal cells. T_h2 cells and immature dendritic cells secrete IL-31, in turn activating dorsal root ganglia neurons and keratinocytes. It is also known that IL-31 is implicated in skin barrier maintenance. Ultimately, IL-31 has been shown to play a role in neuroimmune communication, contributing to the itch sensation.[4,5] Common side effects of nemolizumab include headaches, atopic dermatitis, and increased infections; however, our patient did not experience any side effects to date.[2]

Chronic itch is closely linked to anxiety, depression, and significant quality of life impairment, deserving prompt diagnosis and management.[6] Current treatment regimens for LSC are often ineffective and may not lead to proper symptom resolution.[1] Our observation posits that nemolizumab may play a role in managing LSC and suggests that larger studies are needed to confirm our findings.

DISCLOSURES

None of the authors have any relevant conflicts of interest to disclose.

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FILTER NEEDED: EMERGING SCIENCE IN AND APPROACHES TO SUNSCREEN SAFETY

Sunscreen ... our daily epi/dermal defense, our solar safeguard, our broad-spectrum BFF for life. Yet lurking in the shaded areas are unfounded fears: "Sunscreen causes cancer; Sunscreen is an endocrine disruptor (and I don't know what that means but it sounds scary); Sunscreens ate my homework." Enter Jay Nash, toxicology titan and sunscreen sage, to shed some UV clarity. In this episode, JDD Podcast host Dr. Adam Friedman takes a deep dive into a "Hot Off The Presses" Critical Reviews in Toxicology paper that flips the script on outdated rodent bioassays and shines a bright light on the mode of action (MOA) approach. Spoiler: six of our favorite SPF staples, avobenzone, homosalate, octinoxate, octisalate, octocrylene, and ensulizole, shouldn't make you wobbly in the knees after all. Tune in as we unpack why 2-year rat studies may be feverishly clawing up the wrong tree, how MOA helps connect mechanistic dots, and what this means for patients who just want safe sun protection without sizzling in skepticism. From DNA damage to estrogen activity, immune modulation to cytotoxicity, Jay Nash breaks it all down, no shady business here. If you've ever fielded the, "Is sunscreen safe?" question (and btw, yes, it is), this episode will give you the science, the sass, and the sound bites to answer with confidence. Trust your filters. Trust the data. Trust this episode.



GUEST
Dr. Jay Nash

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CASE REPORT

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Pyoderma Gangrenosum Following Total Colectomy for Ulcerative Colitis

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INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, neutrophilic dermatosis characterized by rapidly enlarging, painful ulcers with violaceous and undermined borders. It is commonly associated with systemic disorders, including rheumatoid arthritis, hematologic malignancies, and inflammatory bowel disease (IBD).[1] While PG often correlates with IBD flares, its pathogenesis is not well understood. Colectomy has been used to treat severe PG, suggesting a link between PG and bowel inflammation.[2] However, rare reports of PG developing after colectomy and ileostomy, with ulcers at peristomal sites, indicate that PG can occur independently of active bowel disease.[3] Here, we present a case of PG that occurred one year after total colectomy for ulcerative colitis (UC). The PG was successfully treated with intralesional triamcinolone and systemic adalimumab. This case supports the observation that PG can manifest independently of bowel disease activity.

Case Presentation

A 55-year-old woman presented with painful ulcerations near her ostomy site one year after undergoing a total colectomy for UC. Her history of UC had been associated with severe refractory diarrhea, fecal incontinence, weight loss, and abdominal pain despite treatment with mesalamine and risankizumab. She also had recurrent *Clostridium difficile* infections, sepsis requiring fecal transplantation, and a prior sigmoid colectomy for diverticulitis with abscess formation. Due to worsening UC despite medical therapy, she underwent total colectomy and ileostomy. Approximately nine months postoperatively, the patient reported pain and irritation around the ostomy site. She was diagnosed with a chronic intraabdominal abscess and underwent drainage on the medial aspect of the ileostomy. Four months later, the patient developed multiple large cribriform ulcers with undermined borders and surrounding erythema surrounding a clean ostomy (Figure 1). Due to increasing pain, history of UC, undermined borders, cribriform appearance, and progression of ulcerations, peristomal PG was suspected. The patient was initially treated with intralesional triamcinolone injections (10 mg/mL x 1 mL) across two visits. Due to the progression of lesions, systemic adalimumab was initiated (160 mg loading dose, followed by 80 mg, then 40 mg every two weeks). Over the following month, her ulcers significantly improved, decreasing from three lesions to a single small ulcer (Figure 2).

FIGURE 1. Multiple erythematous-based cribriform ulcers and erythematous patches around the ostomy site on the lower R abdomen.



FIGURE 2. Reduction in ulceration following treatment with adalimumab and intralesional corticosteroids.



DISCUSSION

This case underscores that PG can occur independently of UC disease activity, even after complete removal of the colon. The pathophysiology of PG post-colectomy likely reflects immune dysregulation despite the absence of active bowel disease, including excessive neutrophil recruitment and elevated pro-inflammatory cytokines such as IL-8, IL-1β, TNFα, and IL-36.[1,4] Colectomy may also induce intestinal dysbiosis and disrupt immune tolerance by eliminating gut-associated lymphoid tissue, which promotes the production of anti-inflammatory

cytokines and regulatory T-cells.[5] This disruption can alter the gut-skin axis and promote immune-related skin diseases such as PG.[5] Pathergy, an exaggerated inflammatory response to minor trauma, is implicated in up to 50% of PG cases and likely also contributes to the development of PG post-colectomy at ostomy sites.[1] Historically, systemic corticosteroids were the primary therapy for PG, but their prolonged use is associated with significant adverse effects. Biologic agents such as TNF-α inhibitors have demonstrated efficacy in PG and are increasingly used. This case provides further evidence that PG can develop after colectomy and in the absence of intestinal inflammation. PG should be in the differential diagnosis for IBD patients who develop ulcerations near peristomal sites, even if they occur after colectomy. Further studies are needed to better understand the relationship between bowel activity and PG pathogenesis.

DISCLOSURES

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Maximizing a Focused Vitiligo Patient Visit: A Practical Approach

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INTRODUCTION

The reality of dermatology practice is that doctor-patient encounters are often limited to minutes, making it critical to optimize each visit, particularly for conditions like non-segmental vitiligo (NSV). Patients frequently present with concerns about disease progression, treatment options, and psychosocial implications. With a structured and efficient approach, dermatologists can address key concerns and provide meaningful care while remaining efficient.

DISCUSSION

Skin Exam and Subjective Assessment

Begin with a thorough history and a full skin examination to assess phototype, disease duration, and extent, as these factors inform therapeutic decisions.[1] NSV is typically diagnosed clinically, with Wood's lamp examination.[2] While Wood's lamp enhances visualization of depigmented areas lacking melanocytes, its utility varies by skin tone. In lighter skin types, the contrast under natural light is subtle, making Wood's lamp particularly valuable. Conversely, in darker skin types (Fitzpatrick IV–VI), the contrast is naturally more pronounced, diminishing the necessity of this tool.[3] In some circumstances, dermatoscopy may be a valuable tool, especially when looking for lesional and/or peri-lesional inflammation or leukotrichia. Gauging lesion severity, stability, and recent progression further refines management. For the estimation of the body surface area (BSA) involved, the palm print method can be utilized, where the patient's palm, with fingers adducted, is considered approximately equivalent to 1% of their total body surface area.[4] Although this method is quick, requires no specialized tools, and is reasonably accurate in clinical settings, it may overestimate BSA by 10–20% since the hand with fingers represents only about 0.8% of BSA in men and 0.7% in women.[4] The 5-point Physician Global Assessment (PGA) scale can be used as a standardized tool with high interrater validity for stratifying disease severity in NSV.[5] An image of a target area or lesion included in the medical record and also on the patient's own phone allows tracking of progression or response to therapy. In addition, for NSV in lighter-skinned individuals, digital images guide topical applications.[2]

Laboratory Assessment

Given NSV's association with autoimmune disorders, relevant laboratory tests include thyroid-stimulating hormone (TSH), thyroid peroxidase (TPO) antibodies, Anti-Nuclear Antibody (ANA), and vitamin D levels.[6] Vitamin D plays a pivotal role in skin pigmentation by enhancing tyrosinase activity and melanogenesis while exerting immunoregulatory effects. Deficiency has been linked to several autoimmune diseases, including systemic lupus erythematosus, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and alopecia areata. However, studies evaluating serum vitamin D levels in vitiligo patients have yielded mixed results, necessitating further research to elucidate its role in disease pathogenesis and treatment response.[7]

Streamlined Treatment Discussion

Therapeutic strategies for NSV may be efficiently categorized into topical and systemic approaches. First-line topical treatments include corticosteroids, calcineurin inhibitors, and vitamin D analogs, particularly for localized or stable disease. Ruxolitinib 1.5% cream, the first FDA-approved topical Janus kinase (JAK)

TABLE 1.

Summary. Key aspects of a structured 10-minute dermatology office visit for NSV, including diagnosis, assessment, treatment, photoprotection, psychosocial support, and follow-up planning.

Key Aspects of Visit	
Diagnosis	Clinical diagnosis; Wood's lamp aids visualization, especially in lighter skin tones (Fitzpatrick I-III).
Severity Assessment	Perform a full skin exam. Evaluate lesion extent by evaluating BSA, PGA. Faster response in facial/body lesions with rapid progression.
Laboratory Work-up	Check TSH, TPO antibodies, ANA and vitamin D levels due to autoimmune link.
Treatment Discussion	First-line topical: Ruxolitinib for repigmentation, especially facial vitiligo. Other options: corticosteroids, calcineurin inhibitors (tacrolimus, pimecrolimus), vitamin D analogs. Systemic: Oral corticosteroids, JAK inhibitors for refractory cases. Phototherapy: NB-UVB, excimer laser for extensive disease.
Photoprotection Counseling	Use sunblock, broad-brimmed hats to minimize contrast.
Psychosocial Support	Address self-esteem concerns; provide resources and referrals.
Follow-Up Plan	Review treatment response and importance of patience with slow re-pigmenations, adjust therapy, provide ongoing support, endorse shared decision-making and taking at-home photographs.

inhibitor for NSV in patients 12 and older, has shown significant repigmentation efficacy with limited side effects, particularly for facial lesions, making it a great first-line topical treatment option as well.[8,9] Systemic therapies, such as oral corticosteroids, immunosuppressants, and oral JAK inhibitors, are reserved for rapidly progressing, widespread, or treatment-refractory cases. Phototherapy, specifically narrowband UVB and excimer laser, serves as an adjunct, particularly in extensive cases where uniform repigmentation is the goal.[10] It is important to note that, to date, these systemic therapies remain off-label. Emphasizing the importance of strict sun protection with sunblock and broad-brimmed hats to prevent burning of involved skin and tanning of normal skin, reducing contrast between affected and unaffected skin.[11] Assessing a patient's distress related to vitiligo is essential. A simple question such as, *"How often does your vitiligo bother you?"* can provide valuable insight into the disease's impact on a patient's well-being. Any associated mental health concerns should be carefully documented and referred appropriately.[12]

Reinforce Key Takeaways and Plan Follow-Up

Before concluding the visit, always good to succinctly summarize the treatment plan and provide educational resources. A nurse or medical assistant can help provide information on support groups or mental health referrals when needed.[13] Encourage patients to take at-home photographs to track disease progression and optimize topical treatment application. Clarify follow-up timelines to monitor disease progression and treatment efficacy. Shared decision-making (SDM) plays a crucial role in enhancing treatment adherence and achieving repigmentation by fostering a collaborative approach between clinicians and patients.[14] In more academic settings, a multidisciplinary approach integrating medical, psychological, and educational interventions is essential in reducing the burden of vitiligo.[13]

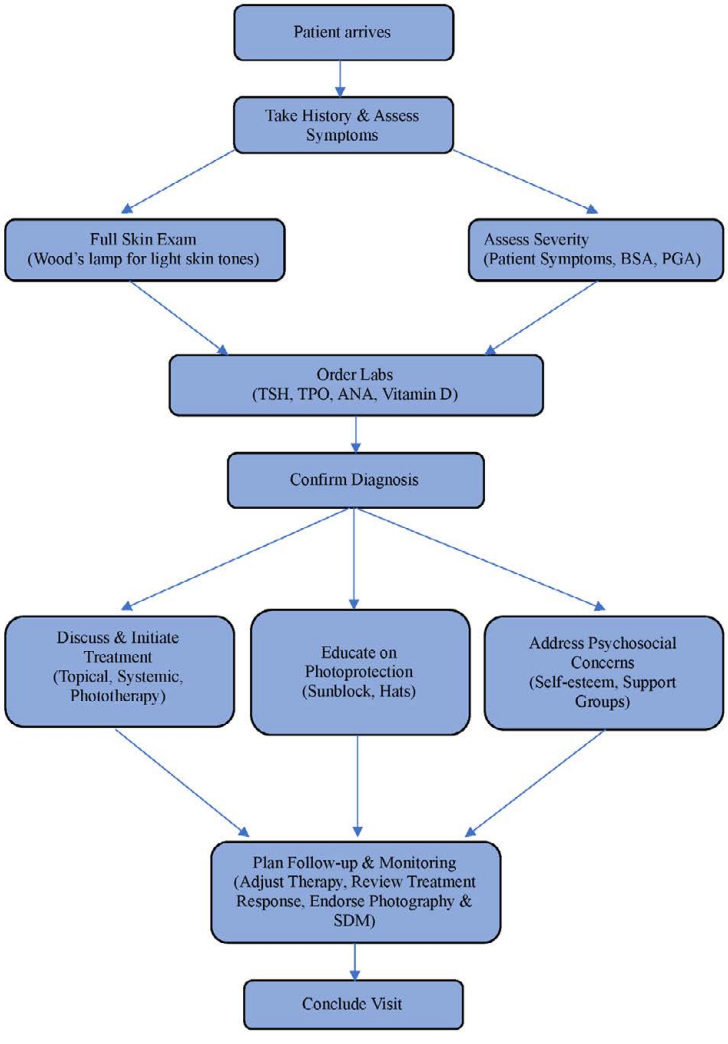
CONCLUSION

While managing NSV through a structured, focused visit, the ensuing approach allows for efficient yet comprehensive care. Above all, patients looking for hope will leave with a plan. Reassurance and reminders to persist with therapy, given NSV's slow response to treatment, are crucial (see Table 1, Figures 1 and 2).

FIGURE 1. Example of Wood's lamp images taken on the patient's phone in the clinic, allowing for at-home monitoring of disease progression and precise topical medication application. (Left) Hypopigmented macules and patches on dorsal hands. (Right) Hypopigmented patch surrounding the peri-oral region and the chin.



FIGURE 2. Optimized flowchart: 10-minute non-segmental vitiligo patient visit.



DISCLOSURES

The authors have no conflicts of interest to disclose.

Data availability statement: The data that supports the findings of this review are available from publicly accessible sources and repositories. All references and citations to the primary studies, datasets, and literature sources utilized in this review are listed in the reference section.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

National Institutes of Health Funding for Vitiligo Research: Trends from 1985 to 2024

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ABSTRACT

Background: The National Institutes of Health (NIH) funds a multitude of dermatology research. This study examines NIH funding for vitiligo studies and highlights key trends.

Methods: The NIH Research Portfolio Online Reporting Tool database was used to identify vitiligo research projects funded between 1985 and 2024, with results limited to project titles containing "vitiligo."

Results/Discussion: The NIH awarded 166 grants for vitiligo research between 1985 and 2024. This study analyzed 144 of these awards, totaling $22,343,119. The greatest increase occurred between 1998 and 1999, with the average funding per grant rising by $124,316, leading to a total funding increase from $269,102 to $1,149,554. The most common funding mechanism was Non-Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR). The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) was the leading administering institute. Medical schools were the most awarded organization type. The most common grant types were R01 (n=59, 41%) and M01 (n=21, 15%). Among the 144 funded projects, 48 were unique, with most focusing on pathophysiology (n=36) and treatment (n=8).

Limitations: Study limitations include incomplete data on NIH research funding, with 22 awards missing total cost information and 25 awards calculated using subproject sums.

Conclusion: From 1985 to 2024, NIH funding for vitiligo research fluctuated with an upward trend in recent years. The most common funding mechanism was Non-SBIR/STTR. Among organization types, medical schools received the most awards. Most vitiligo research projects have been completed and have focused on understanding the pathophysiology and treatment of vitiligo.

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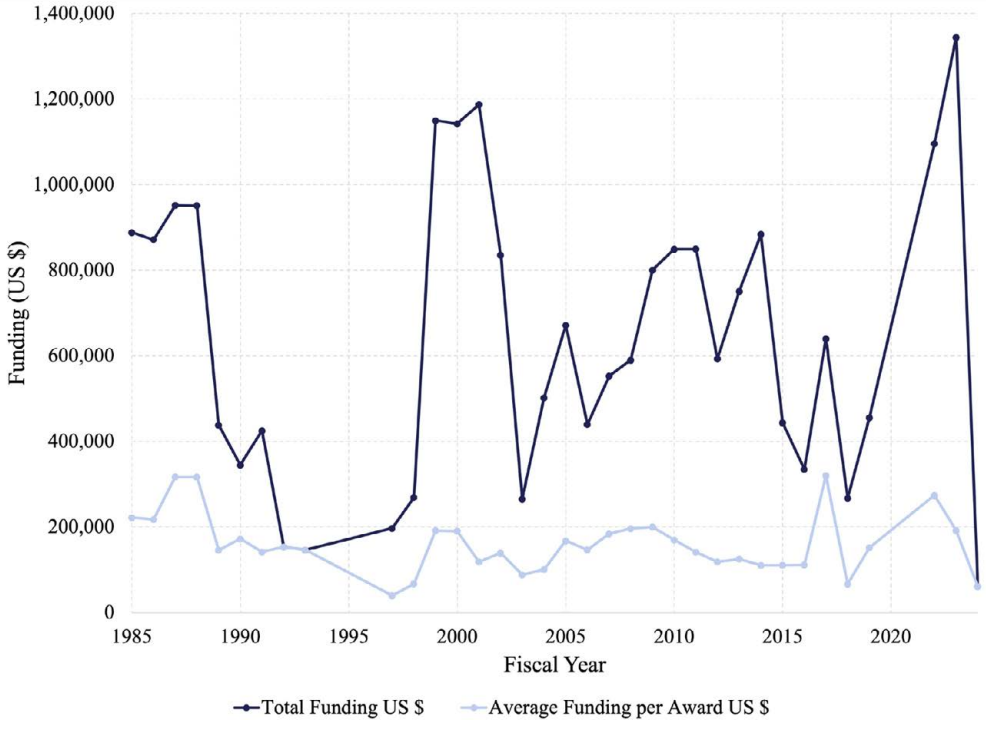
INTRODUCTION

Vitiligo research has seen a gradual increase in publications and citations from 1980 to 2000, with a significant rise after 2005.[1] Vitiligo research peaked in 2016 with 528 published articles and in 2017 with 10,390 citations. The most cited works are original articles from the United States, focusing on melanoma, autoimmunity, and immunotherapy.[1] To guide future research and funding opportunities, this study evaluated trends in National Institutes of Health (NIH) funding of vitiligo research.

The NIH Research Portfolio Online Reporting Tool database was used in July 2024, to identify projects funded between fiscal years 1985 and 2024, limiting the search to project titles containing "vitiligo".[2] Information was collected on the project title, project number, administering institutes or centers (ICs), department, organization name, organization city, organization state, organization type, organization country, grant type, project start and end dates, funding mechanism, fiscal year, total cost, total cost (sub projects), funding IC(s), direct cost IC, indirect cost IC, and total cost IC. NIH funding amounts have been adjusted to 1985 US dollars to account for inflation using Consumer Price Index data from the Bureau of Labor Statistics.[3]

The NIH awarded 166 vitiligo research awards between 1985 and 2024. This study analyzed 144 of these awards, totaling $22,343,119. Vitiligo research funding has fluctuated over the years, but in recent years shows an upward trend. The greatest increase occurred between 1998 and 1999, with the average funding per grant increasing by $124,316, leading to a total funding increase from $269,102 to $1,149,554 (Figure 1).[2]

FIGURE 1. Trends of total funding and average funding per award for vitiligo by fiscal year.*



*Includes data on 144 NIH awards from 1985 to 2024 with available funding information. A total of 22 awards were excluded due to missing data. Data for the years 1994-1996 and 2020-2021 are not included due to incomplete or missing entries in the NIH database.

Among the 144 NIH research awards for vitiligo projects, 125 have been completed, 10 are ongoing, and 9 are missing both start and end dates. These projects were supported by 21 different grant types, with R01 (n=59, 41%) and M01 (n=21, 15%) being the most common.

Several NIH-funded vitiligo projects received multiple awards. Among the 144 funded projects, 48 were unique, with 38 receiving awards more than once. Most of these unique projects focused on the pathophysiology of vitiligo (n=36), treatment of vitiligo (n=8), and one project focused on both pathophysiology and treatment of vitiligo. The project "Mapping of Vitiligo Susceptibility Genes", conducted at the University of Colorado Denver, received the most awards (n=13) and aimed to identify genetic risk factors for vitiligo using genome-wide analyses. This project advanced the understanding of vitiligo genetics, with one of its key findings being the identification of AIS1 on chromosome 1p31 as a major susceptibility locus for vitiligo.[4]

Non-Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) was the most common funding mechanism with 69 awards and total funding of $11,947,869, with an average of $173,158 per award (Table 1).[2] The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) was the most awarded administering ICs with 107 awards, with a total funding of $18,232,371, followed by the National Center for Research Resources (NCRR) with 21 awards, with a total funding of $1,527,286. Together, NIAMS and NCRR accounted for 89% of all awards.[2]

Medical schools were the most awarded organization type with 106 awards and a total funding of $18,357,554, followed by domestic higher education with 24 awards totaling $2,303,214 of funding. These two organization types accounted for 90% of all awards.[2] The University of Colorado Denver was the most awarded organization with 37 awards, with total funding of $6,928,873, followed by the University of Massachusetts Medical School, Worcester, with 15 awards, with a total funding of $2,812,380.[2]

Study limitations include incomplete data on NIH research funding, with 22 awards missing total cost information and 25 awards calculated using subproject sums. Additionally, nine vitiligo research projects are missing both start and end dates.

NIH funding trends illustrate a growing scientific interest in vitiligo. At the time of this study, the NIH ClinicalTrials.gov database shows 100 completed clinical trials and 58 active studies.[5] The use of Janus kinase (JAK) inhibitors represents a significant milestone for vitiligo treatment, with ruxolitinib

TABLE 1.

NIH Funding Distribution for Vitiligo Research by Funding Mechanism, Administering IC, Organization Type, and Name*			
Funding Mechanism	**Total Funding US $**	**Average Funding per Award US $**	**Total Number of Awards**
Non-SBIR/STTR	11,947,869	173,158	69
Unknown	5,463,505	182,117	30
Research Centers	3,220,667	153,365	21
SBIR/STTR	856,384	214,096	4
Other Research-Related	666,500	41,656	16
R and D Contracts	121,901	121,901	1
Training, Individual	66,293	22,098	3
Administering IC			
NIAMS	18,223,271	170,311	107
NCRR	1,527,286	72,728	21
NIAID	1,279,737	182,820	7
NIADDK	879,631	293,210	3
NCI	390,586	97,646	4
NIEHS	42,610	21,305	2
Organization Type			
Medical Schools	18,357,554	173,184	106
Domestic Higher Education	2,303,214	95,967	24
Domestic For-Profits	856,384	214,096	4
Research Institutes	278,874	69,718	4
Earth Sciences/Resources	277,981	92,660	3
Schools Of Arts and Sciences	147,212	73,606	2
Other Domestic Non-Profits	121,901	121,901	1
Top 10 Organization Name			
University Of Colorado Denver	6,928,873	187,267	37
Yale University	3,398,430	308,948	11
University of Massachusetts Medical School, Worcester	2,812,380	187,492	15
Loyola University Chicago	2,071,843	147,989	14
New York University	1,329,780	189,969	7
University of Virginia	1,303,420	162,927	8
University of Cincinnati	791,326	87,925	9
Radikal Therapeutics, Inc.	751,920	250,640	3
UT Southwestern Medical Center	619,593	123,919	5
Howard University	578,927	144,732	4

*Includes data on 144 NIH awards from 1985 to 2024 with available funding information. A total of 22 awards were excluded due to missing data. Funding mechanisms included 30 awards from unknown organizations not listed in the database.

Abbreviations: NIH: National Institutes of Health; ICs: Institutes or centers; non-SBIR/STTR: non-Small Business Innovation Research/Small Business Technology Transfer; R and D Contracts: Research and Development Contracts; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NCRR: National Center for Research Resources; NIAID: National Institute of Allergy and Infectious Diseases; NIADDK: National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; NCI: National Cancer Institute; NIEHS: National Institute of Environmental Health Sciences

being the first FDA-approved treatment for repigmentation.[6] Multiple oral JAK inhibitors are now undergoing phase 3 studies in addition to the study of other systemic and procedural therapies showing additional promise for new future treatment options for vitiligo.[7]

DISCLOSURES

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

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

FDA Boxed Warnings: Should Package Inserts Include Levels of Evidence?

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ABSTRACT

Many medications commonly used in dermatology come with package inserts that contain boxed warnings that are frequently not evidence-based. Boxed warnings are the most serious warnings that the US Food and Drug Administration (FDA) can issue for medications through various methods, like class labeling, despite the absence of factual, high-quality evidence. Currently, there are several medications labeled with these boxed warnings for which there is no evidence, and in many cases, there actually may exist refuting evidence. However, these warnings persist in the package inserts. This has led to much hesitancy in their use, contributing to the undertreatment, or even lack of treatment, of conditions for which these medications are efficacious. Furthermore, the negative physical and mental effects of the lack of effective treatment for patients with skin disorders are well-documented. The authors call for transparency regarding the evidence, or lack thereof, behind these boxed warnings on the part of the FDA.

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INTRODUCTION

New medications are continuously being developed for the treatment of various disorders. The US Food and Drug Administration (FDA) is the regulatory body responsible for protecting public and individual health, overseeing drug approvals, and ensuring food safety and vaccine oversight. Thus, the FDA certifies the safety, efficacy, and proper management of medications that are used in clinical care throughout the United States.

The FDA also oversees safety interventions, which include approving and revising package inserts (PIs). The PI includes information on indications, dosing, adverse effects, interactions, and safety warnings. This ensures that patients are protected by warning them of the potential adverse effects of medications when they are approved for use. However, FDA warnings can occasionally negatively impact patient care by making providers, patients, or both, hesitant to prescribe and use efficacious medications that may ultimately lead to undertreatment or a complete avoidance of a particular therapy. Frequently, FDA warnings, including the most serious boxed warnings, are not supported by clinical evidence. Making matters worse, the FDA is currently not obligated to reveal the fact that such warnings are not evidence-based. This controversial practice of issuing the most serious boxed warnings without clearly referencing the clinical or scientific evidence supporting them is relatively unique to the US FDA; the European Union (EU) and Japan do not follow this practice of issuing non-evidence-based warnings.

The following brief communication reveals this current reality in detail and communicates the authors' recommendations encouraging the FDA to be truthful and transparent about warnings that are not supported by clinical evidence.

Tacrolimus and Pimecrolimus

Boxed warnings are the most serious warnings the FDA can issue regarding a medication. However, within dermatology, there have been examples of the FDA issuing warnings with questionable scientific support, ultimately discouraging the use of many safe medications. One example is topical tacrolimus and pimecrolimus, which are FDA approved for the treatment of atopic dermatitis. Notoriously, the PIs of these medications contain boxed warnings about malignancy despite there being no human studies that support this risk being elevated with topical use. This has likely led to an increase in provider and patient hesitation and a resulting decrease in the use of these medications. Overall, this impacts clinical practices and likely contributes to the undertreatment of patients, especially amongst parents who are deciding on topical therapies for their children. After over twenty years of these medications being on the market, there remains no evidence that either contributes to an increased risk of cancer.[2] Nevertheless, the FDA has yet to retract the boxed warning about malignancy that continues to persist in PIs for these medications.

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Brodalumab

Brodalumab is another example of a medication with an FDA boxed warning that lacks scientific support. Brodalumab is an effective biologic approved approximately seven years ago for the treatment of moderate to severe plaque psoriasis. However, in a clinical trial of 4,464 patients worldwide, there were three cases of suicide, leading to a boxed warning about the increased risk of depression and suicide.[3] This also led to the burdensome requirement that physicians enroll in the FDA's Risk Evaluation and Mitigation Strategy (REMS) program when prescribing the medication. A closer evaluation of these cases of suicide in patients taking brodalumab reveals significant personal risk factors in all three cases that were present before the initiation of brodalumab. Additionally, brodalumab has a lower rate of reported suicide when compared to adalimumab, which does not have a boxed warning.[3] After approximately half a decade of worldwide use, there has only been one suicide documented in a terminal cancer patient in Japan, who may have only received one dose of brodalumab. This medication, arguably the most efficacious biologic at the time of its launch, has been severely under-utilized, likely due to this boxed warning and consequential REMS program.[4]

JAK Inhibitors

Another way the FDA justifies including boxed warnings without evidence is known as "class labeling." Through class labels, the FDA has the power to place warnings on medications that fall into the same class, even when they have a clean side effect profile with no worldwide clinical trial evidence that such risk is increased. A prime example is JAK inhibitors for atopic dermatitis, which have many boxed warnings despite clinical trials that have produced refuting evidence. Many patients and providers are reluctant to use JAK inhibitors because their PI consists of multiple boxed warnings, which include serious infections, all-cause mortality, malignancy, major adverse cardiac events, and thrombosis. Many dermatology providers are likely unaware that these boxed warnings are based on the ORAL surveillance study, which was a rheumatoid arthritis study (which contained no dermatology patients), in which tofacitinib was compared to adalimumab. Results of this study found an increased risk of serious infection, malignancy, and MACE when comparing tofacitinib to adalimumab, but this only reached statistical significance when patients who were both ≥ 65 years of age and smoked were included. After exclusion of these patients from analysis, these serious risks were quite similar between tofacitinib and adalimumab.[1,5] However, in several research studies, those treated with JAK inhibitors compared to placebo were only found to be at higher risk for herpes simplex infections.[6] In fact, a closer look at the data reveals that at week 16 of the clinical trial, those on the highest dose of JAK inhibitors for atopic dermatitis had a serious infection rate lower than those treated with placebo.[7,8] Besides herpes reactivation, none of the boxed warnings are supported by worldwide phase III clinical trial data for JAK inhibitors approved to treat AD.[1] Additionally, even ruxolitinib the FDA-approved topical JAK inhibitor for AD and vitiligo, has these boxed warnings due to class labeling, despite acting locally and causing significantly less systemic absorption. Further, there are inconsistencies within class labeling that are not evidence-based; while topical ruxolitinib has a boxed warning, oral ruxolitinib does not.

Levels of Evidence

Dermatologists today may be hesitant to use these effective and potentially life-changing medications due to their boxed warnings. While it is of the utmost importance to prioritize patient safety and acknowledge all potential risks, ideally, the information included should be evidence-based. And if the warnings are not based on evidence, clinicians should be made aware of that fact. A useful way of considering what "evidence-based" actually means is to think about the levels of evidence. The quality of evidence depends on 1) whether a study was conducted and 2) how it was conducted. For example, prototypical level 1 evidence represents a higher quality of evidence drawn from a large-scale, randomized, placebo-controlled trial in humans.[9] In contrast, level 5 evidence, representing a lower quality of evidence, is synonymous with expert opinion only. The quality of our research influences the quality of our evidence, and it is the high-quality evidence that should be used to drive decision-making in medicine, especially when it comes to advising on serious adverse events of medications.

Recommendations

The authors are not recommending limiting the FDA's jurisdiction to issue warnings as it sees appropriate. However, for the sake of transparency, the authors recommend that the FDA clearly indicate whether boxed warnings are evidence-based, extrapolated from another medication through class labeling, or are purely speculative by explicitly stating the level of evidence that the warning is based upon. While the awareness of clinically significant risks is very important, serious warnings without evidence prevent the safe and efficacious treatment of patients with medications they desperately need if the FDA makes the clinician or the patient too hesitant to use them.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The Overlooked Burden: Psychodermatologic Needs of Hispanic and Latinx Communities in the United States

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INTRODUCTION

Hispanic and Latinx communities in the United States face disproportionate psychological burdens from dermatologic disease. Notably, the prevalence of major depression among US Hispanic individuals ranges from 8 to 15%, with an increasing suicide rate over the past decade.[1] Numerous studies investigating the prevalence of psychiatric illnesses resulting from skin disease indicate that Hispanic patients may be more likely to experience psychiatric comorbidities compared to non-Hispanic Whites (NWH), particularly in the context of chronic or stigmatizing skin disorders.[2,3]

For example, according to a retrospective cohort of 502 US adults with chronic urticaria, psychiatric diagnoses were significantly more prevalent among Hispanic patients (15.2%) compared to NWH (8.3%) (P<.002).[2] Similarly, a cross-sectional analysis of 1,087 vitiligo patients found that Black and Hispanic patients had significantly higher odds of comorbid depression.[3] Additionally, social determinants of health, such as housing instability and lower socioeconomic status, both more frequently experienced by Hispanic populations, were shown as modulating factors in psychiatric diagnoses associated with dermatologic care utilization.[4,5]

Despite their heightened psychosocial needs, Hispanic and Latinx patients often face systemic barriers to both dermatologic and psychiatric care. According to a report from the Center for American Progress, only one in three Hispanic Americans with mental health concerns receives treatment, compared to one in two NWH.[6] Contributing factors may include language barriers, insurance constraints, and a general lack of referral infrastructure in psychodermatologic care. Moreover, cultural and linguistic challenges—such as limitations in the Spanish translation of self-reported emotional health assessments—can result in underreporting of psychological distress.[7] Miscommunication between patients and providers can also contribute to mistrust in the medical system among Hispanic and Latinx individuals. These disparities may be exacerbated by limited workforce diversity, with only 4.2% of dermatologists identifying as Hispanic.[8] Likewise, access to language-specific education remains limited among dermatology clinics, with shortages of Spanish-language materials and in-person translators.[9]

Without timely intervention, these patients may experience chronic disease exacerbation and diminished quality of life. Additionally, untreated psychiatric comorbidities can impair treatment adherence and perpetuate increased healthcare utilization. These challenges underscore the urgent need for culturally competent psychodermatological care. Implementing tailored screening tools in dermatology practices, increasing funding for underserved hospital programs, and enhancing provider education to improve cross-cultural understanding may facilitate earlier identification and intervention of mental health disorders in at-risk populations. Notably, integrated psychocutaneous care has been shown to improve patient quality of life while simultaneously decreasing healthcare utilization and costs.[10] Therefore, a multidisciplinary approach may be needed to effectively address psychodermatological conditions. Future research should aim to quantify the psychological burden of skin disease in larger Hispanic and Latinx cohorts and to develop community-based models of integrated dermatologic and psychiatric care.

DISCLOSURES

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Perspectives and Practice Patterns of Dermatologists Using Laser Hair Removal for Hidradenitis Suppurativa

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INTRODUCTION

Hidradenitis suppurativa (HS) is an inflammatory condition characterized by recurrent abscesses and sinus tract formations in intertriginous areas of the body, which can be difficult to manage.[1,2] Laser hair removal (LHR) has been shown to be an effective and safe treatment for HS.[2] However, there is a paucity of data regarding dermatologists' practice patterns when using LHR for HS and their perspectives on its advantages and barriers.

MATERIALS AND METHODS

This survey-based study, approved by the Association of Academic Cosmetic Dermatology (AACD) Board, included 13 questions targeting attending physicians in both academic and private practice settings who treat HS. It captured information on LHR practices, patient characteristics, barriers to care, treatment outcomes, Hurley staging, and cost-related challenges. Responses were collected anonymously via Qualtrics and analyzed using descriptive and thematic analysis.

The survey was distributed twice to AACD members and promoted at professional events (American Society for Dermatologic Surgery [ASDS] meeting and the 9th Annual Symposium of HS Advances). Additional outreach included pediatric dermatologists and residency program coordinators nationwide.

RESULTS

Survey results (n = 50) are outlined in Table 1. Answers to multiple-choice questions and responses to open-ended questions were quantitatively and qualitatively analyzed, respectively.

DISCUSSION

This survey of board-certified dermatologists provides valuable insights into the current practices and perceptions regarding laser hair removal (LHR) for HS treatment. The majority of respondents (88%) perform LHR, reflecting its widespread adoption in dermatology. However, the frequency of LHR use for HS varied considerably among practitioners, with 51% treating 1-5 patients per month and only 20% treating more than 10 patients monthly. This variability may reflect differences in patient populations or hesitancy to recommend LHR more broadly.

Notably, 86% of respondents would recommend LHR for over half or all of their HS patients if insurance coverage were available. Indeed, cost appears to be a significant barrier to LHR utilization, as insurance coverage and cost were frequently cited in the open-response section as challenges in determining whether or not LHR was an appropriate treatment option for HS. Lack of insurance coverage for LHR in HS management has previously been identified as a major obstacle to its widespread implementation.[1]

67% of dermatologists reported usually observing improvement in HS severity following LHR treatment. Furthermore, 84% of respondents feel confident or very confident in LHR's efficacy for HS management. These findings are consistent with several studies demonstrating the benefits of LHR in reducing HS severity and improving quality of life.[3] Patient preferences emerged as the most influential factor (81%) in deciding to recommend or administer LHR. This patient-centered approach aligns with current recommendations for shared decision-making in HS management.[4,5]

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TABLE 1.

Survey Responses	
Question (n = total responses)	**Responses (n, %)**
Please describe the practice setting(s) in which you routinely practice (choose all that apply). (n = 50)	Academic Teaching Hospital (46, 92%)
	Private Practice (3, 6%)
	Group Practice Setting (5, 10%)
	VA Clinic (4, 8%)
	Federally Qualified Health Center (FQHC) (2, 4%)
	Other (1, 2%)
Do you perform laser hair removal (LHR)? (n = 50)	Yes (44, 88%)
	No (6, 12%)
Over the past year, how frequently did you encounter patients with hidradenitis suppurativa (HS)? (n = 44)	None (3, 7%)
	Less than 5 per month (12, 27%)
	5-10 per month (7, 16%)
	11-15 per month (5, 11%)
	16+ per month (16, 36%)
	Unsure (1, 2%)
Over the past year, how many unique patients with HS did you treat with LHR? (n = 41)	None (5, 12%)
	1-5 per month (21, 51%)
	6-10 per month (7, 17%)
	11-15 per month (4, 10%)
	More than 15 per month (4, 10%)
When performing LHR in patients with HS, what laser/energy device modalities were used? (choose all that apply) (n = 36)	Long-pulsed Nd Yag (LPNdYag) (36, 100%)
	Long-Pulsed Alexandrite (LPAlex) (13, 36%)
	Diode (6, 17%)
If LHR were covered by insurance for the treatment of HS, for what proportion of your HS patients would you recommend LHR? (n = 36)	All of my patients who have hidradenitis suppurativa (13, 36%)
	Over half of my patients who have hidradenitis suppurativa (18, 50%)
	Less than half of my patients who have hidradenitis suppurativa (5, 14%)
For patients with HS for whom you recommend LHR, approximately what percentage were also on systemic medication(s) for HS? (n = 36)	100% (8, 22%)
	More than 50% (20, 56%)
	Less than 50% (7, 19%)
	Unsure (1, 3%)
Which specific body areas do you commonly treat with LHR for HS patients? (choose all that apply) (n = 36)	Axillary (armpits) (35, 97%)
	Groin (35, 97%)
	Buttocks (21, 58%)
	Thighs (22, 61%)
	Inframammary (9, 25%)
	Infra-abdominal pannus (11, 31%)
	Other (2, 6%)
For each patient undergoing LHR for HS, what is the typical treatment area per visit? (choose all that apply) (n = 36)	0-50 cm (9, 25%)
	51-100 cm (14, 39%)
	101-150 cm (5, 14%)
	> 151 cm (11, 31%)
	Unsure (5, 14%)
On average, when you recommend LHR for HS, how many treatment sessions do you advise? (n = 36)	2-5 (7, 19%)
	6-10 (29, 81%)

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TABLE 1. (CONTINUED)

Survey Responses	
Question (n = total responses)	**Responses (n, %)**
At what Hurley stage(s) do you treat HS patients with LHR? (choose all that apply) (n = 36)	Stage 1 (25, 69%)
	Stage 2 (23, 64%)
	Stage 3 (14, 39%)
	Combination of stages (20, 56%)
	Unsure (2, 6%)
In general, do you find that Hurley stage improves after treatment with LHR? (choose all that apply) (n = 36)	Yes, there is usually improvement (24, 67%)
	No significant change (7, 19%)
	Varied among patients (4, 11%)
	Unsure (4, 11%)
How confident do you feel in the efficacy of LHR as a treatment option for managing HS? (n = 36)	Very confident (20, 56%)
	Confident (10, 28%)
	Neutral (5, 14%)
	Unsure (1, 3%)
What factors influence your decision to recommend or administer LHR as part of the treatment plan for patients with HS? (choose all that apply) (n = 36)	Clinical efficacy (27, 75%)
	Patient preferences (29, 81%)
	Cost-effectiveness (25, 69%)
	Safety considerations (17, 47%)
	Other (5, 14%)
Are there specific patient populations or HS subtypes for which you find LHR to be particularly effective or ineffective? (n = 15)	More effective in early or limited disease (13, 87%)
	Men are more likely to refuse LHR (2, 13%)
What challenges, if any, have you faced in incorporating LHR into the overall management of HS? (n = 20)	Insurance coverage/cost (12, 60%)
	Reimbursement (3, 15%)
	Capacity (3, 15%)
	Gender bias (2, 10%)

Limitations include a relatively small sample size and a large proportion of respondents from academic teaching hospitals, which may not be representative of all dermatology practices. Additionally, self-reported data can be subject to recall bias.

In conclusion, this survey demonstrates that board-certified dermatologists generally view LHR as an effective treatment option for HS; Future research should focus on larger, more diverse samples of dermatologists. Additionally, efforts to address insurance coverage barriers for LHR in HS treatment could significantly enhance its accessibility and utilization.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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FEATURED CONTENT
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NEWS, VIEWS, AND REVIEWS

Scar Wars: A Review of Topical Scar Therapies

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BACKGROUND

Scarring is a natural part of the wound healing process, but it may result in disfigurement, functional limitations, psychosocial distress, discomfort, pruritus, and pain, highlighting the need for preventative and therapeutic strategies.[1-3] Given the range of available topical scar treatments, many of which are accessible over-the-counter (OTC), clinicians often encounter patients seeking guidance on their use. This review evaluates the efficacy of common topical therapies, including silicone products, retinoids, pressure therapy, corticosteroids, and cannabinoids, to inform clinical decision-making and support patient counseling.

Pathophysiology of Scar Formation

Scar formation is believed to result from the replacement of normal dermal architecture with fibroblast-driven collagen bundles, producing dense, disorganized tissue.[4] It's hypothesized that scar dehydration, resulting from impaired stratum corneum barrier function and transepidermal water loss (TEWL), may stimulate fibroblast activity and promote hypertrophy.[5]

Silicone

Silicone-based products are currently available in various formulations, including gels, sheets, and liquids, and are considered the gold standard treatment for scar management.[6,7] Silicone enhances stratum corneum hydration, thereby promoting keratinocyte migration and re-epithelialization.[6] It has also been hypothesized to reduce capillary exudation, fibroblast proliferation, and collagen deposition.[6] In a meta-analysis, Wang et al reported that silicone gel demonstrated greater efficacy in post-operative scar prevention compared with placebo or no treatment at six months.[7] Data indicates that silicone gel sheets should be applied for up to 12 hours a day over a duration of 12 to 24 months.[5] In contrast, De Decker et al found that silicone gel was less effective than occlusive moisturizers in reducing TEWL, suggesting that previously observed benefits may derive primarily from their hydrating and occlusive properties rather than from silicone itself.[5] Silicone products are generally safe, but may cause mild irritation and skin maceration.[6] While substantial evidence supports the role of silicone in scar management, emerging data suggest that its benefits may be replicated or even enhanced in other topicals that promote hydration and occlusion.

Retinoids

Retinoids, derived from vitamin A, are frequently utilized in scar remodeling for their ability to enhance follicular epithelial turnover and modulate fibroplasia, collagen synthesis, and angiogenesis.[8,9] In a Phase II study, Loss et al evaluated the efficacy of adapalene gel 0.3% in 20 patients with moderate to severe atrophic acne scars.[10] Patients applied adapalene once daily for four weeks, then twice daily for 20 weeks. After 24 weeks, 55.6% of patients demonstrated a 1-or 2-grade improvement on the global scarring scale.[10] Additionally, 83% of patients reported improved skin texture, and 89% reported improved atrophic scarring, though the results are limited by the absence of a control group and small sample size.[10] Retinoid initiation requires careful management due to potential cutaneous irritation.[9] Common adverse effects include peeling, dryness, and erythema, typically arising during the initial weeks and mitigated through gradual initiation, patient education, and protective skincare.[9]

Pressure Therapy

While the exact mechanism of pressure therapy remains unclear, it is proposed that mechanical compression reduces oxygen delivery to the wounded site.[11] This hypoxic environment may inhibit collagen synthesis and downregulate transforming growth factor-β1 (TGF-β1) activity, thereby limiting fibroblast proliferation and minimizing wound contracture.[11,12] In a prospective cohort study of 18 patients with 26 hypertrophic scars, 10 received pressure therapy and 16 served as controls.[12] Patients in the treatment group wore garments delivering 15 mm Hg of pressure for 23 hours daily over 3 months. Significant improvements in Vancouver Scar Scale, scar thickness, and erythema were observed compared with controls.[12] Despite suggested efficacy, patient adherence remains a challenge due to discomfort and the need for near-continuous wear.[3]

Topical Corticosteroids

The role of topical corticosteroids (TCS) in managing scar-related symptoms, including pain and pruritus, and in promoting scar regression has been proposed based on their well-documented pharmacological effects.[13] Specifically, TCS suppress inflammation, reduce fibroblast proliferation, inhibit angiogenesis, and promote remodeling of the extracellular matrix.[13] In a prospective study of 32 patients with hypertrophic scars and 9 with keloids treated with 0.1% triamcinolone acetonide lotion twice daily for 3-7 months,

improvement rates were 84.4% and 44.4%, respectively.[13] However, evidence supporting their efficacy in scar prevention and treatment remains limited due to the few adequately powered randomized controlled trials. Prolonged or unsupervised use may increase the risks of skin atrophy, depigmentation, pruritus, and telangiectasia, emphasizing the importance of patient education and clinical monitoring.[13]

Cannabinoids

Cannabinoids have been implicated in wound healing and modulation of inflammation, primarily through the activation of cannabinoid receptors.[14] Activation of these receptors, particularly cannabinoid type 2 receptor agonists, has been shown to reduce the expression of pro-inflammatory cytokines, enhance anti-inflammatory mediators, and potentially promote epigenetic changes, such as DNA methylation, which are hypothesized to accelerate the wound healing process.[15,16] Additional studies report accelerated wound closure, enhanced re-epithelialization, decreased collagen deposition, and reduced oxidative stress following cannabinoid treatment.[15] In a case series of three patients with epidermolysis bullosa (EB), topical cannabidiol (CBD) led to significant improvements in pain and wound healing rates, despite the lack of a standardized dosing regimen.[15] Similarly, an international survey of 71 EB patients and their caretakers indicated that both oral and topical CBD use improved pain, pruritus, and wound healing outcomes.[15] In a retrospective study, Kong et al evaluated the effects of a topical CBD-enriched ointment applied twice daily for three months in 20 patients with psoriasis (n=5), atopic dermatitis (n=5), and resulting outcome scars (n=10).[14] The treatment resulted in significant reductions in scarring and cutaneous blemishes, with no reported adverse effects.[14]

CONCLUSIONS

Despite the substantial volume of research on scar management, many studies analyze the same primary data or produce inconclusive or contradictory results, complicating the development of standardized guidelines. This review evaluates the efficacy of topical silicone products, retinoids, pressure therapy, corticosteroids, and cannabinoids. Silicone-based products, which optimize hydration and occlusion, are considered first-line treatment, though similar effects may be achieved with certain OTC occlusive moisturizers, warranting further investigation. Retinoids enhance epithelial turnover, playing an important role in scar treatment. Pressure therapy, while effective, may yield low patient compliance due to discomfort and prolonged wear requirements. Topical corticosteroids and cannabinoids show potential but require evaluation in large, randomized trials. Given the complex pathophysiology of scar formation and variability in individual responses, combination therapies may offer superior outcomes and should be explored in future studies.

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